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

*Daniel P Petrylak, Ronald de Wit, Kim N Chi, Alexandra Drakaki, Cora N Sternberg, Hiroyuki Nishiyama, Daniel Castellano, Syed Hussain, Aude Fléchon, Aristotelis Bamias, Evan Y Yu, Michiel S van der Heijden, Nobuaki Matsubara, Boris Alekseev, Andrea Necchi, Lajos Géczi, Yen-Chuan Ou, Hasan Senol Coskun, Wen-Pin Su, Miriam Hegemann, Ivor J Percent, Jae-Lyun Lee, Marcello Tucci, Andrey Semenov, Fredrik Laestadius, Avivit Peer, Giampaolo Tortora, Sufia Safina, Xavier Garcia del Muro, Alejo Rodriguez-Vida, Irfan Cicin, Hakan Harputluoglu, Ryan C Widau, Astra M Liepa, Richard A Walgren, Oday Hamid, Annamaria H Zimmermann, Katherine M Bell-McGuinn, Thomas Powles, for the RANGE study investigators**

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*A full list of investigators is provided in the appendix

Yale University School of Medicine, New Haven, CT, USA (Prof D P Petrylak MD); Erasmus MC Cancer Institute, Rotterdam, Netherlands (Prof R de Wit PhD); British Columbia Cancer Agency, Vancouver, BC, Canada (Prof K N Chi MD); David Geffen School of Medicine, UCLA, Los Angeles, CA, USA (A Drakaki PhD); San Camillo and Forlanini Hospitals, Rome, Italy (Prof C N Sternberg MD); University of Tsukuba, Tsukuba, Ibaraki, Japan (Prof H Nishiyama PhD); Hospital Universitario 12 de Octubre (CiberOnc), Madrid, Spain (D Castellano MD); Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK (Prof S Hussain MD); Centre Léon Bérard, Lyon, France (A Fléchon MD); National and Kapodistrian University of Athens, Athens, Greece (Prof A Bamias PhD); University of Washington, Seattle, WA, USA (Prof E Y Yu MD); Netherlands Cancer Institute–Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands (Prof M S van der Heijden MD); National Cancer Centre Hospital East, Chiba, Japan (N Matsubara MD); PA Herzen Moscow Oncological Research Institute, Moscow, Russia

Summary

Background Few treatments with a distinct mechanism of action are available for patients with platinum-refractory advanced or metastatic urothelial carcinoma. We assessed the efficacy and safety of treatment with docetaxel plus either ramucirumab—a human IgG1 VEGFR-2 antagonist—or placebo in this patient population.

Methods We did a randomised, double-blind, phase 3 trial in patients with advanced or metastatic urothelial carcinoma who progressed during or after platinum-based chemotherapy. Patients were enrolled from 124 sites in 23 countries. Previous treatment with one immune-checkpoint inhibitor was permitted. Patients were randomised (1:1) using an interactive web response system to receive intravenous docetaxel 75 mg/m² plus either intravenous ramucirumab 10 mg/kg or matching placebo on day 1 of repeating 21-day cycles, until disease progression or other discontinuation criteria were met. The primary endpoint was investigator-assessed progression-free survival, analysed by intention-to-treat in the first 437 randomised patients. This study is registered with ClinicalTrials.gov, number NCT02426125.

Findings Between July, 2015, and April, 2017, 530 patients were randomly allocated either ramucirumab plus docetaxel (n=263) or placebo plus docetaxel (n=267). Progression-free survival was prolonged significantly in patients allocated ramucirumab plus docetaxel versus placebo plus docetaxel (median 4·07 months [95% CI 2·96–4·47] *vs* 2·76 months [2·60–2·96]; hazard ratio [HR] 0·757, 95% CI 0·607–0·943; p=0·0118). A blinded independent central analysis was consistent with these results. An objective response was achieved by 53 (24·5%, 95% CI 18·8–30·3) of 216 patients allocated ramucirumab and 31 (14·0%, 9·4–18·6) of 221 assigned placebo. The most frequently reported treatment-emergent adverse events, regardless of causality, in either treatment group (any grade) were fatigue, alopecia, diarrhoea, decreased appetite, and nausea. These events occurred predominantly at grade 1–2 severity. The frequency of grade 3 or worse adverse events was similar for patients allocated ramucirumab and placebo (156 [60%] of 258 *vs* 163 [62%] of 265 had an adverse event), with no unexpected toxic effects. 63 (24%) of 258 patients allocated ramucirumab and 54 (20%) of 265 assigned placebo had a serious adverse event that was judged by the investigator to be related to treatment. 38 (15%) of 258 patients allocated ramucirumab and 43 (16%) of 265 assigned placebo died on treatment or within 30 days of discontinuation, of which eight (3%) and five (2%) deaths were deemed related to treatment by the investigator. Sepsis was the most common adverse event leading to death on treatment (four [2%] *vs* none [0%]). One fatal event of neutropenic sepsis was reported in a patient allocated ramucirumab.

Interpretation To the best of our knowledge, ramucirumab plus docetaxel is the first regimen in a phase 3 study to show superior progression-free survival over chemotherapy in patients with platinum-refractory advanced urothelial carcinoma. These data validate inhibition of VEGFR-2 signalling as a potential new therapeutic treatment option for patients with urothelial carcinoma.

Funding Eli Lilly and Company.

Introduction

Platinum-based combination chemotherapy is standard front-line treatment for patients with advanced or metastatic urothelial carcinoma, with median overall survival of 11–15 months depending on the type of platinum chemotherapy that can be administered and baseline clinical prognostic factors.[1–4] Despite objective responses of 40–70%, the duration of response is limited and most patients become refractory. Prognosis in refractory patients remains poor, with median overall survival with single-agent cytotoxic therapy of approximately 7 months.[5]

Research in context

Evidence before this study

We searched PubMed, abstracts of major oncology congresses (eg, American Society of Clinical Oncology [ASCO] and ASCO Genitourinary Cancer Symposium, and European Society for Medical Oncology), and clinical trial websites (including ClinicalTrials.gov), with no date restrictions, for preclinical reports and clinical trials (published in English) assessing chemotherapy, antiangiogenic therapies, and a combination of these methods in urothelial carcinoma. Multiple single-agent cytotoxic therapies (eg, docetaxel) showed modest activity in this patient population. Findings of a randomised phase 2 study (NCT01282463) in patients with platinum-refractory advanced or metastatic urothelial carcinoma showed that ramucirumab plus docetaxel significantly improved median progression-free survival versus docetaxel alone. Ramucirumab is an IgG1 monoclonal antibody that binds to the extracellular domain of vascular endothelial growth factor receptor 2 (VEGFR-2), which is an important mediator of tumour angiogenesis. Thus, after review of the scientific literature and discussions with clinicians, researchers, and regulatory agencies, we undertook the phase 3 RANGE trial of ramucirumab plus docetaxel versus placebo plus docetaxel in patients with platinum-refractory advanced or metastatic urothelial carcinoma. As our study protocol was being developed, emerging evidence suggested immune-checkpoint inhibitors targeting the programmed cell death 1 protein (PD-1) and its ligand (PD-L1) had clinical activity in a subset of patients with platinum-refractory urothelial carcinoma. Therefore, we included in our study patients who received one previous immune-checkpoint inhibitor.

Added value of this study

Compared with placebo plus docetaxel, ramucirumab plus docetaxel improved progression-free survival and objective responses without additive toxic effects or compromising quality of life in patients with platinum-refractory advanced or metastatic urothelial carcinoma. The responses reported in our phase 3 trial are in line with those noted with immune-checkpoint inhibitors in other studies.

Implications of all the available evidence

Taken together with results from the previous phase 2 study in a similar patient population, our phase 3 data show that inhibition of VEGFR-2-mediated signalling yields meaningful clinical activity in patients with platinum-refractory advanced or metastatic urothelial carcinoma. To the best of our knowledge, ramucirumab is the only antiangiogenic agent to show such activity in this patient population. Furthermore, RANGE is the first phase 3 trial as far as we are aware to show a progression-free survival advantage over chemotherapy alone in platinum-refractory advanced or metastatic urothelial carcinoma. These results confirm the benefit of adding an anti-VEGFR-2 antibody to standard chemotherapy in this setting and represent progress in the treatment of urothelial carcinoma.

Immune-checkpoint inhibitors targeting the programmed cell death 1 protein (PD-1) and its ligand (PD-L1) have shown clinical activity in patients with platinum-refractory urothelial carcinoma. Accelerated or full approval has been granted in the USA to five agents of this class based on objective responses of 15–21%.[6–10] However, many patients treated with immune-checkpoint inhibitors have progressive disease as their best response, highlighting that other targets and treatments are needed.[6–11]

Vascular endothelial growth factor receptors (VEGFRs) 1 and 2 and their ligands are important mediators of tumour angiogenesis and contribute to the pathogenesis and progression of urothelial carcinoma.[11–19] Ramucirumab is an IgG1 monoclonal antibody that binds to the extracellular domain of VEGFR-2, competing with VEGFA, VEGFC, and VEGFD.[20] There is strong rationale for testing the combination of ramucirumab and docetaxel in platinum-refractory urothelial carcinoma because preclinical data suggest synergy, and docetaxel is used widely as a single agent across the globe in this setting.[21–24] In a randomised phase 2 study in patients with platinum-refractory advanced or metastatic urothelial carcinoma, ramucirumab plus docetaxel significantly improved median progression-free survival compared with docetaxel alone (5·4 months *vs* 2·8 months; hazard ratio [HR] 0·389, 95% CI 0·235–0·643; p=0·0002).[13] To confirm these results, we did a randomised phase 3 trial (RANGE) in a similar patient population. Here, we report the primary analysis of investigator-assessed progression-free survival. Data for overall survival are immature at the time of this publication, prohibiting formal testing of objective response; overall survival outcomes will be reported once mature.

Methods

Study design and participants

We did a double-blind, multicentre, randomised, phase 3 trial at 124 investigative sites in 23 countries (appendix pp 1–10). Full inclusion and exclusion criteria are provided in the study protocol (appendix pp 17–144). Briefly, patients aged 18 years or older were eligible for enrolment if they had: histologically or cytologically confirmed carcinoma of pure or predominant transitional cell histology; locally advanced, unresectable, or metastatic disease extent; primary tumour originating from the bladder, urethra, ureter, or renal pelvis; and progression 14 months or less after platinum-containing chemotherapy (2 additional months were allowed for screening and patient identification over the standard 12 months).[25] We permitted previous treatment with one immune-checkpoint inhibitor for patients who relapsed 24 months or less from the end of a platinum-containing regimen, allowing an additional 10 months for patients who received both platinum and immune-checkpoint inhibitors. Furthermore, patients had

(Prof B Alekseev PhD); **Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy** (A Necchi MD); **National Institute of Oncology, Budapest, Hungary** (L Géczi PhD); **Taichung Veterans General Hospital, Taichung, Taiwan** (Prof Y-C Ou PhD); **Akdeniz University School of Medicine, Antalya, Turkey** (Prof H S Coskun MD); **Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, and Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, Tainan, Taiwan** (Prof W-P Su PhD); **University Hospital, Tübingen, Germany** (M Hegemann MD); **Florida Cancer Specialists, Port Charlotte, FL, USA** (I J Percent MD); **Asan Medical Centre, University of Ulsan College of Medicine, Seoul, Korea** (Prof J-L Lee PhD); **Division of Medical Oncology, Department of Oncology, University of Turin, San Luigi Gonzaga Hospital, Orbassano, Turin, Italy** (M Tucci MD); **RBHI Ivanovo Regional Oncology Dispensary, Ivanovo, Russia** (A Semenov PhD); **Centre Oscar Lambret, Lille, France** (F Laestadius MD); **Rambam Health Care Campus, Haifa, Israel** (A Peer MD); **University of Verona and Azienda Ospedaliera Universitaria Integrata, Verona, Italy** (Prof G Tortora PhD); **Tatarstan Regional Cancer Centre, Kazan, Russia** (S Safina MD); **Institut Català d'Oncologia L'Hospitalet, IDIBELL, University of Barcelona, Barcelona, Spain** (X G del Muro PhD); **Hospital del Mar, Barcelona, Spain** (A Rodriguez-Vida MD); **Trakya University, Edirne, Turkey** (Prof I Cicin MD); **Inonu University, Malatya, Turkey** (Prof H Harputluoglu MD); **Eli Lilly and Company, Indianapolis, IN, USA** (R C Widau PhD, A M Liepa PharmD, R A Walgren PhD, O Hamid PharmD, A H Zimmermann MS, K M Bell-McGuinn PhD); **and Barts Cancer Institute, Queen Mary University of London, London, UK** (Prof T Powles MD)

Correspondence to:
Prof Daniel P Petrylak,
Yale School of Medicine,
New Haven, CT 06520, USA
daniel.petrylak@yale.edu

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to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Key exclusion criteria included more than one previous systemic chemotherapy in the relapsed or metastatic setting (previous systemic therapy in the perioperative setting was not judged a previous line); previous systemic taxane; untreated brain metastases; haemoglobin lower than 9 g/dL; and an arterial or venous thromboembolic event 6 months or less before randomisation.

The trial adhered to the Declaration of Helsinki, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and applicable local regulations. The protocol was approved by the ethics committees of all participating centres, and patients provided written informed consent before study entry. An independent data monitoring committee assessed unblinded safety data throughout the study.

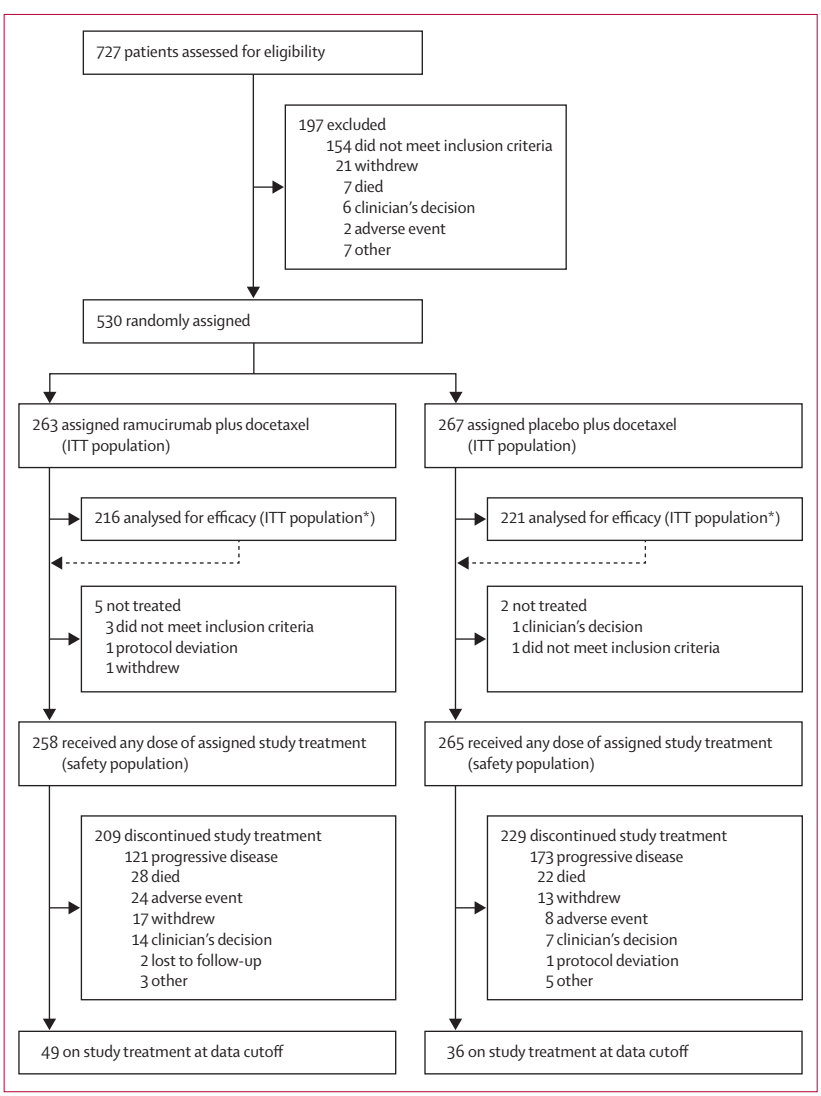

Figure 1: **Trial profile**
ITT=intention to treat. *The primary analysis was done in the first 437 randomised patients.

Randomisation and masking

Patients were randomly allocated treatment using an interactive web response system, with a computer-generated random sequence. Randomisation was stratified by: geographic region (North America, east Asia, and Europe and the rest of the world); ECOG performance status at baseline (0 or 1); and visceral disease (yes or no), when visceral disease involved the liver, lung, bone, or a combination. Patients, study staff, and the study funder were unaware of treatment assignment. For masking, allocated treatments were volume equivalent and in identical-appearing containers.

Procedures

We administered intravenous docetaxel 75 mg/m² (60 mg/m² in Korea, Taiwan, and Japan) to all patients then either intravenous ramucirumab 10 mg/kg or placebo 10 mg/kg volume equivalent, as per the random assignment, on day 1 of a 21-day cycle. Treatments were continued until disease progression or unacceptable toxic effects. Docetaxel was restricted to six cycles; up to four additional cycles could be given after funder approval. There was no planned crossover on disease progression. We allowed dose modifications of any administered study drug, according to protocol-defined criteria. We permitted use of granulocyte-colony stimulating factors based on American Society of Clinical Oncology guidelines.[26]

We assessed tumour response radiographically according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at baseline, every 6 weeks after randomisation for the first year, and then every 12 weeks thereafter. Radiological assessments were analysed by investigators at local sites and reviewed by an independent blinded assessment group (BIOCLINICA, Princeton, NJ, USA). After discontinuation, we followed up patients for survival every 3 months. The appendix (pp 17–144) provides details of the timing of other assessments. We graded adverse events using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. We assessed patient-reported outcomes using European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) version 3.0 and the EQ-5D-5L questionnaire, which measure quality of life and health status, respectively. QLQ-C30 is scored on a scale from 0 to 100, according to the EORTC scoring manual, and the EQ-5D-5L index was calculated using the English value set.[27] For QLQ-C30, we defined time to sustained deterioration as time from randomisation to the first 10 point or greater worsening with no subsequent on-therapy assessment that returned to or improved from baseline score.

Outcomes

The primary endpoint was progression-free survival as assessed by the investigator, defined as the time from

	Ramucirumab plus docetaxel (n=263)	Placebo plus docetaxel (n=267)
Age (years)	65 (34–86)	66 (32–83)
≥65	139 (53%)	152 (57%)
Sex		
Men	213 (81%)	215 (81%)
Women	50 (19%)	52 (19%)
Ethnic origin		
White	204 (78%)	204 (76%)
Asian	54 (21%)	61 (23%)
Other	3 (1%)	2 (<1%)
Missing	2 (<1%)	0
ECOG performance status		
0	121 (46%)	125 (47%)
1	138 (52%)	142 (53%)
Missing	4 (2%)	0
Geographic region		
North America	24 (9%)	24 (9%)
East Asia	53 (20%)	57 (21%)
Europe and rest of the world	186 (71%)	186 (70%)
Histology		
Pure transitional cell	201 (76%)	209 (78%)
Mixed histology	55 (21%)	50 (19%)
Missing	7 (3%)	8 (3%)
Bladder as primary site of tumour	169 (64%)	170 (64%)
Visceral disease	182 (69%)	188 (70%)
Lung metastases	99 (38%)	121 (45%)
Liver metastases	78 (30%)	69 (26%)
Bone metastases	56 (21%)	53 (20%)
Adrenal gland	16 (6%)	12 (4%)
Kidney	12 (5%)	10 (4%)
Spleen	4 (2%)	5 (2%)
Other	35 (13%)	28 (10%)
Lymph-node-only metastases	52 (20%)	45 (17%)
Creatinine clearance (mL/min)		
<60	106 (40%)	118 (44%)
≥60	151 (57%)	146 (55%)
Missing	6 (2%)	3 (1%)
(Table 1 continues in next column)		
(Continued from previous column)		
Haemoglobin concentration <10 g/dL	37 (14%)	36 (13%)
Completion or discontinuation of most recent treatment <3 months	115 (44%)	122 (46%)
Bellmunt risk factors (n)*		
0	61 (23%)	54 (20%)
1	85 (32%)	96 (36%)
2	69 (26%)	82 (31%)
3	47 (18%)	31 (12%)
4	1 (<1%)	4 (1%)
Previous adjuvant treatment		
Adjuvant	38 (14%)	61 (23%)
Neoadjuvant	40 (15%)	37 (14%)
No previous adjuvant	168 (64%)	155 (58%)
Missing	17 (6%)	14 (5%)
Previous treatments†		
Cisplatin-based	159 (60%)	182 (68%)
Carboplatin-based	95 (36%)	78 (29%)
Immune-checkpoint inhibitor	18 (7%)‡	26 (10%)

Data are number of patients (%) or median (range). ECOG=Eastern Cooperative Oncology Group. *Bellmunt risk factors[28,29] included liver metastases, haemoglobin <10 g/dL, ECOG performance status score >0, and time since completion or discontinuation of previous treatment of <3 months. †A summary of previous anticancer treatments is included in the appendix (p 13). ‡Among the first 437 randomised patients, one patient allocated ramucirumab received nivolumab or placebo in a previous clinical trial, but we do not know whether that patient actually received nivolumab, so they are not included in this total.

Table 1: **Baseline demographics and treatment and disease characteristics (intention-to-treat population)**

randomisation until first radiographic documentation of objective progression, or as death from any cause. Secondary endpoints included: overall survival, defined as the time from randomisation to death from any cause; objective response, defined as the proportion of patients with a best overall response of complete or partial response; disease control, defined as the proportion of patients with a best overall response of complete response, partial response, or stable disease; duration of response, defined as the first date of complete or partial response until the first date of objective progression, or death; safety; patient-reported outcomes; pharmacokinetics of ramucirumab; and immunogenicity of ramucirumab. The appendix (pp 17–144) provides the full assessment schedule. Here, we report the primary analysis of investigator-assessed progression-free survival and data for all secondary analyses with the exception of overall survival, for which data were immature at the time of data cutoff.

Statistical analysis

We planned to enrol 524 patients in a 1:1 randomisation, with the primary analysis to be done when at least 331 progression-free survival events were reported. We assumed 15% patient dropout and estimated that roughly 437 patients would be needed to reach 331 progression-free survival events. The number of events provided 90% power to detect progression-free survival superiority of ramucirumab plus docetaxel versus placebo plus docetaxel, assuming an HR of 0·70 with a two-sided α of 0·05. The sample size was also powered to show an overall survival superiority between the two treatment groups, with an assumed HR of 0·75 for ramucirumab plus docetaxel versus placebo plus docetaxel with at least 382 events, power of 80%, and a two-sided type I error of 0·05.

We assessed progression-free survival and response in the first 437 patients of the intention-to-treat (ITT)

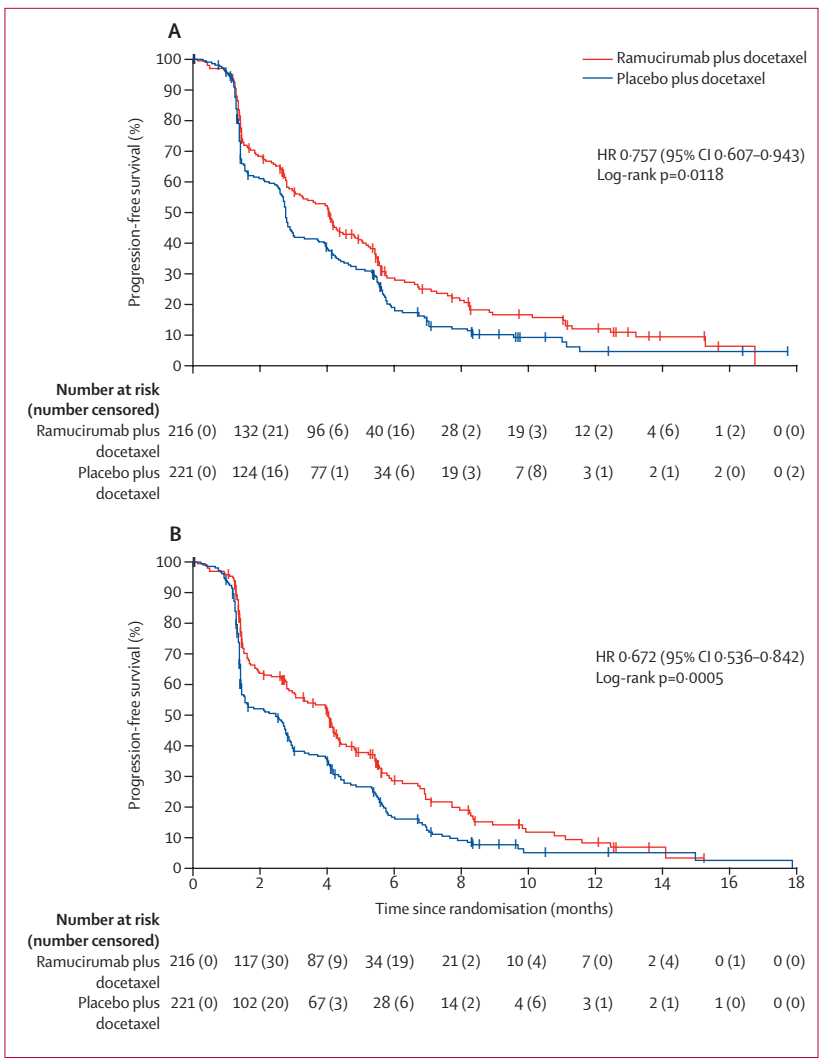

Figure 2: **Kaplan-Meier plots for progression-free survival in the first 437 randomised patients (intention-to-treat population)**
(A) Investigator-assessed. (B) Independent central review. HR=hazard ratio.

population, which included all randomised patients. We used the full ITT population to assess patient-reported outcomes. We estimated progression-free survival using the Kaplan-Meier method, and we compared outcomes between treatment groups using a stratified log-rank test. We estimated HRs and associated 95% CIs using a stratified Cox proportional hazard model. We summarised patient-reported outcome data descriptively. We compared time to sustained deterioration using a non-stratified log-rank test. We assessed safety in all patients who received at least one dose of study medication (safety population). We implemented a gatekeeping design to assess progression-free survival, overall survival, and objective response in a fixed sequential manner.

This study is registered with ClinicalTrials.gov, number NCT02426125.

Role of the funding source

The funder designed the trial, in collaboration with the scientific council (including DPP, RdW, KNC, CNS, HN, and TP), and was responsible for data management and statistical analysis. The funder interpreted data in collaboration with all authors and supported development of the report by providing medical writing and editorial assistance. The corresponding author had full access to all data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Between July, 2015, and April, 2017, 727 patients were screened for study eligibility of whom 197 were excluded mainly for not meeting inclusion criteria (figure 1); 530 patients were randomly allocated either ramucirumab plus docetaxel (n=263) or placebo plus docetaxel (n=267) and comprised the ITT population. Baseline characteristics were balanced between treatment groups in the ITT population (table 1; appendix p 13) and in the first 437 randomised patients (appendix pp 11, 12). 234 (44%) of 530 patients had two or more adverse prognostic risk factors, including liver metastases (n=147 [28%]), haemoglobin lower than 10 g/dL (n=73 [14%]), ECOG performance status score greater than 0 (n=280 [53%]), and time since completion or discontinuation of previous therapy of less than 3 months (n=237 [45%]; table 1). Five patients allocated ramucirumab and two assigned placebo did not receive study treatment; therefore, the safety population comprised 523 patients, of whom 258 were allocated ramucirumab and 265 were assigned placebo.

Data cutoff for the current analysis was April 21, 2017. At data cutoff, 49 (19%) of 263 patients allocated ramucirumab and 36 (13%) of 267 assigned placebo continued to receive study treatment (figure 1). Median duration of follow-up in the full ITT population was 5·0 months (IQR 2·3–8·9). Median treatment duration was 12·1 weeks (IQR 6·0–21·0) with ramucirumab and 9·9 weeks (6·0–20·9) with placebo. The median number of cycles of docetaxel was four (IQR 2–6) in patients allocated ramucirumab and three (2–6) in those assigned placebo (appendix p 14). 93 (36%) of 258 patients allocated ramucirumab and 84 (32%) of 265 assigned placebo completed at least six cycles of docetaxel therapy; median relative dose intensities were 98·3% (IQR 90·9–100·1) and 98·8% (92·9–100·1), respectively. Patients who continued with ramucirumab or placebo monotherapy after the end of docetaxel treatment (64 *vs* 60) received a median of three (IQR 2–7) additional cycles of ramucirumab and two (1–5) of placebo.

At data cutoff, 341 progression-free survival events had occurred in the first 437 patients of the ITT population, 158 (73%) of 216 allocated ramucirumab and 183 (83%) of 221 assigned placebo (appendix p 15). Median progression-free survival was 4·07 months (95% CI 2·96–4·47) in patients allocated ramucirumab

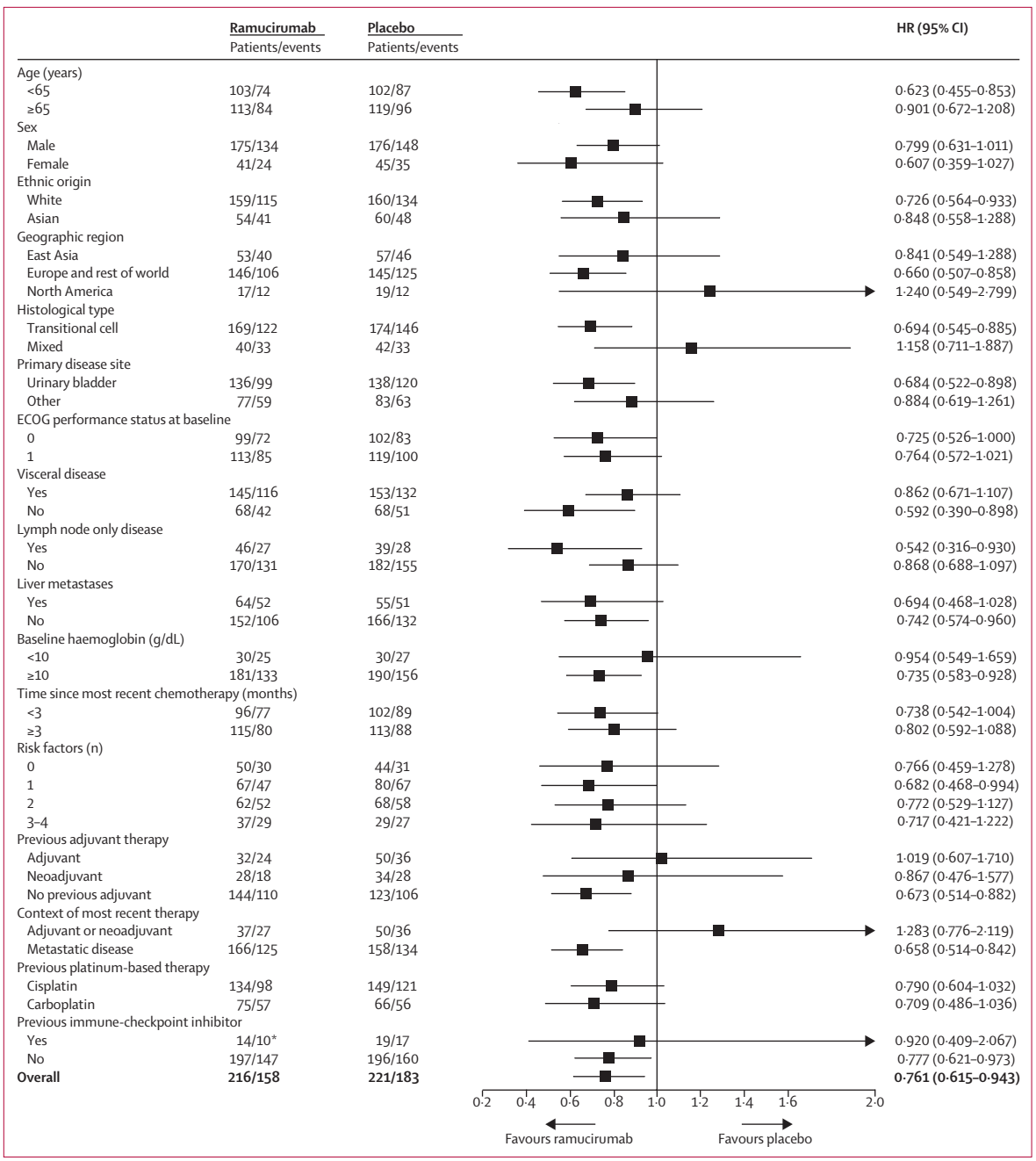

Figure 3: **Progression-free survival subgroup analyses in the first 437 randomised patients (intention-to-treat population)**
ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. *One patient allocated ramucirumab received nivolumab or placebo in a previous clinical trial, but we do not know whether that patient actually received nivolumab, so they are not included in this total for subgroup analysis.

and 2·76 months (2·60–2·96) in those assigned placebo (stratified HR 0·757, 95% CI 0·607–0·943; p=0·0118; figure 2A). Estimated progression-free survival at 12 months was 11·9% (95% CI 7·1–18·0) in patients allocated ramucirumab and 4·5% (1·5–10·1) in those assigned placebo. A blinded independent central analysis was consistent with these results, with median progression-free survival of 4·04 months (95% CI 2·96–4·30) and 2·46 months (1·45–2·83), respectively (stratified HR 0·672, 95% CI 0·536–0·842; p=0·0005; figure 2B). In prespecified subgroup analyses of progression-free survival, addition of ramucirumab to docetaxel improved progression-free survival across most subgroups (figure 3).

Investigator-assessed objective responses in the first 437 patients in the ITT population were achieved by

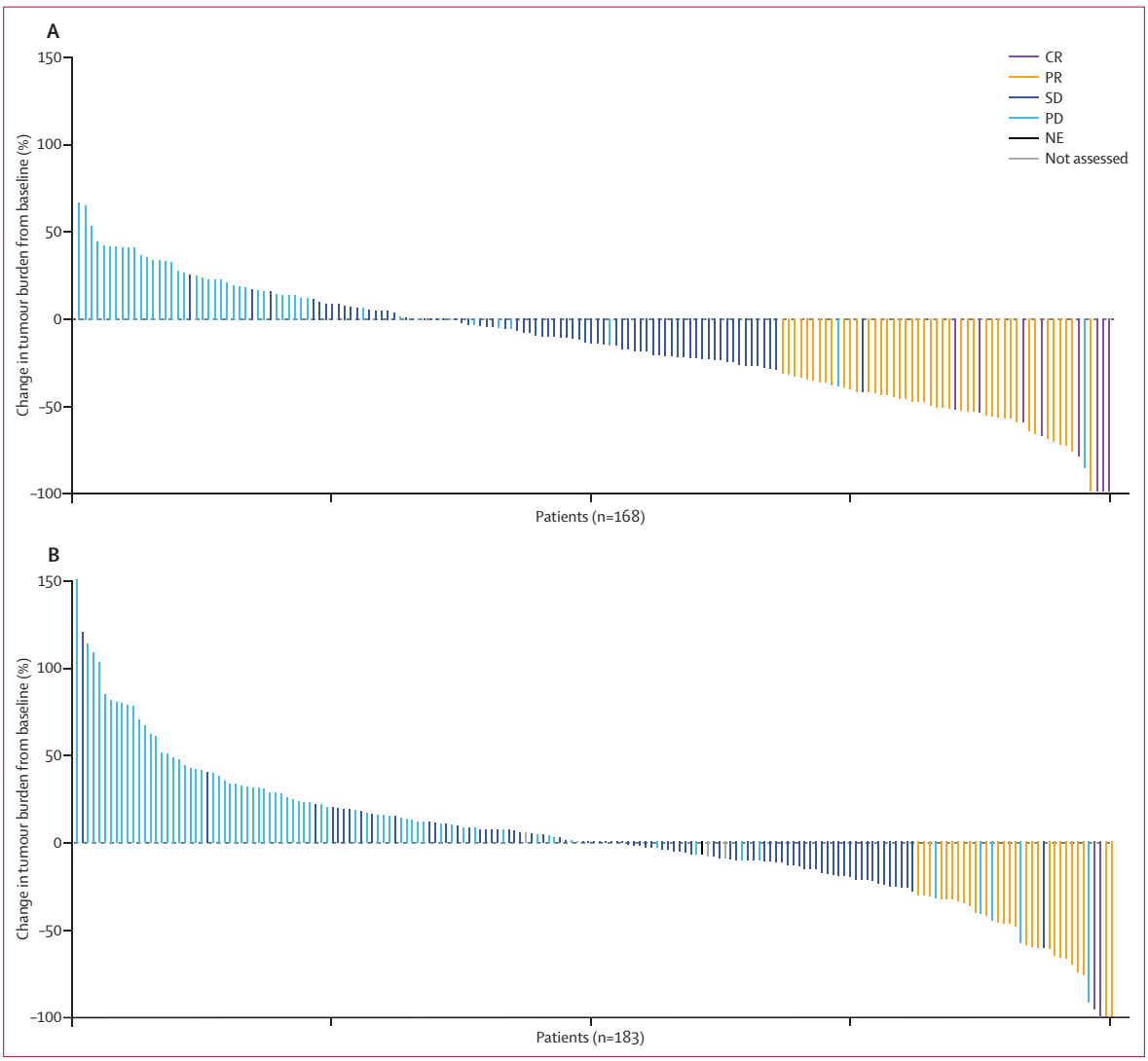

Figure 4: **Best percentage change from baseline in tumour size for patients who had baseline and at least one post–baseline tumour size assessment**
(A) Ramucirumab plus docetaxel (n=168). (B) Placebo plus docetaxel (n=183). Best response assessed according to RECIST version 1.1. CR=complete response. NE=not evaluable. PD=progressive disease. PR=partial response. RECIST=Response Evaluation Criteria in Solid Tumors. SD=stable disease.

53 (24·5%, 95% CI 18·8–30·3) of 216 patients allocated ramucirumab and 31 (14·0%, 9·4–18·6) of 221 assigned placebo (appendix p 15). These included nine (4%) complete responses in patients allocated ramucirumab and three (1%) in those assigned placebo. Objective responses by blinded independent central analysis were achieved by 48 (22·2%, 95% CI 16·7–27·8) of 216 patients allocated ramucirumab and 28 (12·7%, 8·3–17·1) of 221 assigned placebo. Because of the gatekeeping trial design, objective response superiority will be formally tested if the overall survival superiority test is positive. Median duration of response was 5·65 months (95% CI 3·9–7·1) for patients allocated ramucirumab and 4·17 months (2·9–5·5) for those assigned placebo. Of patients who received a previous immune-checkpoint inhibitor, five (36%) of 14 allocated ramucirumab and two (11%) of 19 assigned placebo achieved an objective response to treatment. Disease control occurred in 137 (63·4%, 95% CI 57·0–69·8) of 216 patients allocated ramucirumab and 124 (56·1%, 49·6–62·7) of 221 assigned placebo. Most patients allocated ramucirumab (107 [64%] of 168) had a reduction in tumour burden (figure 4). Reductions in tumour burden were seen less frequently in patients allocated placebo (86 [47%] of 183). At data cutoff, overall survival results were not mature, with 219 events.

Compliance for completion of the questionnaires for patient-reported outcomes in the full ITT population was 97% in both treatment groups at baseline and was 85% or higher at all on-therapy post-baseline visits. Mean scores for global quality of life and the EQ-5D-5L index were similar between treatment groups at baseline

and were relatively unchanged over time, with no differences between treatment groups (figure 5). No difference was recorded in time to sustained deterioration in global quality of life (non-stratified HR 0·931, 95% CI 0·701–1·235; p=0·610).

After administration of ramucirumab 10 mg/kg every 3 weeks in combination with docetaxel to patients with urothelial carcinoma, the geometric mean trough concentrations before doses two, three, and five were 15 µg/mL, 23 µg/mL, and 34 µg/mL, respectively. These data are consistent with those from previous studies in which ramucirumab was administered to patients with various types of cancer using this regimen.[30–32] Of 258 patients allocated ramucirumab who received treatment, 185 had serum samples analysed for the presence of anti-ramucirumab antibodies; 19 (10%) had positive samples at baseline and three (2%) had treatment-emergent anti-ramucirumab antibodies.

The most frequently reported treatment-emergent adverse events, regardless of causality, in either treatment group (any grade) were fatigue, alopecia, diarrhoea, decreased appetite, and nausea (table 2). These events occurred predominantly at grade 1–2 severity. 156 (60%) of 258 patients allocated ramucirumab and 163 (62%) of 265 assigned placebo reported an adverse event of grade 3 or worse. No adverse event of grade 3 or worse was recorded that showed a difference in frequency of 5% or more in patients allocated ramucirumab compared with placebo. Grade 3 or worse anaemia was less common in patients allocated ramucirumab than in those assigned placebo (seven [3%] *vs* 28 [11%]), but the frequency of grade 3 or worse neutropenia was similar in both treatment groups (39 [15%] *vs* 36 [14%]). Use of granulocyte colony-stimulating factor was similar in both treatment groups (106 [41%] of 258 allocated ramucirumab and 112 [42%] of 265 assigned placebo). Adverse events of special interest, based on the known safety profile of other anti-angiogenic therapies and previous clinical experience with ramucirumab, are shown in table 2. Grade 1–2 events of epistaxis (36 [14%] *vs* 13 [5%]), hypertension (29 [11%] *vs* 12 [5%]), haematuria (27 [10%] *vs* 17 [6%]), and proteinuria (23 [9%] *vs* eight [3%]) were each reported more frequently in 258 patients allocated ramucirumab than in 265 assigned placebo. The frequency of venous (six [2%] *vs* 13 [5%]) and arterial (eight [3%] *vs* two [<1%]) thromboembolic events was low and similar in both treatment groups.

Adverse events leading to at least one dose adjustment (reduction, delay, or omission of any study drug) were reported in 88 (34%) of 258 patients allocated ramucirumab and 82 (31%) of 265 assigned placebo. The most common adverse event leading to dose adjustments for ramucirumab compared with placebo was febrile neutropenia (11 [4%] *vs* ten [4%]). Adverse events leading to discontinuation of any study treatment occurred in 39 (15%) of 258 patients allocated ramucirumab and 19 (7%) of 265 assigned placebo; sepsis was the most common adverse event leading to discontinuation of any treatment (five [2%] *vs* none [0%]).

Serious adverse events were reported for 100 (39%) of 258 patients allocated ramucirumab and 104 (39%) of 265 assigned placebo; these events were deemed by the investigator to be related to study treatment in 63 (24%) and 54 (20%) patients, respectively. Including events related by the investigator to disease progression, adverse

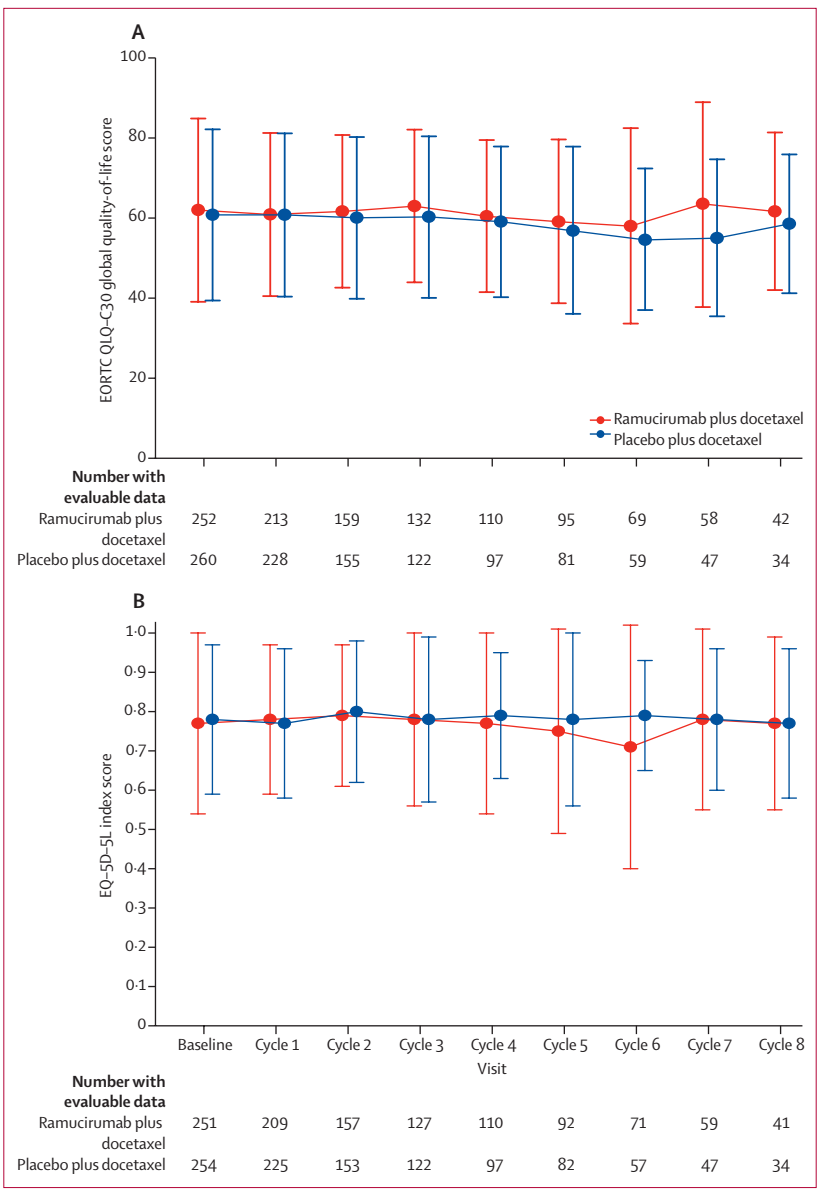

Figure 5: **Patient-reported outcome scores by visit**
Circles represent mean scores and bars represent SD, in patients completing the questionnaire and with a valid score for the scale. Data for treatment groups are offset along the x-axis for legibility, but assessment times were the same for both groups. (A) EORTC QLQ-C30 global quality of life; scores range from 0 to 100, with higher scores representing better quality of life. (B) EQ-5D-5L index; scores range from –0·281 to 1 (displayed as 0–1), with higher scores representing better health status.

	Ramucirumab plus docetaxel (n=258)		Placebo plus docetaxel (n=265)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
All adverse events				
Any	244 (95%)	156 (60%)	251 (95%)	163 (62%)
Fatigue*	110 (43%)	20 (8%)	121 (46%)	25 (9%)
Alopecia	63 (24%)	0	92 (35%)	1 (<1%)
Diarrhoea	75 (29%)	7 (3%)	56 (21%)	7 (3%)
Decreased appetite	73 (28%)	8 (3%)	61 (23%)	5 (2%)
Nausea	63 (24%)	1 (<1%)	52 (20%)	3 (1%)
Stomatitis	61 (24%)	8 (3%)	29 (11%)	0
Pyrexia	42 (16%)	1 (<1%)	41 (15%)	1 (<1%)
Vomiting	38 (15%)	3 (1%)	37 (14%)	2 (<1%)
Neuropathy*	31 (12%)	0	43 (16%)	2 (<1%)
Constipation	29 (11%)	1 (<1%)	43 (16%)	1 (<1%)
Urinary-tract infection	32 (12%)	10 (4%)	38 (14%)	11 (4%)
Peripheral oedema	36 (14%)	0	30 (11%)	1 (<1%)
Dypnoea	30 (12%)	5 (2%)	30 (11%)	5 (2%)
Asthenia	26 (10%)	3 (1%)	22 (8%)	4 (2%)
Dysgeusia	30 (12%)	0	17 (6%)	0
Haematological adverse events				
Neutropenia*	51 (20%)	39 (15%)	44 (17%)	36 (14%)
Febrile neutropenia	25 (10%)	25 (10%)	17 (6%)	17 (6%)
Anaemia	40 (16%)	7 (3%)	64 (24%)	28 (11%)
Leucopenia*	26 (10%)	17 (7%)	24 (9%)	21 (8%)
Adverse events of special interest				
Bleeding or haemorrhage*	67 (26%)	8 (3%)	46 (17%)	12 (5%)
Epistaxis	36 (14%)	0	13 (5%)	0
Haematuria	27 (10%)	5 (2%)	17 (6%)	5 (2%)
Gastrointestinal haemorrhage	10 (4%)	2 (<1%)	10 (4%)	3 (1%)
Pulmonary haemorrhage	1 (<1%)	0	0	0
Hypertension*	29 (11%)	15 (6%)	12 (5%)	5 (2%)
Renal failure*	15 (6%)	8 (3%)	19 (7%)	2 (<1%)
Proteinuria	23 (9%)	2 (<1%)	8 (3%)	1 (<1%)
Venous thromboembolic*	6 (2%)	1 (<1%)	13 (5%)	5 (2%)
Arterial thromboembolic*	8 (3%)	6 (2%)	2 (<1%)	0
Fistula*	5 (2%)	3 (1%)	2 (<1%)	2 (<1%)
Congestive heart failure*	3 (1%)	2 (<1%)	1 (<1%)	1 (<1%)
Gastrointestinal perforation*	3 (1%)	2 (<1%)	1 (<1%)	1 (<1%)

Data are number of patients (%). Data are treatment-emergent adverse events occurring in at least 10% of patients or of special interest irrespective of cause, according to either preferred terms or *consolidated categories.

Table 2: **Treatment-emergent adverse events (safety population)**

events with an outcome of death on treatment or within 30 days of discontinuation were reported for 38 (15%) of 258 patients allocated ramucirumab and 43 (16%) of 265 assigned placebo; these events were deemed by the investigator to be related to study treatment in eight (3%) and five (2%) patients, respectively. Sepsis was the most common adverse event leading to death on treatment (appendix p 16), occurring in four (2%) patients allocated ramucirumab and no patients assigned placebo. One fatal event of neutropenic sepsis was reported in a patient allocated ramucirumab.

Discussion

Findings of the RANGE trial show that addition of ramucirumab to docetaxel is associated with a significant improvement in progression-free survival in patients with platinum-refractory advanced urothelial carcinoma. In this advanced patient population, progression-free survival outcomes were consistent across almost all major subgroups examined and confirmed by blinded central review. 44% of patients in this trial had two or more adverse prognostic risk factors at baseline, including the presence of liver metastases.[28,29] A consistent progression-free survival benefit was seen for patients treated with ramucirumab plus docetaxel, irrespective of the number of associated risk factors, showing broad applicability of this regimen. The median progression-free survival of 2·76 months that was recorded with placebo plus docetaxel is consistent with historical data in the second-line setting, such that the noted improvement with ramucirumab plus docetaxel (4·07 months) was not attributable to underperformance of the control.[5,13]

Data for overall survival are immature at this time, precluding formal statistical analysis of objective response in accordance with the order of analyses specified in the statistical analysis plan. However, a higher proportion of patients allocated ramucirumab achieved an objective response compared with placebo (24·5% *vs* 14·0%), including nine complete responses with ramucirumab versus three with placebo, with non-overlapping 95% CIs. The objective response was consistent with findings of a phase 2 study of this treatment regimen and it was higher when compared indirectly with historical chemotherapy studies.[5,13,23] The objective response recorded in patients allocated ramucirumab in our study is also in line with that seen with immune-checkpoint inhibitors in other studies, although duration of response is longer with immune-checkpoint inhibitors.[6] Disease control was achieved by 63% of patients allocated ramucirumab in our study, which compares favourably with single-agent chemotherapy or immune-checkpoint inhibitors in other studies, underlining the active nature of this regimen in biomarker-unselected patients.[6,13,33]

The combination of ramucirumab and docetaxel revealed no unexpected safety findings. The most common toxic effects were of grade 1–2 severity and manageable with supportive care alone or with dose reductions, as shown by the high median relative dose-intensity for all study drugs. Overall, addition of ramucirumab to docetaxel was not associated with an increase in occurrence of grade 3 or worse toxic effects typically associated with docetaxel in this patient population. Consistent with phase 2 data,[13] the most common haematological toxic effect in our study was neutropenia, reported at a similar frequency in both treatment groups; anaemia was less common in patients allocated ramucirumab. The frequency of toxic effects identified as potential class effects of antiangiogenic therapies—eg, grade 1–2

hypertension and bleeding—occurred at a higher frequency with ramucirumab than with placebo. Yet, the analyses of patient-reported outcomes indicated no negative effect on quality of life. This finding is especially important for these patients, because most have a short life expectancy.

Previous meta-analyses of second-line chemotherapy for patients with metastatic urothelial carcinoma showed that improvements in progression-free survival predict improvements in overall survival.[34] Based on this observation, and the improvement in objective response noted with ramucirumab and docetaxel, we believe our results are clinically significant.

Although our findings are positive, the study and the data available at the time of publication have limitations. Patients were not stratified according to all second-line Bellmunt risk factors and, as such, some imbalances were noted between treatment groups. A higher proportion of patients allocated ramucirumab had liver metastases (30% *vs* 26%) and a total Bellmunt risk score of 3 (18% *vs* 12%) compared with those assigned placebo, which might have affected study outcomes. The trial design allowed for inclusion of patients after treatment with an immune-checkpoint inhibitor. However, only two such agents—atezolizumab (May, 2016) and nivolumab (February, 2017)—received regulatory approval for urothelial carcinoma before the end of the enrolment period of this study, and this approval was restricted to the USA. As a result, enrolment of such patients was limited. Further clinical experience with this cohort and with others in future studies will be needed to fully understand the efficacy of ramucirumab and docetaxel when used after treatment with a platinum-based regimen and immune-checkpoint inhibitors. Overall, median follow-up in the ITT population was fairly short (5 months) at this primary progression-free survival analysis, which can be attributed to the study population being a subset of the full ITT population and the overall rapid disease course leading to a short time to progression in patients with urothelial carcinoma. Survival data are pending maturity and will be informative once available.

Acknowledging the limitations and taken into context, the combination of ramucirumab and docetaxel shows significant activity without clear deleterious effects on quality of life, in a clinical setting of high unmet medical need. A high frequency of disease control will be attractive for patients for whom alternative chemotherapy options are limited and largely ineffective. Data for immune-checkpoint inhibitors have also become available in this setting, resulting in their widespread use in the USA. Inconsistencies have been seen with these agents, although long-term durable remission occurs in a subset of patients, and a survival advantage has been shown for pembrolizumab.[6] Our trial included 43 patients who had previously received immune-checkpoint inhibitors (appendix p 13). Two additional patients had been in clinical trials before RANGE in which they were randomly allocated either an immune-checkpoint inhibitor or placebo. Unfortunately, these numbers are small and only 33 of the 43 patients were included in the primary analysis of progression-free survival. However, responses were seen with ramucirumab and docetaxel in this population (five [36%] of 14 patients), suggesting activity. Further studies in this setting are needed. Based on the reported efficacy and tolerability, ramucirumab plus docetaxel is also an alternative treatment regimen in the setting after immune-checkpoint treatment or in patients ineligible for treatment with an immune-checkpoint inhibitor.

Future studies might also be of interest to investigate potential benefits of combining immune-checkpoint inhibitors and antiangiogenic agents. Findings of phase 2 and phase 3 studies have shown that about 20% of patients with platinum-refractory urothelial carcinoma achieve an objective response to immune-checkpoint inhibition.[6–8] Strategies to increase objective responses include combinations of PD-1 or PD-L1 inhibitors with other immune-checkpoint inhibitors, chemotherapy, or antiangiogenic agents.[5,35–38] Ramucirumab in combination with PD-1 or PD-L1 inhibitors has shown promising clinical activity in multiple tumour types, including urothelial carcinoma, in the phase 1 setting, with no unexpected toxic effects.[36,38,39] More work is needed to understand combinatorial and sequencing approaches of these new classes of treatment for urothelial carcinoma.

In conclusion, the findings of the RANGE trial are consistent with results from a previous phase 2 study in which ramucirumab combined with docetaxel improved progression-free survival in patients with platinum-refractory advanced or metastatic urothelial carcinoma.[13] Up to now, ramucirumab is the only antiangiogenic agent with proven clinical activity in this patient population and, to our knowledge, RANGE represents the first phase 3 study to show a progression-free survival advantage over chemotherapy alone. No additive or unexpected toxic effects were seen when ramucirumab was combined with docetaxel. Together, these phase 2 and phase 3 data suggest a favourable benefit-to-risk ratio for this combination treatment and might represent a new regimen for this patient population.

Contributors

DPP, RdW, KNC, CNS, HN, and TP were members of the scientific council and contributed to study design, data collection, data analysis, data interpretation, and drafting, review, and approval of the submitted report. AML, RAW, OH, and AHZ contributed to study design, data analysis, data interpretation, and drafting, review, and approval of the submitted report. RCW and KMB-M contributed to data analysis, data interpretation, and drafting, review, and approval of the submitted report. BA, IJP, FL, and AR-V contributed to data collection, data analysis, data interpretation, and review and approval of the submitted report. AB, HSC, MH, MT, GT, XGdM, and HH contributed to data collection and review and approval of the submitted report. DC, SH, EYY, and IC contributed to data analysis, data interpretation, and drafting, review, and approval of the submitted report. AD, AF, MSvdH, NM, AN, Y-CO, W-PS, J-LL, AS, AP, and SS contributed to data collection, data interpretation, and drafting, review, and approval of the submitted report. LG contributed to data interpretation, and review and approval of the submitted report.

Declaration of interests

DPP reports grants from Eli Lilly and Company, during the conduct of the study; personal fees from Bayer, Bellicum, Dendreon, Sanofi-Aventis, Johnson & Johnson, Exelixis, Ferring, Millennium, Medivation, Pfizer, Roche Laboratories, and Tyme pharmaceuticals, outside the submitted work; grants from Oncogenix, Progenics, Johnson & Johnson, Merck, Millennium, Dendreon, Sanofi-Aventis, Agensys, Eli Lilly and Company, and Roche Laboratories, outside the submitted work; and ownership interest/investment from Bellicum and Tyme, outside the submitted work. RdW reports personal fees from Eli Lilly and Company, during the conduct of the study; and personal fees from Merck, Roche, and Sanofi, outside the submitted work. KNC reports institutional funding from Eli Lilly and Company, during the conduct of the study. CNS reports personal fees from Eli Lilly and Company, BMS, Merck/Pfizer, and Clovis, outside the submitted work. SH reports personal fees from Roche, Merck, AstraZeneca, Pierre Fabre, and Bayer, outside the submitted work. AF reports personal fees from AstraZeneca, MSD, Pierre Fabre, Pfizer, and Roche, outside the submitted work. AB reports personal fees from AstraZeneca and BMS, outside the submitted work; and grants and personal fees from Roche, outside the submitted work. EYY reports grants and personal fees from Eli Lilly and Company, during the conduct of the study; grants and personal fees from Agensys, Astellas, Bayer, Dendreon, Genentech/Roche, and Merck, outside the submitted work; and personal fees from AstraZeneca, Churchill Pharmaceuticals, EMD Serono, Ferring, Janssen, Medivation, Sanofi, Seattle Genetics, Tolmar, and Tokai, outside the submitted work. MSvdH reports personal fees from Roche/Genentech, AstraZeneca/Medimmune, and BMS, outside the submitted work; and grants and personal fees from Astellas, outside the submitted work. AN reports grants, personal fees, and non-financial support from Roche, during the conduct of the study; grants and personal fees from Merck and AstraZeneca, during the conduct of the study; and personal fees from Seattle Genetics and Bayer, during the conduct of the study. MT reports personal fees from Astellas, Sanofi, Bayer, and Janssen, outside the submitted work. AP reports consultancy fees from MSD, Bayer, BMS, Janssen, Astellas, Novartis, Roche, AstraZeneca, and Pfizer, outside the submitted work. XGdM reports personal fees from Pfizer, BMS, Eli Lilly and Company, Pharmamar, Novartis, Ipsen, and Roche, outside the submitted work. RCW, AML, OH, AHZ, and KMB-M are employees and shareholders at Eli Lilly and Company. RAW is an employee, shareholder, and has a patent pending (CA2961295A1) at Eli Lilly and Company. TP reports grants and research funding from Roche, outside the submitted work; grants from AstraZeneca, outside the submitted work; and personal fees from Roche, Merck, AstraZeneca, BMS, Eli Lilly and Company, and Pfizer, outside the submitted work. AD, HN, DC, NM, BA, LG, Y-CO, HSC, W-PS, MH, IJP, J-LL, AS, FL, GT, SS, AR-V, IC, and HH declare no competing interests.

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