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

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Summary

Background Pre-clinical and clinical evidence suggests that simultaneous blockade of VEGF receptor-2 (VEGFR-2) and PD-1 or PD-L1 enhances antigen-specific T-cell migration, antitumour activity, and has favourable toxicity. In this study, we aimed to assess the safety and preliminary antitumour activity of ramucirumab (an IgG1 VEGFR-2 antagonist) combined with pembrolizumab (an IgG4 PD-1 antagonist) in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma, non-small-cell lung cancer, or urothelial carcinoma.

Methods We did a multicohort, non-randomised, open-label, phase 1a/b trial at 16 academic medical centres, hospitals, and clinics in the USA, France, Germany, Spain, and the UK. We enrolled adult patients aged 18 years or older with histologically confirmed gastric or gastro-oesophageal junction adenocarcinoma (cohorts A and B), non-small-cell lung cancer (cohort C), or urothelial carcinoma (cohort D), whose disease had progressed on one or two lines of previous therapy (for those with gastric or gastro-oesophageal junction adenocarcinoma) or one to three lines of previous therapy (for those with non-small-cell lung cancer and urothelial carcinoma) that included platinum (for all tumour types) or fluoropyrimidine or both (for gastric or gastro-oesophageal junction adenocarcinoma). Eligibility criteria included presence of measurable disease and an Eastern Cooperative Oncology Group performance status of 0–1. Patients with previously untreated gastric or gastro-oesophageal junction adenocarcinoma and non-small-cell lung cancer were also enrolled (in two additional separate cohorts); the results for these cohorts will be reported separately. The first 21-day treatment cycle was a dose-limiting toxicity observation period (phase 1a; safety run-in), followed by a phase 1b cohort expansion stage. Pembrolizumab 200 mg was administered intravenously on day 1, and intravenous ramucirumab was administered at 8 mg/kg on days 1 and 8 for cohort A or at 10 mg/kg on day 1 for cohorts B, C, and D, every 3 weeks, until disease progression or other discontinuation criteria were met. The primary endpoint was the safety and tolerability of ramucirumab in combination with pembrolizumab assessed by the incidence of adverse events in both phase 1a and 1b and as dose-limiting toxicities during phase 1a. The safety and activity analysis set included all patients who received at least one dose of study treatment. This trial is registered with ClinicalTrials.gov, number NCT02443324, and is no longer enrolling patients.

Findings Between July 30, 2015 and June 24, 2016, we enrolled and treated 92 patients (41 with gastric or gastro-oesophageal junction adenocarcinoma, 27 with non-small-cell lung cancer, and 24 with urothelial carcinoma). Median follow-up was 32·8 months (IQR 28·1–33·6). During the first cycle of treatment (phase 1a safety run-in; n=11), one patient with gastro-oesophageal junction adenocarcinoma who received the 8 mg/kg dose of ramucirumab had grade 3 abdominal pain, colitis, hepatitis, interstitial lung disease, and jaundice, and grade 4 cholestasis, and died on treatment on day 40; the death was deemed related to progressive disease. No additional dose-limiting toxicities occurred and the decision was made to maintain the full planned doses of ramucirumab and pembrolizumab in phase 1b (n=81). Treatment-related adverse events occurred in 75 (82%) of 92 patients, the most common of which was fatigue (in 33 patients [36%]), predominantly of grade 1 or 2 severity. 22 patients (24%) had one or more treatment-related adverse events of grade 3 or worse, most commonly hypertension (six patients; 7%) and colitis (five patients; 5%). Serious adverse events occurred in 53 (58%) of 92 patients, and were deemed related to treatment in 22 (24%) patients. The most common treatment-related serious adverse events were abdominal pain in patients with gastric or gastro-oesophageal junction adenocarcinoma (in three [7%] of 41 patients); asthenia and myocardial infarction in patients with non-small-cell lung cancer (two [7%] of 27 patients), and colitis in patients with urothelial carcinoma (two [8%] of 24 patients). Six (7%) of 92 patients discontinued treatment because of treatment-related adverse events, and one death (from pulmonary sepsis in a patient with gastric or gastro-oesophageal junction adenocarcinoma) was deemed related to treatment. The number of patients achieving an objective response was three (7%; 95% CI 1·5–19·9) of 41 in the gastric or gastro-oesophageal junction adenocarcinoma cohort, eight (30%; 13·8–50·2) of 27 in the non-small-cell lung cancer cohort, and three (13%, 2·7–32·4) in the urothelial carcinoma cohort.

Lancet Oncol 2019; 20: 1109–23

Published Online July 10, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30458-9

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Interpretation **Ramucirumab in combination with pembrolizumab showed a manageable safety profile with favourable antitumour activity in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma, non-small-cell lung cancer, and urothelial carcinoma. Our results contribute to the growing evidence that supports dual inhibition of the VEGF–VEGFR2 and PD-1–PD-L1 pathways. This combination could be further explored with or without chemotherapy, especially for patients with tumours for which single-agent checkpoint inhibitors have shown no additional benefit over chemotherapy.**

Funding **Eli Lilly and Company, and Merck and Co.**

Introduction

Tumours can evade T cell-mediated killing through upregulation of PD-L1, which interacts with inhibitory receptor PD-1 expressed on tumour-infiltrating T cells, leading to their functional inactivation. Immune checkpoint inhibitors targeting the PD-L1–PD-1 axis show durable activity in a subset of patients with cancer.[1–3] However, many patients with cancer treated with checkpoint inhibitors have progressive disease as their best response and novel combination treatments are needed. The PD-1 inhibitor pembrolizumab has shown durable antitumour activity in some patients, including those with previously treated advanced non-small-cell lung cancer, gastric or gastro-oesophageal junction adenocarcinomas, and urothelial carcinoma.[1,2,4]

Mechanisms of resistance to checkpoint inhibitors are probably multifactorial and can include an absence of PD-L1, inhibitory effects in the tumour microenvironment, or both. Antiangiogenic therapies targeting VEGF or VEGF receptor-2 (VEGFR-2) can increase trafficking of T cells into tumours and reduce immunosuppressive cytokines and regulatory T cells, and might help to overcome resistance to checkpoint inhibitors.[5,6] Clinical studies with antiangiogenic drugs in combination with checkpoint inhibitors have shown enhanced antigen-specific T-cell migration, antitumour activity, and a favourable toxicity profile.[7–13] A translational study[13] showed that bevacizumab (anti-VEGF) increased antigen-specific T-cell migration and expression of MHC-1 and PD-L1. The addition of atezolizumab to bevacizumab augmented this process and led to deep and durable

Research in context

Evidence before this study

Before trial enrolment began, we searched PubMed, the abstracts of the American Society of Clinical Oncology and European Society for Medical Oncology congresses, and ClinicalTrials.gov with the terms "carcinoma", "cancer", "immune checkpoint inhibitor", "anti-PD-1", "anti-PD-L1", "trials", "clinical trials", "VEGF", and "VEGFR-2" for preclinical reports and clinical trials published in English up to Jan 1, 2015 with no restrictions on the earliest date. We identified reports showing that immune checkpoint inhibitors targeting the PD-L1–PD-1 axis have durable activity in various subsets of patients with cancer, although many patients treated with checkpoint inhibitors had progressive disease as their best response. Much evidence suggests that mechanisms of resistance to checkpoint inhibitors are probably multifactorial, and could potentially be overcome through the addition of anti-angiogenic therapies targeting VEGF or VEGF receptor-2 (VEGFR-2). Preclinical studies provided evidence for a synergistic antitumour effect from blocking VEGFR2 and PD-1 simultaneously in a murine colon cancer model, with this dual blockade inhibiting tumour growth significantly compared with each treatment, individually. Furthermore, in two clinical studies in patients with metastatic colorectal cancer and melanoma, the combination of bevacizumab (anti-VEGF) and immune checkpoint blockade was well tolerated with no unexpected toxicities.

Added value of this study

Our study combined ramucirumab (a VEGFR2 antagonist) and pembrolizumab (a PD-1 antagonist) to simultaneously target both the angiogenesis or tumour microenvironment and immune checkpoint inhibition in biomarker-unselected patients with previously treated advanced non-small-cell lung cancer, gastric or gastrooesophageal junction adenocarcinoma, and urothelial carcinoma. The combination of ramucirumab and pembrolizumab showed a manageable safety profile, with no indication that ramucirumab potentiates pembrolizumab toxicity (or vice versa), and full doses of each individual drug could be administered in combination. Efficacy endpoints in our study showed favourable outcomes compared with immune checkpoint inhibitor monotherapy in other studies.

Implications of all the available evidence

Our results contribute to the growing evidence that supports dual inhibition of the VEGF–VEGFR2 and PD-1–PD-L1 pathways in patients with previously treated advanced or metastatic cancer. Given its manageable safety profile and clinical activity, this combination could be explored in future trials either with or without chemotherapy, especially in patients with tumours for which single-agent immune checkpoint inhibitors have shown no additional benefit to chemotherapy.

responses in patients with metastatic renal cell carcinoma.[13] A randomised phase 2 trial of this treatment combination showed longer median progression-free survival of 11·7 months (95% CI 8·4–17·3) with first-line bevacizumab plus atezolizumab versus 8·4 months (7·0–14·0) with sunitinib in patients with metastatic renal cell carcinoma.[9] In a phase 3 study,[11] combining the antiangiogenic drug axitinib with pembrolizumab in patients with metastatic renal cell carcinoma improved progression-free survival and objective response, compared with sunitinib (median progression-free survival 15·1 months with pembrolizumab–axitinib *vs* 11·1 months with sunitinib [HR for disease progression or death 0·69, 95% CI 0·57–0·84; p<0·001]; proportion of patients achieving an objective response was 59·3%, 95% CI 54·5–63·9 with pembrolizumab–axitinib and 35·7%, 31·1–40·4 with sunitinib group; p<0·001). Furthermore, the boosting effects of bevacizumab on atezolizumab in combination with chemotherapy have been noted in patients with non-small-cell lung cancer, suggesting clinical effectiveness of combining anti-angiogenics with checkpoint inhibitors.[12]

After initial treatment with cytotoxic chemotherapy, persistent toxicities can affect the ability of many patients with cancer to receive second-line therapy; in some tumour types, such as gastric or gastro-oesophageal junction adenocarcinomas, up to 50% of patients do not receive second-line therapy.[14] In these patients, there is an unmet need for possible chemotherapy-free options with similar activity to standard chemotherapeutic regimens but improved toxicity profiles.

Ramucirumab is an IgG1 monoclonal antibody that binds to the extracellular domain of VEGFR2 and has shown antitumour activity in phase 3 trials,[15–18] as monotherapy or in combination with chemotherapy, for several tumour types including non-small-cell lung cancer, gastric or gastro-oesophageal junction adeno-carcinomas, and urothelial carcinomas. Here, we describe results from the JVDF study, a phase 1 trial of ramucirumab with pembrolizumab for patients with previously treated advanced solid tumours. We reported results for patients with previously treated advanced or metastatic biliary tract cancer separately; our results showed that the combination showed no unexpected safety findings but did not improve overall survival when compared with historical controls.[7] Results for ongoing cohorts of untreated non-small-cell lung cancer and gastric or gastro-oesophageal junction adenocarcinoma will be reported separately. Here, we report results for patients with previously treated non-small-cell lung cancer, gastric or gastro-oesophageal junction adeno-carcinomas, and urothelial carcinomas.

Methods

Study design and participants

We did the multicohort, non-randomised, open-label, phase 1a/b JVDF trial at 16 academic medical centres, hospitals, and clinics in the USA, France, Germany, Spain, and the UK. We enrolled adult patients aged at least 18 years with histologically confirmed gastric or gastro-oesophageal junction adenocarcinomas (cohorts A and B; no differences in criteria between these two cohorts), non-small-cell lung cancer (cohort C), or urothelial carcinoma (cohort D); unresectable or metastatic disease; and progression on one or two lines of previous chemotherapy for patients with gastric or gastro-oesophageal junction adenocarcinomas, or one to three lines for those with non-small-cell lung cancer and urothelial carcinoma. Previous therapy for advanced disease must have included platinum (for all tumour types) or fluoropyrimidine or both (for gastric or gastro-oesophageal junction adenocarcinomas). Patients with non-small-cell lung cancer who had known *EGFR* or *ALK* mutations were eligible if they had received one or more previous targeted therapies for these mutations. Also required were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable disease (based on Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), adequate organ function (haematological: absolute neutrophil count ≥1·5×10⁹ cells/L, platelets ≥100×10⁹/L, haemoglobin concentration ≥9 g/dL or ≥5·6 mmol/L; renal: creatinine concentration ≤1·5 times the upper limit of normal [ULN] or ≥60 mL/min; hepatic: total bilirubin concentration ≤1·5×ULN, aspartate amino-transferase and alanine aminotransferase concentration ≤2·5×ULN or ≤5×ULN for patients with liver metastases; coagulation: international normalised ratio ≤1·5×ULN or prothrombin time ≤5 s above ULN; thyroid: thyroid-stimulating hormone within normal limits), and a newly obtained core or excisional biopsy of a tumour lesion before enrolment. Patients were excluded if they had known brain metastases, uncontrolled spinal cord compression, or leptomeningeal disease, or had a serious illness or medical condition including, but not limited to, immunodeficiency, active autoimmune disease, pneumonitis, interstitial lung disease, hepatitis B or hepatitis C virus infection, HIV, liver cirrhosis, or congestive heart failure. For patients with non-small-cell lung cancer, previous treatment with drugs targeting VEGF or VEGF receptors was allowed. For all other patients, previous therapy with drugs targeting the VEGF–VEGFR, PD-1–PDL-1, or PD-1–PDL-2 signalling pathways was not permitted. Patients were not allowed to have had chemotherapy, targeted small molecule therapy, or radiotherapy within 2 weeks or monoclonal antibody treatment within 4 weeks before enrolment. Full eligibility criteria are in the appendix (pp 53–61).

See Online for appendix

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 ethics committees for all participating centres and is available in the web appendix (pp 25–182). All patients provided written, informed consent before study entry.

Procedures

The phase 1a (safety run-in) part of the study was a dose-limiting toxicity observation period which lasted for one 21-day treatment cycle; dose-limiting toxicities are defined in the appendix (pp 63–64). Ramucirumab had two dosing schedules (8 mg/kg on days 1 and 8, or 10 mg/kg on day 1), and the dose of pembrolizumab was fixed at 200 mg on day 1 every 3 weeks. The phase 1a part followed a standard 3+3 design, with up to 12 patients (six per dosing schedule) evaluable for dose-limiting toxicities. Patients in phase 1a could continue to the phase 1b expansion phase.

In the expansion phase 1b part of the trial, patients with gastric or gastro-oesophageal junction adenocarcinomas (cohort B only), non-small-cell lung cancer, and urothelial carcinoma received ramucirumab 10 mg/kg intravenously on day 1 every 3 weeks with pembrolizumab 200 mg intravenously on day 1 every 3 weeks. Patients with gastric or gastro-oesophageal junction adenocarcinomas in cohort A received ramucirumab 8 mg/kg intravenously on days 1 and 8 every 3 weeks with pembrolizumab 200 mg intravenously on day 1 every 3 weeks. Treatments were continued for up to 35 cycles or until disease progression, unacceptable toxicity, or discontinuation for any other reason.

The dosing strategy for ramucirumab is in the appendix (pp 49–51). A ramucirumab dose of 8 mg/kg on days 1 and 8 every 3 weeks was based on exposure-response analyses in the REGARD (8 mg/kg every 2 weeks) and RAINBOW (8 mg/kg on days 1 and 15 of a 28-day cycle) studies.[16,17] Based on pharmacokinetic simulation, 8 mg/kg on days 1 and 8 every 3 weeks should produce higher ramucirumab exposure and potentially better clinical activity outcomes than the regimen of 8 mg/kg every 2 weeks. The ramucirumab-related safety risk was not expected to be significantly increased because this dose is approximately 60% lower than the maximum tolerated weekly dose identified in a phase 1 dose-escalation study (13 mg/kg weekly).[19]

Dose modifications were permitted for non-life-threatening grade 3 clinical adverse events that were considered to be at least possibly related to study treatment. Treatment was generally discontinued for grade 4 clinical adverse events. Further details about permitted dose modifications are in the appendix (pp 65–75). A patient could continue with only one drug while discontinuing the other; therefore, the duration of treatment for the drugs could be different.

Tumour responses were assessed radiographically by the investigator according to RECIST 1.1, with required investigator confirmation for partial and complete responses. Responses were assessed every 6 weeks (or within 7 days either side of this timepoint) for the first 24 weeks and measured every 12 weeks (or within 7 days either side of this point) thereafter. Study treatment was continued until progression was confirmed in a subsequent scan (after at least 4 weeks) per RECIST; once progression was confirmed, treatment was discontinued. Stable disease was confirmed if the duration was at least 39 days. Following discontinuation, patients were followed up for survival approximately every 90 days. Safety was assessed and adverse events were graded throughout the study and for 30 days after treatment discontinuation. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, and judged by the investigator as related or unrelated to study treatment. Laboratory monitoring was done within 7 days before cycle 1 and within 4 days before each subsequent cycle.

Consistent with previous methods,[1,20,21] PD-L1 expression was assessed using immunohistochemistry with an investigational version of PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA, USA), for which the number of stained tumour cells (tumour proportion score) or tumour and immune cells (combined positive score) was relative to the total number of tumour cells. PD-L1 positivity was defined by a combined positive score of at least 1% in patients with gastric or gastro-oesophageal junction adenocarcinomas and urothelial carcinoma, and by a tumour proportion score of at least 1% (PD-L1 positive), 1% to 49% (PD-L1 weak positive), and at least 50% (PD-L1 strong positive) in patients with non-small-cell lung cancer.

Outcomes

The primary endpoint was the safety and tolerability of ramucirumab in combination with pembrolizumab assessed by the incidence of adverse events in phase 1a and 1b and dose-limiting toxicities during the 21-day treatment cycle in the phase 1a safety run-in period. Secondary endpoints were progression-free survival (by investigator review), defined as the time from date of first study treatment until the first radiographic documentation of objective progression, or as death due to any cause; overall survival, defined as the time from date of first study treatment 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; time to response, defined as the time from the date of first study treatment until the first evidence of a confirmed complete or partial response; and the pharmacokinetics of ramucirumab when coadministered with pembrolizumab. Exploratory end-points were the immunogenicity of ramucirumab when co-administered with pembrolizumab; association between biomarkers and clinical outcomes; and biomarker measures of immune functioning and angiogenesis. The exploratory endpoints of immunogenicity and biomarker measures of immune functioning and angiogenesis will be reported separately.

Statistical analysis

For the safety run-in (phase 1a), we used a standard 3+3 design, with a planned enrolment of up to 12 patients (six per dosing schedule) to be evaluable for dose-limiting toxicities. Planned enrolment for each tumour expansion cohort (phase 1b) was 25 to 30 patients. 15 patients each were planned for both the gastric or gastro-oesophageal junction adenocarcinoma cohorts. The sample size was selected to allow adequate assessment of safety and preliminary anti-tumour activity at the recommended doses for ramucirumab and pembrolizumab. For the gastro-oesophageal junction adenocarcinoma, non-small-cell lung cancer, and urothelial carcinoma cohorts, the null hypothesis was based on the assumption that the proportion of patients with an objective response was no greater than 10–15% and that the target treatment effect of the combination therapy on the proportion with an objective response was between 20% and 30%. Based on these proportions, a sample size of 25–30 patients per cohort (n=30 for the combined gastric or gastrooesophageal junction adenocarcinoma cohorts) provided approximately 60–90% power with a one-sided α level of 0·20.

The safety and activity analysis sets were based on all enrolled patients—ie, all those who had been assigned to treatment and had received at least one dose of study treatment.

The 95% CI for the proportion of patients with an objective response were calculated based on the Clopper-Pearson method. Patients who did not have any post-baseline tumour response assessments for any reason were considered non-evaluable and were included in the denominator when calculating the proportion of responding patients.

Time-to-event variables were estimated using Kaplan-Meier methods. Safety was assessed in all patients who received one or more doses of study medication. The time to resolution of an adverse event was calculated from the start date of the first episode of the event, until the resolved or recovered date for the same episode. For the phase 1a part of the study, the available safety and pharmacokinetic data were reviewed on a cohort-by-cohort basis. For the phase 1b part of the study, interim analyses were done at a cohort level when the patients had completed approximately 24 weeks of study treatment or had discontinued for any reason.

The protocol was amended (on Feb 11, 2016) to include three new phase 1b expansion cohorts: first-line gastric or gastro-oesophageal junction adenocarcinoma (cohort A2), first-line non-small-cell lung cancer (cohort E), and second or third-line biliary tract cancer (cohort A1). The rationale for this amendment is in the protocol (appendix pp 146–82); the results for the biliary tract cancer cohort (cohort A1) have already been reported[7] and results for the ongoing cohorts A2 and E will be reported separately. SAS (version 9.4) and R (version 3.5.0) were used for statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT02443324.

Role of the funding source

The funder of the study (Eli Lilly and Company) had a role in study design, data collection, data analysis, data interpretation (in collaboration with all authors), and

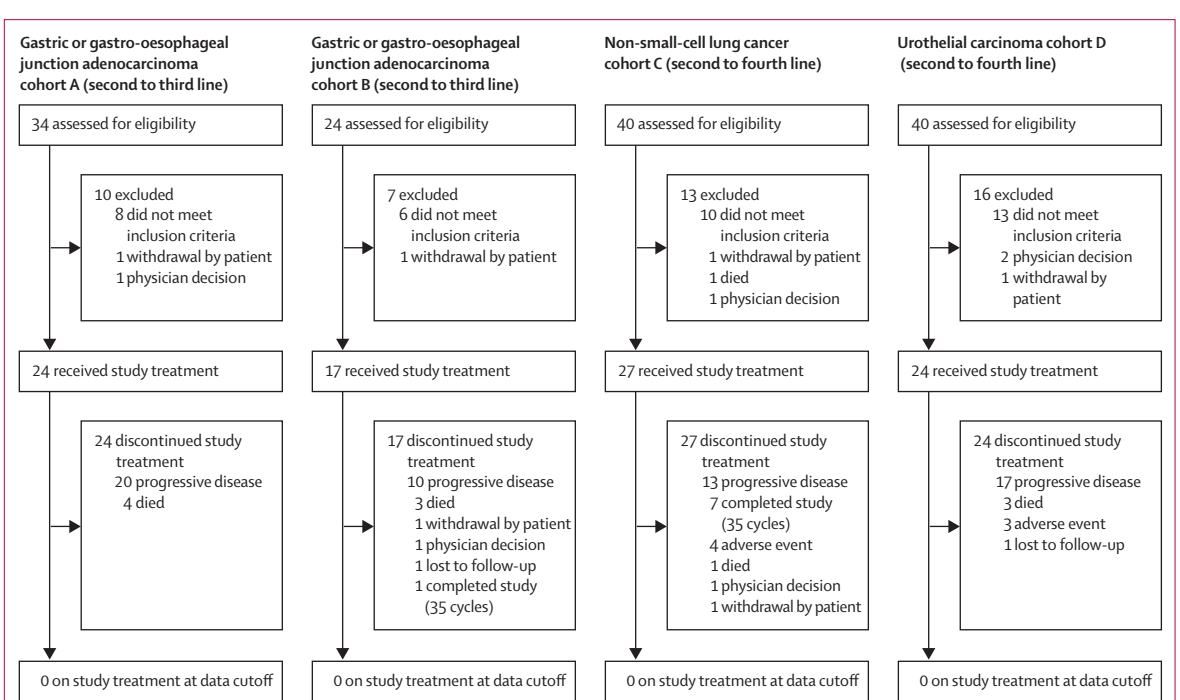

Figure 1: **Trial profile**

	Gastric or gastro-oesophageal junction adenocarcinoma (n=41)	Non-small-cell lung cancer (n=27)	Urothelial carcinoma (n=24)
Age (years)	58 (51–65)	65 (56–72)	63 (56–71)
Sex			
Male	31 (76%)	21 (78%)	14 (58%)
Female	10 (24%)	6 (22%)	10 (42%)
Ethnic origin			
White	35 (85%)	26 (96%)	22 (92%)
Asian	4 (10%)	0	0
Black or African-American	1 (2%)	1 (4%)	0
Missing	1 (2%)	0	2 (8%)
ECOG performance status			
0	13 (32%)	7 (26%)	12 (50%)
1	27 (66%)	20 (74%)	11 (46%)
2*	1 (2%)	0	1 (4%)
PD-L1 status			
Positive	22 (54%)	TPS 1–49%: 4 (15%); TPS ≥50%: 7 (26%)	12 (50%)
Negative	17 (41%)	11 (41%)	11 (46%)
Not reported	2 (5%)	5 (19%)	1 (4%)
Histopathological grade			
Low	1 (2%)	4 (15%)	2 (8%)
Intermediate	8 (20%)	1 (4%)	2 (8%)
High	24 (59%)	8 (30%)	13 (54%)
Unable to determine	7 (17%)	14 (52%)	7 (29%)
Not reported	1 (2%)	0	0
Smoking status			
Former or current	21 (51%)	26 (96%)	17 (71%)
Never	19 (46%)	1 (4%)	7 (29%)
Unknown	1 (2%)	0	0
Previous systemic therapies			
Adjuvant therapy	10 (24%)	4 (15%)	7 (29%)
Neoadjuvant therapy	10 (24%)	2 (7%)	4 (17%)
Previous lines of systemic anticancer therapy for advanced disease†			
1	17 (41%)	13 (48%)	9 (38%)
2	24 (59%)	12 (44%)	12 (50%)
≥3	0	2 (7%)	3 (13%)
Gastric or gastro oesophageal junction adenocarcinoma			
Gastric or gastro oesophageal junction as primary cancer site	25 (61%)	..	..
Previous chemotherapy			
Fluoropyrimidine plus platinum	38 (93%)	..	..
Fluoropyrimidine plus other	1 (2%)	..	..
Platinum plus other	2 (5%)	..	..

(Table 1 continues on next page)

writing of the report. 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 30, 2015, and June 24, 2016, 138 patients were screened, of whom 46 were excluded (figure 1).

	Gastric or gastro oesophageal junction adenocarcinoma (n=41)	Non-small-cell lung cancer (n=27)	Urothelial carcinoma (n=24)
(Continued from previous page)			
HER2 status	24 (100%)	..	..
Negative	18 (75%)	..	..
Not assessed	1 (4%)	..	..
Positive	3 (13%)	..	..
Unknown	2 (8%)	..	..
Non-small-cell lung cancer			
Adenocarcinoma	..	22 (81%)	..
Squamous cell carcinoma	..	4 (15%)	..
Non-small-cell lung cancer-not otherwise specified	..	1 (4%)	..
Previous chemotherapy	..		..
Pemetrexed	..	20 (74%)	..
Carboplatin	..	14 (52%)	..
Cisplatin	..	15 (56%)	..
Taxane	..	14 (52%)	..
EGFR mutation status	..	27 (100%)	..
Negative	..	23 (85%)	..
Not assessed	..	3 (11%)	..
Positive	..	1 (4%)	..
ALK mutation status	..	27 (100%)	..
Negative	..	22 (82%)	..
Not assessed	..	4 (15%)	..
Unknown	..	1 (4%)	..
Urothelial carcinoma	..	..	
Bladder as primary site	..	..	16 (67%)
Haemoglobin concentration <10 g/dL	..	..	3 (13%)
Liver metastases	..	..	7 (29%)
Visceral metastases	..	..	24 (100%)
Bellmunt risk factors	..	..	
0	..	..	2 (8%)
1	..	..	9 (38%)
2	..	..	9 (38%)
3	..	..	4 (17%)
Previous chemotherapy	..	..	
Gemcitabine	..	..	24 (100%)
Cisplatin	..	..	19 (79%)
Carboplatin	..	..	10 (42%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. TPS=tumour proportion score. ..=not applicable. *Although the protocol limited eligibility to those with an ECOG performance status of 0–1, two patients whose ECOG performance status changed from 1 to 2 after screening were included, considered a major protocol violation. †A detailed summary of previous anticancer therapies is in the appendix (pp 3–4).

Table 1: **Baseline characteristics**

92 eligible patients were assigned to receive study treatment (11 in phase 1a, 81 in phase 1b); 41 with gastric or gastro-oesophageal junction adenocarcinoma (24 in cohort A, 17 in cohort B), 27 with non-small-cell lung cancer, and 24 with urothelial carcinoma. Baseline demographic and disease characteristics are summarised in table 1 (with additional detail on previous treatments shown in appendix pp 3–4). Data cutoff for this analysis was Aug 31, 2018, at which time all 92 patients had discontinued treatment. The median follow-up duration was 32·8 months (IQR 28·1–33·6).

	Gastric or gastro-oesophageal junction adenocarcinoma (n=41)			Non-small-cell lung cancer (n=27)			Urothelial carcinoma (n=24)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Fatigue*	16 (39%)	2 (5%)	..	8 (30%)	1 (4%)	..	6 (25%)	..	..
Hypothyroidism	4 (10%)	..	..	7 (26%)	..	..	2 (8%)	..	..
Hypertension	2 (5%)	3 (7%)	..	6 (22%)	2 (7%)	..	2 (8%)	1 (4%)	..
Rash*	8 (20%)	..	..	1 (4%)	..	..	..	..	..
Diarrhoea	1 (2%)	1 (2%)	..	5 (19%)	..	..	1 (4%)	1 (4%)	..
Nausea	3 (7%)	..	..	4 (15%)	..	..	4 (17%)	..	..
Pyrexia	2 (5%)	..	..	..	..	..	4 (17%)	..	..
Epistaxis	3 (7%)	..	..	4 (15%)	..	..	..	..	..
Stomatitis	1 (2%)	1 (2%)	..	4 (15%)	..	..	..	..	..
Proteinuria	1 (2%)	..	..	2 (7%)	1 (4%)	..	3 (13%)	..	..
ALT increased	1 (2%)	..	..	2 (7%)	..	..	3 (13%)	..	..
AST increased	2 (5%)	..	..	2 (7%)	..	..	3 (13%)	..	..
Infusion related reaction	5 (12%)	1 (2%)	..	1 (4%)	1 (4%)	..	1 (4%)	..	..
Decreased appetite	5 (12%)	..	..	3 (11%)	1 (4%)	..	1 (4%)	..	..
Pruritus	5 (12%)	..	..	2 (7%)	..	..	1 (4%)	..	..
Vomiting	1 (2%)	..	..	3 (11%)	..	..	2 (8%)	..	..
Arthralgia	..	..	..	3 (11%)	..	..	1 (4%)	..	..
Headache	1 (2%)	..	..	3 (11%)	..	..	2 (8%)	..	..
Anaemia	1 (2%)	..	1 (2%)	3 (11%)	..	..	1 (4%)	..	..
Dysphonia	1 (2%)	..	..	3 (11%)	..	..	..	..	..
Metrorrhagia†	1/10(10%)	..	..	..	..	..	..	..	..
Colitis	..	3 (7%)	..	..	..	..	..	2 (8%)	..
Abdominal pain*	..	3 (7%)	..	2 (7%)	..	..	1 (4%)	..	..
Myocardial infarction	..	..	..	..	2 (7%)	..	..	..	..
Pneumonitis	..	1 (2%)	..	..	..	..	1 (4%)	..	..
Pulmonary embolism	1 (2%)	1 (2%)	..	..	..	..	..	1 (4%)	..
Hyponatremia	..	..	..	..	1 (4%)	..	..	1 (4%)	..
Hypoalbuminaemia	..	..	..	..	1 (4%)	..	..	..	..
Hypophysitis	..	..	..	1 (4%)	1 (4%)	..	..	..	..
Hypokalaemia	..	..	..	..	..	1 (4%)	..	..	..
Delirium	..	..	..	..	1 (4%)	..	..	..	..
Respiratory failure	..	..	..	..	1 (4%)	..	..	..	..
Adrenal insufficiency	..	..	..	..	1 (4%)	..	1 (4%)	..	..
Dehydration	..	..	..	..	1 (4%)	..	..	..	..
Cholestasis	..	..	1 (2%)	..	..	..	..	..	..
Pneumocystis jirovecii pneumonia	..	..	1 (2%)	..	..	..	..	..	..
Interstitial lung disease	..	1 (2%)	..	..	..	..	..	..	..
Dyspnoea	1 (2%)	1 (2%)	..	..	..	..	..	..	..
Acute kidney injury	..	1 (2%)	..	..	..	..	..	..	..
Peritonitis	..	1 (2%)	..	..	..	..	..	..	..
Jaundice	..	1 (2%)	..	..	..	..	..	..	..
Hepatitis	..	1 (2%)	..	..	..	..	..	..	..

Data are n (%). One patient with gastric or gastro-oesophageal junction adenocarcinoma died from pulmonary sepsis. AST=aspartate aminotransferase. ALT=alanine aminotransferase. The table shows treatment-related adverse events occurring at grades 1–2 in at least 10% of treated patients per tumour type, or at grades 3–4 in one or more patients according to preferred term or *consolidated categories. †Denominator adjusted because sex-specific event for females (n=10).

Table 2: **Treatment-related adverse events**

All patients received one or more doses of ramucirumab and pembrolizumab (appendix p 5). Median duration of treatment for patients with gastric or gastro-oesophageal junction adenocarcinoma was 2·8 months (IQR 1·4–5·5) with ramucirumab and 3·0 months (1·4–7·6) with pembrolizumab. In patients with non-small-cell lung cancer, median treatment duration was 7·0 months (IQR 3·0–16·8) with ramucirumab and 8·3 months (3·3–23·7) with pembrolizumab. In patients with urothelial carcinoma, median treatment duration was 2·1 months (IQR 1·4–4·6) with ramucirumab and 2·4 months (1·5–4·6) with pembrolizumab. Median relative dose intensities were at least 95% for ramucirumab and pembrolizumab for all patients (appendix p 5). The ramucirumab dose was reduced in two patients with gastric or gastro-oesophageal junction adenocarcinoma to 6 mg/kg on days 1 and 8 (because of infusion-related reaction in one patient and fatigue and incarcerated inguinal hernia in the other patient) and in one patient with urothelial carcinoma to 8 mg/kg every 3 weeks (because of proteinuria). No dose reductions of pembrolizumab were required. As of data cutoff, nine (22%) patients with gastric or gastro-oesophageal junction adenocarcinoma, 11 (41%) with non-small-cell lung cancer, and six (25%) with urothelial carcinoma received post-study systemic anticancer therapy (appendix p 6). One patient with gastric or gastro-oesophageal junction adenocarcinoma (in cohort B) and seven with non-small-cell lung cancer discontinued the study after completing the maximum duration of 35 cycles of treatment.

During the first 21-day cycle of treatment in the phase 1a part of the study, one patient with gastro-oesophageal junction adenocarcinoma (who received ramucirumab 8 mg/kg on days 1 and 8 every 3 weeks with pembrolizumab 200 mg on day 1 every 3 weeks) had grade 3 abdominal pain, colitis, hepatitis, interstitial lung disease, and jaundice, and grade 4 cholestasis. This patient died on treatment (day 40) and the death was deemed related to progressive disease. No additional dose-limiting toxicities occurred and the decision was made to maintain the full planned doses of ramucirumab and pembrolizumab in phase 1b. Neither drug was escalated or de-escalated because no dose-limiting toxicities occurred at the initial doses.

In the combined phase 1a and b cohorts, treatment-related adverse events occurred in 75 (82%) of 92 patients. The most frequently reported of these events at any grade occurring in more than 10% of patients were fatigue (in 33 [36%] of 92 patients), hypertension (16 [17%]), hypothyroidism (13 [14%]), nausea (11 [12%]), and decreased appetite (ten [11%]). These occurred predominantly at grade 1 or 2 severity (table 2). Grade 3 or worse treatment-related adverse events occurred in 22 (24%) of 92 patients; most commonly hypertension (in six [7%] patients) and colitis (five [5%]). One patient with gastric or gastro-oesophageal junction adenocarcinoma (in cohort A) died from pulmonary sepsis, deemed related to

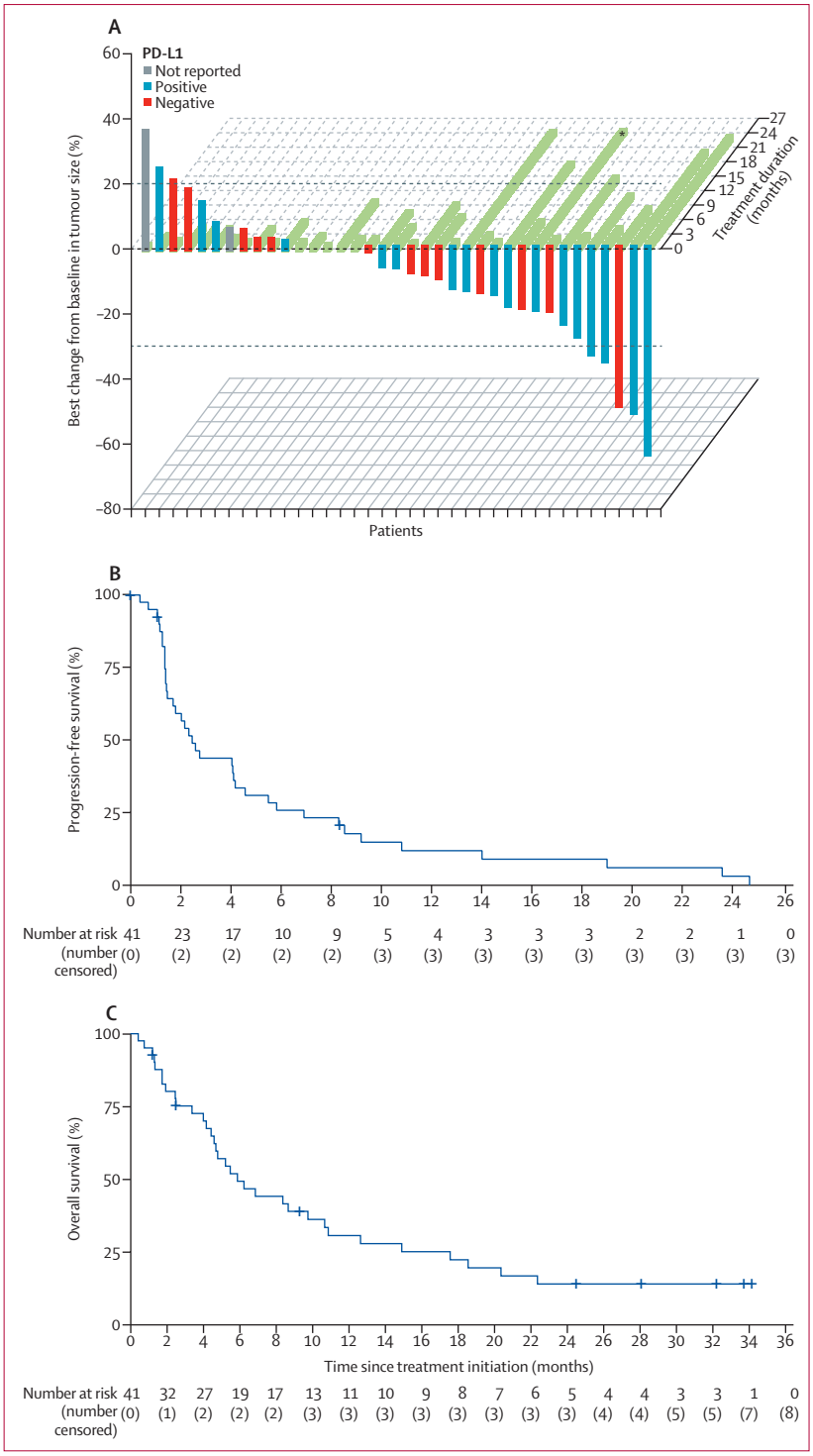

Figure 2: **Secondary outcomes for patients with gastric or gastro-oesophageal junction adenocarcinoma (cohorts A and B)**

(A) Best percentage change of targeted lesions from baseline versus treatment duration in patients with gastric or gastro oesophageal junction adenocarcinoma. Patients (x-axis) are arranged by percentage change in size of targeted lesions from baseline (y-axis) and colour-coded for best response according to PD-L1 expression. Treatment duration (green) is shown on the z-axis. Dotted lines indicate RECIST boundaries (20% to –30%). (B) Progression-free survival. (C) Overall survival. *Completed study (35 cycles).

treatment (the trial was not designed to distinguish attribution to any individual study drug). When including events related by the investigator to disease progression, deaths on treatment or within 30 days of discontinuation, from any cause, were reported for 14 (34%) of 41 patients with gastric or gastro-oesophageal junction adenocarcinoma (ten from study disease; one haematemesis; one pulmonary sepsis; one sudden death; one bowel obstruction), three (11%) of 27 patients with non-small-cell lung cancer (all from study disease), and eight (33%) of 24 patients with urothelial carcinoma (seven from study disease, and one thromboembolic event).

Serious adverse events were reported in 53 (58%) of 92 patients; these were deemed related to treatment in 22 (24%) patients (appendix p 7). The most common related serious adverse events were abdominal pain in the gastric or gastro-oesophageal junction adenocarcinoma cohort (in three [7%] of 41 patients); asthenia (in two [7%] of 27 patients) and myocardial infarction (two patients [7%]) in the non-small-cell lung cancer cohort; and colitis in the urothelial carcinoma cohort (in two [8%] of 24 patients; appendix p 7). Six patients (7%) discontinued treatment because of treatment-related adverse events (grade 1 diarrhoea, grade 2 fatigue, and grade 3 myocardial infarction and grade 3 asthenia in one patient each with non-small-cell lung cancer; and grade 3 pulmonary embolism and grade 3 colitis in one patient each with urothelial carcinoma). There were no obvious differences in safety between the two different schedules of ramucirumab used in the gastric or gastro-oesophageal junction adenocarcinoma cohorts (cohorts A and B). Treatment-related adverse events were reported in 21 (88%) of 24 patients in cohort A, and in 13 (76%) of 17 patients in cohort B; grade 3 or worse treatment-related events occurred in seven (29%) patients in cohort A and four (24%) in cohort B.

Adverse events of special interest, based on the known safety profile of ramucirumab and pembrolizumab, are in the appendix (pp 8–11). Additionally, on the basis of published Trial Reporting in Immuno-oncology recommendations,[22] additional information about immune-related adverse event dose delay, dose discontinuation, timing and duration of toxicity onset, and admissions to hospital is in the appendix (pp 12–13). One fatal event of embolism occurred in one patient with urothelial carcinoma, one fatal event of gastrointestinal

	Gastric or gastro-oesophageal junction adenocarcinoma (n=41)	Non-small-cell lung cancer (n=27)	Urothelial carcinoma (n=24)
Median follow-up, months	32·2 (24·4–33·7)	33·4 (32·8–33·6)	30·7 (11·3–30·9)
Best overall response			
Complete response	0	1 (4%)	0
Partial response	3 (7%)	7 (26%)	3 (13%)
Stable disease	18 (44%)	15 (56%)	9 (38%)
Progressive disease	13 (32%)	3 (11%)	11 (46%)
Not evaluable	7 (17%)	1 (4%)	1 (4%)
Objective response	3 (7%; 1·5–19·9)	8 (30%; 13·8–50·2)	3 (13%; 2·7–32·4)
Disease control	21 (51%; 35·1–67·1)	23 (85%; 66·3–95·8)	12 (50%; 29·1–70·9)
Time to response, months (95% CI)	1·4 (1·4–4·1)	2·1 (1·3–3·0)	2·8 (1·3–5·5)
Duration of response, months (95% CI)	6·7 (4·4–17·5)	NR (11·1–NR)	8·3 (4·6–16·8)
Duration of stable disease, months (95% CI)	5·0 (4·0–8·5)	6·9 (2·8–9·7)	2·8 (1·9–13·1)
Progression-free survival			
Events	38 (93%)	17 (63%)	21 (88%)
Median duration, months (95% CI)	2·5 (1·5–4·2)	9·7 (4·6–27·6)	1·9 (1·2–2·8)
3 months	44% (28·0–58·4)	77% (55·7–88·9)	28%(11·5–47·2)
6 months	26% (13·4–40·0)	65% (43·0–79·9)	23% (8·5–42·2)
12 months	12% (3·9–24·3)	43% (23·4–61·5)	11·6% (2·2–29·9)
Overall survival			
Deaths	33 (81%)	15 (56%)	18 (75%)
Median duration, months (95% CI)	5·9 (4·4–10·6)	26·2 (11·8–NR)	6·4 (2·5–18·7)
6 months	49% (32·9–63·6)	85% (64·5–94·0)	52% (30·5–70·2)
12 months	31% (16·9–45·3)	68% (45·8–82·6)	38% (18·6–57·3)
18 months	22% (10·6–36·5)	59% (37·6–75·8)	32% (13·4–51·8)

Data are median (IQR), n (%), n (%, 95% CI), or % (95% CI), unless indicated otherwise. NR=not reached.

Table 3: **Confirmed efficacy results per Response Evaluation Criteria in Solid Tumors**

haemorrhage causing haematemesis occurred in a patient with gastro-oesophageal junction adenocarcinoma (in cohort B), and one fatal event of intestinal obstruction occurred in a patient with gastro-oesophageal junction adenocarcinoma (cohort B); all three deaths were deemed unrelated to study treatment.

In the combined gastric or gastro-oesophageal junction adenocarcinoma cohorts, at data cutoff, 38 (93%) of 41 patients had disease progression, of whom 33 (80%) had died. 21 (57%) of 37 evaluable patients had a decrease in target lesion size. Confirmed objective responses (all partial responses) occurred in three (7%) of 41 patients (figure 2A, table 3). Results for the other secondary activity outcomes are shown in table 3, figure 2, and the the appendix (p 18). Visual inspection of the survival curves and the objective responses to treatment did not suggest any differences in activity between the two dose schedules used for the patients with gastric or gastro-oesophageal junction adenocarcinoma (data not shown). Patients with PD-L1-positive tumours (n=22) had numerically higher antitumour activity outcomes compared with patients with PD-L1-negative disease (n=17), including median overall survival of 12·6 months (95% CI 4·7–20·3) versus 5·2 months (1·3–8·6), respectively, although this was not statistically compared (appendix pp 14, 21); this was a pre-specified exploratory endpoint of activity by biomarker analysis.

In the non-small-cell lung cancer cohort, at data cutoff, 17 (63%) of 27 patients had disease progression and 15 (56%) of 27 patients had died. 20 (77%) of 26 evaluable patients had a decrease in target lesion size. Confirmed objective responses were recorded in eight (30%) of 27 patients: one patient (4%) had a complete response and seven (26%) had a partial response (figure 3A, table 3). Responses were durable and occurred regardless of PD-L1 status, with a median duration of response not reached (table 3; appendix pp 14, 19). Results for the other secondary activity outcomes are shown in table 3 and figure 3. Activity results by PD-L1 expression are in the appendix (pp 14, 22). One patient with non-small-cell lung cancer was positive for EGFR at baseline and their previous treatment included erlotinib. This patient was PD-L1 positive, had a best overall response to study treatment of stable disease, and discontinued treatment at cycle 9 because of progressive disease.

In the urothelial carcinoma cohort, at the time of data cutoff, 21 (88%) of 24 patients had disease progression, of whom 18 (75%) patients had died. Ten (45%) of 21 evaluable patients had a decrease in target lesion size. Confirmed objective responses (all partial responses) were recorded in three (13%) of 24 patients (figure 4A, table 3) and only occurred in patients who were positive for PD-L1. Results for the other secondary activity outcomes are shown in table 3, figure 4, and appendix p 20. Activity results by PD-L1 expression are in the appendix (pp 14, 23).

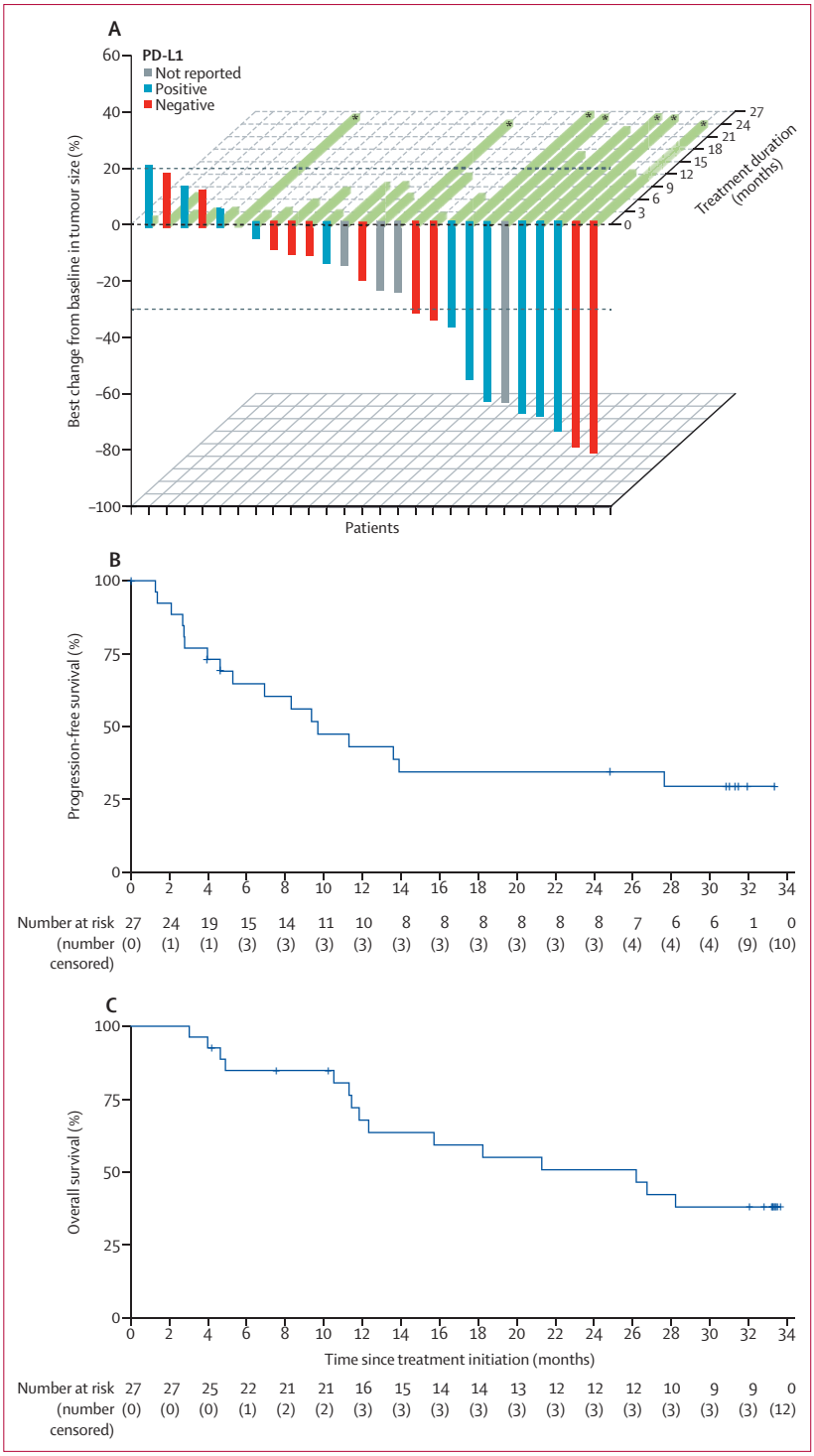

Figure 3: **Secondary outcomes for patients with non-small-cell lung cancer (cohort C)**
(A) Best percentage change in size of targeted lesions from baseline versus treatment duration in patients with non-small-cell lung cancer. Patients (x-axis) were ordered by percentage change of targeted lesions from baseline (y-axis) and colour-coded for best response according to PD-L1 expression. Treatment duration (green) is shown on the z-axis. Dotted lines indicate RECIST boundaries (20% to –30%). (B) Progression-free survival. (C) Overall survival. *Completed study (35 cycles).

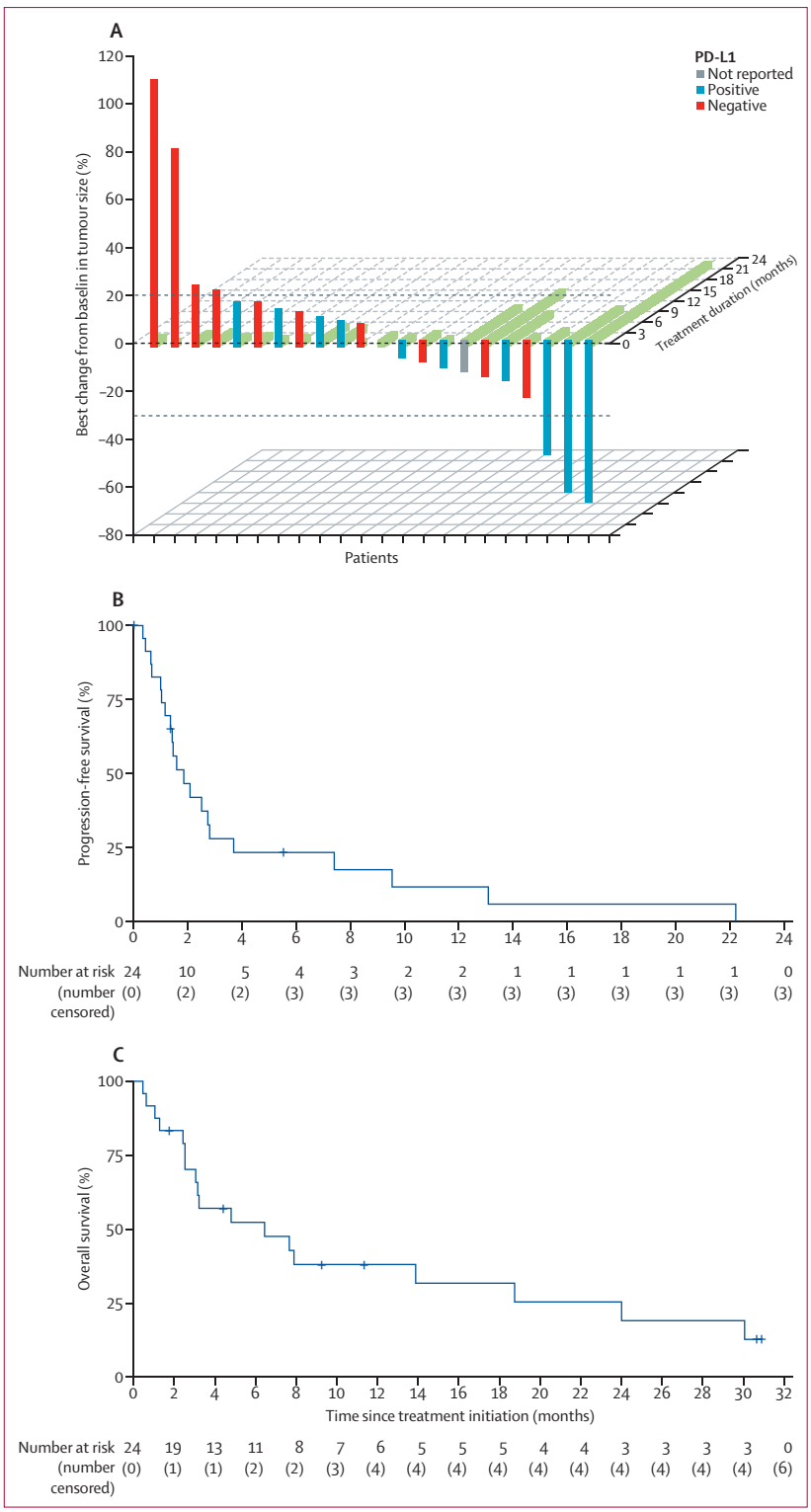

Figure 4: **Secondary outcomes for patients with urothelial carcinoma (cohort D)**
(A) Best percentage change in size of targeted lesions from baseline versus treatment duration in patients with urothelial carcinoma. Patients (x-axis) were ordered by percentage change of targeted lesions from baseline (y-axis) and colour-coded for best response according to PD-L1 expression. Treatment duration (green) is shown on the z-axis. Dotted lines indicate RECIST boundaries (20% to –30%). (B) Progression-free survival. (C) Overall survival.

Ramucirumab exposure concentrations seemed to be similar in patients with different cancer indications when ramucirumab was administered following the same schedule. Dose-related ramucirumab exposure increases were noted between the regimens of 8 mg/kg on days 1 and 8 every 3 weeks and 10 mg/kg every 3 weeks. As expected, the regimen of 8 mg/kg on days 1 and 8 every 3 weeks produced higher trough concentrations, but similar peak concentrations (appendix pp 15–17).

Discussion

In 92 patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (second-line to thirdline), non-small-cell lung cancer (second-line to fourthline), or urothelial carcinoma (second-line to fourthline), ramucirumab in combination with pembrolizumab showed no unexpected safety findings. The most common toxic effects were of grade 1 or 2 severity and were manageable with supportive care or with dose reductions or delays, with few patients discontinuing treatment because of treatment-related adverse events.

Most serious adverse events were of grade 3 or lower severity, and the proportions of patients having a serious adverse event were similar or lower to those previously reported for ramucirumab or pembrolizumab monotherapy.[1,16] Most of these events were recovered, resolved, or were resolving by data cutoff. The occurrences of specific adverse events identified as potential class effects of antiangiogenic therapies, such as hypertension and bleeding (mainly grade 1 or 2 epistaxis), were in the range observed in a meta-analysis of 4996 patients in randomised ramucirumab trials.[23] Similarly, the occurrence of all-grade arterial (3%) and venous (8%) thromboembolic events (appendix) was similar to the frequencies reported in a late-phase meta-analysis[23] (1·4% and 3·9%, respectively). Adverse events identified as potential class effects of checkpoint inhibitors, such as colitis, hypothyroidism, and pneumonitis, were uncommon and mainly occurred at grade 1 or 2 severity. The frequency of events of grade 3 colitis (5%) and pneumonitis (1%) were in the range reported by meta-analyses for checkpoint inhibitors.[24,25] Acknowledging the limitations of the sample size, our safety results show no indication that ramucirumab potentiates pembrolizumab toxicity (or vice versa) and full doses of each individual drug could be administered in combination.

The pharmacokinetic results for ramucirumab were consistent with those from previous studies[15–18] in which ramucirumab was administered to patients with various types of cancer using the same regimens. Different dose schedules were used in the gastric or gastro-oesophageal junction adenocarcinoma cohorts, because when this trial started, key questions remained about the optimum dose of ramucirumab. Subsequent dose–response studies have shown that higher doses of ramucirumab

were not proven to provide significantly improved clinical benefits compared with the approved regimen.[26] In our study, the results suggested no safety or activity differences between the two different schedules of ramucirumab used in the patients with gastric or gastro-oesophageal junction adenocarcinoma.

Expression of PD-L1 on tumour and immune cells is associated with increased clinical benefit from PD-1 or PD-L1 inhibitors in many tumour types.[3] We did not restrict enrolment based on PD-L1 status and only half (49%) of the tested biopsies were positive for PD-L1. Similar to previous reports, activity was generally better in PD-L1-positive patients and this was most evident in patients with gastric or gastro-oesophageal junction adenocarcinoma (second-line to third-line). However, durable antitumour activity also occurred in patients who were negative for PD-L1, most evidently in patients with non-small-cell lung cancer. Future randomised trial designs should consider stratification by PD-L1 status.

In patients with gastric or gastro-oesophageal junction adenocarcinoma in the ATTRACTION-2 trial, the clinical activity of nivolumab (anti-PD-1) monotherapy versus placebo was recorded in a third-line and subsequent line trial of patients, with a median progression-free survival of 1·61 months (95% CI 1·54–2·30) and a 12-month overall survival of 26·2% (20·7–32·0).[27] Similarly, activity of pembrolizumab monotherapy was shown in a single-arm cohort of largely third-line patients (KEYNOTE-059), with a median progression-free survival of 2·0 months (95% CI 2·0–2·1) and a 12-month overall survival of 23·4% (17·6–29·7); PD-L1-positive patients had a median overall survival of 5·8 months (95% CI 4·5–7·9).[28] Data from the phase 3 KEYNOTE-061 trial[20] showed that pembrolizumab was not better than paclitaxel alone in the second-line treatment of patients with PD-L1-positive gastric or gastro-oesophageal junction adenocarcinoma, with median progression-free survival reported for pembrolizumab monotherapy as 1·5 months (95% CI 1·4–2·0) and 4·1 months (3·1–4·2) with paclitaxel (hazard ratio 1·27, 95% CI 1·03–1·57).

Response to pembrolizumab in patients with gastric or gastro-oesophageal junction adenocarcinoma decreased with further lines of therapy, perhaps because patients might be less likely to manifest an immune response after several lines of therapy.[28] The combination of ramucirumab and pembrolizumab might help to overcome this decline, and might be even more effective in earlier lines of therapy. In the current study, we reported a median progression-free survival of 4·6 months and overall survival of 12·6 months in PD-L1-positive patients with gastric or gastro-oesophageal junction adenocarcinoma, of whom 59% were being treated in the third-line setting. Seven (17%) of patients with gastric or gastro-oesophageal junction adenocarcinoma were not evaluable for response. This might have been due to chance, with a larger proportion of patients with this type of cancer having had clinical disease progression before radiological assessment and therefore not being evaluable, although there is no reason that this proportion should be larger than in the other disease cohorts.

Checkpoint inhibitors have shown notable benefit in patients with non-small-cell lung cancer.[29] The activity of pembrolizumab monotherapy was first shown in a large single-arm phase 1 study of PD-L1 allcomers in KEYNOTE-001, with a median progression-free survival of 3·0 months (95% CI 2·2–4·0), a median overall survival of 9·3 months (95% CI 8·4–12·4), and 18% of patients achieving an objective response, in patients previously treated for non-small-cell lung cancer.[30] Broadly, in the second-line setting, the activity of pembrolizumab monotherapy was superior to docetaxel in patients with PD-L1-positive tumours in KEYNOTE-010,[2] with 18% of patients achieving an objective response, a median progression-free survival of 3·9 months (95% CI 3·1–4·1), and median overall survival of 10·4 months (95% CI 9·4–11·9) in patients receiving a dose of 2 mg/kg. The activity of pembrolizumab monotherapy correlated with PD-L1 expression, with the most favourable clinical outcomes in patients with PD-L1 expression on at least 50% of tumour cells.[2,21] Here, we reported that in a PD-L1-allcomer population of patients with non-small-cell lung cancer, 30% of patients achieved an objective response, median progression-free survival was 9·7 months, and median overall survival was 26·2 months, 44% of whom were being treated in the third-line setting. The interpretive challenges of cross-trial comparisons notwithstanding, activity endpoints in our study compared favourably with checkpoint inhibitors in other studies, underlining the potential activity of this regimen in biomarker-unselected patients.[2,29–31]

In a previous study of patients with platinum-refractory advanced urothelial cancer, ramucirumab plus docetaxel improved progression-free survival compared with placebo plus docetaxel (median 4·07 months (95% CI 2·96–4·47) *vs* 2·76 months (2·60–2·96) and the proportion of patients achieving an objective response (25% *vs* 14%).[18] Inconsistencies have been noted with checkpoint inhibitor treatment in such patients, although a survival advantage has been shown for pembrolizumab over docetaxel.[1] Here, we reported that 13% of 24 patients with urothelial cancer achieved an objective response, median progression-free survival was 1·9 months, and median overall survival was 6·4 months in PD-L1 all-comers, 12 (50%) of whom were being treated in the third-line setting, all of whom had visceral metastases at baseline, and 13 (54%) of whom were high-risk by Bellmunt scoring. Patients who were PD-L1-positive had better outcomes than PD-L1-negative patients, including a tail in the overall survival curve. No responses were seen in PD-L1-negative patients.

Our results contribute to the growing evidence that supports dual inhibition of the VEGF–VEGFR2 and PD-1–PD-L1 pathways in patients with previously treated advanced or metastatic cancer.[7–13] Antitumour activity

outcomes in the non-small-cell lung cancer cohort were particularly striking when compared with the other tumour types in this study, which could be driven by the robust activity results in both PD-L1-negative and PD-L1-positive non-small-cell lung tumours. Promising anti-tumour activity results in the gastric or gastro-oesophageal junction adenocarcinoma and urothelial cancer cohorts mainly occurred in PD-L1-positive tumours.

Limitations of our study included the small size of the expansion cohorts. We did not include p values because the study was not designed to have sufficient power for subgroup analyses (by PD-L1 status); the even smaller sample sizes from those subgroups would render p values non-informative. An improved understanding of tumour biology and its interaction with the immune system is needed in patients treated with antiangiogenic drugs in combination with immune checkpoint inhibitors. Our study was limited in providing greater understanding of this complex interaction because the protocol did not allow for collection of post-treatment biopsy samples. Additionally, the single-treatment arm design of the study limited our ability to directly compare findings with other available therapies for each tumour type studied.

Given the manageable safety profile and clinical activity shown in this study, the combination of ramucirumab with pembrolizumab could be explored in future trials either with or without chemotherapy, especially in tumours for which single-agent checkpoint inhibitors have failed to show benefit over chemotherapy.

Contributors

RSH, CSF, DPP, and IC contributed to study design, data collection, data interpretation, and drafting, review, and approval of the submitted report. H-TA, RS-D, EC, LP-A, PAC, JB, NP, MGK, JM-L, NI, AS, MW, and JC contributed to data collection, data interpretation, and drafting, review, and approval of the submitted report. GM, DF, and LG contributed to study design, data analysis, data interpretation, and drafting, review, and approval of the submitted report. RCW and JJ contributed to data analysis, data interpretation, and drafting, review, and approval of the submitted report.

Declaration of interests

RSH has received honoraria for consulting from Abbvie Pharmaceuticals, ARMO Biosciences, AstraZeneca, Biodesix, Bristol-Myers Squibb (BMS), Eli Lilly and Company, EMD Serrano, Genentech/Roche, Genmab, Halozyme, Heat Biologics, Infinity Pharmaceuticals, Loxo Oncology, Merck and Company, Nektar, Neon Therapeutics, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, Tesaro, and Tocagen; honoraria for research support from AstraZeneca, Eli Lilly and Company, and Merck and Company; and is a member of the board of directors (non-executive/independent) for Junshi Pharmaceuticals. RS-D reports research grants from Eli Lilly and Company. EC reports research grants from AbbVie, Amcure, Amgen, AstraZeneca, BMS, Boehringer-Ingelheim, CytomX, Eli Lilly and Company, H3, Incyte, Kura, LOXO, Macrogenics, Menarini, Merc, Merck Serono, Merus, Millenium, Nanobiotix, Janssen, Nektar, Novartis, Pfizer, PharmaMar, Principia Bayer, PsiOxus, PUMA, Rigontec, Roche/Genentech, Sanofi, Taiho, and Tearo; consulting fees from AbbVie, Amcure, AstraZeneca, Boehringer Ingelheim, Celgene, Cerulean Pharma, EUSA, GLG, Guidepoint Global, Janssen-Cilag, Nanobiotix, Janssen, Novartis, Pfizer, Pierre Fabre, PsiOxus Therapeutics, Roche/Genentech, Seattle Genetics, and Servier; speakers' bureau work for Novartis; employment/ownership/leadership of START; employment and honoraria from HM Hospitals Group; and is the president and founder of NPO Foundation Intheos (Investigational Therapeutics in Oncological Sciences). LP-A reports advisory fees from Roche, Eli Lilly and Company, Merck Sharp & Dohme (MSD), BMS, AstraZeneca, Boehringer Ingelheim, Pfizer, Amgen, Takeda, Pharma Mar, Novartis, and Celgene. PAC reports personal fees and non-financial support from AstraZeneca; non-financial support from Roche; grants, personal fees and non-financial support from MSD; non-financial support from Plexxikon; and grants and non-financial support from Novartis. JB reports grants from AbbVie, Acerta Pharma, ADC, Agios, Amgen, Apexigen, Arch Oncology, ARMO, Array, Arrys, AstraZeneca, Bayer, BI, Blueprint, BMS, Boston Biomedical, Calithera, Celgene, Celldex, Cytomx, Daiichi Sankyo, Effector, Eisai, EMD Serono, Evelo, Five Prime, FORMA, Forty Seven, Genentech/Roche, Gilead, GlaxoSmithKline (GSK), Harpoon, Imclone, Incyte, Innate, Ipsen, Jacobio, Koltan, LEAP, Lilly, Macrogenics, Marshall Edwards, MedImmune, Merck, Merrimack, Mersana, Merus, Millennium, Nektar, Novartis, Novocare, Oncogenex, OncoMed, Onyx, Pfizer, Pieris, Prelude Oncology, Regenix, Sanofi, Sierra, SynDevRex, Taiho, Takeda, Tarveda, TG Therapeutics, Tracon, Tyrogenex, Unum Therapeutics, and Vyriad; consulting services for Amgen, Apexigen, Arch Oncology, ARMO, Array, AstraZeneca, Bayer, Beigene, BMS, Celgene, Continuum Clinical, Cyteir, Daiichi Sankyo, Five Prime, FORMA, Genentech/Roche, Gilead, GSK, Incyte, Innate, Ipsen, Janssen, LEAP, Lilly, Macrogenics, MedImmune, Merck, Merrimack, Modern Therapeutics, Molecular Partners, Novartis, Oncogenex, OncoMed, Phoenix Bio, Prelude Therapeutics, Sanofi, Seattle Genetics, Taiho, Tanabe Research Laboratories, TD2 (Translational Drug Development), TG Therapeutics, Tizona, Tolero, and Torque; and personal fees from ARMO, BI, BMS, Celgene, FORMA, Genentech/Roche, Gilead, Ipsen, Lilly, MedImmune, Merck, Novartis, Oncogenex, OncoMed, and Taiho. MGK reports personal fees from Roche, Janssen, Achilles Therapeutics, Octimet, AstraZeneca, and BerGenBio; non-financial support from MSD; and grants and non-financial support from BerGenBio. JM-L reports personal fees from Astellas, Bristol-Myers Squibb, MSD, Novartis, Pierre Fabre, Pfizer, and Roche; and other funding from Astellas, Bristol-Myers Squibb, Ipsen, MSD, Novartis, Pierre Fabre, Pfizer, and Roche. MW reports personal fees from Roche, non-financial support from BMS, and personal fees from Merck and Novartis. JC reports speaker bureau participation for Celgene, Spectrum, and Amgen; and acts as consultant and on advisory boards for Spectrum. CSF reports a consulting role for Agios, Bain Capital, Bayer, Celgene, Dicerna, Five Prime Therapeutics, Gilead Sciences, Eli Lilly and Company, Entrinsic Health, Genentech, KEW, Merck, Merrimack Pharmaceuticals, Pfizer, Sanofi, Taiho, and Unum Therapeutics; serves as a Director for CytomX Therapeutics; and owns unexercised stock options for CytomX and Entrinsic Health. DPP reports consultant fees from Ada Cap, Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Meyers Squibb, Clovis, Eli Lilly and Company, Exelixis, Incyte, Janseen, Pfizer, Pharmacyclics, Roche, Seattle Genetics, and Urogen; grant support from Ada Cap, Amgen, Astellas, AstraZeneca, Bayer, BMS, Clovis, Eli Lilly and Company, Endocyte, Genentech, Innocrin, MedImmune, Merck, Novartis, Pfizer, Progenics, Roche, Sanofi Aventis, and Seattle Genetics; and ownership interest/investment in Bellicum/Tyme. IC reports personal fees for advisory boards from AstraZeneca, Bayer, Bristol-Meyers Squibb, Eli Lilly and Company, Merck-Serono, MSD, Oncologie International, and Roche; research grants from Eli Lilly and Company, Janssen-Cilag, Merck-Serono, and Sanofi Oncology; and honoraria from Five Prime Therapeutics. LG, GM, RCW, JJ, and DF are employees of Eli Lilly and Company. H-TA, NP, NI, and AS declare no competing interests.

Data sharing

Eli Lilly provides access, after anonymisation, to all individual participant data collected during the trial, except for pharmacokinetic and genetic data. Data can be requested 6 months after the indication studied has been approved in the USA and EU or after primary publication acceptance, whichever is later. No expiration date for data requests is set once the data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose, and after receipt of a signed data-sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

Further details about submitting a data request are available at https://www.clinicalstudydatarequest.com.

Acknowledgments

This study was sponsored by Eli Lilly and Company, in collaboration with Merck and Company. We thank the patients, their families, and the study personnel across all sites for participating in this study. Writing assistance was provided by John Bilbruck (ProScribe [Horsham, UK], part of the Envision Pharma Group), who was funded by Eli Lilly and Company. Editorial assistance was provided by Atasi Laha and Purnima Chandra, employees of Eli Lilly and Company.

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