ORIGINAL ARTICLE

Phase 1 Expansion Cohort of Ramucirumab Plus Pembrolizumab in Advanced Treatment-Naive NSCLC

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ABSTRACT

Introduction: Data of first-line ramucirumab plus pembrolizumab treatment of programmed death-ligand 1 (PD-L1)–positive NSCLC (cohort E) are reported (NCT02443324).

Methods: In this multicenter, open-label phase 1a/b trial, patients received ramucirumab 10 mg/kg and pembrolizumab 200 mg every 21 days for up to 35 cycles. PD-L1 positivity was defined as tumor proportion score (TPS) greater than or equal to 1%. Exploratory NanoString biomarker analyses included three T-cell signatures (T-cell–inflamed, Gajewski, and effector T cells) and CD274 gene expression.

Results: Cohort E included 26 patients. Treatment-related adverse events of any grade occurred in 22 patients (84.6%). Treatment-related adverse events of grade greater than or equal to 3 were reported in 11 patients (42.3%); the most frequent was hypertension (n = 4, 15.4%). Objective response rate was 42.3% in the treated population and 56.3% and 22.2% for patients with high (TPS $\geq$ 50%) and lower levels (TPS 1%–49%) of PD-L1 expression, respectively. Median progression-free survival (PFS) in the treated population was 9.3 months, and 12-month and 18-month PFS rates were 45% each. Median PFS was not reached in patients with PD-L1 TPS greater than or equal to 50% and was 4.2 months in patients with PD-L1 TPS 1% to 49%. Median overall survival was not reached in the treated population, and 12-month and 18-month overall survival rates were 73% and 64%, respectively. Biomarker data suggested a positive association among clinical response, three T-cell signatures, CD274 gene expression, and PD-L1 immunohistochemistry.

Conclusions: First-line therapy with ramucirumab plus pembrolizumab has a manageable safety profile in patients with NSCLC, and the efficacy signal seems to be strongest in tumors with high PD-L1 expression.

Keywords: Non–small cell lung cancer; Treatment-naive; Ramucirumab; Pembrolizumab

Introduction

The programmed death-ligand 1 (PD-L1) inhibits antitumor immune responses by binding to the programmed cell death-protein-1 (PD-1) located on $CD8^+$ cells, which inactivates T cells and enables tumor cells to evade immune surveillance and destruction by immune cells in the tumor microenvironment.[1] Immune checkpoint inhibitors that target PD-1 or PD-L1 were found to have efficacy in the treatment of NSCLC.[2] Pembrolizumab is a PD-1 inhibitor that is indicated in combination with chemotherapy for the first-line treatment of NSCLC and as a monotherapy for first-line and second-line treatments of NSCLC in patients whose tumors express PD-L1.[3] Objective response rates (ORRs) ranging from 27% to 45% have been reported after pembrolizumab monotherapy in treatment-naive patients with NSCLC, depending on PD-L1 expression and other factors,[4,5] suggesting some tumors may be resistant to PD-1 inhibition. Combination therapy with an agent that has a different mechanism of action may improve outcomes.

Responses to checkpoint inhibitor therapy have improved with the addition of vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-2 (VEGFR2) inhibitors, possibly by increasing access of T cells to tumors and blockade of immunosuppressive cytokines and regulatory T cells in the tumor microenvironment.[6-8] Ramucirumab is a VEGFR2 inhibitor that has promising efficacy in different tumor types, including gastric or gastroesophageal junction adenocarcinoma,[9,10] metastatic urothelial carcinoma,[11] NSCLC,[12] metastatic colorectal cancer,[13] and hepatocellular carcinoma.[14]

Emerging data reveal that dual blockade of VEGFR2 with ramucirumab and PD-1 with pembrolizumab has antitumor activity as evidenced by the JVDF trial evaluating the safety and efficacy of ramucirumab plus pembrolizumab in locally advanced and unresectable or metastatic gastric or gastroesophageal junction adenocarcinoma, NSCLC, urothelial carcinoma, and biliary tract cancer.[15,16] Here, we report the first presentation of data from the JVDF trial of the first-line treatment with the combination of ramucirumab and pembrolizumab in patients with NSCLC (cohort E).

Materials and Methods

Study Design and Patients

The multicohort, nonrandomized, open-label, phase 1a/b JVDF trial was conducted at 16 academic medical centers, hospitals, and clinics in the United States, France, Germany, Spain, and the United Kingdom. This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice, and applicable local regulations. The protocol and informed consent forms were approved by ethical review boards at all participating centers. All patients provided written, informed consent and agreed to all study protocols and

testing before study entry. The JVDF trial is registered at ClinicalTrials.gov (NCT02443324).[3]

For cohort E, adults aged 18 years and older with treatment-naive, locally advanced unresectable or metastatic, NSCLC were enrolled. Eligible patients had tumor specimens available for PD-L1 expression analysis for central confirmation of PD-L1 tumor proportion score (TPS) greater than or equal to 1%. Other inclusion criteria were an Eastern Cooperative Oncology Group performance status of 0 or 1, measurable disease on the basis of the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1), and adequate organ function (hematological: absolute neutrophil count $\geq 1.5 \times 10^9$ cells/liter, platelets $\geq 100 \times 10^9$/liter, hemoglobin concentration ≥ 9 g/dL or ≥ 5.6 mmol/liter; renal: creatinine concentration ≤ 1.5 times the upper limit of normal [ULN] or creatinine clearance ≥ 60 mL/min; hepatic: total bilirubin concentration $\leq 1.5 \times$ ULN, aspartate aminotransferase and alanine aminotransferase concentration $\leq 2.5 \times$ ULN or $\leq 5 \times$ ULN for patients with liver metastases; coagulation: international normalized ratio $\leq 1.5 \times$ ULN or prothrombin time ≤ 5 seconds above the ULN; thyroid: thyroid-stimulating hormone within normal limits). Key exclusion criteria were previous systemic chemotherapy or radiation for NSCLC, known brain metastases, EGFR- or ALK-positive NSCLC, uncontrolled spinal cord compression, or leptomeningeal disease or a serious illness or medical condition, including, but not limited to, immunodeficiency, active autoimmune disease, pneumonitis, interstitial lung disease, hepatitis B or C virus infection, HIV, liver cirrhosis, or congestive heart failure.

Study Treatments and Procedures

The rationale for ramucirumab and pembrolizumab dosing was based on pharmacokinetic modeling and previous trial results in NSCLC.[15] On study entry, patients received ramucirumab 10 mg/kg intravenously plus pembrolizumab 200 mg intravenously on day 1 every 3 weeks. The treatment continued for up to 35 cycles or until disease progression, unacceptable toxicity, or discontinuation for any reason. Treatment discontinuation was defined as discontinuing both pembrolizumab and ramucirumab; treatment with either pembrolizumab or ramucirumab monotherapy was permitted. Ramucirumab dose reductions or delays were permitted for nonlife-threatening grade less than or equal to 3 adverse events (AEs) considered at least possibly related to study treatment. Grade 4 AEs generally resulted in discontinuation of ramucirumab. Pembrolizumab dose delays or discontinuation were allowed for drug-related and severe or life-threatening AEs; dose reductions of pembrolizumab were not permitted.

Tumor responses were assessed by means of computed tomography according to RECIST v1.1, with confirmation for partial responses (PRs) and complete responses (CRs) no less than 4 weeks from the time the first response was observed. Responses were assessed every 6 weeks ($\pm$7 d) for the first 24 weeks and then every 12 weeks ($\pm$7 d). Patients were treated until confirmed disease progression per RECIST v1.1 (by a second scan after $\geq$ 4 wk), unacceptable toxicity, or discontinuation for other reasons. After the discontinuation, the patients were followed up for survival approximately every 90 days for up to 2 years.

Safety was assessed and AEs were graded throughout the study and every 90 days during long-term follow-up. AEs were graded in severity according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.0 and judged by the investigator as related or unrelated to study treatment. AEs of special interest that could occur during treatment with ramucirumab (i.e., hypertension, proteinuria, thromboembolic events, bleeding/hemorrhage, gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome, congestive heart failure, fistula formation, impaired wound healing, and liver toxicity) were monitored. Immune-related AEs of special interest to pembrolizumab that could occur were monitored (e.g., pneumonitis, diarrhea or colitis, type 1 diabetes or hyperglycemia, hypophysitis, hyperthyroidism, hypothyroidism, liver toxicity, and renal failure or nephritis). Laboratory monitoring was done within 7 days before cycle 1 and within 3 days before each subsequent cycle.

The PD-L1 immunohistochemistry (IHC) for the JVDF trial was sponsored by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. (Kenilworth, NJ), and performed at Q2 Solutions using an investigational version of the 22C3 pharmDx assay (Agilent, Carpinteria, CA). Testing procedures have been previously described.[15] The number of stained tumor cells was scored relative to the total number of tumor cells (TPS). For patients with NSCLC in cohort E, the TPS was used to determine PD-L1 status defined as low PD-L1 expression (TPS of 1%–49%) or high PD-L1 expression (TPS $\geq$ 50%).

Outcomes

The primary study end point was safety and tolerability of the combination of ramucirumab and pembrolizumab. Key secondary end points were efficacy outcomes, including best objective response, ORR, disease control rate (defined as a best objective response of CR, PR, or stable disease [SD]), progression-free survival (PFS), and overall survival (OS) (censored on the last date the patient was known to be alive). The relationship between PD-L1

expression level at baseline and clinical outcomes (ORR, PFS, and OS) was an exploratory end point.

Statistical Analysis

Using an exact binomial test, a sample size of 25 to 30 patients was selected to allow for adequate assessment of safety and preliminary efficacy of ramucirumab and pembrolizumab at recommended doses. The null hypothesis was based on the assumption that the proportion of patients with an objective response was not greater than 30% to 35%, and the target treatment effect of the combination therapy on the ORR was greater than 45% to 55%. A sample size of 25 to 30 patients therefore provided approximately 65% to 90% power with a one-sided α level of 0.20. The safety and efficacy analysis populations comprised all patients who received at least one dose of the study treatment. 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.

Exploratory Analysis

An exploratory biomarker analysis using the NanoString nCounter PanCancer Immune Profiling Panel (NanoString Technologies, Inc., Seattle, WA) was conducted on RNA extracted from formalin-fixed, paraffin-embedded tumor tissue collected at baseline or within 3 months before enrollment. In this analysis, CD274 gene expression (which encodes for PD-L1) and gene expression signatures reflecting an inflamed or infiltrated tumor microenvironment were assessed for correlation with PD-L1 IHC status and objective response.

Gene Expression Analysis

NanoString Workflow. nCounter RNA count data (.RCC files) were normalized using the geometric mean of the positive controls and housekeeping genes using an in-house implementation of the NanoStringNorm R package.[17] The lower limit of detection for counts was set as the maximum count of the background (i.e., negative) controls. A total of 114 genes with normalized counts less than the lower limit of detection were flagged as low-expressing genes and removed from the downstream analyses; 616 genes passed quality control and were further investigated.

Gene Expression Signatures

Three gene expression signatures found to reflect an inflamed, immune-infiltrated tumor microenvironment were selected for in-depth analysis. These signatures have established prognostic utility for immunotherapy outcomes and largely cover different sets of genes (Supplementary Table 1). The T-cell–inflamed signature (TIS) of Gajewski contains chemokines (CCL2, -3, -4, -5) indicative of T-cell recruitment, including CXCL9 and CXCL10, which are associated with the trafficking of activated $CD8^+$ T cells into tumors.[18] The TIS of Ayers contains genes with diverse functions, such as major histocompatibility complex class I (HLA-E), major histocompatibility complex class II (HLA-DQA1), interferon production (STAT1), lymphocyte activation (LAG3), and checkpoints (IDO1, TIGIT), including the PD-L1 gene (CD274) and PD-L1 ligand 2 (PDCD1LG2).[19] A union set of T-effector signature genes with direct cytotoxic effector activity (GZMA, GZMB, PRF1)[20] and T-helper cell induction of interferon gamma expression (TBX21, INFG)[21] was also investigated. Patient signature scores were calculated by first z-scoring each signature gene, scaling across the 10 patients with NSCLC, and then obtaining the average of the z-scored genes comprising the signature for each patient sample. All the respective genes comprising the signatures, except one (HLA-DOA not covered on immune panel), were included in these calculations.

Results

Patients

As of data cutoff on April 21, 2019, 78 patients were screened, 51 patients were excluded (with the main reason being not meeting the inclusion criterion of PD-L1 $\geq$ 1%), 27 patients were enrolled, one patient withdrew from the study before receiving any study treatment, and 26 patients were treated (Supplementary Fig. 2). All safety and efficacy analyses are based on the treated patients (n = 26). At time of data cutoff, three patients remained on treatment; the main reasons for discontinuation of treatment were progressive disease (n = 10), AE (n = 4), and completing the maximum of 35 cycles of treatment (n = 4). Baseline characteristics for the treated population were as expected for first-line NSCLC (Table 1). Median patient age was 63 years (range: 42–85 y). Most patients had an Eastern Cooperative Oncology Group score of 1 (57.7%), were current or former tobacco users (92.3%), had adenocarcinoma of the lung (65.4%), and had metastatic disease (76.9%). A total of 16 patients (61.5%) had tumors with high PD-L1 expression (TPS $\geq$ 50%).

All the patients received one or more doses of ramucirumab and pembrolizumab. Median duration of treatment was 4.5 months for ramucirumab (interquartile range: 2.1–11.8 mo) and 8.4 months for pembrolizumab (interquartile range: 3.1–21.1 mo). Median duration of follow-up was 23.5 months (range: 3.2+ [censored observation] to 28.1 mo).

Table 1. Baseline Demographic and Disease Characteristics

Cohort E, N = 26	n (%)
Age, median (range), y	63 (42-85)
Sex	
Female	14 (53.8)
Male	12 (46.2)
Race	
White	22 (84.6)
Black	1 (3.8)
Not reported	3 (11.5)
ECOG PS	
0	11 (42.3)
1	15 (57.7)
PD-L1 TPS[a]	
≥ 50%	16 (61.5)
1%-49%	9 (34.6)
Negative[b]	1 (3.8)
Tobacco use	
Current	6 (23.1)
Former	18 (69.2)
Never	2 (7.7)
Histology	
Adenocarcinoma of lung	17 (65.4)
Large cell carcinoma	2 (7.7)
NSCLC, NOS	3 (11.5)
Squamous cell carcinoma of lung[c]	4 (15.4)
Disease stage	
Metastatic	20 (76.9)
Nonmetastatic	4 (15.4)
Not reported	2 (7.7)

[a]As determined by 22C3 assay.
[b]One patient with a PD-L1 expression level less than 1% was inadvertently enrolled.
[c]One designated by investigator as epidermoid lung carcinoma.
ECOG PS, Eastern Cooperative Oncology Group performance status; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; TPS, tumor proportion score.

Efficacy

At data cutoff, confirmed objective responses occurred in 11 patients (42.3%), with one CR and 10 PRs; 11 patients had SD (42.3%), three patients had progressive disease (11.5%), and one patient's response status was not assessable (3.8%; Table 2). The disease control rate, consisting of CRs, PRs, and SD, was 84.6%. The ORR was 56.3% for patients (nine of 16) with high PD-L1 expression (TPS ≥ 50%) and 22.2% for patients (two of nine) with lower levels of PD-L1 expression (TPS 1%–49%).

In the overall treated population, median PFS was 9.3 months, and the 12-month and 18-month PFS rates were 45% at both time points (Fig. 1*A*). Median PFS in patients whose tumors had high PD-L1 expression (TPS ≥ 50%) was not reached, whereas median PFS in patients with tumors that had lower levels of PD-L1 expression (TPS 1%–49%) was 4.2 months. Rates of PFS at 12-month and 18-month landmarks were greater in patients with high PD-L1 expression (56% for both) versus lower levels of PD-L1 expression (33% for both).

Median OS follow-up time was 23.5 months (95% confidence interval: 19.6–24.9) (patients were followed for a median of 21.2 and 24.8 mo for the PD-L1 high and low subgroups, respectively). In the overall treated population, median OS was not reached at data cutoff, and the 12-month and 18-month OS rates were 73% and 64%, respectively (Fig. 1*B*). Median OS was not reached, regardless of PD-L1 expression. Rates of OS at 12-month and 18-month landmarks were higher in patients with high PD-L1 expression (75% and 68%, respectively) versus lower levels of PD-L1 expression (67% and 53%, respectively).

Safety

Treatment-emergent AEs (TEAEs) of grade 3 or higher occurred in 18 patients (69.2%) (Table 3). Serious TEAEs were reported in 14 patients (53.8%), and three patients (11.5%) discontinued study treatment owing to TEAEs. One death related to a TEAE (grade 5) was observed during study treatment (related to treatment, as described subsequently).

Treatment-related AEs (TRAEs) of any grade occurred in 22 patients (84.6%). TRAEs of grade greater

Table 2. Response by RECIST v1.1

Response	PD-L1 TPS 1%-49% (n = 9)	PD-L1 TPS ≥ 50% (n = 16)	Total (N = 26)[a]
BOR, n (%; 95% CI)			
CR	0 (0; 0-33.6)	1 (6.3; 0.2-30.2)	1 (3.8; 0.1-19.6)
PR	2 (22.2; 2.8-60)	8 (50.0; 24.7-75.3)	10 (38.5; 20.2-59.4)
SD	6 (66.7; 29.9-92.5)	5 (31.3; 11-58.7)	11 (42.3; 23.4-63.1)
PD	1 (11.1; 0.3-48.2)	1 (6.3; 0.2-30.2)	3 (11.5; 2.4-30.2)
NA	0	1 (6.3)	1 (3.8)
ORR, % (95% CI)	2 (22.2; 2.8-60)	9 (56.3; 29.9-80.2)	11 (42.3; 23.4-63.1)
DCR,[b] % (95% CI)	8 (88.9; 51.8-99.7)	14 (87.5; 61.7-98.4)	22 (84.6; 65.1-95.6)

[a]Includes one PD-L1-negative patient (< 1%); this patient had a BOR of PD.
[b]DCR, proportion of patients with a BOR of CR, PR, or SD.
BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; NA, not assessable; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TPS, tumor proportion score.

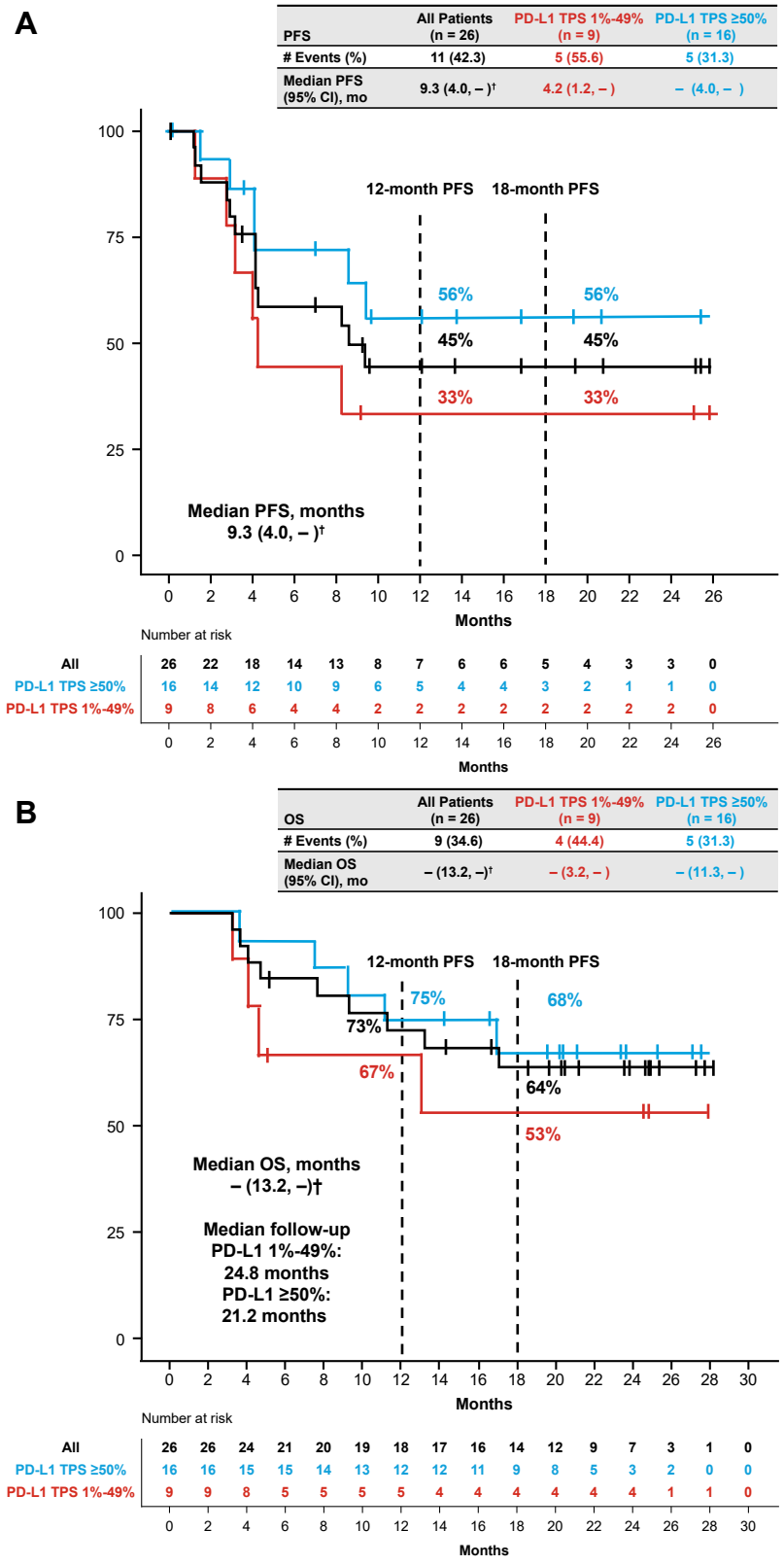


Figure 1. (*A*) PFS. (*B*) OS. †Data include the one PD-L1–negative patient. CI, confidence interval; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

Table 3. Overall Safety Summary

JVDF Cohort E (N = 26)	n (%)
Patients with ≥ 1 TEAE	26 (100.0)
Related to study treatment	22 (84.6)
Patients with grade ≥ 3 TEAE	18 (69.2)
Related to study treatment	11 (42.3)
Patients with ≥ 1 SAE	14 (53.8)
Related to study treatment	6 (23.1)
Patients who discontinued study treatment owing to AE	3 (11.5)
Related to study treatment	1 (3.8)
Patients who discontinued study treatment owing to SAE	2 (7.7)
Related to study treatment	1 (3.8)
Deaths related to AE (grade 5) on study treatment	1 (3.8)
Related to study treatment	1 (3.8)
Deaths related to AE (grade 5) within 30 d of discontinuation of study treatment	0
Related to study treatment	0

AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.

than or equal to 3 were reported in 11 patients (42.3%); the most frequent grade greater than or equal to 3 TRAE was hypertension (n = 4, 15.4%) (Table 4). Acute myocardial infarctions occurred in two patients (grades 3–4 [7.7%]). One patient died from congestive heart failure, judged to be possibly related to treatment. The trial was not designed to attribute AEs to individual study drugs.

Serious TRAEs occurred in six patients (23.1%): acute myocardial infarction (n = 2); congestive heart failure (n = 1); limbic encephalitis (n = 1); transient ischemic attack and pericardial effusion (n = 1); and chronic obstructive pulmonary disease, abdominal pain, and increased hepatic enzymes (n = 1). Deaths occurring on treatment or within 30 days of study treatment discontinuation owing to disease progression were reported for three of 26 patients (11.5%).

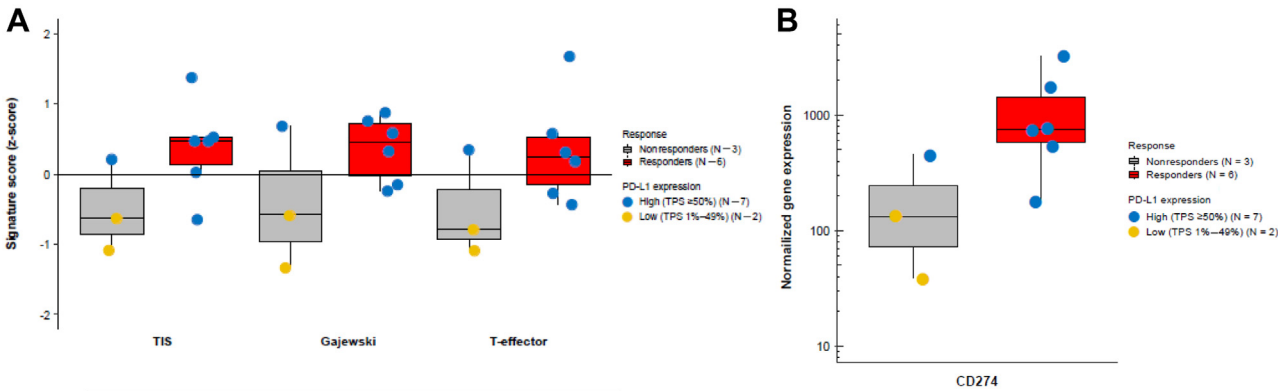
AEs of special interest for ramucirumab and pembrolizumab, based on the known safety profile of these agents, are reported in Supplementary Tables 3 and 4, respectively. TRAEs of special interest for ramucirumab occurred in 13 patients (50.0%), and eight patients (30.8%) had TRAEs of grade greater than or equal to 3. The most often reported grade greater than or equal to 3 TRAE was hypertension (n = 4, 15.4%).

Immune-related TEAEs (irTEAEs) for pembrolizumab were reported in 20 patients (76.9%), and three patients (11.5%) had grade 3 irTEAEs. No grade 4 or 5 irTEAEs were reported (Supplementary Table 4). Grade 3 increased γ-glutamyltransferase that occurred in one

Table 4. TRAEs

	Any Grade	Grade 3, 4, or 5
TRAEs[a]	n (%)	n (%)
Patients with ≥ 1 TRAE	22 (84.6)	11 (42.3)
Rash[b]	7 (26.9)	–
Hypertension	5 (19.2)	4 (15.4)
Fatigue	5 (19.2)	–
Pruritus[c]	4 (15.4)	1 (3.8)
Diarrhea	3 (11.5)	–
Nausea	3 (11.5)	–
Epistaxis	3 (11.5)	–
Dry skin	3 (11.5)	–
Infusion-related reaction	3 (11.5)	1 (3.8)
Acute myocardial infarction	–	2 (7.7)
Congestive heart failure	–	1 (3.8)[d]
Pericardial effusion	–	1 (3.8)
Abdominal pain	–	1 (3.8)
Stomatitis	–	1 (3.8)
Gamma-glutamyl transferase increased	–	1 (3.8)
Hepatic enzyme increased	–	1 (3.8)
Limbic encephalitis	–	1 (3.8)
Chronic obstructive pulmonary disease	–	1 (3.8)
Laryngeal inflammation	–	1 (3.8)
Embolism	–	1 (3.8)

Note: – indicates not applicable.
[a]TRAEs occurring at any grades in at least 10% of patients and at grades 3, 4, or 5 in one or more patients.
[b]Includes patients with rash, rash erythematous, and rash maculopapular.
[c]Includes patients with pruritus and pruritus generalized.
[d]Death related to AE (grade 5) on study treatment.
AE, adverse event; TRAE, treatment-related AE.



		TIS	Gajewski	T-effector
t test *p* value		0.134	0.319	0.185
Mean (SD)	Nonresponder	−0.50 (0.66)	−0.41 (1.02)	−0.51 (0.76)
	Responder	0.37 (0.67)	0.36 (0.47)	0.34 (0.75)
Median	Nonresponder	−0.63	−0.58	−0.79
	Responder	0.47	0.46	0.25

		CD274
t test *p* value		0.102
Mean (SD)	Nonresponder	209 (218)
	Responder	1200 (1127)
Median	Nonresponder	133
	Responder	749

Figure 2. T-cell signatures and CD274 gene expression correlate with BOR per RECIST v1.1. (*A*) TIS, Gajewski signature, and T-effector signatures. (*B*) CD274 gene expression. BOR, best overall response; PD-L1, programmed death-ligand 1; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; Sig, signature; TIS, T-cell-inflamed signature; TPS, tumor proportion score.

patient. Two patients had two grade 3 irTEAEs; one patient had infusion-related reaction and pruritus, and one patient had pancreatitis and hepatic enzyme increased.

Exploratory Biomarker Analysis

A total of 22 treated patients within the 27-patient cohort had tissue specimens submitted for NanoString analyses, of which nine specimens were assessable. Reasons for testing failure included insufficient tissue, neoplastic cells, or extracted RNA. High levels of three T-cell signatures (TIS, Gajewski, and effector T cells) and CD274 gene expression positively correlated with objective response (Fig. 2*A* and *B*). Each of these biomarkers was also positively correlated with high (TPS $\geq$ 50%) compared with low (TPS 1%–49%) PD-L1 expression (Supplementary Figs. 5 and 6).

Discussion

The primary end point of the JVDF trial, including cohort E in the first-line treatment of patients with NSCLC, was to evaluate the safety and tolerability of the combination of ramucirumab and pembrolizumab. A total of 26 patients with NSCLC in cohort E were treated. AE profiles were mostly consistent with those previously reported with ramucirumab[22] and pembrolizumab.[23,24] Although there are apparent numerical differences in the rate of infusion-related reactions between that reported in this and previous studies,[12] it is hard to draw conclusions owing to small sample size of JVDF cohort E.

Consistent with the literature, comparing the high PD-L1 to the low PD-L1 subgroups, higher ORR (56.3%, 22.2%) and longer median PFS (not reached, 4.2 mo) were observed in this study. There were few OS events at the time of data cutoff. Median OS was not reached in either subgroup (as of the data cutoff date, patients were followed for a median of 21.2 and 24.8 mo for the PD-L1 high and low subgroups, respectively).

There are no direct, head-to-head trials of pembrolizumab monotherapy versus the combination of ramucirumab and pembrolizumab in patients with NSCLC, or any tumor type. In KEYNOTE-042, pembrolizumab monotherapy resulted in a median OS of 20.0 months in patients with PD-L1 TPS greater than or equal to 50%.[25] The estimated percentage of patients alive at 24 months was 45% for patients with PD-L1 TPS greater than or equal to 50% and approximately 35% for patients with PD-L1 TPS 1% to 49%.[25] The combination of pembrolizumab and ramucirumab in the JVDF cohort E resulted in a median OS that was not reached in patients with high PD-L1 expression (TPS $\geq$ 50%) or lower levels of PD-L1 expression (TPS 1%–49%). The estimated percentage of patients alive at 24 months was 68% in PD-L1 TPS greater than or equal to 50% and 53% in PD-L1 TPS 1% to 49%. These observations, albeit indirect, suggest that the addition of ramucirumab to pembrolizumab may result in improved clinical outcomes in treatment-naive patients with NSCLC compared with pembrolizumab alone. Such inferences are speculative given the small sample size and single-arm design of the JVDF trial;

however, this is consistent with our hypothesis that VEGFR2 inhibitors such as ramucirumab may enhance the efficacy of a checkpoint inhibitor. In the context of novel immunotherapy combinations that do not involve chemotherapy in first-line PD-L1–positive (TPS $\geq$ 1%) NSCLC, the median PFS of 9.3 months for ramucirumab plus pembrolizumab appears encouraging, whereas median PFS of 5.1 months and 5.6 months was reported for ipilimumab plus nivolumab and tiragolumab plus atezolizumab, respectively,[26,27] although comparisons are limited across different study designs and by different PD-L1 assays determining positivity. The combination of ramucirumab to pembrolizumab in the treatment of NSCLC is being evaluated in other trials that are currently enrolling (NCT03971474 and NCT04040361).

PD-L1 is an established predictive biomarker for checkpoint inhibitor therapy in patients with NSCLC.[28] However, the requirement for sufficient amount of tumor tissue specimens for PD-L1 IHC remains a challenge. RNA analysis has a different tumor tissue requirement. In this small cohort of treatment-naive patients with NSCLC who were treated with the combination of ramucirumab and pembrolizumab, high levels of CD274 expression correlated with PD-L1 expression and clinical response. Specific T-cell profiles also positively correlated with clinical response. In a meta-analysis conducted by Lu et al.,[29] PD-L1 IHC was reported to be comparable with gene expression profiling in predicting response to checkpoint inhibitor therapy. Our findings are in agreement and suggest that T-cell signatures and CD274 expression are biomarker candidates that, in the future, may provide additional options to PD-L1 IHC to inform patient selection for immunotherapy, especially if technology for RNA analysis improves and results in a lower tumor tissue requirement. Additional studies are warranted.

First-line systemic therapy with the combination of ramucirumab and pembrolizumab has a manageable safety profile in patients with NSCLC, and the efficacy signal appears to be greater in tumors with high levels of PD-L1 expression. Results from JVDF cohort E, while preliminary and requiring validation in larger randomized comparative trials, suggest that the addition of ramucirumab to pembrolizumab in PD-L1–positive first-line NSCLC could be beneficial.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2020.10.004.

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