21. Cascinu S, Labianca R, Barone C et al. Adjuvant treatment of high-risk, radically resected gastric cancer patients with 5-fluorouracil, leucovorin, cisplatin, and epidoxorubicin in a randomized controlled trial. J Natl Cancer Inst 2007; 8: 601–607.
22. Bajetta E, Floriani I, Di Bartolomeo M et al. Randomized trial on adjuvant treatment with FOLFIRI followed by docetaxel and cisplatin versus 5-fluorouracil and folinic acid for radically resected gastric cancer. Ann Oncol 2014; 25: 1373–1378.
23. Schuhmacher C, Gretschel S, Lordick F et al. Neoadjuvant chemotherapy compared with surgery alone for locally advanced cancer of the stomach and cardia: European Organisation for Research and Treatment of Cancer Randomized Trial 40954. J Clin Oncol 2010; 28(35): 5210–5218.
24. Becker K, Langer R, Reim D et al. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas: a summary of 480 cases. Ann Surg 2011; 253(5): 934–939.
25. Jiang L, Yang KH, Guan QL et al. Survival benefit of neoadjuvant chemotherapy for resectable cancer of the gastric and gastroesophageal junction: a meta-analysis. J Clin Gastroenterol 2015; 5: 387–394.
26. Tsuburaya A, Yoshida K, Kobayashi M et al. Sequential paclitaxel followed by tegafur and uracil (UFT) or S-1 versus UFT or S-1 monotherapy as adjuvant chemotherapy for T4a/b gastric cancer (SAMIT): a phase 3 factorial randomised controlled trial. Lancet Oncol 2014; 15(8): 886–893.
27. Hartgrink HH, van de Velde CJH, Putter H et al. Neo-adjuvant chemotherapy for operable gastric cancer: long term results of the Dutch randomised FAMTX trial. Eur J Surg Oncol 2004; 6: 643–649.
28. Pauligk C, Tannapfel A, Meiler J et al. Pathological response to neoadjuvant 5-FU, oxaliplatin, and docetaxel (FLOT) versus epirubicin, cisplatin, and 5-FU (ECF) in patients with locally advanced, resectable gastric/esophagogastric junction (EGJ) cancer: data from the phase II part of the FLOT4 phase III study of the AIO. J Clin Oncol 2015; 33(suppl): abstr 4016.

Annals of Oncology 27: 673–679, 2016
doi:10.1093/annonc/mdv625
Published online 7 January 2016

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†

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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

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†Some of the quality-of-life results were presented as a poster presentation at the American Society of Clinical Oncology (ASCO) 50th Annual Meeting, 30 May–3 June 2014, in Chicago, IL, and as an oral presentation at the European Society for Medical Oncology (ESMO) 16th World Congress on Gastrointestinal Cancer, 25–28 June 2014, in Barcelona, Spain. Data associated with the primary efficacy endpoints and baseline/end-of-treatment quality of life scores were published in *Lancet Oncol* 15:1224–1235, 2014.

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/m^2) 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 therapy 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-5D 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[a]

Time point (weeks)	Ramucirumab + paclitaxel ($N = 330$)			Placebo + paclitaxel ($N = 335$)		
	No. of patients expected to complete QLQ-C30	No. of completed QLQ-C30[b]	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

[a]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.

[b]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[a]				
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[b]				
Index	323	0.74 (0.23)	323	0.73 (0.25)
VAS	318	65.2 (20.9)	324	63.2 (20.1)

[a]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.
[b]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.

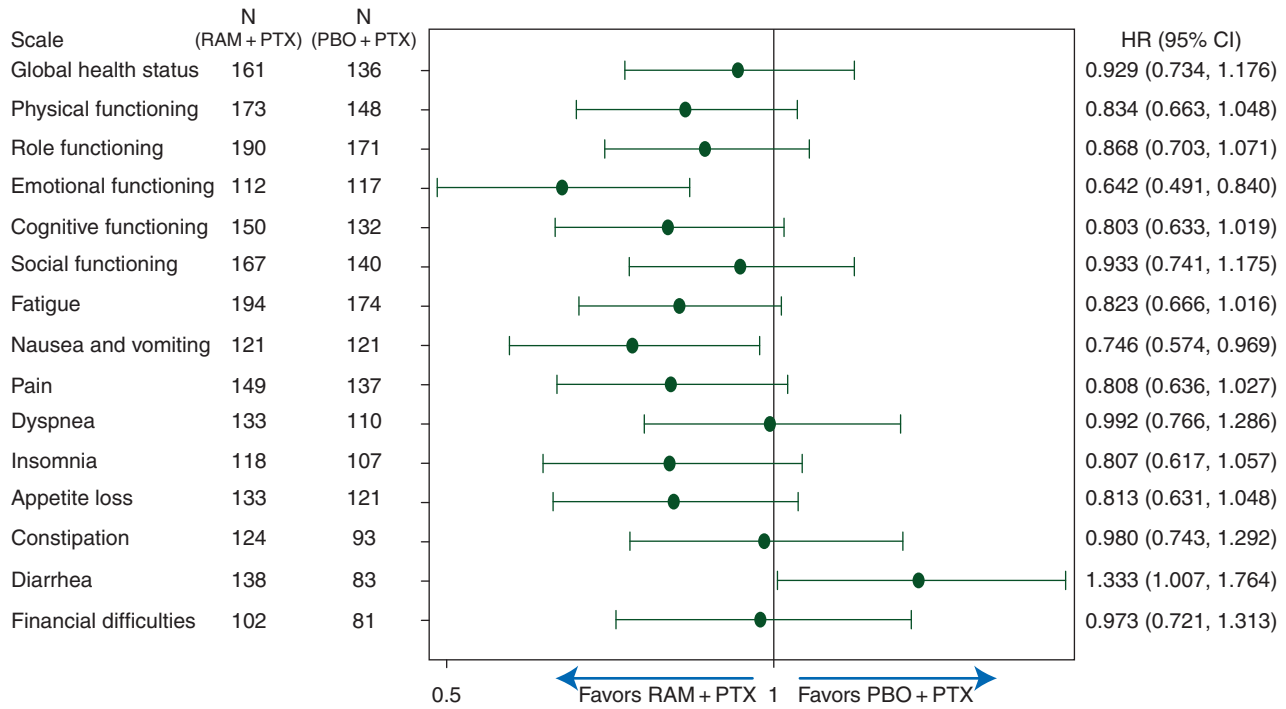

Figure 1. Time to deterioration in EORTC QLQ-C30 scales. Hazard ratios are shown for time to deterioration for each of the EORTC QLQ-C30 scales in the ramucirumab + paclitaxel group, when compared with the placebo + paclitaxel arm. Horizontal bars represent 95% confidence limits. CI, confidence interval; HR, hazard ratio; *N*, number of patients with deterioration; PBO, placebo; PTX, paclitaxel; RAM, ramucirumab.

(favored ramucirumab + paclitaxel) except for diarrhea (Figure 1), indicating similar or longer TtD of function time before worsening of symptoms for patients treated with ramucirumab + paclitaxel over those treated with placebo + paclitaxel. Adjustment for independent baseline factors yielded consistent results with unadjusted analyses. Sensitivity analyses that varied the definition of deterioration also yielded consistent results with those derived from the 10-point definition, with HRs showing the same directionality for each scale.

QLQ-C30 response analysis

Response analysis of each of the 15 QLQ-C30 scales supported the TtD analysis. Visual representation of the QLQ-C30 response is provided for the global health status score, physical and role functioning scores, and pain, fatigue, and appetite loss symptom scores (supplementary Figure S1A–F, available at *Annals of Oncology* online). A consistently higher percentage of 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 ≥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 ≥ 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, $P = 0.0063$) (Figure 2B–D). The analyses must be interpreted with caution due to the high censoring rate (≥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 that 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.

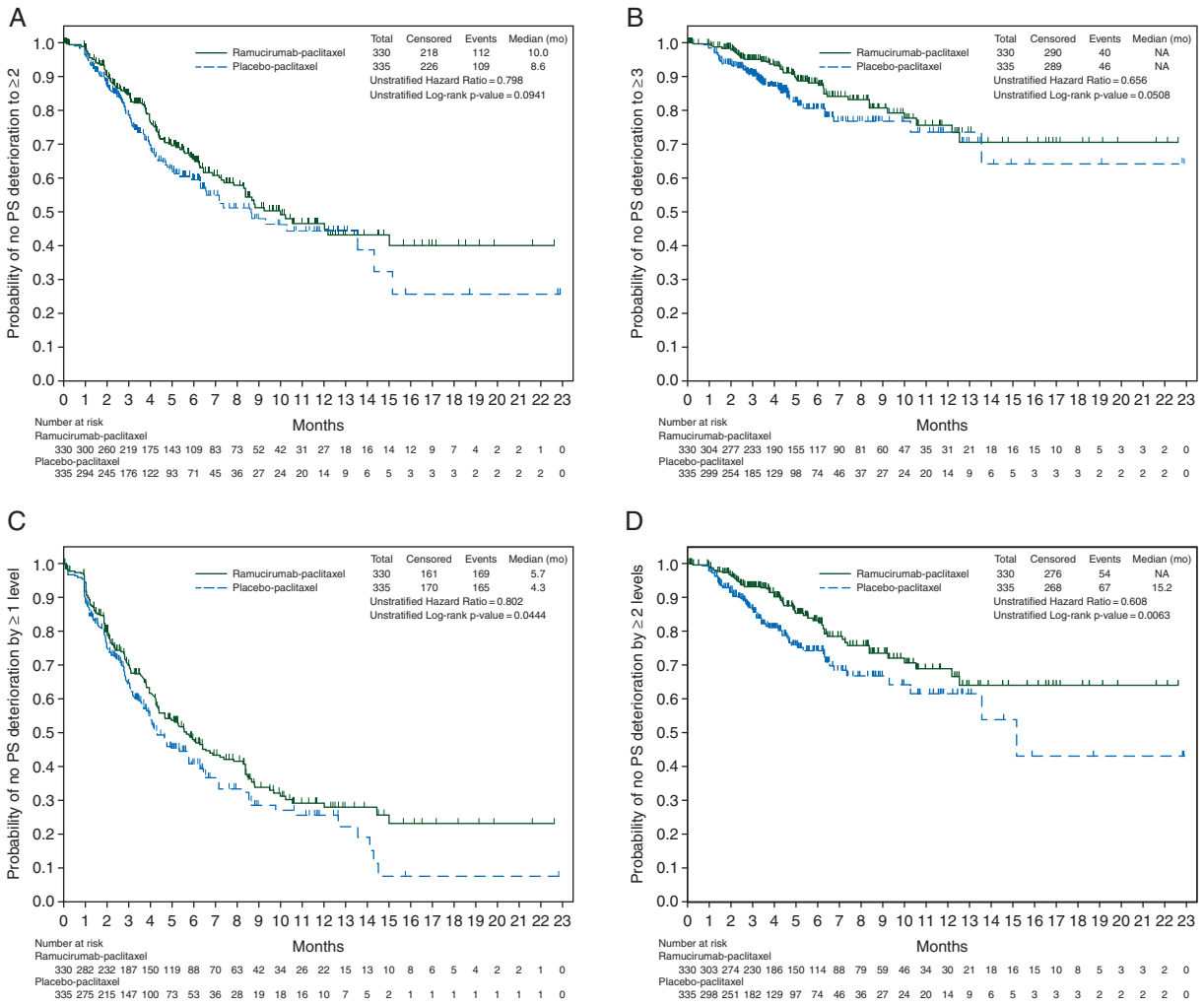

Figure 2. (A–D) Kaplan–Meier plots of time to deterioration of performance status. Time to deterioration defined as a decline in ECOG PS: (A) to ≥2; (B) to ≥3; (C) by ≥1 level; (D) by ≥2 levels. The *y*-axis shows the probability that patients will not deteriorate to these specific PS thresholds. Median TtD (months) is shown, along with the total number of patients, the number of TtD events and the number of censored patients. NA, not available; PS, Eastern Cooperative Oncology Group performance status; TtD, time to deterioration.

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

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 (REGARD): an international, randomised, multicenter, placebo-controlled, phase 3 trial. Lancet 2014; 383: 31–39.
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 double-blind, randomised phase 3 trial. Lancet Oncol 2014; 15: 1224–1235.
9. Wilke H, Van Cutsem E, Oh SC et al. 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.
10. Al-Batran SE, Ajani JA. Impact of chemotherapy on quality of life in patients with metastatic esophagogastric cancer. Cancer 2010; 116: 2511–2518.
11. Satoh T, Bang YJ, Gotovkin EA et al. Quality of life in the trastuzumab for gastric cancer trial. Oncologist 2014; 19: 712–719.
12. 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.
13. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199–208.
14. Oken MM, Creech RH, Tormey DC et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649–655.
15. 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.
16. Osoba D, Rodrigues G, Myles J et al. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998; 16: 139–144.
17. Cox DR, Snell EJ. Analysis of Binary Data, 2nd edition. Chapman & Hall: London, 1989.
18. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997; 35: 1095–1108.
19. 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 (QoliTax). Ann Oncol 2015; 26: 1244–1248.