HHS Public Access

Author manuscript

Lancet Oncol. Author manuscript; available in PMC 2021 January 01.

Published in final edited form as:

Lancet Oncol. 2020 January ; 21(1): 105–120. doi:10.1016/S1470-2045(19)30668-0.

‡See appendix for full list of investigators

Correspondence to: Prof Daniel P Petrylak, Yale School of Medicine, Yale University, New Haven, CT 06520-8028, USA, daniel.petrylak@yale.edu.

Contributors

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

*Current affiliation: New York-Presbyterian/Weill Cornell Medical Center, New York, NY, USA

†Current affiliation: Fondazione Policlinico Universitario A Gemelli IRCCS, Rome, Italy

See **Online** for appendix

Declaration of interests

DPP reports grants from Eli Lilly and Company, during the conduct of the study; and consultant fees from Ada Cap, Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis, Eli Lilly, Exelixis, Incyte, Janssen, Pfizer, Pharmacyclics, Roche Laboratories, Seattle Genetics, and Urogen, grants from Ada Cap, Astellas, AstraZeneca, Bayer, Bristol-Myers Squibb, Clovis, Eli Lilly, Endocyte, Genentech, Innocrin, MedImmune, Merck, Novartis, Pfizer, Progenics, Roche Laboratories, Sanofi Aventis, and Seattle Genetics, and ownership interest or investments in Bellicum and Tyme, outside the submitted work. RdW reports personal fees from Eli Lilly and Company, during the conduct of the study; and grants (paid to institution) from Sanofi and personal fees from Merck, Roche, Bayer, Janssen, Clovis, and Sanofi, outside the submitted work. KNC reports institutional funding from Eli Lilly and Company, during the conduct of the study. AD reports travel reimbursements from Eli Lilly and Company, consulting fees from Bristol-Myers Squibb, travel and consulting fees from AstraZeneca, and equity in Kynan Pharma, Allogene, and Urogen, outside the submitted work. CNS reports personal fees from Eli Lilly and Company, Bristol-Myers Squibb, Merck/Pfizer, and Clovis, outside the submitted work. SAH reports personal fees from Roche, Merck, AstraZeneca, Pierre Fabre, Sotio, Pfizer, Janssen, and Bayer, outside the submitted work. AF reports honoraria from AstraZeneca, Merck Sharp & Dohme, and Roche, outside the submitted work. AB reports personal fees from AstraZeneca and Bristol-Myers Squibb, and grants and personal fees from Roche, outside the submitted work. EYY reports grants and personal fees from Eli Lilly, during the conduct of the study; and grants and personal fees from Agensys, Astellas, Bayer, Dendreon, Genentech/Roche, Merck, and Seattle Genetics and personal fees from AstraZeneca, Churchill Pharmaceuticals, EMD Serono, Ferring, Janssen, Medivation, Sanofi, Tolmar, Tokai, QED, Amgen, Pharmacyclics, and InCyte, outside the submitted work. MSvdH reports grants (paid to institution) from Roche and AstraZeneca and consultation and grant support (both to institute) from Bristol-Myers Squibb, outside the submitted work.

NM reports research grants from Janssen, AstraZeneca, Merck Sharp & Dohme, Bayer, Lilly, Roche, and Taiho, outside the submitted work. AN reports grants, personal fees, and non-financial support from Roche, grants and personal fees from Merck and AstraZeneca, and personal fees from Seattle Genetics and Bayer, during the conduct of the study. JB reports grants from Eli Lilly and Company, during the conduct of the study; and personal fees from AstraZeneca, Astellas, and Eusa Pharma and grants and personal fees from Bristol-Myers Squibb, Eisai, Ipsen, Merck Sharp & Dohme, Novartis, Roche, and Pfizer, and personal fees from Eusa Pharma, outside the submitted work. J-LL reports grants, personal fees, and advisory board fees from Pfizer Korea and Ipsen Korea, personal fees and advisory board fees from Janssen, Astellas Korea, Bristol-Myers Squibb Korea, and Sanofi Aventis, and personal fees from Novartis Korea, outside the submitted work. MT reports personal fees from Astellas, Sanofi, Bayer, and Janssen, outside the submitted work. AP reports consultant fees from Merck Sharp & Dohme, Bayer, Bristol-Myers Squibb, Janssen, Astellas, Novartis, Roche, AstraZeneca, and Pfizer, outside the submitted work. XGdM reports personal fees from Pfizer, Bristol-Myers Squibb, Eli Lilly and Company, Pharmamar, Novartis, Ipsen, and Roche, outside the submitted work. AR-V reports grants from Takeda, grants and personal fees from Merck Sharp and Dohme, and grants and personal fees from Pfizer, Janssen, Astellas, Roche, Bristol-Myers Squibb, Clovis, Bayer, and Sanofi-Aventis, outside the submitted work. STT reports institutional research support from Eli Lilly during the conduct of the study, and prior honoraria from Sanofi; and consulting and advisory roles for Medivation, Astellas Pharma, Dendreon, Janssen, Bayer, Genentech, Sanofi, Endocyte, Immunomedics, Karyopharm Therapeutics, Abbvie, Tolmark, QED, institutional research support from Janssen, Astellas Pharma, Progenics, Millennium, Amgen, Bristol-Myers Squibb, Dendreon, Rexahn Pharmaceuticals, Bayer, Genentech, Newlink Genetics, Inovio Pharmaceuticals, AstraZeneca, Immunomedics, Novartis, AVEO, Boehringer Ingelheim, Merck Sharp & Dohme, Stem CentRx, Karyopharm Therapeutics, Abbvie, Medivation, Endocyte, Exelixis, and Clovis Oncology, and travel, accommodations, and expenses received from Sanofi and Amgen, outside the submitted work. UV reports personal fees (honoraria) and other (consulting, advisory, or speaker bureau payments) from Bayer and Sanofi, grants, personal fees, and consulting, advisory, or speaker bureau payments from Bristol-Myers Squibb, Exelixis, and Pfizer, and grants and consulting or advisory role payments from Astellas Pharma, outside the submitted work. JBA-C reports personal fees from Bristol-Myers Squibb, Sanofi, Janssen, and EMD Serono outside the submitted work. OH and FR were employees of Eli Lilly and Company during the conduct of the study and are shareholders at Eli Lilly and Company. AML, SW, RRH, AHZ, and KMB-M are employees and shareholders at Eli Lilly and Company. RAW is an employee, shareholder, and has patents pending at Eli Lilly and Company. TP reports strategic or advisory fees and grants from Roche, strategic or advisory and consultant or honoraria fees from Pfizer, Bristol-Myers Squibb, and AstraZeneca, and consultant or honoraria fees from Exelexis, Incyte, Ipsen, Merck, and Seattle Genetics, all outside the submitted work. All other authors declare no competing interests.

Data sharing

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

Daniel P Petrylak, **Ronald de Wit**, **Kim N Chi**, **Alexandra Drakaki**, **Cora N Sternberg**[*], **Hiroyuki Nishiyama**, **Daniel Castellano**, **Syed A 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**, **Jens Bedke**, **Georgios Gakis**, **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**, **Scott T Tagawa**, **Ulka Vaishampayan**, **Jeanny B Aragon-Ching**, **Oday Hamid**, **Astra M Liepa**, **Sameera Wijayawardana**, **Francesca Russo**, **Richard A Walgren**, **Annamaria H Zimmermann**, **Rebecca R Hozak**, **Katherine M Bell-McGuinn**, **Thomas Powles**, **RANGE study investigators**[‡]

Yale School of Medicine, Yale University, 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, University of California Los Angeles, Los Angeles, CA, USA (A Drakaki MD); 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); Department of Oncology and Metabolism, Medical School, University of Sheffield, Sheffield, UK (Prof S A 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 (M S van der Heijden PhD); National Cancer Center Hospital East, Chiba, Japan (N Matsubara MD); P.A. Herzen Moscow Oncological Research Institute, Moscow, Russia (Prof B Alekseev PhD); Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale dei Tumori, Milan, Italy (A Necchi MD); National Institute of Oncology, Budapest, Hungary (L Géczi PhD); Tungs' Taichung Metro Harbor 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 & Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan (Prof W-P Su PhD);

Eli Lilly and company will provide access to all individual participant data collected during the trial, after anonymisation, except for pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the USA and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data have been made available. Access to data will be 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.

Department of Urology, University of Tübingen, Tübingen, Germany (Prof J Bedke MD, Prof G Gakis MD); Pediatric Urology, Julius Maximillians University, Würzburg, Germany (Prof G Gakis); Florida Cancer Specialists, Port Charlotte, FL, USA (I J Percent MD); Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea (Prof J-L Lee PhD); Division of Medical Oncology, Department of Oncology, University of Turin, San Luigi Gonzaga Hospital, 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 Center, Kazan, Russia (S Safina MD); Institut Català d'Oncologia L'Hospitalet, Institut d'Investigacio Biomedica de Bellvitge, University of Barcelona, Barcelona, Spain (X Garcia 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); New York-Presbyterian/Weill Cornell Medical Center, New York, NY, USA (S T Tagawa MD); Karmanos Cancer Institute, Detroit, MI, USA (Prof U Vaishampayan MD); Inova Schar Cancer Institute, Fairfax, VA, USA (J B Aragon-Ching MD); Eli Lilly and Company, Indianapolis, IN, USA (O Hamid PharmD, A M Liepa PharmD, S Wijayawardana PhD, F Russo MD, R A Walgren MD, A H Zimmermann MS, R R Hozak PhD, K M Bell-McGuinn MD); and Barts Cancer Institute, Queen Mary University of London, London, UK (Prof T Powles MD)

Summary

Background—Ramucirumab—an IgG1 vascular endothelial growth factor receptor 2 antagonist—plus docetaxel was previously reported to improve progression-free survival in platinum-refractory, advanced urothelial carcinoma. Here, we report the secondary endpoint of overall survival results for the RANGE trial.

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 investigative sites (hospitals, clinics, and academic centres) in 23 countries. Previous treatment with one immune checkpoint inhibitor was permitted. Patients were randomly assigned (1:1) using an interactive web response system to receive intravenous ramucirumab 10 mg/kg or placebo 10 mg/kg volume equivalent followed by intravenous docetaxel 75 mg/m^2 (60 mg/m^2 in Korea, Taiwan, and Japan) on day 1 of a 21-day cycle. Treatment continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Randomisation was stratified by geographical region, Eastern Cooperative Oncology Group performance status at baseline, and visceral metastasis. Progression-free survival (the primary endpoint) and overall survival (a key secondary endpoint) were assessed in the intention-to-treat population. The study is registered with ClinicalTrials.gov, ; patient enrolment is complete and the last patient on treatment is being followed up for safety issues.

Findings—Between July 20, 2015, and April 4, 2017, 530 patients were randomly allocated to ramucirumab plus docetaxel (n=263) or placebo plus docetaxel (n=267) and comprised the intention-to-treat population. At database lock (March 21, 2018) for the final overall survival analysis, median follow-up was 7·4 months (IQR 3·5–13·9). In our sensitivity analysis of investigator-assessed progression-free survival at the overall survival database lock, median progression-free survival remained significantly improved with ramucirumab compared with

placebo (4·1 months [95% CI 3·3–4·8] *vs* 2·8 months [2·6–2·9]; HR 0·696 [95% CI 0·573–0·845]; p=0·0002). Median overall survival was 9·4 months (95% CI 7·9–11·4) in the ramucirumab group versus 7·9 months (7·0–9·3) in the placebo group (stratified HR 0·887 [95% CI 0·724–1·086]; p=0·25). Grade 3 or worse treatment-related treatment-emergent adverse events in 5% or more of patients and with an incidence more than 2% higher with ramucirumab than with placebo were febrile neutropenia (24 [9%] of 258 patients in the ramucirumab group *vs* 16 [6%] of 265 patients in the placebo group) and neutropenia (17 [7%] of 258 *vs* six [2%] of 265). Serious adverse events were similar between groups (112 [43%] of 258 patients in the ramucirumab group *vs* 107 [40%] of 265 patients in the placebo group). Adverse events related to study treatment and leading to death occurred in eight (3%) patients in the ramucirumab group versus five (2%) patients in the placebo group.

Interpretation—Additional follow-up supports that ramucirumab plus docetaxel significantly improves progression-free survival, without a significant improvement in overall survival, for patients with platinum-refractory advanced urothelial carcinoma. Clinically meaningful benefit might be restricted in an unselected population.

Funding—Eli Lilly and Company.

Introduction

Prognosis for patients with locally advanced or metastatic urothelial carcinoma who have progressed on a previous frontline platinum-based chemotherapy remains poor. The 7–8 month median overall survival for patients who receive second-line single-agent therapy underscores the need to develop more efficacious and tolerable therapies for this treatment setting.[1–5] Immune therapy targeting the PD-1 protein and its ligand PD-L1 has largely superseded chemotherapy in this setting, although few patients benefit from durable remissions. Currently, five immunotherapy agents are approved in several regions, including the USA, Europe, and Japan, based on second-line phase 2 and phase 3 data.[1,6–9] The proportion of patients who achieved an objective response on these regimens ranged between 13% and 21%, with durable responses also being recorded.[1,6–9] Only pembrolizumab has shown an overall survival benefit compared with chemotherapy in a randomised phase 3 study in patients with advanced urothelial carcinoma and no treatment, to our knowledge, has shown a progression-free survival benefit.[1] There remains a high unmet need for other therapeutic targets and treatments in these patients.[1,6–10]

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.[10–18] Ramucirumab is an IgG1 monoclonal antibody VEGFR-2 antagonist.[19] RANGE is a randomised, double-blind, placebo-controlled, phase 3 study assessing ramucirumab combined with docetaxel versus placebo plus docetaxel in patients with locally advanced, unresectable or metastatic urothelial carcinoma whose disease had progressed on or after previous platinum-based chemotherapy.[20] The primary endpoint of progression-free survival was met and reported for the first 437 randomised patients.[20] Median progression-free survival improved from 2·8 months (95% CI 2·6–3·0) with placebo plus docetaxel to 4·1 months (3·0–4·5) with ramucirumab plus docetaxel. (hazard ratio [HR] 0·757, 95% CI 0·607–0·943; p=0·0118).[20] The proportion of patients who

achieved an objective response was also higher in the ramucirumab plus docetaxel group than in the placebo plus docetaxel group (53 [25%] of 216 patients [95% CI 18·8–30·3] *vs* 31 [14%] of 221 patients [9·4–18·6]). Here, we report the secondary endpoint of overall survival, updated progression-free survival and overall response results in the full intention-to-treat population, as well as updated safety and quality of life, immunogenicity, and pharmacokinetics. Exploratory biomarker analyses of efficacy endpoints by baseline PD-L1 combined positive score are also presented.

Methods

Study design and participants

RANGE was a double-blind, multicentre, placebo-controlled, randomised, phase 3 trial at 124 investigative sites (hospitals, clinics, and academic centres) in 23 countries (appendix pp 2–8). The overall study design was previously reported[20] and is summarised in the study protocol (appendix p 30).

Full inclusion and exclusion criteria are provided in the study protocol (appendix p 30). Key eligibility criteria included adults aged 18 years or older with histologically or cytologically confirmed urothelial carcinoma of the bladder, urethra, ureter, or renal pelvis of predominantly transitional cell histology; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; locally advanced, unresectable, or metastatic disease extent; life expectancy of at least 3 months; and disease progression according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 14 months or less after receipt of platinum-containing chemotherapy (2 additional months were allowed for screening and patient identification over the standard 12 months).[21] 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. Patients were ineligible for inclusion if they had received more than one previous systemic chemotherapy in the relapsed or metastatic setting (previous systemic therapy in the perioperative setting was not considered a previous line of treatment). Complete eligibility criteria, including laboratory tests required to assess eligibility and exclusionary comorbidities, are in the study protocol (appendix pp 58–63). Briefly, laboratory tests were done to assess adequate haematological, coagulation, hepatic, and renal function, and urinary protein levels. Existing comorbidities that were exclusionary included, but were not limited to, Child-Pugh class B (or worse), cirrhosis (any degree), uncontrolled hypertension, symptomatic anaemia, symptomatic congestive heart failure, unstable angina pectoris, known untreated brain metastases, or any other serious uncontrolled medical disorders in the opinion of the investigator.

The trial complied with 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.

Randomisation and masking

After enrolment, eligible patients were randomly assigned (1:1) to ramucirumab plus docetaxel or ramucirumab plus placebo by an interactive web response system, with a computer-generated random sequence. Randomisation was stratified by geographical region (North America *vs* east Asia *vs* Europe and the rest of the world); ECOG performance status at baseline (0 *vs* 1); and visceral metastasis (yes *vs* no), with visceral metastases involving the liver, lung, bone, or a combination. Patients, investigators, site study staff, and the study funder were masked to treatment assignment throughout the study. Allocated treatments were volume equivalent and in identical-appearing containers. Employees of the study funder who were unblinded at the time of progression-free survival analysis no longer managed patient-level decisions between the progression-free survival and overall survival database locks.

Procedures

Patients received intravenous ramucirumab 10 mg/kg (Eli Lilly and Company; Indianapolis, IN, USA) or placebo 10 mg/kg volume equivalent followed by intravenous docetaxel 75 mg/m^2 (60 mg/m^2 in Korea, Taiwan, and Japan) on day 1 of a 21-day cycle. Treatment continued until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Docetaxel was limited to six cycles, with up to four additional cycles allowed after sponsor approval. Ramucirumab or placebo was continued as monotherapy once docetaxel treatment was completed. There was no planned crossover on disease progression. We allowed dose modifications according to protocol-defined criteria (appendix p 80). Specifically, up to two dose-level decreases of ramucirumab or placebo, of 2 mg/kg each, were allowed during the study; if further dose reductions were required, the patient discontinued ramucirumab or placebo. Dose modifications were permanent; no dose escalations were permitted after a dose reduction. If a toxic effect related to ramucirumab or placebo did not resolve in the same treatment cycle, administration of the next dose could be delayed for up to 42 days; if symptoms were not resolved at this point, ramucirumab or placebo was discontinued. Docetaxel treatment continued as scheduled if there was a delay or modification of ramucirumab or placebo. Docetaxel dose modifications were permitted as per the manufacturer's instructions. Ramucirumab or placebo therapy continued as scheduled if there was a delay or discontinuation of docetaxel. We permitted use of granulocyte-colony-stimulating factor based on American Society of Clinical Oncology guidelines.[22]

Investigators at local sites assessed tumour responses radiographically according to RECIST version 1·1 at baseline, every 6 weeks after randomisation for the first year, and every 12 weeks thereafter. Radiological assessments were then centrally reviewed by an independent, blinded group (BIOCLINICA; Princeton, NJ, USA). After discontinuation, we followed up patients for survival every 3 months. The appendix (p 97) provides details of the timing of other efficacy assessments.

Safety data were collected at baseline, and at each subsequent study visit (appendix p 100) or as medically necessary. Patients were instructed to call their physician to report any adverse events between study visits. Clinical laboratory assessments including, but not

limited to, haematology, clinical chemistry, coagulation, and urinalysis were collected at baseline, each subsequent study visit, and if a patient required a visit because of a toxic effect between study visits. We graded adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Before each treatment cycle, we assessed patient-reported outcomes with the 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. Each of the QLQ-C30 scales was scored 0 to 100, according to the EORTC scoring manual, and the EQ-5D-5L index was calculated using the English value set.[23] For QLQ-C30, we defined time to sustained deterioration as time from randomisation to the first 10-point or greater worsening in score, with no subsequent on-therapy assessment that returned to or improved from the baseline score.

In pretreatment archival tumour samples, PD-L1 was visualised with the 22C3 PD-L1 pharmDx assay (Dako; Santa Clara, CA, USA), verified in bladder cancer. Scoring was done with the combined positive score algorithm as described in the PD-L1 IHC 22C3 pharmDx Interpretation Manual.[24]

Follow-up was calculated as the time from randomisation to death or date of censoring. Time to treatment discontinuation was defined as the time from randomisation to treatment discontinuation. Censoring for survival at the last known treatment date before the primary data cutoff occurred for patients who remained on treatment.

Outcomes

The primary endpoint of RANGE was progression-free survival as assessed by the investigator, defined as the time from randomisation until first radiographic documentation of progression, or death from any cause.[20] Secondary endpoints were 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 time from the first date of complete or partial response until the first date of progression or death; safety; patient-reported outcomes; pharmacokinetics of ramucirumab; and immunogenicity of ramucirumab.[20] Detailed analyses of patient-reported outcomes and pharmacokinetic exposure response are not reported in this Article and will be reported separately in future publications. Exploratory objectives included assessment of the change in tumour size in patients with measurable disease and biomarker associations with clinical outcomes.

Statistical analysis

The full intention-to-treat population that included all randomised patients was used for efficacy and patient-reported outcome assessments. A gatekeeping design to control type I error was implemented to assess the primary endpoint of progression-free survival, followed by the secondary endpoints of overall survival and then achievement of an objective response by RECIST in a fixed sequential manner. The primary statistical analyses were

reported previously.[20] Briefly, the primary progression-free analysis was done when at least 331 progression-free survival events were observed in the first 437 randomly assigned patients.[20] The planned sample size of 524 randomly assigned patients was powered to test the secondary endpoint of overall survival, with an assumed HR of 0·75 for ramucirumab plus docetaxel versus placebo plus docetaxel, with at least 382 events, 80% power, and two-sided type I error of 0·049.[20] Median overall survival was assumed to be 9 months for the placebo group, such that an HR of 0·75 would show an improvement from 9 months to 12 months in the ramucirumab group. We estimated progression-free survival and overall survival using the Kaplan-Meier method, and 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. The assumption of proportional hazards was met for overall survival and was verified visually through inspection of the graph of log(-log(S(t)) versus log(t) for the two treatment groups, as well as a test of the interaction between treatment and log(time) in the proportional hazards model, which was not significant (Wald's test p=0·90). A sensitivity analysis of investigator-assessed progression-free survival and achievement of an overall response from time of randomisation in the intention-to-treat population at the time of overall survival database lock was done. Unless otherwise stated, efficacy analyses were stratified by interactive web response system factors. We estimated overall survival HRs for treatment effect and corresponding 95% CIs using the unstratified Cox proportional hazard model for each of the subgroups on the forest plot. If the number of events in a particular subgroup was less than 15, this subgroup might not be presented in the forest plot.

We assessed safety in all patients who received at least one dose of study medication and incidences of adverse events were reported using descriptive statistics. We summarised serum concentrations of ramucirumab before infusion using descriptive statistics. Immunogenicity in response to treatment for the subset of patients with available samples in the safety population was evaluated and summary statistics presented. We tabulated immunogenicity incidence and assessed correlations with ramucirumab drug level, activity, and safety. In an exploratory analysis, patients with available PD-L1 combined positive score data made up the translational research population. We used Cox proportional hazards modelling, Kaplan-Meier estimation, and the log-rank test to evaluate efficacy outcomes by PD-L1 combined positive score.

For patient-reported outcomes, HRs and associated 95% CIs were evaluated using an unstratified Cox proportional hazards model.

An independent data monitoring committee assessed unblinded safety data throughout the study (appendix p 9).

All statistical analyses were done using SAS version 9.1.2 or later. The study is registered with ClinicalTrials.gov, number .

Role of the funding source

The funder of the study 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 the data in the study and all authors had final responsibility for the decision to submit for publication.

Results

Between July 20, 2015, and April 4, 2017, 727 patients were screened for study eligibility, of whom 197 (27%) were excluded (figure 1); 530 patients were enrolled and randomly allocated to ramucirumab plus docetaxel (n=263) or placebo plus docetaxel (n=267) and comprised the intention-to-treat population. Five patients allocated to ramucirumab and two allocated to placebo did not receive study treatment; therefore, the safety population comprised 523 patients, of whom 258 were allocated to ramucirumab and 265 were allocated to placebo. At the data cutoff for the current analysis (March 21, 2018), three (1%) of 263 patients in the ramucirumab group and three (1%) of 267 patients in the placebo group continued to receive study treatment.

Baseline characteristics were similar between the treatment groups (table 1). Similar to the primary progression-free survival analysis of the first 437 randomly assigned patients,[20] many patients had one or more adverse prognostic risk factors, including liver metastases (147 [28%] of 530 patients), haemoglobin less than 10 g/dL (70 [13%]), and ECOG performance status score greater than zero (281 [53%]) and time since completion or discontinuation of previous therapy of less than 3 months (241 [45%]; table 1). Proportions of previous therapies received across RANGE treatment groups were similar and included surgery, radiotherapy, or both, and platinum-based and non-platinum-based therapies (appendix p 12). Additionally, 17 (6%) of 263 patients in the ramucirumab group and 28 (10%) of 267 patients in the placebo group received an immune checkpoint inhibitor. One additional patient in the ramucirumab group might have received either immunotherapy or placebo and was excluded from our analyses of this subset.

Median duration of follow-up in the full intention-to-treat population was 7·4 months (range 0·1–31·1, IQR 3·5–13·9). In the intention-to-treat population, 448 progression-free survival events occurred (212 [81%] of 263 patients in the ramucirumab group *vs* 236 [88%] of 267 patients in the placebo group; table 2). Our sensitivity analysis of progression-free survival and the proportion of patients achieving an overall response at overall survival database lock were consistent with results reported at the primary analysis (figure 2; table 2).[20] Median progression-free survival was 4·1 months (95% CI 3·3–4·8) in the ramucirumab group and 2·8 months (2·6–2·9) in the placebo group. The stratified HR for progression-free survival decreased from 0·757 (95% CI 0·607–0·943; p=0·0118) at the primary analysis[20] to 0·696 (0·573–0·845, p=0·0002) in the current analysis (figure 2). We observed improvements in progression-free survival in the ramucirumab group versus the placebo group at landmark timepoints of 3 months, 6 months, 9 months, and 12 months (table 2).

In the intention-to-treat population, 385 patients died (185 [70%] of 263 patients in the ramucirumab group *vs* 200 [75%] of 267 in the placebo group). Median overall survival was 9·4 months (95% CI 7·9–11·4) in the ramucirumab group and 7·9 months (7·0–9·3) in the placebo group (stratified HR 0·887 [95% CI 0·724–1·086]; p=0·25; figure 2, table 2). Overall

survival in the ramucirumab group compared with the placebo group was not statistically different at 6 months, 9 months, 12 months, and 24 months. Results of a prespecified subgroup analysis for overall survival are shown in figure 3.

Formal statistical analysis of the proportion of patients with an objective response was not done because of the gatekeeping design of the study. Table 2 shows the responses recorded in both treatment groups. The two patients in the placebo group with a complete response had lymph-node-only disease. Six (60%) of ten patients with complete response in the ramucirumab group had lymph-node-only disease, three had lymph-node disease in addition to spleen, soft tissue, or bladder lesions (one patient for each), and one had a bladder tumour only. 12 (18%) of 68 patients in the ramucirumab group and five (14%) of 37 patients in the placebo group were censored during the investigator-assessed duration of response analysis. Median duration of response in the full intention-to-treat population was 5·3 months (95% CI 3·9–6·9) in the ramucirumab group and 4·2 months (3·3–5·6) in the placebo group (unstratified HR 0·740, 95% CI 0·473–1·158, p=0·19; appendix p 21).

In pre-specified exploratory subgroup analyses for overall survival, median overall survival was longer in the ramucirumab group compared with the placebo group for patients with a primary tumour site of bladder (appendix p 24). However, no difference in overall survival between the treatment groups was seen for patients with the primary tumour outside the bladder (appendix p 24). We observed no overall survival benefit in the ramucirumab group in patients from east Asia or in patients who were not from east Asia (appendix p 25). Patients from east Asia had a lower proportion of bladder primary tumours and a higher proportion of nonbladder primary tumours in both treatment groups compared with patients from other regions (appendix p 20).

Five (29%) of 17 patients in the ramucirumab group and two (7%) of 28 patients in the placebo group who received previous treatment with an immune checkpoint inhibitor had a best overall response of partial response. Six (35%) of 17 patients in the ramucirumab group and 16 (57%) of 28 patients in the placebo group had a best response of stable disease, and three (18%) of 17 patients in the ramucirumab group and seven (25%) of 28 patients in the placebo group had a best response of progressive disease. Progression-free survival and overall survival did not differ between the ramucirumab and placebo treatment groups for this subset of patients, although patient numbers were small for this exploratory analysis (data not shown).

Post-discontinuation therapy, specifically systematic anticancer therapy, was received by 70 (27%) of 263 patients in the ramucirumab group and 71 (27%) of 267 patients in the placebo group (appendix p 13). Chemotherapy was the most commonly received post-discontinuation therapy (44 [17%] of 263 patients in the ramucirumab group and 53 [20%] of 267 patients in the placebo group). 33 (13%) of 263 patients in the ramucirumab group and 23 (9%) of 267 patients in the placebo group received a biological therapy after discontinuation. Post-discontinuation biological therapies received were predominantly antibodies targeting PD-1, PD-L1, or cytotoxic T-lymphocyte-associated protein 4 and, between treatment groups, similar percentages of patients received these therapies.

In the safety population, the most frequently reported any-grade treatment-emergent adverse events were similar between treatment groups and were mostly grades 1–2 in severity (appendix p 14). The incidence of grade 3 or worse treatment-emergent adverse events was similar between treatment groups (appendix p 14). Grade 3 or worse treatment-related treatment-emergent adverse events occurred in 123 (48%) of 258 patients in the ramucirumab group and 108 (41%) of 265 patients in the placebo group; however, treatment-related treatment-emergent adverse events were mostly grades 1–2 (table 3). Grade 3 or worse treatment-related treatment-emergent febrile neutropenia and neutropenia occurred in at least 5% of patients in the ramucirumab group and were at least 2% more frequent in the ramucirumab group than in the placebo group (table 3). Adverse events of special interest (adverse events of any grade that occurred with ramucirumab in previous clinical studies or have been associated with other anti-angiogenic therapies) that were 5% more frequent in the ramucirumab group than in the placebo group included epistaxis, hypertension, haematuria, and proteinuria (appendix p 14). Grade 3 or worse adverse events of special interest occurred in 52 (20%) of 258 patients in the ramucirumab group and 29 (11%) of 265 patients in the placebo group.

Fatigue was the most common adverse event leading to dose adjustments of any study treatment and was mostly grade 1–2 (appendix p 15). Adverse events leading to discontinuation of any study treatment occurred in 50 (19%) of 258 patients in the ramucirumab group and 20 (8%) of 265 in the placebo group (appendix p 16). The most common adverse event leading to treatment discontinuation of any therapy was sepsis, which occurred in five (2%) of 258 patients in the ramucirumab group and no patients in the placebo group. Despite a higher proportion of patients discontinuing treatment in the ramucirumab group than in the placebo group, time to treatment discontinuation was longer in the ramucirumab group than in the placebo group (median 3·4 months [95% CI 2·8–4·1] *vs* 2·8 months [2·4–2·9]); unstratified HR 0·835, 95% CI 0·702–0·993; p=0·042).

Serious adverse events were reported in 112 (43%) of 258 patients in the ramucirumab group and 107 (40%) of 265 patients in the placebo group (appendix p 17). Serious adverse events related to study treatment occurred in 66 (26%) of 258 patients in the ramucirumab group and 57 (22%) of 265 patients in the placebo group (appendix p 17). Febrile neutropenia was the only treatment-related serious adverse event that occurred in more than 2% of patients in either group (17 [7%] of 258 patients in the ramucirumab group *vs* 11 [4%] of 265 patients in the placebo group). 48 (19%) of 258 patients in the ramucirumab group and 53 (20%) of 265 patients in the placebo group died on therapy or within 30 days of treatment discontinuation. The incidence of adverse events leading to death on therapy or within 30 days of discontinuation, regardless of causality, was 15 (6%) of 258 patients in the ramucirumab group versus 12 (5%) of 265 patients in the placebo group, with the most common adverse events leading to death being sepsis (four [2%] of 258 patients in the ramucirumab group *vs* none in the placebo group), renal failure (two [<1%] of 258 patients in the ramucirumab group group *vs* none in the placebo group), and pneumonia (none in the ramucirumab group *vs* two [<1%] of 265 patients in the placebo group; appendix p 18). Adverse events related to study treatment and leading to death occurred in eight (3%) patients in the ramucirumab group versus five (2%) patients in the placebo group (appendix p 18). In the ramucirumab group, adverse events leading to death included one case of each

of the following: basilar artery thrombosis, cardiac arrest, enterovesical fistula, gastric haemorrhage, neutropenic sepsis, renal failure, and sepsis. In the placebo group, adverse events leading to death included one of each of the following: asthenia, lung infection, pneumonitis, and pulmonary embolism. In each of the treatment groups, there was one adverse event-related death deemed to be related to study treatment, but for which no further information on cause was available.

Two patients with treatment-emergent ramucirumab antidrug antibody positivity (one in each treatment group) reported infusion-related reaction events (appendix p 19). The frequency of infusion-related reactions was not higher in treatment-emergent antidrug antibody-positive patients (two [18%] of 11 patients) compared with treatment-emergent antidrug antibody-negative patients (116 [29%] of 401 patients; appendix pp 10, 19). Although numbers were small, evaluation of data did not support that infusion-related reactions were mediated by immunogenicity and we noted no new safety concerns (appendix pp 10, 19).

245 patients in the ramucirumab group had 697 blood samples evaluable for pharmacokinetic analyses at the overall survival database lock. After administration of 10 mg/kg ramucirumab every 3 weeks in combination with docetaxel, the geometric mean trough concentrations of ramucirumab before doses 2, 3, 5, and 9 were 14·9 μg/mL, 23·5 μg/mL, 32·5 μg/mL, and 48·9 μg/mL, respectively (data not shown). These findings were consistent with those of the primary progression-free survival analysis in the first 437 randomised patients.[25]

Our previous primary progression-free survival analysis summarised patient-reported outcome data.[20] Baseline mean scores at the overall survival database lock were similar between the ramucirumab group and placebo group for both the QLQ-C30 and EQ-5D-5L (data not shown). Updated data from the overall survival database lock for time to sustained deterioration analysis of the QLQ-C30 quality of life scales are in appendix p 22. An exploratory post-hoc analysis of best pain improvement by maximum tumour shrinkage in patients in each treatment group suggested pain palliation and reduction in tumour size might be positively associated, particularly in the ramucirumab group (appendix p 23).

To gain potential clinical insights into the efficacy of ramucirumab plus docetaxel in the era of immunotherapy, the RANGE trial included a pre-planned exploratory subgroup analysis of treatment efficacy by PD-L1 expression measured at baseline (appendix p 11). 240 (45%) of 530 patients in the intention-to-treat population were evaluable for PD-L1 combined positive score determination (translational research population). We divided patients into subgroups by high PD-L1 expression (105 [44%] of 240 patients with combined positive score ≥10) and low PD-L1 expression (135 [56%] of 240 patients with combined positive score <10). Exploratory efficacy analyses by PD-L1 expression showed that ramucirumab led to longer progression-free survival in patients with high PD-L1 expression (table 4). We observed a treatment difference in median overall survival in patients with PD-L1 combined positive score of 10 or higher that favoured the ramucirumab group (table 4), but no such effect was observed in patients with PD-L1 combined positive score less than 10 (table 4). A treatment by PD-L1 level interaction was observed for overall survival (p=0·037). The

proportion of patients who achieved an overall response was higher in the ramucirumab group than in the placebo group, regardless of PD-L1 combined positive score (table 4).

Discussion

To our knowledge, ramucirumab is the only angiogenesis inhibitor, in combination with docetaxel, to show significant improvement in progression-free survival compared with placebo plus docetaxel in a phase 3 trial of platinum-refractory urothelial carcinoma. Platinum-refractory urothelial carcinoma is a challenging disease with typically short overall survival, poor achievement of overall response, and multiple failed trials. To our knowledge, pembrolizumab is the only therapy to achieve a statistically significant improvement in overall survival compared with chemotherapy in this population.[1]

The RANGE trial was designed to test the primary efficacy endpoint of progression-free survival, which was achieved. The progression-free survival benefit was maintained with longer follow-up in the intention-to-treat sensitivity analysis (HR 0·696 [95% CI 0·573–0·845]). The proportion of patients with an objective response also remained consistent with that in the intention-to-treat sensitivity analysis, with an almost doubling of responses in the ramucirumab group compared with the placebo group. Duration of response was also longer in the ramucirumab group than in the placebo group. The higher proportion of patients with a response and duration of response probably contributed to the longer progression-free survival we observed in the ramucirumab group compared with the placebo group. Our safety and quality of life findings were also consistent with previously reported results.[20] No new safety issues emerged with longer follow-up, and quality of life was maintained.

Overall survival was not significantly improved with the addition of ramucirumab to docetaxel compared with placebo plus docetaxel in the intention-to-treat population. Post-discontinuation therapies, including use of immune therapies, were similar between the treatment groups and unlikely to have contributed to any overall survival differences observed. The overall survival endpoint was designed to test a clinically meaningful improvement with an assumed HR of 0·75 and a 3-month improvement in overall survival from 9 months to 12 months with the addition of ramucirumab to docetaxel. RANGE did not meet this endpoint in the intention-to-treat population. Since pembrolizumab has previously shown a statistically significant overall survival benefit in a similar population compared with taxane monotherapy or vinflunine in a randomised phase 3 trial,[1] pembrolizumab could be accepted over ramucirumab as a preferred standard of care. Atezolizumab did not show superiority versus chemotherapy in a randomised phase 3 study[2] but is still used to treat patients with locally advanced or metastatic urothelial carcinoma after progression with platinum-based chemotherapy. Given the few treatment options for platinum-refractory disease and the potential use of PD-1 and PD-L1 agents in frontline combinations, pending the results of several key phase 3 trials (eg, pembrolizumab with or without standard chemotherapy [], atezolizumab with or without platinum-based chemotherapy [], and durvalumab with or without tremelimumab []), our trial results are important for treatment decisions in the second-line setting.

The pre-specified subgroup overall survival analyses in RANGE, although exploratory in nature, warrant further consideration. We observed an almost 3-month improvement in overall survival with the addition of ramucirumab for patients with a primary bladder tumour, but found no difference for patients with non-bladder primary tumours (appendix p 24). A similar finding was reported in the randomised phase 3 EORTC Intergroup study, which evaluated the addition of paclitaxel to cisplatin and gemcitabine.[26] Paclitaxel has been reported to have potential anti-angiogenic effects, which raises the question of whether the tumour site of origin within urothelial carcinoma might result in a variable response to anti-angiogenic therapy.[27] In the RANGE study, patients from east Asia had no overall survival benefit with ramucirumab compared with patients not from east Asia. Patients from east Asia also had a lower proportion of bladder primary tumours (42% in the ramucirumab group and 49% in the placebo group) compared with patients from other geographical regions (where bladder primary tumours ranged from 67–76%). Genomic and molecular characterisation of upper urinary tract and lower urinary tract tumours, and knowledge of how different urinary carcinoma molecular classifications might respond to chemotherapy, is evolving.[28–30] The molecular alterations and relative proportions of different genomic subgroups might vary between upper-tract and lower-tract disease. Biomarker research to explore potential genomic drivers of response to ramucirumab and the differences seen in upper-tract versus lower-tract tumours in the RANGE trial is ongoing.

We enrolled a population that was characteristic of patients with platinum-refractory urothelial carcinoma; however, this might have been a limitation of the study. The short median follow-up duration of 7·4 months (IQR 3·5–13·9) reflects the poor prognosis of the patients enrolled in this study, with many patients succumbing to their disease within a few months. Approxiately a quarter of patients enrolled in the study died in the first 4·5 months of the study, which might have restricted our ability to see any treatment effects. The RANGE team has previously reported that overall survival varies with clinical characteristics, with median overall survival in the placebo group ranging from 6·1 months to 10·5 months, depending on baseline characteristics, and ramucirumab having the greatest overall survival effect in patients with more favourable clinical characteristics.[31] We plan to report pharmacokinetic analysis of exposure response in a future publication. Enrolling a broad population might dilute the effect of anti-angiogenic treatment if only a small group of patients truly benefit; this might also have affected the results of CALGB 90601,[32] which also did not show a significant improvement in overall survival and only a modest improvement in progression-free survival with the addition of bevacizumab to frontline platinum treatment in patients with metastatic urothelial carcinoma. To date, to our knowledge, a selection strategy to identify patients who are most likely to benefit from anti-angiogenic therapy has not been successful in any solid tumour. Biomarker analysis in specimens obtained from patients in the RANGE trial is ongoing.

Standard-of-care therapy has evolved since the initial design and enrolment of the RANGE trial, with five immune checkpoint inhibitors targeting PD-1 or PD-L1 approved for platinum-refractory urothelial carcinoma in various regions. The RANGE trial allowed previous immune checkpoint inhibitor therapy, although such patients represented a small subgroup given the availability of these agents during trial enrolment. Efficacy results in this subgroup were consistent with the intention-to-treat population.[33] In our exploratory

analysis of PD-L1 expression and efficacy, a higher proportion of patients achieving an objective response was seen in the ramucirumab group than in the placebo group, regardless of PD-L1 expression. Progression-free survival and overall survival had substantially improved HRs in patients with a PD-L1 combined positive score of 10 or higher. These results are hypothesis-generating and warrant exploration of the potential effects of ramucirumab on the tumour immune microenvironment. We used the combined positive scoring system for this analysis because a previous trial of pembrolizumab, the only therapy approved in platinum-refractory urothelial carcinoma based on phase 3 data showing a statistical overall survival benefit, used this approach.[1] We also obtained tumour cell and immune cell scores and ongoing analyses of these will be presented in a future manuscript.

The VEGF axis has been implicated in immune suppression.[34] Dual blockade of PD-L1 and VEGF pathways has been shown to increase intratumoural CD8 T cells, MHC class 1 molecules, Th1 cells, and T-effector markers and significantly improve progression-free survival compared with PD-L1 monotherapy in PD-L1-positive patients with renal cell carcinoma.[35,36] Given the results of the RANGE trial for patients with a PD-L1 combined positive score of 10 or higher, combining ramucirumab with PD-1 or PD-L1 therapy in the appropriate patients warrants evaluation. Results from a phase 1b study across select tumour types, including urothelial carcinoma, were recently published.[37] In that study, molecular subtypes and ramucirumab exposures achieved were unknown.[37] A more thorough understanding of the interaction between clinical factors, exposure response, molecular subtypes, and PD-L1 status of the tumour and microenvironment will help to identify patients who are most likely to benefit from a combined ramucirumab and PD-1-directed or PD-L1-directed therapy combination. Such analyses are ongoing and will be reported separately.

In conclusion, our results support the progression-free survival benefit of the addition of an anti-VEGFR2 antibody to standard chemotherapy in patients with locally advanced or metastatic urothelial carcinoma after platinum-based therapy and represent, to our knowledge, the first positive randomised phase 3 data to evaluate anti-angiogenic therapy in patients with urothelial carcinoma. Appropriately designed trials testing the hypotheses derived from our subgroup and exploratory analyses are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was funded by Eli Lilly and Company. We thank the patients, their families, and the study personnel across all sites for participating in this study. We thank the independent data monitoring committee, and the entire RANGE clinical trial team.

Susan P Whitman, an employee of Eli Lilly and Company, provided medical writing support. Ling Gao, an employee of Eli Lilly and Company, contributed to pharmacokinetic schedule design, data analysis, and interpretation. Ryan Rhodes, formerly employed by Eli Lilly and Company, contributed to biomarker data generation and analysis.

References

1. Bellmunt J, de Wit R, Vaughn DJ, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017; 376: 1015–26. [PubMed: 28212060]
2. Powles T, Durán I, van der Heijden MS, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2018;391: 748–57. [PubMed: 29268948]
3. Raggi D, Miceli R, Sonpavde G, et al. Second-line single-agent versus doublet chemotherapy as salvage therapy for metastatic urothelial cancer: a systematic review and meta-analysis. Ann Oncol 2016; 27: 49–61. [PubMed: 26487582]
4. Bellmunt J, Théodore C, Demkov T, et al. Phase 3 trial of vinflunine plus best supportive care compared with best supportive care alone after a platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol 2009; 27: 4454–61. [PubMed: 19687335]
5. Vaughn DJ, Srinivas S, Stadler WM, et al. Vinflunine in platinum-pretreated patients with locally advanced or metastatic urothelial carcinoma: results of a large phase 2 study. Cancer 2009; 115: 4110–17. [PubMed: 19536904]
6. Rosenberg JE, Hoffman-Censits J, Powles T, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016; 387: 1909–20. [PubMed: 26952546]
7. Sharma P, Retz M, Siefker-Radtke A, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017; 18: 312–22. [PubMed: 28131785]
8. Apolo AB, Infante JR, Balmanoukian A, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase 1b study. J Clin Oncol 2017; 35: 2117–24. [PubMed: 28375787]
9. Powles T, O'Donnell PH, Massard C, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 2017; 3: e172411. [PubMed: 28817753]
10. Dickinson AJ, Fox SB, Persad RA, Hollyer J, Sibley GN, Harris AL. Quantification of angiogenesis as an independent predictor of prognosis in invasive bladder carcinomas. Br J Urol 1994;74: 762–66. [PubMed: 7530131]
11. Necchi A, Mariani L, Zaffaroni N, et al. Pazopanib in advanced and platinum-resistant urothelial cancer: an open-label, single group, phase 2 trial. Lancet Oncol 2012; 13: 810–16. [PubMed: 22819172]
12. Petrylak DP, Tagawa ST, Kohli M, et al. Docetaxel as monotherapy or combined with ramucirumab or icrucumab in second-line treatment for locally advanced or metastatic urothelial carcinoma: an open-label, three-arm, randomized controlled phase 2 trial. J Clin Oncol 2016; 34: 1500–09. [PubMed: 26926681]
13. Jaeger TM, Weidner N, Chew K, et al. Tumor angiogenesis correlates with lymph node metastases in invasive bladder cancer. J Urol 1995; 154: 69–71. [PubMed: 7539869]
14. Sato K, Sasaki R, Ogura Y, et al. Expression of vascular endothelial growth factor gene and its receptor (flt-1) gene in urinary bladder cancer. Tohoku J Exp Med 1998; 185: 173–84. [PubMed: 9823778]
15. Crew JP, O'Brien T, Bicknell R, Fuggle S, Cranston D, Harris AL. Urinary vascular endothelial growth factor and its correlation with bladder cancer recurrence rates. J Urol 1999; 161: 799–804. [PubMed: 10022687]
16. Inoue K, Slaton JW, Karashima T, et al. The prognostic value of angiogenesis factor expression for predicting recurrence and metastasis of bladder cancer after neoadjuvant chemotherapy and radical cystectomy. Clin Cancer Res 2000; 6: 4866–73. [PubMed: 11156246]
17. Xia G, Kumar SR, Hawes D, et al. Expression and significance of vascular endothelial growth factor receptor 2 in bladder cancer.J Urol 2006; 175: 1245–52. [PubMed: 16515971]

18. Balar AV, Apolo AB, Ostrovnaya I, et al. Phase 2 study of gemcitabine, carboplatin, and bevacizumab in patients with advanced unresectable or metastatic urothelial cancer. J Clin Oncol 2013; 31: 724–30. [PubMed: 23341513]
19. Spratlin JL, Cohen RB, Eadens M, et al. Phase 1 pharmacologic and biologic study of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor-2. J Clin Oncol 2010; 28: 780–87. [PubMed: 20048182]
20. Petrylak DP, de Wit R, Chi KN, et al.; RANGE study investigators. 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: 2266–77. [PubMed: 28916371]
21. Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25 (Suppl 3): iii40–48. [PubMed: 25096609]
22. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006; 24: 3187–205. [PubMed: 16682719]
23. Devlin NJ, Shah KK, Feng Y, Mulhern B, van Hout B. Valuing health-related quality of life: an EQ-5D-5L value set for England. Health Econ 2018; 27: 7–22. [PubMed: 28833869]
24. Agilent Dako. PD-L1 IHC 22C3 pharmDxInterpretation Manual – Urothelial CarcinomaFDA-approved for in vitro diagnostic use. 2018 https://www.agilent.com/cs/library/usermanuals/public/29276_22C3_pharmdx_uc_interpretation_manual_us.pdf (accessed Nov 15, 2019).
25. De Wit R, Powles T, Castellano DE, et al. Ramucirumab (RAM) exposure-response (ER) relationship in RANGE, a randomized phase 3 trial of docetaxel (DOC) with or without RAM in advanced urothelial carcinoma (UC) patients (pts) who progressed on or after platinum therapy. J Clin Oncol 2018; 36 (15 Suppl): 4526.
26. Bellmunt J, von der Maase H, Mead GM, et al. Randomized phase 3 study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012; 30: 1107–13. [PubMed: 22370319]
27. Belotti D, Vergani V, Drudis T, et al. The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res 1996;2: 1843–49. [PubMed: 9816139]
28. Moss TJ, Qi Y, Xi L, et al. Comprehensive genomic characterization of upper tract urothelial carcinoma. Eur Urol 2017; 72: 641–49. [PubMed: 28601352]
29. Robertson AG, Kim J, Al-Ahmadie H, et al. Comprehensive molecular characterization of muscle-invasive bladder cancer. Cell 2017; 171: 540–56. [PubMed: 28988769]
30. Seiler R, Oo HZ, Tortora D, et al. An oncofetal glycosaminoglycan modification provides therapeutic access to cisplatin-resistant bladder cancer. Eur Urol 2017; 72: 142–50. [PubMed: 28408175]
31. De Wit R, Powles T, Castellano DE, et al. Ramucirumab (RAM) exposure-response (ER) relationship in RANGE: a randomized phase 3 trial of RAM plus docetaxel (DOC) versus placebo (P) plus DOC in advanced platinum-refractory urothelial carcinoma (UC) patients (pts). J Clin Oncol 2019; 37 (7 Suppl): 353.
32. Rosenberg JE, Ballman KV, Halabi S, et al. CALGB 90601 (Alliance): Randomized, double-blind, placebo-controlled phase 3 trial comparing gemcitabine and cisplatin with bevacizumab or placebo in patients with metastatic urothelial carcinoma. Proc Am Soc Clin Oncol 2019; 37 (15 Suppl): 4503.
33. Drakaki A, Kirby CJ, Van Der Heijden MS, et al. Docetaxel with or without ramucirumab after immune checkpoint inhibition in platinum-refractory metastatic urothelial carcinoma (mUC): Prespecified subgroup analysis from the phase 3 RANGE trial. J Clin Oncol 2018; 36 (6 Suppl): 434 (abstr).
34. Elamin YY, Rafee S, Toomey S, Hennessy BT. Immune effects of bevacizumab: killing two birds with one stone. Cancer Microenviron 2015; 8: 15–21. [PubMed: 25326055]

35. McDermott DF, Huseni MA, Atkins MB, et al. Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med 2018; 24: 749–57. [PubMed: 29867230]

36. Wallin JJ, Bendell JC, Funke R, et al. Atezolizumab in combination with bevacizumab enhances antigen-specific T-cell migration in metastatic renal cell carcinoma. Nat Commun 2016; 7: 12624. [PubMed: 27571927]

37. Herbst RS, Arkenau HT, Santana-Davila R, et al. Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or urothelial carcinomas (JVDF): a multicohort, non-randomised, open-label, phase 1a/b trial. Lancet Oncol 2019; 20: 1109–23. [PubMed: 31301962]

Research in context

Evidence before this study

We searched PubMed, abstracts of major oncology congresses (eg, American Society of Clinical Oncology [ASCO], ASCO Genitourinary Cancer Symposium, and European Society for Medical Oncology), and ClinicalTrials.gov from inception to Sept 5, 2014 (the time of the RANGE study design and protocol development), for clinical trials published in English with the search terms “chemotherapy”, “anti-angiogenic therapies”, and “platinum-refractory advanced” or “metastatic urothelial carcinoma”. Multiple cytotoxic monotherapies, including docetaxel, showed modest clinical benefit in patients with advanced or metastatic urothelial carcinoma. Early clinical evidence suggested that patients with platinum-refractory urothelial carcinoma might respond to anti-angiogenic therapy. Findings from a randomised phase 2 study () in patients with platinum-refractory advanced or metastatic urothelial carcinoma showed that ramucirumab plus docetaxel significantly improved median progression-free survival versus docetaxel alone, and provided support for the phase 3 RANGE clinical trial. In a previous study, a subset of patients with platinum-refractory urothelial carcinoma was found to be sensitive to immune checkpoint inhibitors targeting PD-1 and its ligand PD-L1. However, to date, evidence to support checkpoint inhibitor efficacy in second-line advanced or metastatic urothelial carcinoma has been scarce, with only pembrolizumab monotherapy providing an overall survival benefit versus chemotherapy. To our knowledge, no immunotherapy so far has provided a progression-free survival improvement compared with single-agent chemotherapy and the proportion of patients that achieved an objective response ranges from 13% to 21% in intention-to-treat populations with second-line advanced urothelial carcinoma.

Added value of this study

Consistent with our primary progression-free survival analysis published in 2017, this updated analysis further supports that ramucirumab combined with docetaxel provides a progression-free survival benefit versus placebo and docetaxel. Moreover, this benefit occurred while safety and quality of life were maintained. To our knowledge, this is the first analysis of overall survival in a phase 3 trial investigating an anti-angiogenic drug combined with docetaxel in platinum-refractory advanced urothelial cancer. However, we observed no statistically significant improvement in overall survival in the intention-to-treat population. We could not statistically test the proportion of patients with an overall response because of the gated study design but this was higher in the ramucirumab and docetaxel group than in the placebo and docetaxel group. The subgroup of patients with high baseline PD-L1 expression also had a greater clinical benefit compared with patients with lower baseline PD-L1 expression. Ramucirumab plus docetaxel was associated with a progression-free survival benefit regardless of PD-L1 combined positive score status and irrespective of primary tumour site. To our knowledge, ramucirumab is the only antiangiogenic agent to show benefit in a randomised, phase 3, placebo-controlled trial of platinum-refractory advanced urothelial carcinoma, and RANGE is the only phase 3 study to show a progression-free survival advantage versus chemotherapy alone in platinum-refractory advanced urothelial carcinoma.

Implications of all the available evidence

Our results further support the progression-free survival benefit of the addition of an anti-vascular endothelial growth factor receptor 2 antibody to standard chemotherapy in this setting and represent, to our knowledge, the first positive randomised phase 3 data evaluating anti-angiogenic therapy in the treatment of patients with urothelial carcinoma. Appropriately designed trials testing the hypotheses derived from the results of subgroup and exploratory analyses in RANGE are warranted.

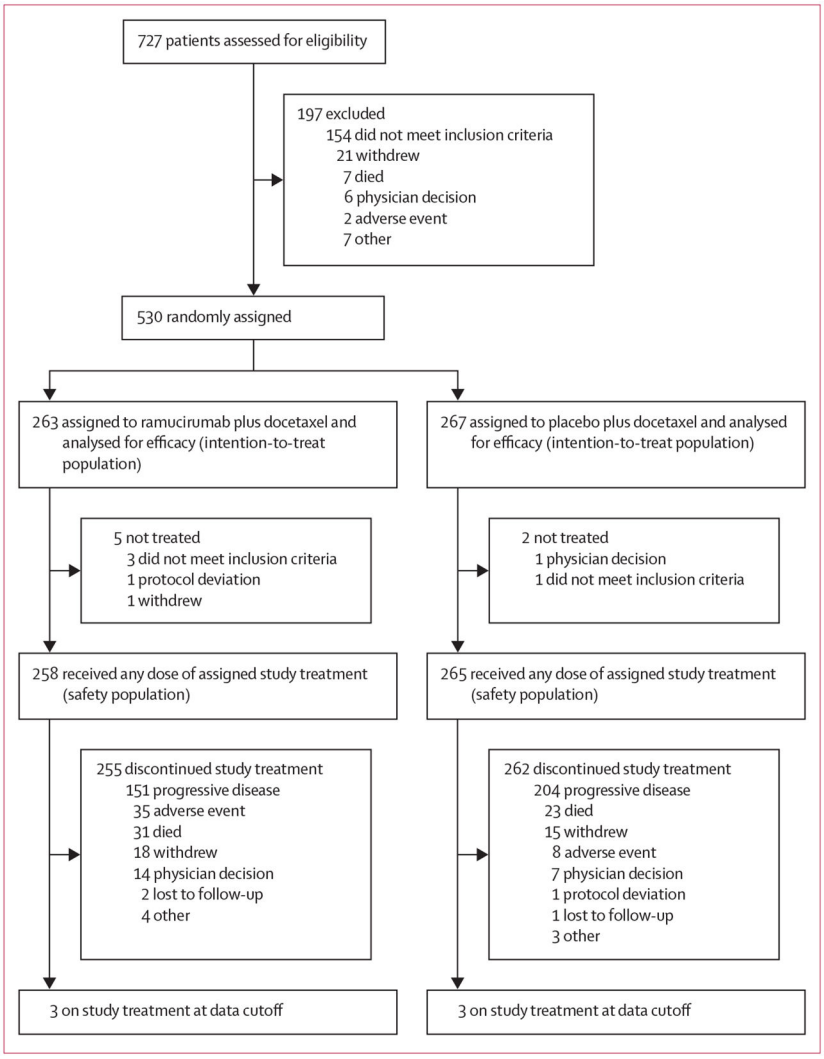

Figure 1:
Trial profile

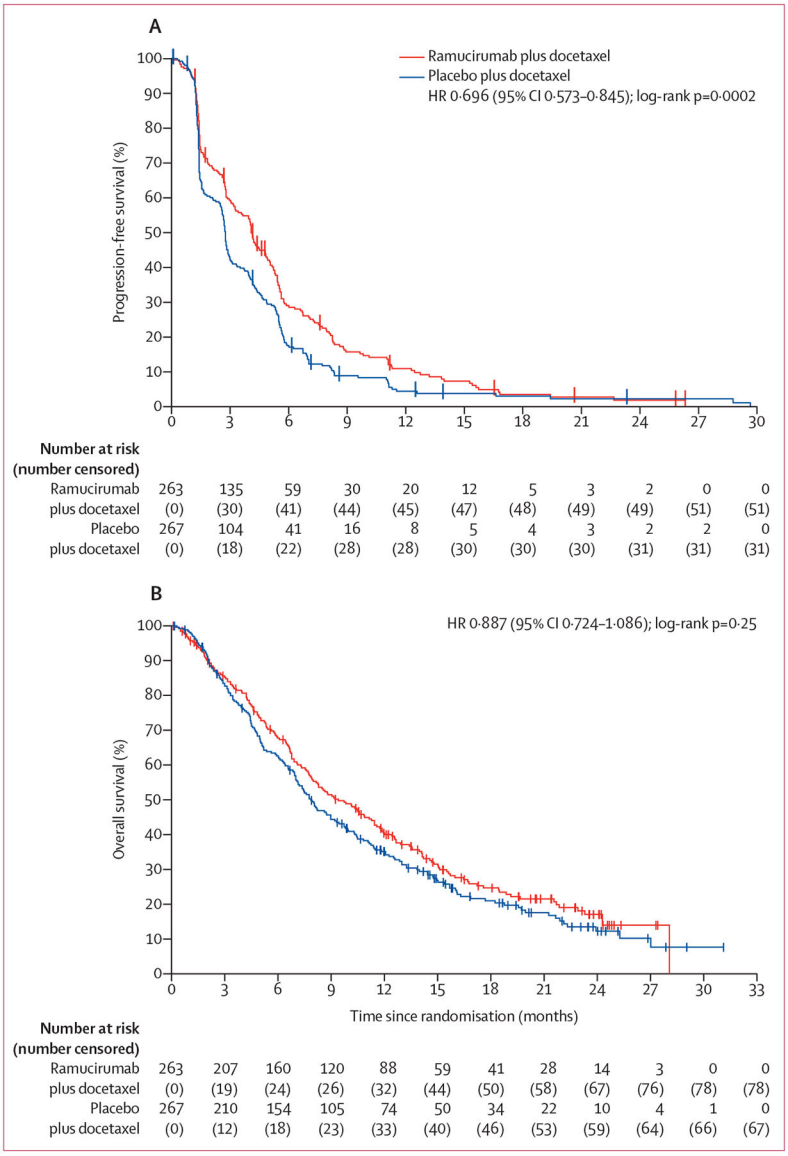

Figure 2: Progression-free survival (A) and overall survival (B) in the intention-to-treat population

Analyses are stratified by randomisation factors. HR=hazard ratio.

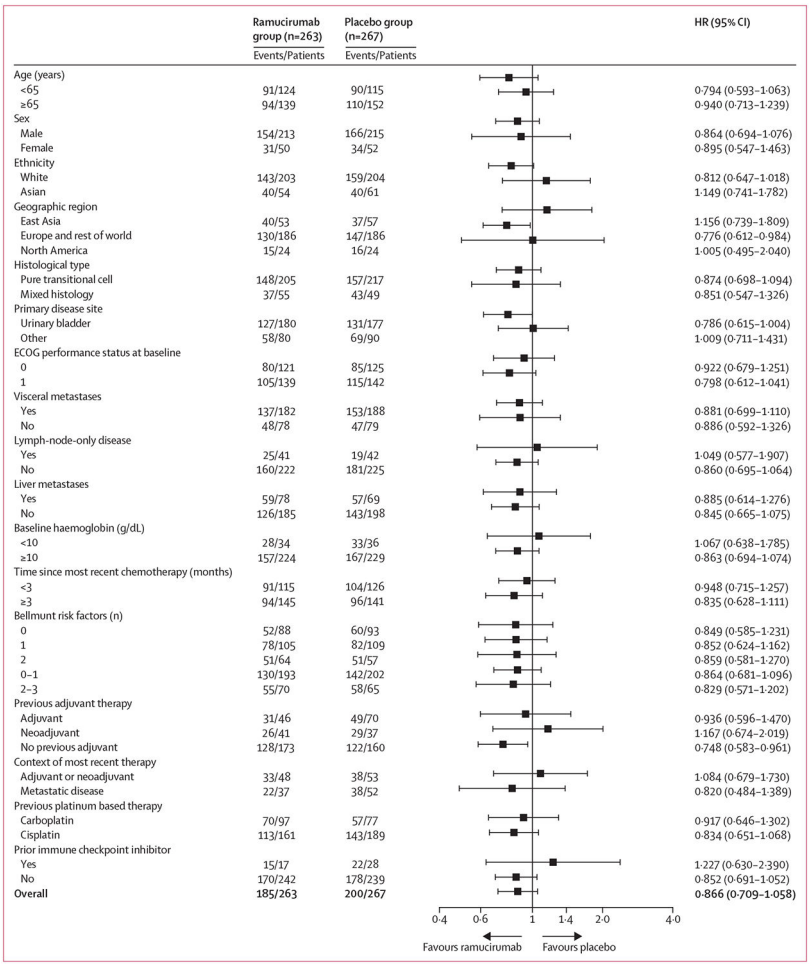

Figure 3: Forest plot of overall survival by subgroups in the intention-to-treat population (unstratified)

Bellmunt risk factors are liver metastases, haemoglobin <10 g/dL, and ECOG performance score >0. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio.

Table 1:

Baseline characteristics of the intention-to-treat population

	Ramucirumab plus docetaxel (n=263)	Placebo plus docetaxel (n=267)
Age (years)	65 (59–72)	66 (59–72)
≥65	139 (53%)	152 (57%)
Sex		
Male	213 (81%)	215 (81%)
Female	50 (19%)	52 (19%)
Ethnicity		
White	203 (77%)	204 (76%)
Asian	54 (21%)	61 (23%)
Other	4 (2%)	2 (<1%)
Missing	2 (<1%)	0
ECOG performance status		
0	121 (46%)	125 (47%)
1	139 (53%)	142 (53%)
Missing	3 (1%)	0
Geographic region		
North America	24 (9%)	24 (9%)
Europe and rest of the world	186 (71%)	186 (70%)
East Asia	53 (20%)	57 (21%)
Histology		
Pure transitional cell	205 (78%)	217 (81%)
Mixed histology	55 (21%)	49 (18%)
Missing	3 (1%)	1 (<1%)
Duration of disease (months) *	18·0 (10·4–36·4)	17·0 (11·0–34·6)
Bladder as primary site of tumour	180 (68%)	177 (66%)
Visceral metastases	182 (69%)	188 (70%)
Lung metastases	98 (37%)	121 (45%)
Liver metastases	78 (30%)	69 (26%)
Bone metastases	56 (21%)	53 (20%)
Adrenal gland	15 (6%)	12 (4%)
Kidney	13 (5%)	10 (4%)
Spleen	4 (2%)	5 (2%)
Other	35 (13%)	28 (10%)
Lymph-node-only disease	41 (16%)	42 (16%)
Creatinine clearance (mL/min)		
<60	106 (40%)	118 (44%)
≥60	151 (57%)	146 (55%)
Missing	6 (2%)	3 (1%)
Haemoglobin concentration <10 g/dL	34 (13%)	36 (13%)
Completion or discontinuation of most recent therapy <3 months	115 (44%)	126 (47%)

	Ramucirumab plus docetaxel (n=263)	Placebo plus docetaxel (n=267)
Bellmunt risk factors (n)†		
0	88 (33%)	93 (35%)
1	105 (40%)	109 (41%)
2	64 (24%)	57 (21%)
3	6 (2%)	8 (3%)
Previous adjuvant treatment		
Adjuvant	46 (17%)	70 (26%)
Neoadjuvant	41 (16%)	37 (14%)
No previous adjuvant	173 (66%)	160 (60%)
Missing	3 (1%)	0
Previous treatments‡		
Cisplatin-based	161 (61%)	189 (71%)
Carboplatin-based	97 (37%)	77 (29%)
Immune checkpoint inhibitor	17 (6%)	28 (10%)

Data are median (IQR) or n (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group.

*Data are median (IQR).

†Bellmunt risk factors included liver metastases, haemoglobin <10 g/dL, and ECOG performance status score >0.

‡A summary of previous anticancer treatments is included in the appendix (p 12).

Table 2:

Investigator-assessed efficacy outcomes (intention-to-treat population)

	Ramucirumab plus docetaxel (n=263)	Placebo plus docetaxel (n=267)	HR (95% CI)*	p value*
Overall survival				
Deaths	185 (70%)	200 (75%)	..	..
Median overall survival, months	9·4 (7·9–11·4)	7·9 (7·0–9·3)	0·887 (0·724–1·086)	0·25
6-month overall survival	67·7% (61·5–73·2)	62·6% (56·4–68·3)	..	0·23
9-month overall survival	51·5% (45·0–57·6)	44·4% (38·1–50·5)	..	0·12
12-month overall survival	40·0% (33·7–46·2)	35–2% (29·2–41·2)	..	0·27
24-month overall survival	17·1% (11·8–23·2)	12·3% (7·6–18·1)	..	0·23
Progression-free survival				
Deaths or disease progressions	212 (81%)	236 (88%)	..	..
Median progression-free survival, months	4·1 (3·3–4·8)	2·8 (2·6–2·9)	0·696 (0·573–0·845)	0·0002
3-month progression-free survival	59·3% (52·8–65·2)	42·2% (36·1–48·3)	..	0·0001
6-month progression-free survival	29·1% (23·2–35·2)	17·6% (13·1–22·6)	..	0·0035
9-month progression-free survival	15·7% (11·1–21·1)	8·9% (5·7–13·1)	..	0·031
12-month progression-free survival	11·0% (7·1–15·8)	4·5% (2·2–8·0)	..	0·014
Best overall response	..	..	..	..
Complete response	10 (4%)	2 (<1%)	..	..
Partial response	58 (22%)	35 (13%)	..	..
Stable disease	104 (40%)	110 (41%)	..	..
Progressive disease	56 (21%)	92 (34%)	..	..
Not evaluable	35 (13%)	28 (10%)	..	..
Objective response	25·9% (20·6–31·1)	13·9% (9·7–18·0)	..	..
Disease control	65·4% (59·7–71·1)	55·1% (49·1–61·0)	..	..

Data are n (%), median (95% CI), or % (95% CI), unless otherwise specified. Confidence intervals are based on normal approximation.

*Stratified by interactive web response system factors.

Table 3:

Grade 1–2 treatment-related treatment-emergent adverse events occurring in ≥10% of patients and all grade 3–5 treatment-related treatment emergent adverse events

	Ramucirumab plus docetaxel (n=258)				Placebo plus docetaxel (n=265)			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Patients with ≥1 treatment-related treatment-emergent adverse event	98 (38%)	86 (33%)	29 (11%)	8 (3%)	115 (43%)	73 (28%)	30 (11%)	5 (2%)
Fatigue *	84 (33%)	17 (7%)	0	0	80 (30%)	16 (6%)	0	0
Alopecia	61 (24%)	0	0	0	80 (30%)	1 (<1%)	0	0
Diarrhoea	53 (21%)	8 (3%)	0	0	41 (15%)	3 (1%)	0	0
Decreased appetite	53 (21%)	4 (2%)	0	0	44 (17%)	1 (<1%)	0	0
Nausea	55 (21%)	2 (<1%)	0	0	35 (13%)	2 (<1%)	0	0
Stomatitis	51 (20%)	9 (3%)	0	0	24 (9%)	0	0	0
Vomiting	27 (10%)	2 (<1%)	0	0	25 (9%)	1 (<1%)	0	0
Hypertension *	12 (5%)	11 (4%)	1 (<1%)	0	6 (2%)	0	0	0
Constipation	16 (6%)	1 (<1%)	0	0	21 (8%)	0	0	0
Hyperuricaemia	3 (1%)	0	0	0	0	0	1 (<1%)	0
Hypokalaemia	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Hypophosphataemia	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Epistaxis	31 (12%)	0	0	0	11 (4%)	0	0	0
Pyrexia	22 (9%)	1 (<1%)	0	0	15 (6%)	1 (<1%)	0	0
Hyponatraemia	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Dysgeusia	27 (10%)	0	0	0	14 (5%)	0	0	0
Malaise	12 (5%)	1 (<1%)	0	0	8 (3%)	0	0	0
Mucosal inflammation	10 (4%)	3 (1%)	0	0	3 (1%)	1 (<1%)	0	0
Dyspnoea	7 (3%)	4 (2%)	0	0	10 (4%)	1 (<1%)	0	0
Pain	3 (1%)	1 (<1%)	0	0	0	1 (<1%)	0	0
Non-cardiac chest pain	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Neuropathy *	27 (10%)	0	0	0	31 (12%)	3 (1%)	0	0
Abdominal pain *	10 (4%)	1 (<1%)	0	0	8 (3%)	0	0	0
Death (unknown cause)	0	0	0	1 (<1%)	0	0	0	1 (<1%)
Hepatic failure	0	1 (<1%)	0	0	0	0	0	0

	Ramucirumab plus docetaxel (n=258)				Placebo plus docetaxel (n=265)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
General physical health deterioration	0	1 (<1%)	0	0	0	0	0	0
Generalised oedema	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Anal fistula	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Colitis	1 (<1%)	1 (<1%)	0	0	0	1 (<1%)	0	0
Gastric haemorrhage	0	0	0	1 (<1%)	0	0	0	0
Small intestinal perforation	0	0	1 (<1%)	0	0	0	0	0
Upper gastrointestinal haemorrhage	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Rectal haemorrhage	1 (<1%)	0	0	0	2 (<1%)	1 (<1%)	0	0
Enterovesical fistula	0	0	0	1 (<1%)	0	0	0	0
Oesophagitis	0	1 (<1%)	0	0	0	0	0	0
Tooth disorder	0	0	0	0	0	1 (<1%)	0	0
Lymphopenia	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Neutropenia	5 (2%)	8 (3%)	9 (3%)	0	5 (2%)	3 (1%)	3 (1%)	0
Febrile neutropenia	0	22 (9%)	2 (<1%)	0	0	15 (6%)	1 (<1%)	0
Anaemia	25 (10%)	5 (2%)	0	0	29 (11%)	14 (5%)	0	0
Leukopenia	4 (2%)	2 (<1%)	1 (<1%)	0	0	4 (2%)	1 (<1%)	0
Thrombocytopenia	4 (2%)	1 (<1%)	0	0	0	0	0	0
Haemorrhagic anaemia	0	1 (<1%)	0	0	0	0	0	0
Pancytopenia	0	0	0	0	0	0	1 (<1%)	0
Decreased neutrophil count	7 (3%)	8 (3%)	15 (6%)	0	1 (<1%)	8 (3%)	19 (7%)	0
Decreased platelet count	15 (6%)	1 (<1%)	1 (<1%)	0	5 (2%)	1 (<1%)	0	0
Decreased white blood cell count	6 (2%)	6 (2%)	5 (2%)	0	3 (1%)	13 (5%)	4 (2%)	0
Increased alanine aminotransferase	4 (2%)	1 (<1%)	0	0	3 (1%)	1 (<1%)	0	0
Decreased lymphocyte count	2 (<1%)	3 (1%)	0	0	4 (2%)	2 (<1%)	0	0
Elevated blood pressure	0	2 (<1%)	0	0	1 (<1%)	0	0	0
Increased gamma-glutamyltransferase	0	1 (<1%)	0	0	0	2 (<1%)	0	0
Decreased blood pressure	0	0	0	0	0	1 (<1%)	0	0
Decreased creatinine renal clearance	0	0	0	0	0	1 (<1%)	0	0
Increased lymphocyte count	0	0	0	0	0	1 (<1%)	0	0
Coronary arteriospasm	0	1 (<1%)	0	0	0	0	0	0

	Ramucirumab plus docetaxel (n=258)				Placebo plus docetaxel (n=265)			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Cardiac arrest	0	0	0	1 (<1%)	0	0	0	0
Left ventricular dysfunction	0	1 (<1%)	0	0	0	0	0	0
Intracardiac thrombus	0	0	0	0	0	1 (<1%)	0	0
Hypoacusis	0	0	0	0	0	1 (<1%)	0	0
Adrenal insufficiency	0	0	0	0	0	0	1 (<1%)	0
Urinary tract infection	4 (2%)	3 (1%)	0	0	4 (2%)	2 (<1%)	0	0
Tooth infection	1 (<1%)	1 (<1%)	0	0	0	0	0	0
Gingivitis	4 (2%)	0	0	0	0	1 (<1%)	0	0
Pneumonia	0	2 (<1%)	1 (<1%)	0	0	0	1 (<1%)	0
Sepsis	0	0	2 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)	4 (2%)	0
Neutropenic sepsis	0	0	0	1 (<1%)	0	0	0	0
Abdominal abscess	0	1 (<1%)	0	0	0	0	0	0
Bronchitis	1 (<1%)	0	0	0	0	1 (<1%)	0	0
Cellulitis	1 (<1%)	0	0	0	1 (<1%)	1 (<1%)	0	0
Clostridium difficile colitis	0	1 (<1%)	0	0	0	0	0	0
Gastroenteritis	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Pyelonephritis	0	1 (<1%)	0	0	0	1 (<1%)	0	0
Acute pyelonephritis	0	1 (<1%)	0	0	0	0	0	0
Bacteraemia	0	0	0	0	0	1 (<1%)	0	0
Diverticulitis	0	0	0	0	0	1 (<1%)	0	0
Kidney infection	0	0	0	0	0	1 (<1%)	0	0
Lung infection	0	0	0	0	1 (<1%)	1 (<1%)	0	1 (<1%)
Urosepsis	0	0	0	0	0	1 (<1%)	2 (<1%)	0
Infusion-related reaction	8 (3%)	1 (<1%)	0	0	7 (3%)	0	0	0
Myalgia	20 (8%)	1 (<1%)	0	0	17 (6%)	0	0	0
Arthralgia	10 (4%)	0	0	0	9 (3%)	2 (<1%)	0	0
Back pain	5 (2%)	1 (<1%)	0	0	2 (<1%)	0	0	0
Muscular weakness	4 (2%)	0	0	0	3 (1%)	1 (<1%)	0	0
Lethargy	2 (<1%)	1 (<1%)	0	0	0	0	0	0
Insomnia	5 (2%)	1 (<1%)	0	0	4 (2%)	0	0	0

	Ramucirumab plus docetaxel (n=258)				Placebo plus docetaxel (n=265)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Proteinuria	20 (8%)	2 (<1%)	0	0	8 (3%)	1 (<1%)	0	0
Haematuria	12 (5%)	1 (<1%)	0	0	4 (2%)	1 (<1%)	0	0
Renal failure	0	0	0	1 (<1%)	1 (<1%)	0	0	0
Female genital tract fistula[†]	0	1 (2%)	0	0	0	0	0	0
Oropharyngeal pain	6 (2%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Pleural effusion	1 (<1%)	0	0	0	2 (<1%)	1 (<1%)	0	0
Pneumonitis	0	1 (<1%)	0	0	1 (<1%)	0	0	1 (<1%)
Laryngeal inflammation	0	0	0	0	0	1 (<1%)	0	0
Pulmonary embolism	0	0	0	0	0	2 (<1%)	0	1 (<1%)
Palmar-plantar erythrodysaesthesia syndrome	18 (7%)	1 (<1%)	0	0	5 (2%)	1 (<1%)	0	0
Generalised rash	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0
Onychalgia	0	1 (<1%)	0	0	0	0	0	0
Hypotension	4 (2%)	0	0	0	2 (<1%)	1 (<1%)	0	0
Deep vein thrombosis	2 (<1%)	1 (<1%)	0	0	2 (<1%)	0	0	0

Data are n (%).

[*] Data for drug-related treatment-emergent adverse events are shown as consolidated terms, defined as fatigue (fatigue and asthenia), hypertension (hypertension and increased blood pressure), neuropathy (peripheral sensory neuropathy, peripheral motor neuropathy, peripheral neuropathy, polyneuropathy, hypoaesthesia, and neuralgia), and abdominal pain (abdominal pain and upper abdominal pain).

[†] The denominator is adjusted for sex-specific events for women (ramucirumab group n=49; placebo group n=51).

Table 4:

Prespecified exploratory analysis of efficacy endpoints by PD-L1 expression

	PD-L1 combined positive score <10				PD-L1 combined positive score ≥10			
	Ramucirumab plus docetaxel (n=72)	**Placebo plus docetaxel (n=63)**	**HR (95% CI)**	**p value**	**Ramucirumab plus docetaxel (n=57)**	**Placebo plus docetaxel (n=48)**	**HR (95% CI)**	**p value**
Progression-free survival (months)	4·2 (2·8–5·8)	2·7 (14·2–9)	0·672 (0·451–1·001);	0·0507	5·2 (3·3–5·6)	2·8 (1·5–3·0)	0·530 (0·339–0·830)	0·0060
Overall survival (months)	8·5 (6·8–11·6)	6·9 (44·9–9)	0·999 (0·664–1·502)	0·9955	9·2 (5·4–12·7)	6·4 (3·9–7·4)	0·519 (0·331–0·816)	0·0048
Patients achieving an overall response *	18; 25% (15·0–35·0)	2; 3% (0·0–7·5)	..	<0·001	16; 28% (16·4–39·7)	6; 13% (3·1–21·9)	..	0·042
Patients achieving disease control *	45; 63% (51·3–73·7)	33; 52% (40·1–64·7)	..	0·24	41; 72% (60·3–83·6)	27; 56% (42·2–70·3)	..	0·070

Data are median (95% CI) unless otherwise indicated. PD-L1=programmed cell death 1. HR=hazard ratio.

* Data are n; % (95% CI).