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Health-related quality of life in the randomized phase 3 study of ramucirumab plus docetaxel versus placebo plus docetaxel in platinum-refractory advanced urothelial carcinoma (RANGE)

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Abstract

Background: To evaluate patient-reported outcomes with ramucirumab plus docetaxel, a regimen which improved progression-free survival in platinum-refractory advanced urothelial carcinoma (aUC).

Methods: RANGE—a randomized, double-blinded, phase 3 trial in patients with platinum-refractory aUC. Ramucirumab (10 mg/kg) plus docetaxel (75 mg/m^2) or placebo plus docetaxel were administered every 21 days until disease progression or unacceptable toxicity. Patients received maximum 10 cycles of docetaxel. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) and EuroQoL five-dimensions (EQ-5D-5L) were administered at baseline, start of each cycle, and 30-day follow-up visit. A $\geq$ 10-point change in QLQ-C30 scores was considered meaningful. Rates of improved/stable scores were compared between treatment arms using Fisher's exact test. Time to deterioration (TtD) was estimated and compared using Kaplan–Meier estimation and log-rank test.

Results: Of the 530 patients, ~ 97% patients in each arm provided baseline QLQ-C30 data. On-treatment compliance was $\geq$ 88% for first 8 cycles. Mean baseline QLQ-C30 scores were similar between arms, with global quality of life (QoL), fatigue, pain, and insomnia having greatest impairment. Postbaseline rates of improved/stable QLQ-C30 scores were similar between treatment arms except for greater improvement in pain score with ramucirumab. TtD of QLQ-C30 scales favored ramucirumab arm. Baseline EQ-5D-5L index and visual analogue scale scores were similar between arms, followed by relatively stable on-treatment scores. EQ-5D-5L scores worsened at post-discontinuation follow-up visit.

Conclusions: Ramucirumab plus docetaxel did not negatively impact QoL compared with docetaxel alone in platinum-refractory aUC. Improved TtD and tumor associated rates of pain favored ramucirumab treatment.

Clinical trail registration: NCT02426125. https://clinicaltrials.gov/ct2/show/NCT02426125. Date of registration: April 24th 2015

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Keyword: Antiangiogenesis, Bladder cancer, Neoplasm metastatsis, Patient-reported outcomes, Quality of life, Ramucirumab, Urinary bladder neoplasm, Urothelial carcinoma

Background

Advanced/metastatic urothelial carcinoma (UC), including carcinomas arising in the bladder, urethra, ureter, and/or renal pelvis, has a poor prognosis. Median survival is approximately 12–14 months with standard first-line platinum-based chemotherapy for advanced/metastatic disease [1]. Despite approvals of various targeted therapies for platinum-refractory advanced UC, most patients have limited treatment options as they experience disease progression. Ramucirumab plus docetaxel has shown higher response rate and improved progression-free survival (PFS) compared to placebo plus docetaxel in the platinum-refractory population [2, 3]. In the refractory setting, quality of life (QoL) is an important factor in the treatment decision-making process for patients with cancer where symptom palliation is the primary goal of therapy [4, 5]. Monitoring of QoL via patient-reported symptoms is also associated with better outcomes than observed with usual care [6].

UCs overexpress the vascular endothelial growth factor (VEGF) ligand and its receptor, vascular endothelial growth factor receptor (VEGFR)-2 [7, 8]. Ramucirumab (a human IgG1 monoclonal antibody and a VEGFR-2 antagonist) [9, 10] plus docetaxel improved PFS (hazard ratio [HR] = 0.757; 95% confidence interval [CI] [0.607, 0.943]) compared with placebo plus docetaxel in the randomized phase 3 trial for platinum-refractory advanced UC (RANGE; NCT02426125) [2]. Whereas other antiangiogenic drugs have failed thus far in refractory UC [1, 11, 12]. Patients treated in the ramucirumab arm also had a numerically higher objective response rate (24.50%, 95% CI [18.80, 30.30] vs 14.0%, 95% CI [9.40, 18.60]) [2]. Although not statistically significant, overall survival (OS) at the final analysis favored the ramucirumab arm (HR = 0.887; 95% CI [0.724, 1.086]; $p = 0.25$) [3]. The most frequent adverse events (AEs) of any grade reported for both the ramucirumab and placebo arms were fatigue (39.1% vs 36.2%), alopecia (23.6% vs 30.6%), diarrhea (23.6% vs 16.6%), decreased appetite (22.1% vs 17.0%), nausea (22.1% vs 14.0%), and stomatitis (23.2% vs 9.0%). Of these AEs, only fatigue had an incidence of ≥ 5% for grade 3/4 (7.0% vs 6.0%). On-study, treatment-related deaths were relatively rare (8 [3.0%] and 5 [2.0%], respectively) [3]. Overall, the proportion of patients with AEs receiving ramucirumab plus docetaxel was similar to the proportion of patients with AEs in the placebo plus docetaxel arm. No new safety signals were detected for ramucirumab plus docetaxel, and the safety profile was considered manageable [2].

The impact of treatment on QoL is not widely reported in refractory advanced UC (aUC), particularly for chemotherapy and anti-VEGFR-2 drug combination therapies. Therefore, we assessed the patient-reported outcomes (PROs) as secondary endpoints in the RANGE trial to evaluate the benefit-risk profile of the addition of ramucirumab to docetaxel from the patient perspective [3]. We hypothesized that patients would experience more symptomatic improvement without experiencing detriment in QoL.

Methods

Study design

The RANGE trial design and the outcome of its primary endpoint were previously published [2]. The trial was conducted during July 2015 and April 2017 and approved by appropriate review boards/ethics committees and followed the principles outlined in the Declaration of Helsinki. All patients provided written informed consent. This study adhered to the CONSORT guidelines.

Patient eligibility criteria

Eligibility criteria included patients with Eastern Cooperative Oncology Group (ECOG) performance status of zero or one and whose advanced disease progressed during or ≤ 14 months after first-line platinum-based chemotherapy. Patients may have also received one checkpoint inhibitor therapy prior to enrollment onto RANGE, in which case prior platinum-containing chemotherapy in ≤ 24 months was allowed. Patients were excluded if they had received a taxane previously [2].

Eligible patients were randomized to receive docetaxel (75 mg/m^2, intravenously [IV]) plus ramucirumab (10 mg/kg, IV) or docetaxel plus placebo, administered on day 1 of each 21-day cycle. Randomization was stratified by geographic region (North America, East Asia, or Europe/other), ECOG performance status at baseline (0 or 1), and visceral metastasis (present or absent). Ramucirumab treatment continued until there was documented disease progression, toxicity or intolerance requiring discontinuation, withdrawal of consent, or noncompliance. Docetaxel could continue, if no prespecified discontinuation criteria were met, for up to six cycles with an additional four cycles allowed if an adequate treatment response was observed. Tumor responses were

assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [13].

Outcomes and assessments

Assessment of PROs, a secondary endpoint of the RANGE trial, was conducted through use of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30), version 3 and the EuroQoL five-dimensions, 5 level (EQ-5D-5L) questionnaire, which measure QoL (functional domains and symptoms) and health status, respectively [14, 15]. Patients completed the questionnaires only if there were cross-culturally validated translations in which they were fluent. Prior to any extensive contact with clinical personnel, patients were asked to complete the questionnaires at baseline, prior to the start of each cycle, and within 30 days after treatment discontinuation (follow-up). QLQ-C30 data were scored according to the EORTC guidelines, using a 0–100 scale with higher scores for global QoL and functional scales representing better QoL and lower scores for symptom scales representing less burden. A $\geq$ 10-point change was considered clinically meaningful [16]. EQ-5D-5L index values were based on the value set for England with a range of -0.281 to 1, with zero representing death and one representing perfect health [17]. Additionally, patients indicated their current health status by marking on a visual analogue scale (VAS) ranging from 0 (worst-imaginable health state) to 100 (best-imaginable health state) [15].

Statistical analysis

Analyses were conducted in the intention-to-treat (ITT) population except for descriptive statistics that were limited to the number of patients who provided data at a given assessment. Compliance rates were calculated based on the number of patients expected to provide data at a given assessment (i.e., those patients still receiving study therapy). Descriptive statistics were used to summarize data, including change from baseline as well as for the EQ-5D-5L scores. QLQ-C30 scores were classified as improved or worsened if change from baseline was $\geq$ 10 points; change < 10 points was classified as stable. For each scale at each postbaseline assessment, the proportion of patients with improved or stable scores was compared using the Fisher's exact test. Time to sustained deterioration (TtD) was defined as time from randomization date to first worsening of $\geq$ 10 points with no subsequent non-worsened assessment relative to baseline. If there were no subsequent assessments, the patient was classified as deteriorated. The follow-up assessment after treatment discontinuation could not be considered as a subsequent non-worsened assessment. Patients without deterioration were censored at the last non-deteriorated assessment. Kaplan–Meier method was used to estimate the probability of TtD, and unstratified log-rank test was used to investigate significance between treatment groups. Univariable Cox regression analysis was performed to test the association of treatment with TtD. No adjustments were made for multiplicity, but p-values < 0.05 were used to identify potential trends. These analyses discussed here were performed on the ITT population at the time of the OS database lock [3]. All the analyses were conducted using SAS software (SAS, Version 9.1.2 or higher).

Results

RANGE patients and questionnaire compliance

In the randomly assigned patients (N = 530, ITT population) from the 727 screened for eligibility (Fig. 1), baseline characteristics were similar between treatment arms (Table 1). At baseline, 254 (96.6%) of patients in the ramucirumab arm and 260 (97.4%) in the placebo arm provided QLQ-C30 and EQ-5D-5L data (Table 2). For the first 8 cycles, compliance was $\geq$ 88% for both the QLQ-C30 and EQ-5D-5L, (Table 2). The most common reasons for noncompliance were failure by the site to administer and patient refusal to complete the questionnaires (Fig. 1). At the post-discontinuation follow-up visit, compliance was lower overall, with 52–54% of patients providing data. When grouped by those who provided data at follow-up and those who did not, the groups were similar in baseline patient characteristics, time on therapy, BOR, and reasons for discontinuation.

Descriptive summaries

Mean baseline scores for both questionnaires were similar between treatment arms (Table 3). With high scores being favorable for global QoL and functional domains of the QLQ-C30, the lowest mean scores were reported for global QoL, indicating the domain with greatest impairment at baseline. With low scores being favorable for symptoms, the highest mean scores were reported for fatigue, pain, and insomnia, indicating the symptoms of greatest burden at baseline.

When considering high-level assessment of QoL and health status, no clear differences were observed between the treatment arms for changes in mean scores from baseline of the QLQ-C30 global QoL scale, EQ-5D-5L index, and EQ-5D-5L VAS (Fig. 2a–c). Although scores within arms worsened over time, the mean changes for on-treatment assessments were small. Similar patterns of no differences between arms in changes from baseline were observed for the other QoL scales, with the exception of pain (Additional file 1: Figure S1). For the functional scales, worsened scores over time were observed for physical and role functioning. For symptom scales,

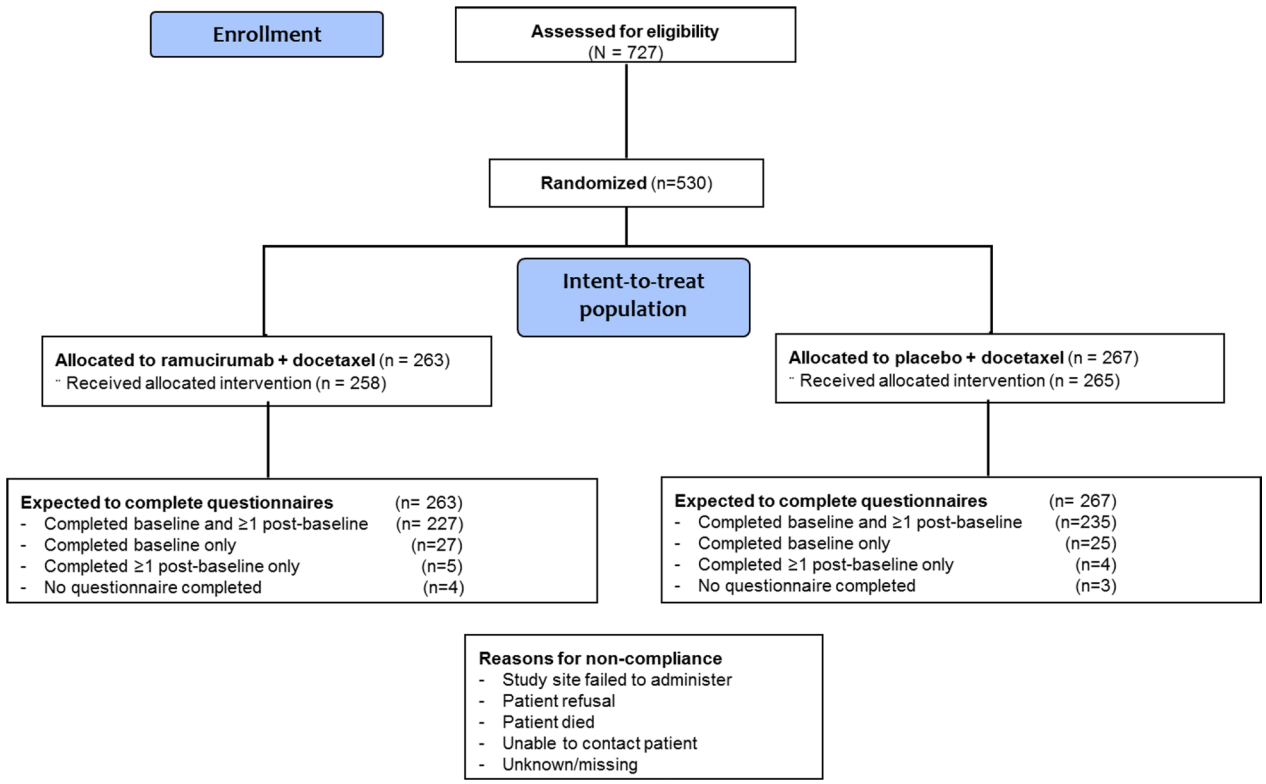

Fig. 1 Patient disposition. *n* = number of patients

fatigue, dyspnea, and diarrhea had the greatest worsening over time. In the case of pain, improved scores were observed in the ramucirumab arm over the first five cycles, while scores worsened in the placebo arm. Additional file 1: Figure S2 summarizes the distribution of EQ-5D-5L responses over time. At baseline, the highest levels of impairment (i.e., moderate or more severe) were reported for pain/discomfort. In general, the distributions of responses for all dimensions were similar over time for on-treatment assessments (Additional file 1: Figure S2A-E). For all scales, change from baseline was worst at the post-discontinuation follow-up assessment. Thus, in general, findings of the QLQ-C30 and the EQ-5D-5L were consistent.

Time to sustained deterioration

Results for TtD of QLQ-C30 scales are summarized in Fig. 3. The HR was < 1 for all scales (range 0.76–0.96), indicating a trend towards longer TtD in the ramucirumab arm. Kaplan–Meier figures are presented for those scales with ˂65% censoring of events (Additional file 1: Figure S3A-I). Median TtD for global QoL was 6.9 months (95% CI 4.2 months—8.9 months) vs. 4.6 months (95% CI 3.5 months—5.5 months) (HR 0.88, 95% CI 0.7–1.2).

Rates of improved or stable scores

The proportion of patients whose QoL scores improved, remained stable, or deteriorated from baseline at each postbaseline assessment are shown in Fig. 4, for the scales with the greatest impairment at baseline; Additional file 1: Figure S4 depicts these results for all other scales. For each scale, rates of improved/stable were similar between treatment arms in early cycles. Of note, a higher proportion of patients in the ramucirumab arm had either improved or stable pain scores at cycles 4, 5, and 7 compared to the placebo arm (Fig. 4d). Indeed, across all cycles, the pain scale, relative to the other scales (Fig. 3a and Additional file 1: S4), exhibited consistency with respect to having the greatest proportion of patients with improvement in pain within the ramucirumab arm.

Exploratory analyses

Considering all prespecified analyses, the consistency of the pain results prompted an exploratory analysis evaluating the association with best overall response to treatment (Fig. 5). Because the global QoL scale provides the most holistic assessment, it was similarly evaluated. During the first four cycles, the range of patients achieving complete response (CR)/partial response (PR) with

Table 1 Baseline demographics and disease characteristics

	RAM + DOC (n = 263)	PL + DOC (n = 267)
Median age, years (range)	65 (34–86)	66 (32–83)
Male	213 (81)	215 (81)
Race		
White	203 (77)	204 (76)
Asian	54 (20)	61 (23)
ECOG performance status		
0	121 (46)	125 (47)
1	139 (53)	142 (53)
Geography		
North America	24 (9)	24 (9)
East Asia	53 (20)	57 (21)
Europe/Other	186 (71)	186 (70)
Primary tumor site		
Bladder	180 (68)	177 (66)
Urethra	7 (3)	6 (2)
Renal pelvis	39 (15)	42 (16)
Ureter	33 (13)	37 (14)
Other	1 (< 1)	5 (2)
Sites of metastases		
Lymph node only	41 (16)	42 (16)
Visceral	182 (69)	188 (70)
Liver	78 (30)	69 (26)
Lung	98 (37)	121(45)
Bone	56 (21)	53 (20)
Hemoglobin < 10 g/dL	34 (13)	36 (13)
Patients with time since previous chemotherapy < 3mo	115 (44)	126 (47)
Bellmunt risk factors		
0	88 (33)	93 (35)
1	105 (40)	109 (41)
2	64 (24)	57 (21)
3	6 (2)	8 (3)
Prior neoadjuvant or adjuvant therapy	87 (33)	107 (40)
Prior platinum-based therapy:		
Cisplatin	161 (61)	189 (71)
Carboplatin	97 (37)	77 (29)
Prior immune checkpoint inhibitor	17 (7)	28 (10)

DOC docetaxel, *ECOG* Eastern Cooperative Oncology Group, *mo* months, *n* number of patients, *PL* placebo, *RAM* ramucirumab

Data are n (%), unless otherwise indicated

For a full list of patient demographics and disease characteristics at baseline in the intention-to-treat population [2]

improved global QoL was 17.6–25.0% for ramucirumab and 10.8–21.6% for placebo; the range for patients with stable disease (SD) was 9.6–17.3% for ramucirumab and 10.0–21.8% for placebo (Fig. 5a). During the first four cycles, the range of patients achieving CR/PR with

Table 2 EORTC QLQ-C30 and EQ-5D-5L compliance rates from baseline through cycle 8 and 30-day follow-up (ITT population)

Assessment time point	QLQ-C30		EQ-5D-5L	
	RAM + DOC (n = 263)	PL + DOC (n = 267)	RAM + DOC (n = 263)	PL + DOC (n = 267)
Baseline	254/263 (97)	260/267 (97)	254/263 (97)	260/267 (97)
Cycle 1	214/229 (93)	226/237 (95)	212/229 (93)	225/237 (95)
Cycle 2	159/165 (96)	159/165 (96)	158/165 (96)	159/165 (96)
Cycle 3	139/147 (95)	133/138 (96)	136/147 (93)	133/138 (96)
Cycle 4	114/126 (90)	100/105 (95)	114/126 (90)	100/105 (95)
Cycle 5	108/114 (95)	88/94 (94)	107/114 (94)	88/94 (94)
Cycle 6	79/87 (91)	64/71 (90)	83/87 (95)	63/71 (89)
Cycle 7	64/68 (94)	52/59 (88)	66/68 (97)	52/59 (88)
Cycle 8	52/56 (93)	36/41 (88)	51/56 (91)	36/41 (88)
Follow-up	116/215 (54)	119/231 (52)	113/215 (53)	121/231 (52)

DOC docetaxel, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, *EQ-5D-5L* EuroQoL five-dimensions, *ITT* intention-to-treat, *PL* placebo, *RAM* ramucirumab

Data are presented as number/total number (%)

For compliance, the total number is the number expected to complete at the assessment time point

On-treatment compliance reporting is truncated at cycle 8, but similar rates were reported for later cycles

The median number of cycles administered in both treatment arms was 4

Table 3 Baseline Scores (Mean [standard deviation])

	RAM + DOC (n = 263)	PL + DOC (n = 267)
EORTC QLQ-C30 Scales[a]		
Global QoL	62.0 (22.9)	60.8 (21.4)
Physical functioning	75.9 (22.4)	74.2 (21.7)
Role functioning	73.3 (29.5)	72.1 (29.9)
Emotional functioning	76.0 (22.4)	75.0 (21.2)
Cognitive functioning	85.9 (18.3)	84.6 (20.3)
Social functioning	74.6 (28.8)	71.2 (30.2)
Fatigue	33.1 (25.9)	36.0 (24.8)
Nausea/vomiting	8.0 (16.1)	9.0 (17.5)
Pain	32.0 (31.1)	33.8 (30.7)
Dyspnea	17.4 (24.6)	17.9 (25.4)
Insomnia	27.7 (30.9)	28.8 (29.9)
Appetite loss	22.4 (29.2)	23.3 (31.9)
Constipation	21.0 (28.3)	24.6 (30.0)
Diarrhea	8.1 (16.6)	6.3 (16.0)
EQ-5D-5L Index Score[b]	0.77 (0.23)	0.78 (0.19)
EQ-5D-5L VAS	67.2 (21.7)	67.3 (18.7)

DOC docetaxel, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, *EQ-5D-5L* EuroQoL five-dimensions, *n* number of patients, *PL* placebo, *QoL* quality of life, *RAM* ramucirumab, *SD* standard deviation, *VAS* visual analogue score

[a] For the EORTC QLQ-C30, high scores are favorable for functional domains and global QoL; low scores are favorable for symptoms

[b] For the EQ-5D-5L, high scores are favorable. The range for Index Score is -0.281 to 1 and the range for VAS is 0 to 100 (higher scores are favorable)

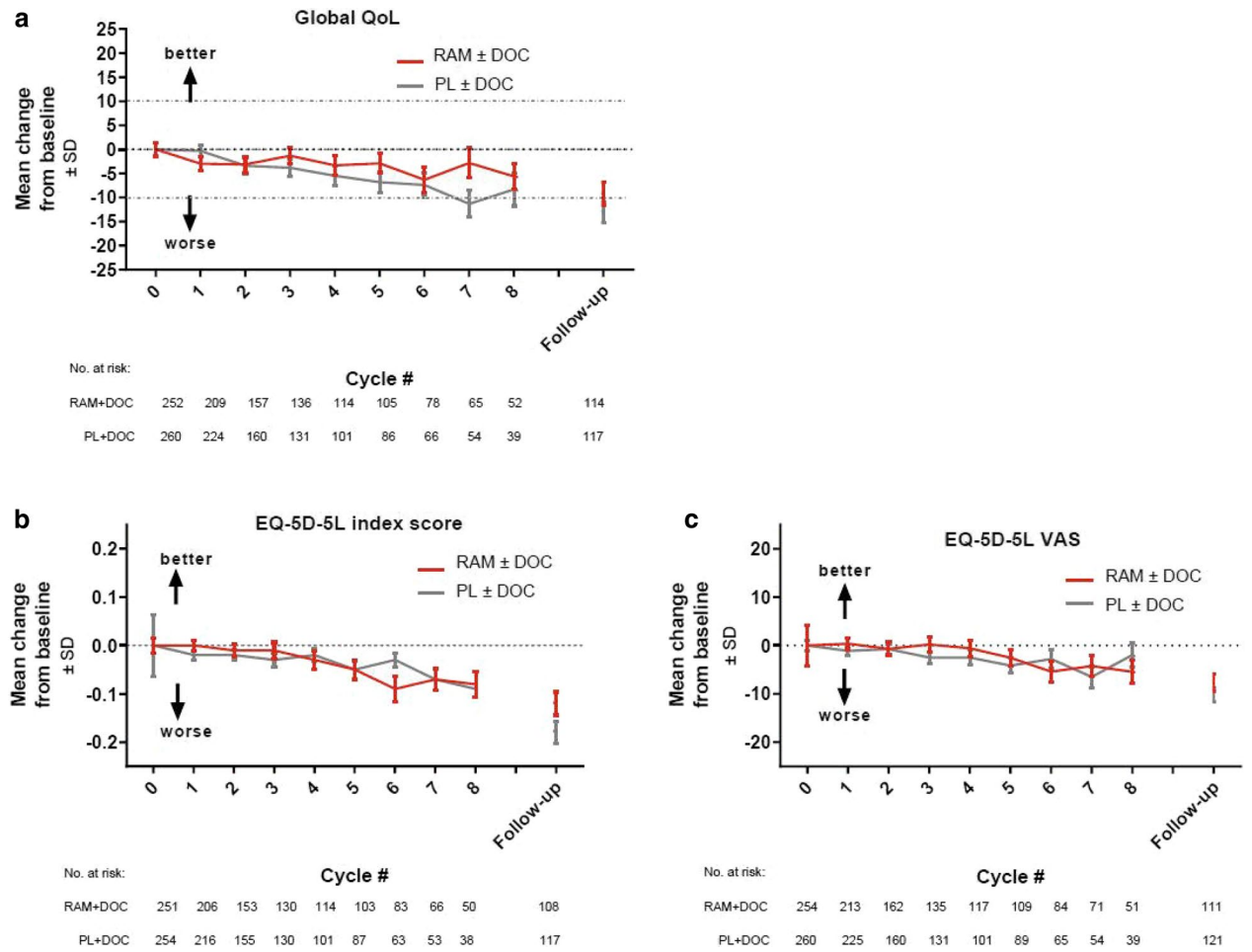

Fig. 2 Mean change from baseline in the mean scores of the EORTC QLQ-C30 global QoL scale (**a**), EQ-5D-5L index (**b**) and visual analogue scale scores (**c**). *DOC* docetaxel, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, *EQ-5D-5L* EuroQoL five-dimensions, *RAM* ramucirumab, *SD* standard deviation, *VAS* visual analogue scale

improved pain was 29.4–30.9% for ramucirumab and 13.5–27.0% for placebo; the range for patients with SD was 17.3–28.8% for ramucirumab and 16.4–29.1% for placebo (Fig. 5b).

In general, a higher proportion of patients who achieved CR/PR had improved pain scores in the ramucirumab arm versus the placebo arm. No apparent difference in pain palliation was seen between arms for patients who achieved SD. Similar results were observed for improved global QoL between ramucirumab versus placebo arms in patients who achieved CR/PR and SD (Fig. 5).

Discussion

QoL is of utmost importance when considering therapeutic options for patients in the palliative setting [4, 18]. There can be concerns when a second agent is added to chemotherapy if gains in efficacy are also accompanied by increased toxicity [19], such as in the RANGE study where there were numerically higher rates of any-grade diarrhea, decreased appetite, nausea, and stomatitis in the ramucirumab plus docetaxel arm compared with the placebo plus docetaxel arm [3]. Thus, evaluating the effects on QoL through PROs when ramucirumab plus docetaxel was compared to placebo plus docetaxel was a key secondary endpoint in the RANGE trial. While on therapy, patients in the placebo plus docetaxel arm generally maintained global QoL and health status. Results were similar for the ramucirumab plus docetaxel arm, suggesting no detrimental impact. Worsening at the 30-day follow-up visit in both treatment arms was potentially associated with the negative impact of disease progression, which was the most common reason for treatment discontinuation. The longer PFS was consistent with trend for longer TtD in global QoL in the ramucirumab plus docetaxel arm. These findings may be

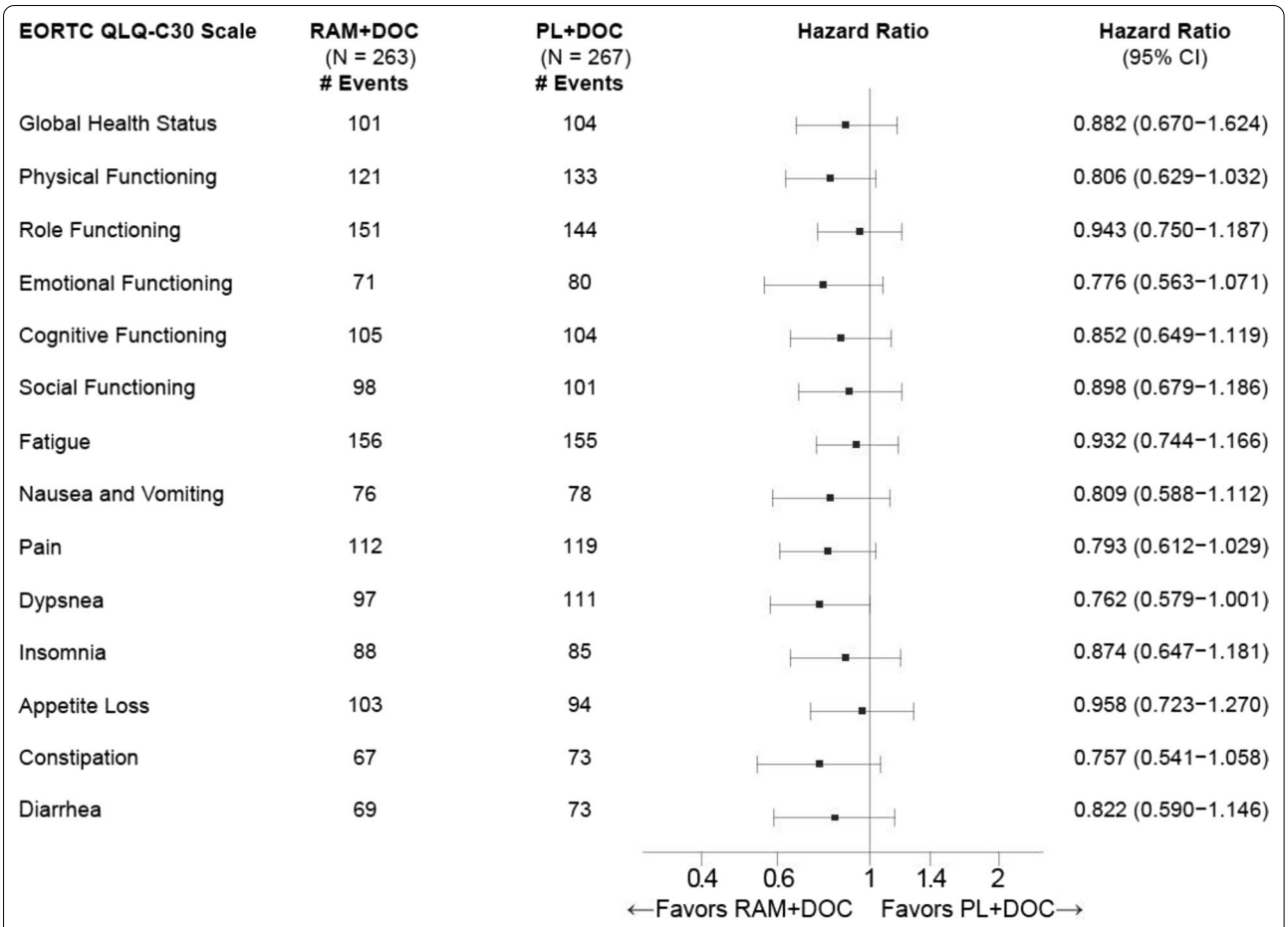

Fig. 3 Time to sustained deterioration of QLQ-C30 scales. *CI* confidence interval; *DOC* docetaxel, *EORTC QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30, *N* number of patients, *HR* hazard ratio, *PL* placebo, *QoL* quality of life; *RAM* ramucirumab. Forest plot of time to sustained deterioration, HRs (unstratified) for each functional and symptom scale are depicted. HRs were estimated using a Cox regression model. 2-sided p-values were based on normal approximation

helpful when considering the value of delaying disease progression and the balance of benefit and risk of combination therapy from the patient perspective.

In our study, all of the more specific aspects of QoL were at least maintained in the ramucirumab plus docetaxel arm relative to the placebo plus docetaxel arm. The strongest trend of delay in deterioration among the functional scales favoring ramucirumab plus docetaxel was for physical functioning which addresses mobility and self-care. Fatigue and insomnia were two of the most prominent symptoms reported by patients at baseline. Changes in fatigue were similar between arms, with patients more likely to report worsening. Insomnia scores generally remained similar both between and within arms.

Of all of the dimensions assessed by the QLQ-C30 and the EQ-5D-5L, pain may be the one most closely associated with disease symptoms and treatment efficacy, with less confounding by toxicity of treatment [20–22]. At baseline, the mean score for pain from the QLQ-C30 indicated high levels of pain and < 30% of patients reported no pain or discomfort on the EQ-5D-5L. All analyses of pain from the QLQ-C30 suggested a differential effect between arms. In the descriptive summaries, mean scores generally improved for the ramucirumab plus docetaxel arm, but worsened for the placebo plus docetaxel arm. At later cycles, more patients in the ramucirumab plus docetaxel arm reported improved or stable pain scores. The HR for TtD was 0.79 (95% CI 0.61, 1.0). In the exploratory analysis conducted, patients treated with ramucirumab plus docetaxel, who achieved a complete or partial response, often reported improvement in pain. The observed relative benefit in pain palliation may be associated with the greater extent of tumor shrinkage among responders and longer duration of response seen in the ramucirumab plus docetaxel arm. The association of symptom palliation with tumor response in other populations has been previously reported [23, 24].

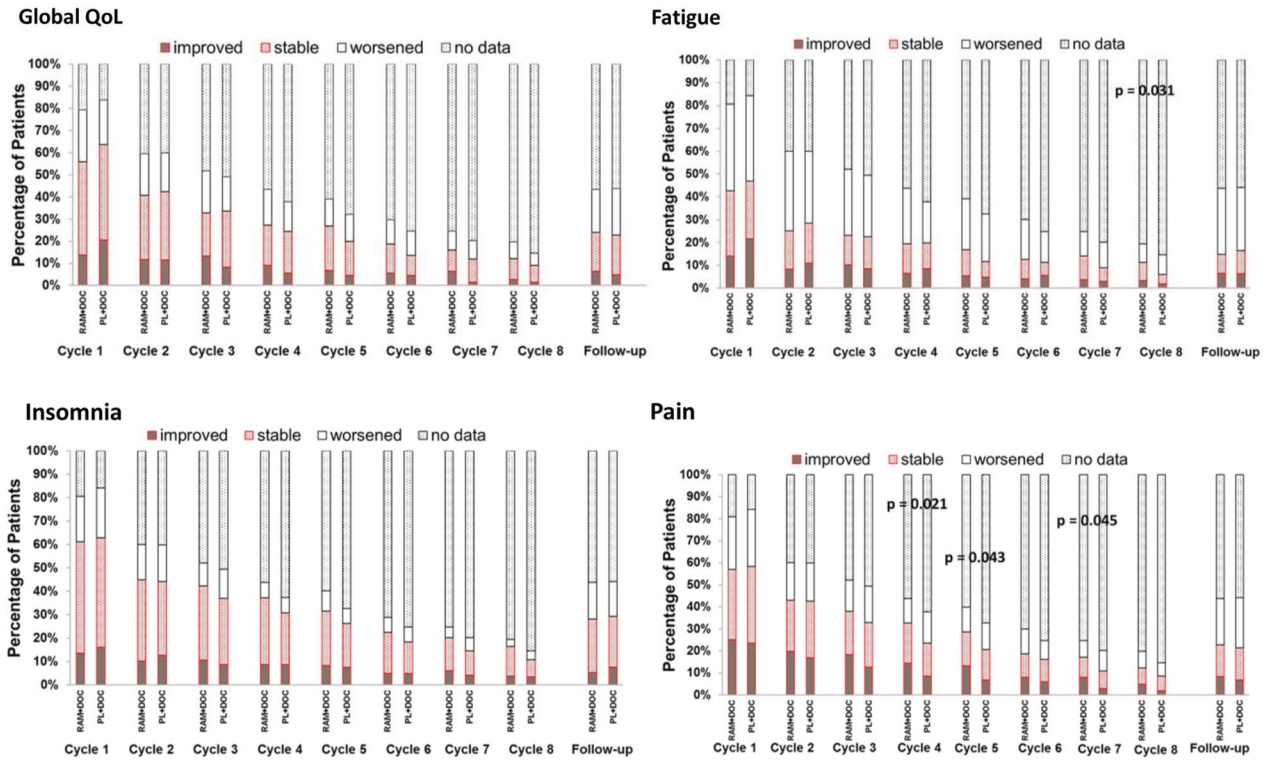

Fig. 4 Proportion of patients in ITT population with improved, stable or worsened QoL of the scales with greatest impairment at baseline. *QoL* quality of life, *ITT* intention-to-treat. For each scale at each postbaseline assessment, proportion of patients with improved or stable scores was compared using the Fisher's exact test

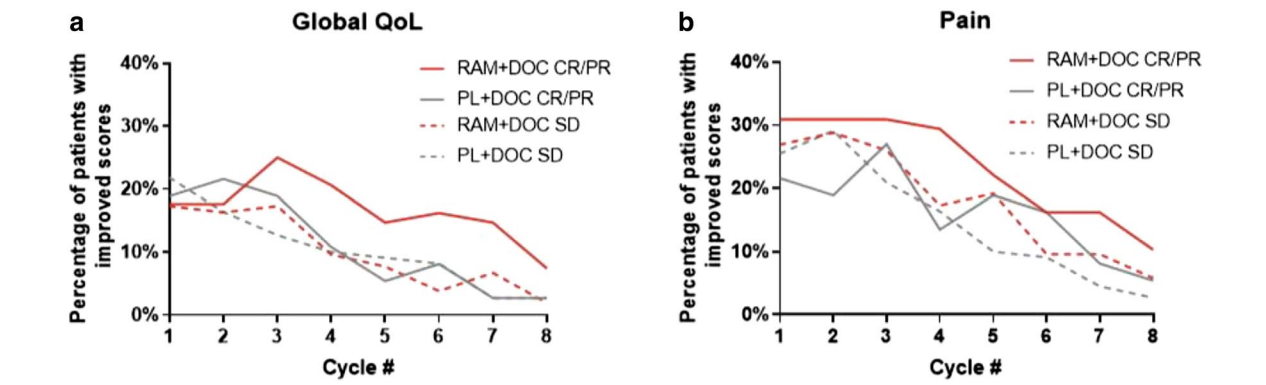

Fig. 5 Proportion of patients with improvement in global QoL (**a**) and pain (**b**) scales among those patients with BOR of CR/PR or SD. *BOR* best overall response, *CR* complete response, *DOC* docetaxel, *n* number of patients, *PL* placebo, *PR* partial response, *QoL* quality of life; *RAM* ramucirumab, *SD* stable disease. For each scale at each postbaseline assessment, proportion of patients with improved or stable scores between treatment and placebo arms was compared using the Fisher's exact test. PR/CR as BOR: RAM + DOC (n = 68) and PL + DOC (n = 37). SD as BOR: RAM + DOC (n = 104) and PL + DOC (n = 110)

Recent phase 3 studies of immune checkpoint inhibitors in similar study populations also assessed QoL [25, 26]. Although trial designs differed, the control arms were single-agent chemotherapy, and QoL was assessed with the QLQ-C30. However, different analysis approaches limit comparisons across the studies. In general, chemotherapy-based regimens were associated with within-arm worsening in global QoL over time and checkpoint inhibitors were associated with no within-arm improvement or worsening. In KEYNOTE-045, the HR for time to first

deterioration in global QoL was0.72, indicating a longer time to first deterioration for pembrolizumab compared to chemotherapy [25]. In IMvigor211, the HR for time to sustained deterioration in global QoL was not reported, but median values were the same for atezoluzimab and chemotherapy [26].The HR for time to sustained deterioration in global QoL in RANGE was 0.887, trending for a longer time to deterioration for ramucirumab plus docetaxel compared to chemotherapy (docetaxel). In RANGE, the addition of ramucirumab to chemotherapy did not further worsen QoL but demonstrated within-arm improvements in pain scores. Both RANGE and KEYNOTE-045 [25] observed a worsening of QoL associated with disease progression. This supports our findings that disease-related symptoms may have a more prominent effect on QoL in this setting.

This study used robust analytical methods. The analysis was prespecified and completion rate of questionnaires was high during the study. The ramucirumab and placebo groups were similar at baseline in PROs and patient and disease characteristics. This study showed no deterioration of QoL with addition of ramucirumab, with consistency observed across QLQ-C30 global QoL scale, EQ-5D-5L index, and VAS scores. The completion rate at the post-discontinuation follow-up visit in our study was comparable to other studies in advanced cancer [27, 28]. In our study slightly more than half of patients provided post-discontinuation data, limiting the characterization of QoL and health status for that time period.

Limitations in the study include PRO instruments, patient characteristics, and incomplete follow-up data. Although cancer-specific and the most widely used in aUC trials, the QLQ-C30 is not specific to UC. No validated tumor-specific module to supplement the QLQ-C30 is available for use to assess additional concerns of aUC patients [29, 30]. With the baseline eligibility criterion of ECOG performance status of zero or one, there is less opportunity for patients to report improvements in PROs. As is common in advanced cancer trials, early discontinuation of patients results in non-random missing data; therefore, we attempted to minimize the impact by conducting cycle-by-cycle analysis to explore data trend instead of focusing on only certain cycle as a snapshot. We also made the general assumption that patients who discontinued therapy likely have worsened QoL, as might be expected with disease progression which was most common reason for study discontinuation. While PRO completion rates were lower at follow-up, characteristics and outcomes of patients who provided follow-up data were similar to those who did not. However, despite these limitations, trends in differences between arms were observed that were consistent with other clinical outcomes.

As the term itself suggests, PROs are reported by patients themselves without any interpretation from a physician or anyone else. PROs can be used to support evaluation of response to treatment and to increase clinician-patient engagement [31]. Integration of PROs to the care demonstrated a survival benefit in patients with cancer compared with patients undergoing usual care (median 31.2 months vs. median 26.0 months, $p=0.03$) [6]. In addition, PROs provide patients with a mechanism to self-report symptoms, minimize a decline in QoL, reduce hospitalization and emergency room admissions, and prolonged time on chemotherapy [32]. As newer agents become available for aUC, PRO/QoL data should be provided to help clinicians make informed treatment decisions [33–35].

Conclusions

In summary, QoL outcomes of the phase 3 RANGE trial presented here provided additional insights regarding no negative impact of ramucirumab plus docetaxel on QoL compared with placebo plus docetaxel. The association of pain palliation with tumor response and disease control observed in this study may be used when considering therapeutic choices for advanced UC.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12894-020-00752-w.

Additional file 1. Figure S1. Change from baseline in QLQ-C30 scales (except Global QoL). DOC = docetaxel; PL = placebo; QLQ-C30 = Cancer Quality of Life Questionnaire C30; RAM = ramucirumab; SEM = standard error of the mean. **Figure S2.** Distributions of dimension responses for EQ-5D-5L (patients who provided data) DOC = docetaxel; EQ-5D-5L = EQ-5D-5L = EuroQoL five-dimensions; n = number of patients; PL = placebo; RAM = ramucirumab. **Figure S3.** Kaplan-Meier TtD plots of QLQ-C30 scales with less than 65% censoring CI = confidence interval; HR = hazard ratio. **Figure S4.** Proportion of patients with improved, stable, or worsened QLQ-C30 scales (except global QoL, fatigue, pain, insomnia) DOC = docetaxel; PL = placebo; QLQ-C30 = Cancer Quality of Life Questionnaire C30; QoL = quality of life; RAM = ramucirumab.

Abbreviations

aUC: Advanced urothelial carcinoma; CI: Confidence interval; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; EQ-5D-5L: EuroQoL five-dimensions, 5 level; HR: Hazard ratio; IV: Intravenously; OS: Overall survival; PRO: Patient-reported outcome; QoL: Quality of life; VEGF: Vascular endothelial growth factor; VEGFR: Vascular endothelial growth factor receptor.

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Authors' contributions

Study Concept and Design: RdW, AML, DPP. Acquisition of Data: AN, HN, NM, JLL, RdW. Analysis and interpretation of data: AN, HN, NM, JLL, DPP, RdW, AD,

AML, HM, KBM. Drafting of the manuscript: AN, HN, JLL, DPP, RdW, AML, KBM, TP. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: HM. Administrative, technical, or material support: KBM. Supervision: KBM. All authors have read and approved the manuscript.

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Eli Lilly and Company. The funders were involved in the design of the study, analysis and interpretation of the data, and writing and critical revision of the manuscript. This study was reported, in part, at the American Society of Clinical Oncology-Genitourinary Cancers Symposium, February 2018.

Availability of data and materials
Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal. The data that support the findings of this study are available from Clinicalstudydatarequest.com, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of www.clinicalstudydatarequest.com. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com under "How it works".

Ethics approval and consent to participate
The study protocol was approved by: Comitato Etico, Fondazione IRCCS (Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; internal reference. no. INT 47/16); Institutional Review Board of University of Tsukuba Hospital (University of Tsukuba, Tsukuba, Japan; internal reference. no. 15-32); National Cancer Center Hospital East Institutional Review Board (National Cancer Center Hospital East, Chiba, Japan; internal reference. no. K0471); Ethics Review Board of Asan Medical Center (Asan Medical Center, Seoul, Republic of Korea; internal reference. no. 2015-0375); Yale University Institutional Review Board #2, 3, 4B, 5—Human Investigation Committee I, II, III, IV (Yale University, New Haven, CT, USA; internal reference. no. 1505015871); METC Brabant gebouw Hasseltveste Tilburg Netherlands (internal reference. no. P1513); OHRPP IRB UCLA Medical Center (University of California Los Angeles, Los Angeles, CA, USA; internal reference. no. 15-000632-AM-0003); NRES Committee South Central – Berkshire, UK (internal reference. no. 15/SC/0306). The study followed the principles outlined in the Declaration of Helsinki. All patients provided written informed consent.

Consent for publication
Not Applicable.

Competing interests
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