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ORIGINAL ARTICLE

Exposure-response relationship of ramucirumab in RANGE, a randomized phase III trial in advanced urothelial carcinoma refractory to platinum therapy

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Aims: Patients with advanced urothelial carcinoma (UC) who progress after platinum-based chemotherapy have a poor prognosis, and there is a medical need to improve current treatment options. Ramucirumab plus docetaxel significantly improved progression-free survival but not overall survival (OS) in platinum-refractory advanced UC (RANGE trial; NCT02426125). Here, we report the exposure-response (ER) of ramucirumab plus docetaxel using data from the RANGE trial.

Methods: Pharmacokinetic (PK) samples were collected (cycle 1-3, 5, 9 [day 1] and 30 days from treatment discontinuation), and PK data were analysed using population PK (popPK) analysis. The minimum ramucirumab concentration after first dose administration ($C_{min,1}$, or trough concentration immediately prior to the second dose) was derived by popPK analysis and used as the exposure parameter for ER analysis. Cox proportional hazards regression models and matched case-control analyses were used to evaluate the relationship between $C_{min,1}$ and OS. The $C_{min,1}$ relationship with safety was assessed descriptively.

Results: Several poor prognostic factors (ECOG 1, haemoglobin concentration <100 g/L, presence of liver metastases) appeared more frequently in the lower exposure quartiles, suggesting a possible disease-PK interaction. A significant association

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was identified between $C_{min,1}$ and OS ($P = .0108$). Higher exposure quartiles were associated with longer survival and smaller hazard ratios compared to placebo. No new exposure-safety trends were observed within the exposure range (ramucirumab 10 mg/kg once every 3 weeks).

Conclusions: This prespecified ER analyses suggests a positive relationship between efficacy and ramucirumab exposure, with an imbalance associated with disease prognostic factors. Further investigation may elucidate a possible disease-PK relationship.

KEYWORDS
exposure-response, overall survival, progression-free survival, ramucirumab, urothelial carcinoma

1 | INTRODUCTION

Ramucirumab, a fully human IgG1 monoclonal antibody, is a selective antagonist of VEGFR-2.[1,2] Ramucirumab exposure was associated with improvements in overall survival (OS) and progression-free survival (PFS) in the advanced setting of several solid tumours, including gastric, colorectal and non-small-cell lung cancers.[3–5] RANGE, a phase 3, randomized trial, evaluated ramucirumab plus docetaxel vs placebo plus docetaxel for patients with locally advanced or metastatic urothelial carcinoma (UC) after disease progression on platinum-based chemotherapy.

The primary endpoint of RANGE, PFS, was met; PFS was significantly improved in the ramucirumab treatment arm compared to the placebo arm (median PFS 4.1 vs 2.8 months, hazard ratio [HR] = 0.696, $P = .0002$).[1] OS was not significantly different, but a trend towards prolonged OS in the ramucirumab arm compared to placebo was observed (median OS 9.4 months vs 7.9 months, HR = 0.887, $P = .25$).[6] No major ramucirumab-related toxicity was observed.[1,6]

Monoclonal antibody (mAb) pharmacokinetics (PK) are variable and influenced by a multitude of factors, including antibody disposition, target occupancy and antibody clearance.[7] Determining the optimal dose for efficacy and safety has proven challenging and more studies are needed to improve individual dosing strategies. Typically, increased exposure results in increased efficacy, but also increased risk of adverse events and a lack of improvement in the risk-benefit ratio. In addition, the catabolic activity of the disease state and immunogenicity/antidrug antibody formation can contribute to tissue clearance, decreased exposure and nonlinear elimination kinetics.[7,8] In several clinical trials, including those of nivolumab and pembrolizumab, baseline clearance has been significantly associated with OS. Nivolumab exposure-response (ER) analyses using overall response rate as an efficacy measure found that baseline clearance, not exposure, was a significant covariate.[9,10] Furthermore, recent studies have highlighted a potential challenge in characterization and interpretation of the ER relationship for therapeutic mAb which can be often confounded by various factors due to the complex interplay of patient disease

What is already known about this subject

- RANGE was a phase 3 randomized trial of ramucirumab or placebo (plus docetaxel) for patients with advanced metastatic urothelial carcinoma after disease progression on platinum-based chemotherapy.
- In platinum-refractory advanced urothelial carcinoma, ramucirumab plus docetaxel improved progression-free survival significantly over placebo plus docetaxel, and there was a numerical but not statistically significant difference in overall survival (OS).

What this study adds

- Increased ramucirumab exposure may be associated with improved OS benefit compared to placebo.
- Several poor prognostic factors (ECOG 1, haemoglobin concentration <100 g/L, presence of liver metastases) appeared more frequently in the lower exposure quartiles, suggesting a possible disease-pharmacokinetic interaction.
- Lower exposure quartiles are possibly associated with poor disease prognostic factors and shorter OS. Exposure-response findings highlight the importance of disease state's involvement in pharmacokinetics and overall survival.

characteristics, drug clearance and clinical outcomes.[11,12] Ramucirumab as a single-agent or in combination with chemotherapy has been approved in second-line gastric, lung, colorectal and liver cancers.[13–18] In addition, ramucirumab in combination with erlotinib is approved in first-line EGFR-mutated NSCLC.[19]

Here, we report exposure-efficacy and exposure-safety analyses on data from patients with UC treated with ramucirumab plus docetaxel from the RANGE trial. Population PK analysis was performed to determine the minimum ramucirumab concentration after first dose administration ($C_{min,1}$, or trough concentration immediately prior to the second dose), which was then used as the exposure parameter for the ER analysis. The main objectives of these analyses were to evaluate the relationships between ramucirumab exposure and OS, PFS and commonly reported treatment-emergent adverse events (TEAEs) in patients with advanced or metastatic urothelial cancer previously treated with platinum-based chemotherapy.

2 | METHODS

2.1 | Study design and participants

The study design and participant characteristics of the full RANGE trial have been previously reported.[1,6] Patients with locally advanced unresectable or metastatic UC with disease progression after prior platinum therapy and an Eastern Oncology Cooperative Group performance status (ECOG PS) of 0 or 1 were enrolled. Full inclusion and exclusion criteria, as well as a complete study protocol, can be found in Petrylak et al.[1] The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice criteria, including institutional ethical review board approval and the required use of written informed consent of the study participants.[1,6]

The primary outcome of the RANGE trial was investigator-assessed PFS as defined by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1).[1,6] Secondary endpoints included OS, overall response rate (ORR), disease control rate, duration of response, safety, patient-reported outcomes, PK, and immunogenicity. Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. In the current prespecified secondary-endpoint analysis, patients in the RANGE intent-to-treat (ITT) population who had evaluable PK data (ie, patients who received at least one full dose of ramucirumab and collected at least one post-treatment PK sample) were analysed to assess the ER relationships with both PFS and OS. In addition, a descriptive analysis of adverse events of special interest (AESI) and selected safety endpoints were examined in the RANGE trial safety population with evaluable PK data.

2.2 | Procedures

In RANGE, patients were randomized 1:1 to intravenous administration of either 10 mg/kg ramucirumab plus 75 mg/mg^2 docetaxel (60 mg/m^2 for patients at East Asian study sites) or placebo plus docetaxel on day 1 of a 21-day cycle until disease progression or withdrawal criteria were met. Treatment with docetaxel may continue for up to six 21-day cycles (up to four additional cycles of docetaxel [maximum of 10 cycles total] may be administered after sponsor approval).

Blood samples were collected prior to ramucirumab infusion on day 1 of cycles 1, 2, 3, 5 and 9 at the end of ramucirumab infusion on day 1 of cycles 1 and 9 for the determination of ramucirumab concentrations. Serum ramucirumab concentration was determined using a validated enzyme-linked immunosorbent assay at Intertek Pharmaceutical Services (San Diego, CA, USA).

A previously developed population PK (popPK) model for ramucirumab used a linear two-compartment pharmaco-statistical model with static clearance (CL) for ramucirumab.[20] Emerging evidence has suggested that monoclonal antibodies may exhibit time-dependent CL due to changes in oncologic disease status.[10,21] The ramucirumab popPK model has been updated based on a published time-varying CL model[10] using PK data collected from 2522 patients in 17 clinical studies (data on file, Eli Lilly and Company), including PK data collected in RANGE.[20,22] PopPK model-predicted minimum concentration after first dose administration ($C_{min,1}$) was used to assess the exposure-response relationship. This approach is supported by review and analysis from the FDA on ER analysis of nivolumab.[21] To investigate the ER relationship, subgroup analyses were performed after separation of the ramucirumab plus docetaxel treatment arm data into four quartiles (Q) based on the exposure parameter of interest, $C_{min,1}$ (Q1 [lowest, 3.2-10.9 ug/mL], Q2 [11.2-16.1 ug/mL], Q3 [16.2-20.5 ug/mL] and Q4 [highest, 20.5-54.6 ug/mL]). Given the total number of patients with PK information in the ramucirumab arm, such quartile analysis will provide a meaningful number of patients (approximately 60) for each of the subgroup analyses.

2.3 | Exposure-efficacy analyses

Univariate and multivariate Cox proportional hazard models and case-control matched analyses were used to evaluate the exposure-efficacy relationship. Data from the control group were not included in the multivariate Cox model. Only patients with evaluable ramucirumab PK data from the ramucirumab-treated group were included in the analysis. Log_2 transformation was applied to the PK parameter prior to fitting the model. The HR should be interpreted as the change in hazard when the PK parameter doubles its value. A stepwise Cox regression, as pre-specified in the statistical analysis plan with entry P value <.05 and exit P value ≥.10, was used to identify the baseline factors that were prognostic for OS or PFS. These significant factors were either adjusted in the multivariate models as covariates or used as matching factors for evaluating the relationship between efficacy and ramucirumab exposure measures.

Additional case-control matched analyses for OS and PFS were explored to adjust for potential imbalance in significant prognostic factors between the treatments within each exposure quartile group. In these analyses, the case groups were the four exposure quartiles of predicted $C_{min,1}$ in the ramucirumab treatment groups ($C_{min,1}$: <25% [Q1], 25% to <50% [Q2], 50% to <75% [Q3] and ≥75% [Q4]). For every patient in each case group, a matched control patient was selected from all patients receiving placebo (with replacement) through a matching scheme based on the significant potential

prognostic factors identified in the stepwise Cox regression analyses (albumin, Bellmunt risk factor score, number of metastatic sites, visceral metastasis, prior immune checkpoint inhibitor, primary tumour location, haemoglobin level, sex and race). To prevent potential collinearity, docetaxel was not a variable included in the model because reduced docetaxel dose was only adopted in the East Asian region. Missing values in any of the matching factors excluded the patients from the matched analysis (Mahalanobis metric matching).

The balance of the selected significant prognostic factors between the two treatments was assessed in each case-control group, before and after matching, using Fisher's exact test or t-test. Kaplan-Meier survival analysis and Cox models were performed to compare the two treatments in each of the matched case-control groups.

Estimates of exposure obtained from population PK modelling were combined with demographic data, clinical laboratory results, and efficacy and safety data using SAS, version 9.1.2 or higher, and S PLUS version 8.2, to produce the datasets used in the ER analyses.

2.4 | Exposure-safety analysis

The relationship between ramucirumab $C_{min,1}$ and incidence of AESIs was assessed descriptively. The AESIs included neutropenia and febrile neutropenia, which were the only grade ≥3 TEAEs occurring in ≥5% of the ramucirumab treatment group with a ≥2% difference in incidence from the placebo treatment group.[6] In addition, grade ≥3 hypertension and fatigue were evaluated as AESIs along with any treatment discontinuations or deaths that were due to an adverse event. Safety endpoints were graded per the National Cancer Institute CTCAE, version 4.0.

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY.[21,23,24]

3 | RESULTS

3.1 | Exposure-response population

Data from a total of 246 patients from the ramucirumab plus docetaxel arm and 267 patients from the placebo plus docetaxel arm were included in the ER analyses. Ramucirumab concentration data were grouped into $C_{min,1}$ quartiles as previously described.[3–5] Baseline demographics and disease characteristics are presented by $C_{min,1}$ quartiles in Table 1, Q1 being the lowest exposure and Q4 being the highest. Similar baseline data were found between the ramucirumab and placebo arms in the ER population, consistent with the overall study population (ITT) enrolled in RANGE.

Unbalanced known prognostic factors ECOG status, primary tumour site, number of metastatic sites, site of metastases, haemoglobin level and Bellmunt risk factors had trending distributions across the exposure quartiles. Lower exposure quartiles were associated with worse disease characteristics than the higher exposure quartiles, such as the number of metastasis site, lower haemoglobin level, Bellmunt risk score and presence of liver metastasis.

3.2 | Exposure-efficacy

A univariate Cox regression analysis with $C_{min,1}$ as the continuous covariate identified a statistically significant positive association with OS (HR = 0.597, 95% confidence interval [CI] 0.492, 0.724; P < .0001). A multivariate Cox regression analysis identified several factors significantly associated with OS, including albumin, Bellmunt risk factor score, number of metastatic sites, visceral metastasis, prior immune checkpoint inhibitor, primary tumour location, haemoglobin level, sex and race. After adjusting for these factors, the association between $C_{min,1}$ and OS remained statistically significant (HR = 0.750, 95% CI 0.601, 0.936; P = .0108). Similar to OS, a univariate Cox regression analysis with $C_{min,1}$ as the continuous covariate identified a positive association with PFS (HR = 0.771, 95% CI 0.642, 0.926; P = .0055). When adjusted for factors significantly associated with PFS, including Bellmunt risk factor, number of metastatic sites, albumin and ECOG performance status, this association did not remain significant (HR = 0.904, 95% CI 0.740, 1.104; P = .3217).

Ramucirumab exposure was evaluated as a categorical variable (multivariate) to compare with the placebo arm. Kaplan-Meier plots of OS and PFS by $C_{min,1}$ quartiles are shown in Figure 1 and Supplementary Figure S1. The median OS was 6.8, 7.9, 10.8 and 17.2 months for the ramucirumab $C_{min,1}$ Q1, Q2, Q3 and Q4 groups, respectively (Figure 1). The median OS for the placebo arm was 7.9 months. OS HRs were adjusted for prognostic factors from Table 1. The higher exposure quartiles demonstrated greater separation and longer OS. Similarly, PFS Kaplan-Meier plots demonstrated greater separation and longer PFS with the higher exposure quartiles. The median PFS was 4.1, 4.2, 3.6 and 5.6 months for the ramucirumab $C_{min,1}$ Q1, Q2, Q3 and Q4 groups, respectively (Supporting Information Figure S1). The median PFS for placebo was 2.8 months.

To adjust for imbalances in baseline clinical characteristics of patients between $C_{min,1}$ quartiles and to evaluate the ER-OS relationship, a matched case-control analysis was performed (Table 2). Patients from both the ramucirumab and placebo groups were included in the analysis and the matching was performed separately for each of the four quartiles in the treatment arm. As compared to match controls and consistent with the ER association observed earlier, higher ramucirumab exposure quartiles displayed longer median OS and PFS (Table 2 and Supporting Information Table S1). Interestingly, the median OS in the placebo arm also increased noticeably from 6.1 months in Q1 to 10.5 months in Q4 when patients were matched for clinical characteristics, which may be due to poor

TABLE 1 Baseline demographics and disease characteristics by RAM $C_{min,1}$ quartile in the exposure-response analysis population

%	PBO + DOC Total N = 267	RAM + DOC Q1 n = 61	Q2 n = 62	Q3 n = 61	Q4 n = 62
Sex, male	80.5	80.3	93.5	80.3	69.4
Age, years, median (range)	66 (32-83)	62 (34-86)	66.5 (34-85)	63 (48-82)	68 (43-82)
<65	43.1	57.4	43.5	50.8	38.7
≥65	56.9	42.6	56.5	49.2	61.3
Race					
Asian	22.8	14.8	16.1	21.3	35.5
White	76.4	82.0	80.6	78.7	61.3
Region					
Europe/other	69.7	77.0	71.0	70.5	56.5
East Asia	21.3	14.8	16.1	21.3	33.9
Japan	11.2	4.9	4.8	6.6	22.6
North America	9.0	8.2	12.9	8.2	9.7
ECOG PS[a]					
0	46.8	44.3	40.3	54.1	56.5
1	53.2	55.7	59.7	45.9	43.5
Pure urothelial histology	81.3	75.4	79.0	77.0	82.3
Primary tumour site[a]					
Lower tract	68.5	75.4	75.8	70.5	62.9
Upper tract	29.6	24.6	24.2	27.9	37.1
Other	1.9	0.0	0.0	1.6	0.0
Number of metastatic sites[a]					
≤2	66.3	57.4	74.2	72.1	83.9
≥3	30.0	37.7	25.8	26.2	14.5
Missing	3.7	4.9	0.0	1.6	1.6
Sites of metastases					
Lymph node only	15.7	4.9	14.5	19.7	27.4
Visceral	70.4	75.4	77.4	67.2	56.5
Liver[a]	25.8	34.4	29.0	26.2	24.2
Hemoglobin <100 g/L[a]	135	230	145	115	48
Time since previous therapy <3 mo	47.2	47.5	45.2	39.3	45.2
Bellmunt risk factors[a,b]					
0	34.8	26.2	27.4	42.6	40.3
1	40.8	37.7	46.8	32.8	46.8
2	21.3	32.8	21.0	23.0	12.9
3	3.0	3.3	4.8	1.6	0.0

Abbreviations: $C_{min,1}$, concentration after first dose administration; DOC, docetaxel; N, number of patients; n, number of patients in a subgroup; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PBO, placebo; Q, quartile; RAM, ramucirumab; SD, standard deviation.
[a]An imbalance in the patient characteristics among the exposure quartiles was observed, including in some known prognostic factors.
[b]Bellmunt risk factors[25,26] include ECOG PS > 0, haemoglobin concentration <100 g/L and the presence of liver metastases.

prognostic factors in the lower ramucirumab exposure quartile. The ORR was also greater in the higher ramucirumab exposure quartiles (Q4: ORR = 43.5%) with patients in Q1 displaying the lowest ORR (Q1: ORR = 16.4%); the ORR for the placebo plus docetaxel was 13.9%. The two treatment arms in each of the four matched case-control groups were compared using Kaplan-Meier plots for OS

(Supporting Information Figure S2A) and PFS (Supporting Information Figure S2B). Consistent with the previous results, higher ramucirumab exposure quartiles (Q2-Q4) displayed greater clinical benefits when compared to matched controls.

To further investigate the interplay between clinical factors and OS outcomes, an unstratified univariate Cox analysis was used to
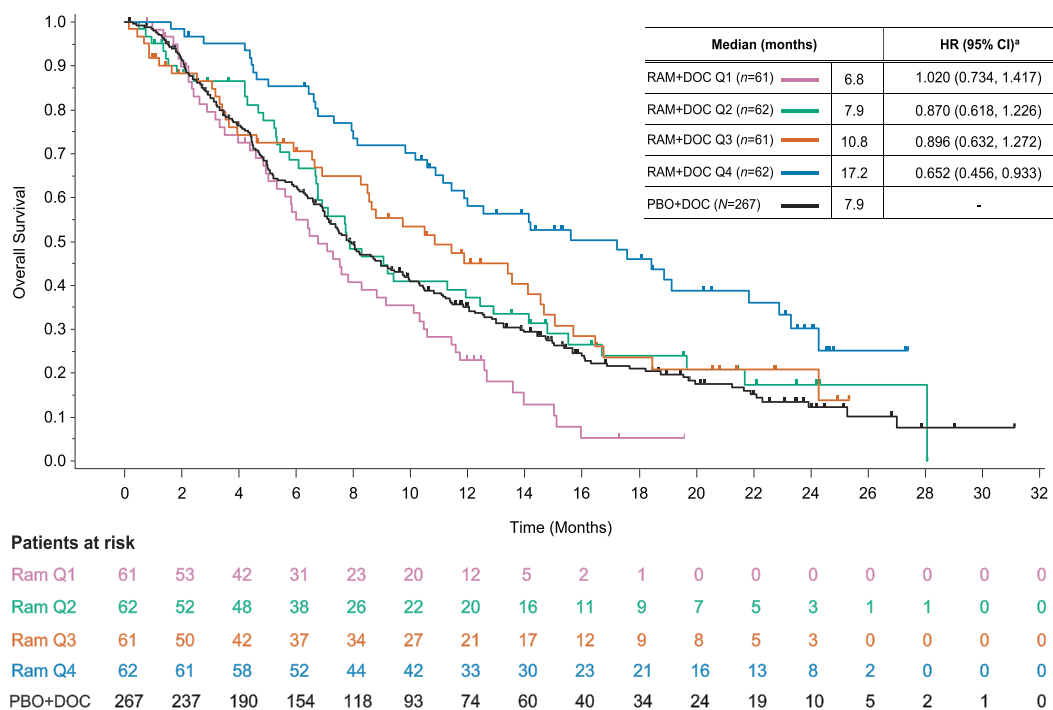
	Median (months)	HR (95% CI)[a]
RAM+DOC Q1 (n=61)	6.8	1.020 (0.734, 1.417)
RAM+DOC Q2 (n=62)	7.9	0.870 (0.618, 1.226)
RAM+DOC Q3 (n=61)	10.8	0.896 (0.632, 1.272)
RAM+DOC Q4 (n=62)	17.2	0.652 (0.456, 0.933)
PBO+DOC (N=267)	7.9	-

Patients at risk

Ram Q1	61	53	42	31	23	20	12	5	2	1	0	0	0	0	0	0
Ram Q2	62	52	48	38	26	22	20	16	11	9	7	5	3	1	1	0
Ram Q3	61	50	42	37	34	27	21	17	12	9	8	5	3	0	0	0
Ram Q4	62	61	58	52	44	42	33	30	23	21	16	13	8	2	0	0
PBO+DOC	267	237	190	154	118	93	74	60	40	34	24	19	10	5	2	1	0

FIGURE 1   Overall survival by RAM $C_{min,1}$ quartile compared to control arm in the exposure-response population. CI, confidence interval; DOC, docetaxel; HR, hazard ratio; N, number of patients; n, the number of patients in a subgroup; OS, overall survival; PBO, placebo; Q1, lowest RAM exposure; Q4, highest RAM exposure; RAM, ramucirumab; Q, quartile. [a]OS HRs are after adjustment for the prognostic factors (albumin, Bellmunt risk factor score, number of metastatic sites, visceral metastasis, prior immune checkpoint inhibitor, primary tumour location, haemoglobin, sex and race)

TABLE 2   Overall survival and overall response rate by $C_{min,1}$ quartile in the exposure-response population (matched case-control)

	OS, median (months)				ORR (%)[a]		
Exposure	**Qn[b]**	**PBO + DOC**	**RAM + DOC**	**HR (95% CI)**	**QN**	**RAM + DOC**	**PBO + DOC[c]**
Q1 (lowest)	58	6.1	6.5	1.084 (0.731, 1.606)	61	16.4	
Q2	62	7.1	7.9	0.837 (0.557, 1.257)	62	27.4	
Q3	59	7.1	11.4	0.813 (0.528, 1.252)	61	23.0	13.9
Q4 (highest)	60	10.5	15.6	0.720 (0.464, 1.118)	62	43.5	

Abbreviations: CI, confidence interval; $C_{min,1}$, concentration after first dose administration; DOC, docetaxel; HR, hazard ratio; N, number of patients; OS, overall survival; ORR, overall response rate; PBO, placebo; Qn, number of patients in the matched case-control analysis for each quartile; QN, total number of patients per quartile; RAM, ramucirumab.
[a]RAM arm with non-missing concentration data vs placebo arm.
[b]The total number of patients per quartile, QN: Q1 = 61, Q2 = 62, Q3 = 61 and Q4 = 62.
[c]Percentage of patients in intent-to-treat population (N = 267).

compare OS and PFS in ramucirumab high- and low-$C_{min,1}$ groups compared to placebo (Table 3 and Supporting Information Table S2, respectively). All clinical factors were prespecified except albumin. As expected, OS in the placebo arm was notably lower for patients with the Bellmunt risk factors of liver metastases, haemoglobin <100 g/L or ECOG PS > 0 compared to their counterpart groups without these risk factors. Patients with albumin <35 g/L or ≥3 metastatic sites also had shorter OS in the placebo arm compared to those with albumin ≥35 g/L or ≤2 metastatic sites, respectively. Twelve of the 20 subgroups defined by baseline clinical factors showed significantly longer

OS with the ramucirumab higher $C_{min,1}$ group versus placebo plus docetaxel group (P < .05). Across these 12 groups, the absolute improvements in median OS ranged from 2.6 to 9.1 additional months for the ramucirumab higher $C_{min,1}$ group compared to the placebo plus docetaxel arm median OS (range 5.1-10.5 months). Imbalances across exposure quartiles were observed for several baseline demographic and disease characteristics (Table 1). In Supporting Information Table S2, six subgroups previously defined showed longer PFS with the ramucirumab higher $C_{min,1}$ group versus the placebo plus docetaxel group (P < .05).

TABLE 3 Subgroup analyses of overall survival in RAM high- and low-$C_{min,1}$ groups compared to placebo in the exposure-response population[a]

Subgroup analyses of overall survival				
Clinical subgroup		OS, median (months) (HR; 95% CI)		
ECOG PS	N	PBO + DOC	RAM + DOC (high)	RAM + DOC (low)
>0	265	7.0	11.4* (0.618; 0.438, 0.873)	7.1 (0.945; 0.671, 1.332)
0	248	10.5	16.8* (0.609; 0.408, 0.911)	8.5 (1.395; 0.981, 1.984)
Metastatic lines of therapy				
>0	389	7.5	12.6* (0.573; 0.426, 0.770)	7.8 (0.934; 0.709, 1.232)
0	124	9.7	14.7 (0.717; 0.401, 1.283)	5.9* (1.923; 1.135, 3.257)
Primary tumour site				
Bladder	346	7.0	13.4* (0.602; 0.440, 0.824)	7.5 (0.969; 0.716, 1.311)
Other	167	9.2	13.5 (0.650; 0.408, 1.037)	6.8* (1.533; 1.001, 2.348)
Histology				
Pure TCC	410	8.0	14.2* (0.609; 0.453, 0.819)	7.6 (1.194; 0.908, 1.569)
Mixed	102	7.6	10.9 (0.740; 0.421, 1.300)	7.5 (0.900; 0.516, 1.570)
Time from prior therapy				
≥ 3 months	278	9.4	18.5* (0.524; 0.357, 0.770)	8.8 (1.235; 0.879, 1.736)
< 3 months	235	6.3	8.0 (0.771; 0.538, 1.105)	6.8 (1.100; 0.773, 1.565)
Liver metastases				
Absent	374	9.8	15.6* (0.612; 0.446, 0.839)	8.6 (1.145; 0.857, 1.528)
Present	139	4.7	6.6 (0.623; 0.385, 1.009)	5.3 (1.053; 0.672, 1.649)
Bellmunt score				
0-1	387	9.9	15.7* (0.586; 0.427, 0.805)	7.9 (1.255; 0.944, 1.667)
2-3	126	4.5	6.4 (0.773; 0.485, 1.233)	6.5 (0.729; 0.448, 1.185)
Albumin				
≥35 g/L	478	8.2	14.1* (0.626; 0.477, 0.822)	7.6 (1.171; 0.909, 1.508)
<35 g/L	32	4.1	3.2 (0.828; 0.295, 2.324)	4.3 (1.080; 0.419, 2.782)
Haemoglobin				
≥100 g/L	442	8.2	14.7* (0.583; 0.436, 0.780)	7.7 (1.174; 0.902, 1.528)
<100 g/L	69	3.8	2.8 (1.699; 0.899, 3.210)	7.5 (0.757; 0.395, 1.449)
Number of metastatic sites				
≤2	354	9.9	14.1* (0.690; 0.503, 0.946)	8.5 (1.186; 0.880, 1.597)
≥3	144	5.1	7.7* (0.566; 0.343, 0.936)	5.2 (1.112; 0.721, 1.714)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; OS, overall survival; PBO, placebo; RAM, ramucirumab; TCC, transitional cell carcinoma.
*P < .05.
[a]Unstratified univariate Cox analysis was used to compare OS in ramucirumab high- and low-$C_{min,1}$ groups to placebo.

3.3 | Exposure-safety

Details of AEs associated with treatment have been published previously.[1] The observed incidence of AESIs by $C_{min,1}$ quartiles is shown in Figure 2. No clear trends were detected across Q1-Q4 in the grade ≥3 AESIs. The only exception was the higher incidence of grade ≥3 neutropenia reported for the Q4 group when compared to placebo and lower exposure quartiles.

4 | DISCUSSION

RANGE was a positive phase 3 trial investigating ramucirumab plus docetaxel in patients with locally advanced or metastatic UC after disease progression on platinum-based chemotherapy.[1,6] ER analyses identified that OS, PFS and ORR improvement may be associated with higher ramucirumab exposure. Here we also show that the lower exposure quartiles are associated with baseline demographics and

FIGURE 2 Discontinuation due to AE, death or grade ≥3 AESIs by RAM $C_{min,1}$ quartile compared to control arm in the safety populations. AE, adverse event; AESI, adverse event of special interest; $C_{min,1}$, concentration after first dose administration; DOC, docetaxel; N, number of patients; PBO, placebo; Q, quartile; RAM, ramucirumab. [a]Consolidated term. [b]Preferred term. [c]AESI term
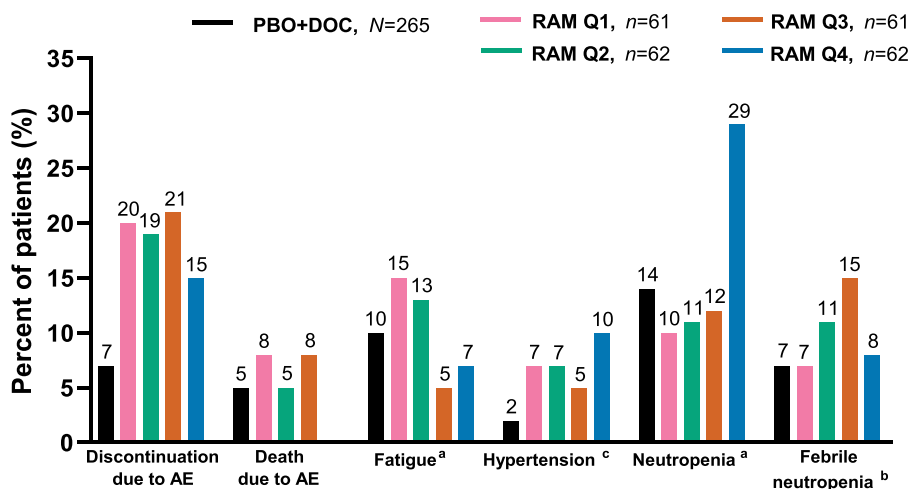
adverse clinical characteristics, including Bellmunt risk factor score, number of metastatic sites, visceral metastasis, primary tumour location, low haemoglobin, sex and race (Table 1). This relationship between ramucirumab exposure and OS was maintained in unadjusted analyses and matched pair analysis. The exposure quartiles demonstrated increasingly greater separation in the Kaplan-Meier plots along with lower hazard ratios as ramucirumab exposure increased, with the greatest benefit seen in Q4 (Figure 1, Supporting Information Figure S1 and Table 2).

It is important to note that no patient factors were found to have a significant effect on ramucirumab PK in the population PK analysis based on predefined criteria.[20] However, consistent with observation from other monoclonal antibodies used in oncology, the lower exposure quartiles were associated with poor disease characteristics, suggesting a disease state contribution to PK.[9,21,27–30] The difference in OS observed with docetaxel plus placebo across the case-matched series highlights a potential issue with early phase 1b/2 trials (small number of patients in each cohort) in UC, in which the main endpoint is efficacy; if only patients with "favourable" prognostic factors are enrolled, the drugs' reported efficacy may not reflect results seen in a larger population with increased diversity of prognostic factors.

ER analysis of ramucirumab (8 mg/kg, biweekly) as a monotherapy (REGARD) or in combination with paclitaxel (RAINBOW) suggested a positive association between efficacy and ramucirumab-exposure with manageable toxicities in patients with gastric or GEJ.[2] Similarly, an ER analysis of ramucirumab (10 mg/kg, every 3 weeks) plus docetaxel for the REVEL trial revealed higher exposure to ramucirumab was associated with improved clinical outcome in patients with non-small-cell lung cancer.[3] These findings suggested that higher doses of ramucirumab may be beneficial. However, several post-marketing commitment (PMC) studies have been conducted to evaluate whether a higher dose may improve efficacy, but study results are mixed. With trastuzumab, higher doses did not equate to increased efficacy.[31] The opposite was true for ipilimumab, with higher doses being associated with improved outcomes.[32] There are a limited number of studies on the bevacizumab ER relationship, and results are conflicting on whether higher bevacizumab levels are associated with

a better response.[33–35] Ramucirumab's own PMC study in gastro-esophageal cancer showed no further improvement on PFS when dose was increased from 8 to 12 mg/kg.[36] These findings indicate that the ER relationship needs to be interpreted with caution and suggest that it may not be possible to achieve higher exposures and thus greater efficacy in all patients just by increasing dose. Further understanding of how intrinsic patient and disease characteristics may be interacting to lead to greater clearance and lower exposure is needed. Moreover, there is a possibility that baseline prognostic factors confounded the ER results, therefore future trials may benefit from considering a randomized dose ranging design.[11,12]

The safety profile was consistent in RANGE with previous ramucirumab ER studies. Likewise, docetaxel did not affect PK as in other ramucirumab trials.[4] The combination of ramucirumab plus docetaxel in the RANGE ITT population was well tolerated with no unexpected adverse events. There was no clear trend observed between ramucirumab exposure and grade ≥3 febrile neutropenia, neutropenia, fatigue or hypertension in OS. Neutropenia is the only grade ≥3 AE showing an apparent trend towards increasing from Q1 to Q4 in PFS. Higher ramucirumab exposure may have led to an increased incidence of grade ≥3 neutropenia in Q4. However, ramucirumab exposure was not associated with a higher likelihood of developing grade ≥3 febrile neutropenia, a known clinically meaningful toxicity. Interpretation of this data is limited due to the relatively small sample size of the individual quartiles (∼60 patients per ramucirumab exposure quartile) and longer exposure to chemotherapy in the Q4 group. However, this analysis does suggest that toxicities do not increase with ramucirumab exposure.

In summary, this ER analysis of RANGE PK data suggests a positive association of efficacy and higher ramucirumab exposures (Q2-Q4) in combination with docetaxel. The outcomes of the ER analysis support the RANGE trial's primary endpoint findings (PFS). The ramucirumab dose of 10 mg/kg plus 75 mg/m^{2} docetaxel on day 1 of a 21-day cycle had manageable toxicities and offers a favourable benefit-to-risk profile in patients with locally advanced or metastatic UC after disease progression on platinum-based chemotherapy.[6] The association of lower ramucirumab exposures (Q1) and poor disease

prognostic factors suggests a connection between the disease state and ramucirumab PK/clearance and may help to explain why the RANGE trial reported no significant improvement in overall survival. The addition of ramucirumab to the standard of care may result in several months of OS benefit for the population of patients with favourable disease characteristics who achieved high ramucirumab exposure, and further defining this subset within UC may be important for optimizing treatment regimens in future studies. Further studies are needed to understand and predict exposure based on disease characteristics and antibody clearance.

COMPETING INTERESTS

R.deW. serves as an advisor for Merck, Sanofi-Genzyme, Astellas, Eli Lilly and Company, Bayer and Janssen; reports speaker fees from Sanofi and Merck; grants (institutional) from Bayer and Sanofi; and travel support from Bayer.

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A.D. reports participation in advisory boards for Roche/Genentech, Merck, Exelixis, Seattle Genetics, Jansen, Infinity, and Astra Zeneca.

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A.H.Z., A.L. and R.A.W. are employees and shareholders of Eli Lilly and Company.

L.G. was an employee of Eli Lilly and Company and was previously a shareholder of Eli Lilly and Company.

K.M.B.-McG. is a former employee of Eli Lilly and Company and is a current shareholder of Eli Lilly and Company.

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CONTRIBUTORS

R.dW. contributed to the study design, conduct of the study, data acquisition, data interpretation and writing of the original draft. T.P. contributed to the study design, conduct of the study, data analysis, data interpretation and writing of the original draft. D.C. contributed to data interpretation. A.N. contributed to data acquisition, data analysis and data interpretation. J.L.L. contributed to the study design, conduct of the study, data analysis and writing of

the original draft. M.vdH. contributed to the conduct of the study and data interpretation. N.M. contributed to data acquisition, data interpretation and writing the original draft. A.B. contributed to the conduct of the study and data acquisition. A.F. contributed to data acquisition and data interpretation. C.N.S. contributed to the conduct of the study, data acquisition, data analysis, data interpretation and writing of the original draft. A.D. contributed to the conduct of the study, data acquisition, data analysis, data interpretation and writing of the original draft. E.Y.Y. contributed to the conduct of the study, data acquisition and data interpretation. A.H.Z. contributed to the study design, data acquisition, data analysis, data interpretation and writing of the original draft. A.L. contributed to data analysis and data interpretation. R.A.W. contributed to the study design, conduct of the study and data interpretation. L.G. contributed to the study design, data acquisition, data analysis and data interpretation. K.B.M. contributed to the study design, conduct of the study, data acquisition, data analysis, data interpretation and writing of the original draft. D.P.P. contributed to the study design, conduct of the study, data analysis and data interpretation. All authors participated in the critical revision (reviewing and editing) of the manuscript and approved the manuscript to be submitted for publication.

ROLE OF THE FUNDING SOURCE

As previously described with RANGE, the study sponsor collaborated with external investigators to design the trial, as well as to manage the data collection and to perform the statistical analysis.[1,6] The study sponsor also collaborated with the listed authors to interpret the data and provided medical writing support for the manuscript. All authors had full access to all the study data and maintained final responsibility for deciding to submit the manuscript for publication.

DATA AVAILABILITY STATEMENT

Eli Lilly and Company 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 United States and the European Union, and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data 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 details on submitting a request, see the instructions provided at www.vivli.org.

REFERENCES

1. Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): a randomised, double-blind, phase 3 trial. *Lancet*. 2017;390(10109):2266-2277. doi:10.1016/S0140-6736(17)32365-6

2. Falcon BL, Chintharlapalli S, Uhlik MT, Pytowski B. Antagonist antibodies to vascular endothelial growth factor receptor 2 (VEGFR-2) as anti-angiogenic agents. *Pharmacol Ther*. 2016;164:204-225. doi:10.1016/j.pharmthera.2016.06.001

3. Tabernero J, Ohtsu A, Muro K, et al. Exposure-response analyses of ramucirumab from two randomized, phase III trials of second-line treatment for advanced gastric or gastroesophageal junction cancer. *Mol Cancer Ther*. 2017;16(10):2215-2222. doi:10.1158/1535-7163.Mct-16-0895

4. Smit EF, Garon EB, Reck M, et al. Exposure-response relationship for ramucirumab from the randomized, double-blind, phase 3 REVEL trial (docetaxel versus docetaxel plus ramucirumab) in second-line treatment of metastatic non-small cell lung cancer. *Cancer Chemother Pharmacol*. 2018;82(1):77-86. doi:10.1007/s00280-018-3560-5

5. Cohn AL, Yoshino T, Heinemann V, et al. Exposure-response relationship of ramucirumab in patients with advanced second-line colorectal cancer: exploratory analysis of the RAISE trial. *Cancer Chemother Pharmacol*. 2017;80(3):599-608. doi:10.1007/s00280-017-3380-z

6. Petrylak DP, de Wit R, Chi KN, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy (RANGE): overall survival and updated results of a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2020;21(1):105-120. doi:10.1016/S1470-2045(19)30668-0

7. Ovacik M, Lin K. Tutorial on monoclonal antibody pharmacokinetics and its considerations in early development. *Clin Transl Sci*. 2018;11(6):540-552. doi:10.1111/cts.12567

8. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*. 2008;84(5):548-558. doi:10.1038/clpt.2008.170

9. Feng Y, Wang X, Bajaj G, et al. Nivolumab exposure-response analyses of efficacy and safety in previously treated squamous or nonsquamous non-small cell lung cancer. *Clin Cancer Res*. 2017;23(18):5394-5405. doi:10.1158/1078-0432.Ccr-16-2842

10. Wang X, Feng Y, Bajaj G, et al. Quantitative characterization of the exposure-response relationship for cancer immunotherapy: A case study of nivolumab in patients with advanced melanoma. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(1):40-48. doi:10.1002/psp4.12133

11. Dai HI, Vugmeyster Y, Mangal N. Characterizing exposure-response relationship for therapeutic monoclonal antibodies in immuno-oncology and beyond: Challenges, perspectives, and prospects. *Clin Pharmacol Ther*. 2020;108(6):1156-1170. doi:10.1002/cpt.1953

12. Kawakatsu S, Bruno R, Kagedal M, et al. Confounding factors in exposure-response analyses and mitigation strategies for monoclonal antibodies in oncology. *Br J Clin Pharmacol*. 2021;87(6):2493-2501. doi:10.1111/bcp.14662

13. Effing SMA, Gyawali B. Assessing the risk-benefit profile of ramucirumab in patients with advanced solid tumors: A meta-analysis of randomized controlled trials. *EClinicalMedicine*. 2020;25:100458. doi:10.1016/j.eclinm.2020.100458

14. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet*. 2014;384(9944):665-673. doi:10.1016/S0140-6736(14)60845-X

15. 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(11):1224-1235. doi:10.1016/S1470-2045(14)70420-6

16. Fuchs CS, Shitara K, Di Bartolomeo M, et al. Ramucirumab with cisplatin and fluoropyrimidine as first-line therapy in patients with metastatic gastric or junctional adenocarcinoma (RAINFALL): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(3):420-435. doi:10.1016/S1470-2045(18)30791-5

17. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study. *Lancet Oncol.* 2015;16(5):499-508. doi:10.1016/S1470-2045(15)70127-0

18. Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol.* 2015;16(7):859-870. doi:10.1016/S1470-2045(15)00050-9

19. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2019;20(12):1655-1669. doi:10.1016/S1470-2045(19)30634-5

20. O'Brien L, Westwood P, Gao L, Heathman M. Population pharmacokinetic meta-analysis of ramucirumab in cancer patients. *Br J Clin Pharmacol.* 2017;83(12):2741-2751. doi:10.1111/bcp.13403

21. Liu C, Yu J, Li H, et al. Association of time-varying clearance of nivolumab with disease dynamics and its implications on exposure response analysis. *Clin Pharmacol Ther.* 2017;101(5):657-666. doi:10.1002/cpt.656

22. Gao L, Lau YK, Wei R, et al. Evaluating clinical impact of a shortened infusion duration for ramucirumab: a model-based approach. *Cancer Chemother Pharmacol.* 2021;87(5):635-645. doi:10.1007/s00280-020-04223-9

23. Alexander SPH, Fabbro D, Kelly E, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Catalytic receptors. *Br J Pharmacol.* 2021;178(S1):S247-S296. doi:10.1111/bph.15541

24. Alexander SPH, Kelly E, Mathie A, et al. THE CONCISE GUIDE TO PHARMACOLOGY 2021/22: Introduction and Other Protein Targets. *Br J Pharmacol.* 2021;178(S1):S1-S20. doi:10.1111/bph.15537

25. Bellmunt J, Choueiri TK, Fougeray R, et al. Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. *J Clin Oncol.* 2010;28(11):1850-1855. doi:10.1200/jco.2009.25.4599

26. Sonpavde G, Pond GR, Fougeray R, et al. Time from prior chemotherapy enhances prognostic risk grouping in the second-line setting of advanced urothelial carcinoma: a retrospective analysis of pooled, prospective phase 2 trials. *Eur Urol.* 2013;63(4):717-723. doi:10.1016/j.eururo.2012.11.042

27. Bajaj G, Gupta M, Feng Y, Statkevich P, Roy A. Exposure-response analysis of nivolumab in patients with previously treated or untreated advanced melanoma. *J Clin Pharmacol.* 2017;57(12):1527-1533. doi:10.1002/jcph.962

28. Turner DC, Kondic AG, Anderson KM, et al. Pembrolizumab exposure-response assessments challenged by association of cancer cachexia and catabolic clearance. *Clin Cancer Res.* 2018;24(23):5841-5849. doi:10.1158/1078-0432.Ccr-18-0415

29. Ribas A, Hamid O, Daud A, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. *JAMA.* 2016;315(15):1600-1609. doi:10.1001/jama.2016.4059

30. Nghiem PT, Bhatia S, Lipson EJ, et al. PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. *N Engl J Med.* 2016;374(26):2542-2552. doi:10.1056/NEJMoa1603702

31. Shah MA, Xu R-h, Bang Y-J, et al. HELOISE: Phase IIIb randomized multicenter study comparing standard-of-care and higher-dose trastuzumab regimens combined with chemotherapy as first-line therapy in patients with human epidermal growth factor receptor 2-positive metastatic gastric or gastroesophageal junction adenocarcinoma. *J Clin Oncol.* 2017;35(22):2558-2567. doi:10.1200/jco.2016.71.6852

32. Feng Y, Roy A, Masson E, Chen T-T, Humphrey R, Weber JS. Exposure-response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. *Clin Cancer Res.* 2013;19(14):3977-3986. doi:10.1158/1078-0432.Ccr-12-3243

33. Pena-Cabia S, Royuela Vicente A, Ramos Diaz R, et al. Assessment of exposure-response relationship for bevacizumab in patients with metastatic colorectal cancer. *Biomed Pharmacother.* 2021;141:111827. doi:10.1016/j.biopha.2021.111827

34. Papachristos A, Kemos P, Kalofonos H, Sivolapenko G. Correlation between bevacizumab exposure and survival in patients with metastatic colorectal cancer. *Oncologist.* 2020;25(10):853-858. doi:10.1634/theoncologist.2019-0835

35. Lu JF, Bruno R, Eppler S, Novotny W, Lum B, Gaudreault J. Clinical pharmacokinetics of bevacizumab in patients with solid tumors. *Cancer Chemother Pharmacol.* 2008;62(5):779-786. doi:10.1007/s00280-007-0664-8

36. Ajani JA, Udrea A, Sarosiek T, et al. A dose-response study of ramucirumab treatment in patients with gastric cancer/gastroesophageal junction adenocarcinoma: Primary results of 4 dosing regimens in the phase 2 trial I4T-MC-JVDB. *Ann Oncol.* 2017;28:v238. doi:10.1093/annonc/mdx369.082

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.