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Clinical Trial Results

Ramucirumab Plus Pembrolizumab in Patients with Previously Treated Advanced or Metastatic Biliary Tract Cancer: Nonrandomized, Open-Label, Phase I Trial (JVDF)

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Disclosures of potential conflicts of interest may be found at the end of this article.

Trial Information

- **ClinicalTrials.gov Identifier**: NCT02443324
- **Sponsors**: Eli Lilly and Company in collaboration with Merck & Co., Inc.
- **Principal Investigator**: Roy S. Herbst
- **IRB Approved:** Yes

Lessons Learned

- Ramucirumab plus pembrolizumab revealed no unexpected safety findings in patients with advanced or metastatic biliary tract cancer, which is consistent with reports of other tumor cohorts within this phase Ia/b trial.
- Ramucirumab plus pembrolizumab did not demonstrate an improvement in overall survival when compared with historical controls in biomarker unselected, heavily pretreated patients with advanced or metastatic biliary tract cancer.
- Patients with programmed death-ligand 1 (PD-L1)-positive tumors had improved overall survival compared with patients with PD-L1-negative disease.

Abstract

Background. Few treatment options exist for patients with advanced biliary tract cancer (BTC) following progression on gemcitabine-cisplatin. Preclinical evidence suggests that simultaneous blockade of vascular endothelial growth factor receptor 2 (VEGFR-2) and programmed death 1 (PD-1) or programmed death-ligand 1 (PD-L1) enhances antitumor effects. We assessed the safety and efficacy of ramucirumab, an IgG1 VEGFR-2 antagonist, with pembrolizumab, an IgG4 PD-1 antagonist, in biomarker-unselected patients with previously treated advanced or metastatic BTC.

Methods. Patients had previously treated advanced or metastatic adenocarcinoma of the gallbladder, intrahepatic and extrahepatic bile ducts, or ampulla of Vater. Ramucirumab 8 mg/kg was administered intravenously on days 1 and 8 with intravenous pembrolizumab 200 mg on day 1 every 3 weeks. The primary endpoint was safety and tolerability of the combination. Secondary endpoints included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS).

Results. Twenty-six patients were treated at 12 centers in five countries. Hypertension was the most common grade 3 treatment-related adverse event (TRAE), occurring in five patients. One patient experienced a grade 4 TRAE (neutropenia), and no treatment-related deaths occurred. Objective response rate was 4%. Median progression-free survival and overall survival were 1.6 months and 6.4 months, respectively.

Conclusion. Ramucirumab-pembrolizumab showed limited clinical activity with infrequent grade 3–4 TRAEs in patients with biomarker-unselected progressive BTC. ***The Oncologist*** 2018;23:1407–e136

Discussion

BTCs are highly aggressive with poor prognosis and few treatment options following progression on gemcitabine-cisplatin

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chemotherapy. Preclinical evidence suggests that simultaneous blockade of VEGFR-2 and PD-1 or PD-L1 induces additive antitumor effects [1–3]. This is the first study to combine an antiangiogenic agent (ramucirumab, an IgG1 VEGFR-2 antagonist) with an immune checkpoint inhibitor (pembrolizumab, an IgG4 PD-1 antagonist) to simultaneously target both processes in patients with previously treated advanced BTC.

Twenty-six patients received at least one dose of ramucirumab and pembrolizumab. Baseline demographics and characteristics were as expected for an advanced, previously treated population. The majority of patients had intrahepatic (42.3%) or extrahepatic (34.6%) cholangiocarcinoma. Median therapy duration was 9 weeks with ramucirumab and 9.3 weeks with pembrolizumab. Median follow-up duration was 15.7 (95% confidence interval [CI] 10.3–17.0) months.

TRAEs occurred in most patients and were predominantly of grade 1–2 severity. The most frequently reported TRAEs (any grade) were fatigue, hypertension, nausea, diarrhea, and hypothyroidism. Nine (34.6%) patients experienced a grade 3 TRAE. One patient experienced grade 4 treatment-related neutropenia. Serious adverse events (AEs) were reported for 15 (57.7%) patients; these were deemed related to treatment by the investigator in seven (26.9%) patients. One patient discontinued treatment due to treatment-related elevation of transaminases. There were no treatment-related deaths.

Reduction in tumor size from baseline in target lesions was observed in 9 (37.5%) of 24 patients; two patients were not evaluable due to no postbaseline tumor assessment (Fig. 1). One (3.8%) patient had a partial response, nine (34.6%) had stable disease, and 13 (50%) had progressive disease as their best response to treatment. Disease control occurred in 10 (38.5%) patients; median duration of stable disease was 3.9 months. Median PFS was 1.6 months. Median PFS in patients with PD-L1-positive ($n = 12$) and -negative ($n = 12$) tumors

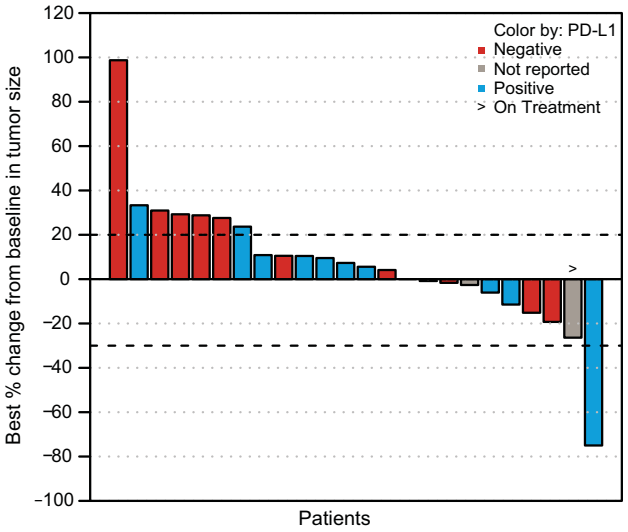

Figure 1. Maximum change in tumor size from baseline.
Abbreviation: PD-L1, programmed death-ligand 1.

was 1.5 months and 1.6 months, respectively. Limited analyses of efficacy by primary tumor site and line of therapy did not demonstrate any clear trends. Median OS was 6.4 months. Median OS in patients with PD-L1-positive and -negative tumors was 11.3 months and 6.1 months, respectively. One patient remained on treatment. Of the seven (26.9%) patients who received postdiscontinuation systemic anticancer therapy, six were PD-L1 positive and one was PD-L1 negative. Although the chemotherapy-free combination in our study reported a tolerable toxicity profile, ramucirumab plus pembrolizumab did not demonstrate an improvement in survival when compared with historical controls in biomarker-unselected, heavily pretreated patients with advanced or metastatic BTC.

Trial Information	
Disease	Biliary tract: gallbladder cancer and cholangiocarcinoma
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1–2 prior regimens
Type of Study - 1	Phase I
Primary Endpoint	Safety and tolerability
Secondary Endpoint	Progression-free survival, overall survival, objective response rate, disease control rate, duration of response, time to response, and pharmacokinetics of ramucirumab

Additional Details of Endpoints or Study Design
Phase I, multicohort, nonrandomized, open-label study. Patients ≥18 years of age were eligible for enrollment if they had histologically or cytologically confirmed biliary tract adenocarcinoma (gallbladder, intrahepatic and extrahepatic cholangiocarcinoma, or ampulla of Vater); unresectable, recurrent, or metastatic disease extent; and progression on 1–2 lines of prior chemotherapy or biological therapy. Prior therapy for advanced disease must have included gemcitabine and cisplatin. Prior therapy in an adjuvant or neoadjuvant setting was not considered a prior line of systemic chemotherapy, unless the patient had rapidly progressed, as defined by there having been ≤6 months since the last dose of chemotherapy. Furthermore, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, measurable disease (RECIST; version 1.1), adequate organ function, and baseline tumor tissue for biomarker analysis. PD-L1 expression was assessed using a provisional cutoff by immunohistochemistry with an investigational version of the PD-L1 IHC 22C3 pharmDx (Agilent, Carpinteria, CA). The "combined positive score" (CPS) is the number of staining tumor and immune cells relative to total tumor cells. PD-L1 status was classified by using CPS as positive (≥1%) or negative (<1%) for biliary tract cancer [4]. The trial adhered to the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulations. The protocol was approved by the ethics committees of all participating centers, and all patients provided written informed consent before study entry. Tumor response was assessed radiographically by the investigator at baseline, every 6 weeks (±7 days) after date of first study treatment for the first 24 weeks, and then every 12 weeks (±7 days) thereafter. Confirmation of partial or complete response was required at the next scheduled assessment, 6 weeks (±7 days) later. If radiographic assessment indicated progressive disease, a confirmatory assessment was required at least 4 weeks later; patients could continue receiving

study treatment during this period. Study treatment was to be discontinued if the repeat scan confirmed progression. Following discontinuation, patients were followed up for survival every 90 days. Safety was assessed and graded throughout the study and for 30 days after treatment discontinuation. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, and judged by the investigator to be related or nonrelated to study treatment. The study planned to enroll approximately 25–30 patients. The sample size was selected to allow adequate assessment of safety at the recommended doses for ramucirumab and pembrolizumab. The exact binomial test was used in the power analysis: Assuming a 10%–15% increase between the null and target response rate, and the target treatment effect on ORR is between 20% and 30%, a sample size of 25–30 will provide approximately 60%–80% power with a one-sided α level of 0.20. Data cutoff for the current analysis was February 1, 2018. Other disease cohorts from this same trial (NCT02443324) will be published separately.	
Investigator's Analysis	Manageable safety profile with limited clinical activity

Drug Information	
Drug 1	
Generic/Working Name	Ramucirumab
Trade Name	Cyramza
Company Name	Eli Lilly and Company
Drug Type	Antibody
Drug Class	Antiangiogenic: anti-VEGFR-2
Dose	8 mg/kg
Route	IV
Schedule of Administration	Ramucirumab days 1 and 8 every 3 weeks until disease progression or other discontinuation criteria met.
Drug 2	
Generic/Working Name	Pembrolizumab
Trade Name	Keytruda
Company Name	Merck and Co., Inc.
Drug Type	Antibody
Drug Class	Immunotherapy: anti-PD-1
Dose	200 mg per flat dose
Route	IV
Schedule of Administration	Pembrolizumab day 1 every 3 weeks until disease progression or other discontinuation criteria met.

Patient Characteristics for Phase I Experimental	
Number of Patients, Male	8
Number of Patients, Female	18
Stage	Nonresectable, recurrent, or metastatic
Age	Median (range): 63 (36–78)
Number of Prior Systemic Therapies	Median (range): 1 (1–3)
Performance Status: ECOG	0 — 12 1 — 14
Other	Complete baseline demographic and disease characteristics are presented in Table 1

Primary Assessment Method	
Title	Total patient population
Number of Patients Screened	33
Number of Patients Enrolled	26
Number of Patients Evaluable for Toxicity	26
Number of Patients Evaluated for Efficacy	26
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 1$ (4%)
Response Assessment SD	$n = 9$ (35%)
Response Assessment PD	$n = 13$ (50%)

Response Assessment OTHER	$n = 3$ (12%)
(Median) Duration Assessments PFS	1.64 months, CI: 1.38–2.76
(Median) Duration Assessments OS	6.44 months, CI: 4.17–13.27
(Median) Duration Assessments Response Duration	6 months
Outcome Notes	Further graphical details on maximum change in tumor size over time, duration of treatment, and efficacy results by PD-L1 status are presented in the extended discussion.

Adverse Events

Adverse events	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Fatigue[a]	3 (11.5)	6 (23.1)	0	—	—	9 (34.6)
Hypertension	0	3 (11.5)	5 (19.2)	0	0	8 (30.8)
Nausea	7 (26.9)	0	0	—	—	7 (26.9)
Diarrhea	4 (15.4)	1 (3.8)	0	0	0	5 (19.2)
Hypothyroidism	1 (3.8)	3 (11.5)	0	0	0	4 (15.4)
Decreased appetite	2 (7.7)	1 (3.8)	0	0	0	3 (11.5)
Epistaxis	3 (11.5)	0	0	0	0	3 (11.5)
Infusion-related reaction	1 (3.8)	2 (7.7)	0	0	0	3 (11.5)
Pyrexia	3 (11.5)	0	0	0	0	3 (11.5)
Stomatitis	2 (7.7)	1 (3.8)	0	0	0	3 (11.5)
Rash[b]	3 (11.5)	0	0	0	0	3 (11.5)
Alanine aminotransferase increased	0	1 (3.8)	1 (3.8)	0	—	2 (7.7)
Aspartate aminotransferase increased	1 (3.8)	0	1 (3.8)	0	—	2 (7.7)
Peripheral edema	2 (7.7)	0	0	—	—	2 (7.7)
Gingival bleeding	2 (7.7)	0	0	—	—	2 (7.7)
Pruritus	1 (3.8)	1 (3.8)	0	—	—	2 (7.7)
Vomiting	2 (7.7)	0	0	0	0	2 (7.7)

Data are *n* (%). The table shows treatment-related adverse events occurring in at least two patients, according to preferred term or consolidated category.
[a]Consolidated category (fatigue and asthenia).
[b]Consolidated category (rash and maculopapular rash).
Abbreviation: —, indicates a grade is not available per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Serious Adverse Events

Name	Grade	Attribution
Colitis	3	Possible
Duodenal ulcer	3	Possible
Gastrointestinal inflammation	3	Possible
Hepatocellular injury	3	Possible
Hypertension	3	Possible
Hypophysitis	3	Possible
Liver abscess	3	Possible
Transaminases increased	3	Possible

Assessment, Analysis, and Discussion

Completion	Study completed; one patient remains on study treatment.
Investigator's Assessment	Manageable safety profile with limited clinical activity

Biliary tract cancer (BTC) arises from the epithelial lining of the gallbladder, intrahepatic and extrahepatic bile ducts, and ampulla of Vater. There are more than 186,000 new cases of BTC diagnosed worldwide each year [5]. The incidence of BTC is increasing in the U.S. and some European countries, largely due to an increase in diagnosis of intrahepatic cholangiocarcinoma [6, 7]. Lymph node involvement and distance metastases are early characteristics of BTC, preventing up to 90% of patients from receiving curative intent surgery [8].

Gemcitabine in combination with cisplatin is standard first-line palliative treatment for advanced BTC, with a median overall survival (OS) of 11.2–11.7 months [9, 10]. There is no established standard of care following progression on gemcitabine-cisplatin, and chemotherapeutic agents have modest activity in this setting. A recent systematic review that included 14 phase II trials indicated an objective response rate of 7.7%, mean progression-free survival (PFS) of 3.2 months, and mean OS of 7.2 months with second-line therapy [11]. Outcomes are suboptimal, and a substantial unmet need persists to improve outcomes for patients with advanced BTC.

Antiangiogenic therapies have several noted immunostimulatory effects including increased trafficking of T cells into tumors as well as reduction of immunosuppressive cytokines and T regulatory cells, suggesting antiangiogenic therapies may complement subsequent or concurrent immunostimulatory therapies [1, 2, 12–15]. Despite reports of vascular endothelial growth factor and programmed death-ligand 1 (PD-L1) expression in a subset of patients with advanced BTC, there have been no published clinical studies combining an antiangiogenic agent with an immune checkpoint inhibitor in this patient population [16–22]. Herein we report the combination of ramucirumab plus pembrolizumab in 26 patients revealed no unexpected safety findings, which is consistent with reports of other tumor cohorts within this trial (Fig. 2) [23–25]. The most common toxic effects were of grade 1–2 severity and were manageable with supportive care alone or with dose reductions or delays, without substantial reduction in the planned dose intensity for either study drug (Table 2). Grade 3 treatment-related adverse events, most commonly hypertension, were experienced by 9 (34.6%) of 26 patients.

PD-L1 expression on tumor and immune cells has been associated with increased clinical benefit from programmed death 1 (PD-1)- and PD-L1-targeted therapies in various tumor types [26, 27]. PD-1 and PD-L1 expression is upregulated in intrahepatic cholangiocarcinoma tumor tissues and was associated with both poor differentiation and stage, whereas increased $CD8^+$ T cells in tumors was associated with better tumor differentiation [28, 29]. Bang et al. enrolled only PD-L1-positive advanced BTC patients in the KEYNOTE-028 study and reported that 4 (17%) of 23 evaluable patients responded to pembrolizumab monotherapy [30]. We did not restrict enrollment based on PD-L1 status, and less than half (46.2%) of patients had tumors that scored positive for PD-L1 expression, as defined by a combined positive score of ≥1% (Table 1). The only patient with an objective response in our study had extrahepatic cholangiocarcinoma that was positive for PD-L1, a time to response of 2.7 months, and a total duration of response of 6.0 months (Table 3). Acknowledging limitations of cross-trial comparison and sample size, baseline characteristics and demographics were similar between both studies with the exception of PD-L1 status and ethnicity, with white as the majority in our study compared with Asian as the majority in the KEYNOTE-028 study (Table 1) [30]. At this time, it is unclear if differences in outcome and toxicity exist between Asian and white patients treated with an immune checkpoint inhibitor. A subset of patients in both studies had prolonged periods of disease stability (three patients in our study on treatment ≥38 weeks; Fig. 3A, 3B), highlighting the need to identify biomarkers that predict clinical efficacy of pembrolizumab and ramucirumab in advanced biliary tract cancers. Although no difference in median PFS was observed by PD-L1 status (Fig. 5A), patients whose tumors were PD-L1 positive had improved OS compared with those whose tumors were PD-L1 negative in our study (Fig. 5B). The survival signal in PD-L1-positive patients is interesting, but we are limited by sample size and have no historical reference for the natural history of patients with PD-L1 positivity relative to the wider population, and it may represent selection bias. Consistent with improved survival in PD-L1-positive patients, six of the seven patients who received postdiscontinuation systemic anticancer therapy were positive for PD-L1 (Table 4).

In addition to PD-L1 expression, high microsatellite instability (MSI-H) has been reported to correlate with the clinical activity of PD-1 and PD-L1 inhibitors in multiple tumor types [31–33]. The incidence of MSI-H in biliary tract cancer has not been comprehensively studied but is reported to be infrequent, occurring in approximately 5% or lower each for gallbladder carcinoma and extrahepatic cholangiocarcinoma and 10% or lower each for intrahepatic cholangiocarcinoma and ampullary carcinoma [34, 35]. In the limited number of samples tested for MSI in our study, including the patient with an objective response, we did not observe any patients with MSI-H. The MSI status has not been reported for KEYNOTE-028.

In summary, ramucirumab plus pembrolizumab did not demonstrate an improvement in survival when compared with historical controls in biomarker-unselected, heavily pretreated patients with advanced or metastatic BTC (Table 5; Fig. 4). However, median OS in patients with PD-L1-positive tumors is interesting, and additional biomarker data will guide the future development of this combination. Ramucirumab is concurrently being investigated in the phase II setting for advanced or metastatic BTC in combination with gemcitabine-cisplatin for first-line treatment (NCT02711553) and as monotherapy in patients previously treated with a gemcitabine-based regimen (NCT02520141) [36].

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Disclosures

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Figures and Tables

Table 1. Baseline demographics and characteristics

Baseline demographics and characteristics	Ramucirumab + pembrolizumab, *n* = 26
Median age, years (range)	63 (36–78)
≤65 years	16 (61.5)
Sex	
Female	18 (69.2)
Male	8 (30.8)
Ethnic origin	
White	23 (88.5)
American Indian or Alaska native	1 (3.8)
Missing	2 (7.7)
ECOG performance status	
0	12 (46.2)
1	14 (53.8)
Tobacco use	
Former	11 (42.3)
Never	15 (57.7)
PD-L1 Status	
Positive (combined positive score ≥1%)	12 (46.2)
Negative (combined positive score <1%)	12 (46.2)
Not reported	2 (7.7)
Site of primary tumor	
Intrahepatic cholangiocarcinoma	11 (42.3)
Extrahepatic cholangiocarcinoma	9 (34.6)
Gallbladder	4 (15.4)
Ampulla of Vater	1 (3.8)
Metastatic cholangiocarcinoma (NOS)	1 (3.8)
Histopathological grade	
Well differentiated (low grade)	3 (11.5)
Moderately differentiated (intermediate grade)	10 (38.5)
Poorly differentiated (high grade)	4 (15.4)
Unable to determine	8 (30.8)
Not reported	1 (3.8)
Prior systemic therapies[a]	26 (100)
1 prior line	15 (57.7)
2 prior lines	10 (38.5)
3 prior lines	1 (3.8)
Prior gemcitabine-cisplatin	24 (92.3)
Prior gemcitabine-carboplatin	1 (3.8)
Prior gemcitabine-oxaliplatin	1 (3.8)

Data are *n* (%) unless otherwise indicated.
[a]A detailed summary of prior anticancer therapies is included in Table 5.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified; PD-L1, programmed death-ligand 1.

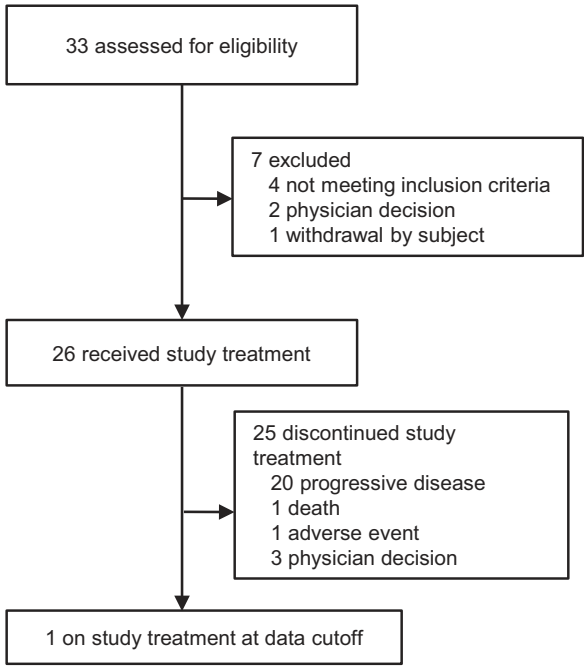

Figure 2. Consolidated Standards of Reporting Trials diagram.

Table 2. Treatment duration

	Ramucirumab + pembrolizumab
Ramucirumab	
Number of patients	26
Median duration of therapy, weeks (IQR)	9 (6–16.6)
Median number of cycles (IQR)	3 (2–5)
Median relative dose intensity, % (IQR)	88.2 (76.2–99.4)
Pembrolizumab	
Number of patients	26
Median duration of therapy, weeks (IQR)	9.3 (6–18)
Median number of cycles (IQR)	3 (2–6)
Median relative dose intensity, % (IQR)	100 (92.3–100)

Abbreviation: IQR, interquartile range.

Table 3. Confirmed efficacy results per RECIST v1.1

	Ramucirumab + pembrolizumab, *n* = 26
Best overall response, *n* (%)	
Complete response	0
Partial response	1 (3.8)
Stable disease	9 (34.6)
Progressive disease	13 (50)
Not evaluable	3 (11.5)
Objective response rate, % (95% CI)	3.8 (0.1–19.6)
Disease control rate, % (95% CI)	38.5 (20.2–59.4)
Time to response, months	2.7
Duration of response, months	6.0
Median duration of stable disease, months (95% CI)	3.9 (2.2–9.8)
Progression-free survival	
Events, *n* (%)	22 (84.6)
Median, months (95% CI)	1.64 (1.38–2.76)
3-month rate, % (95% CI)	27.0 (11.1–45.8)
6-month rate, % (95% CI)	18.0 (5.7–35.9)
Overall survival	
Deaths, *n* (%)	17 (65.4)
Median, months (95% CI)	6.44 (4.17–13.27)
6-month rate, % (95% CI)	61.8 (37.8–78.8)
12-month rate, % (95% CI)	30.0 (11.9–50.7)

Abbreviations: CI, confidence interval; NR, not reported.

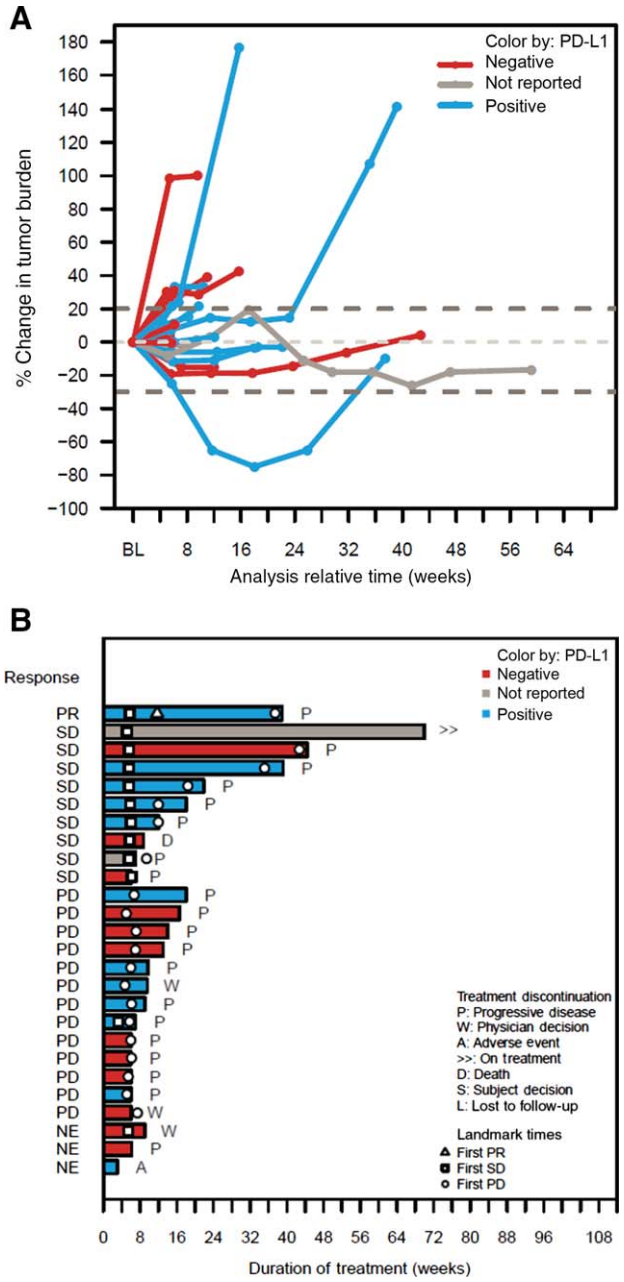

Figure 3. Tumor response assessment per RECIST v1.1 by investigator review. **(A)**: Change in tumor size over time. **(B)**: Treatment duration and response.

Abbreviations: CR, complete response; NE, not evaluable; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease.

Table 4. Poststudy systemic anticancer therapy

Therapy	**Ramucirumab + pembrolizumab, *n* = 26**
Any, *n* (%)	7 (26.9)
Fluorouracil/leucovorin/oxaliplatin	2 (8)
Fluorouracil/oxaliplatin	1 (4)
Dasatinib	1 (4)
Cisplatin	1 (4)
Gemcitabine/cisplatin	1 (4)
Oxaliplatin/capcitabine	1 (4)

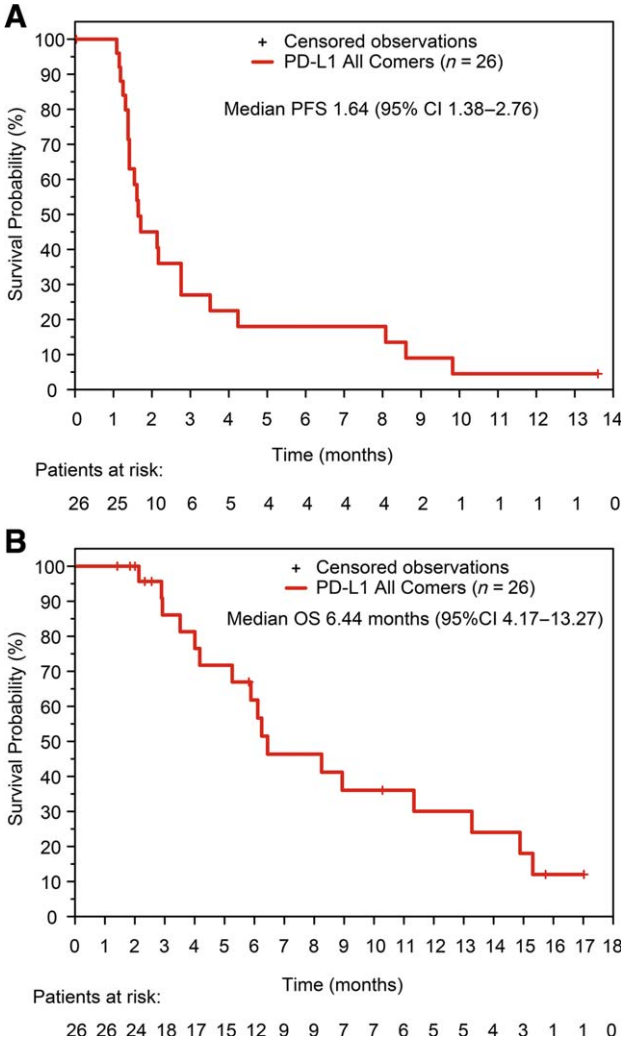

Figure 4. Kaplan-Meier plot. **(A)**: Progression-free survival. **(B)**: Overall survival.

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival.

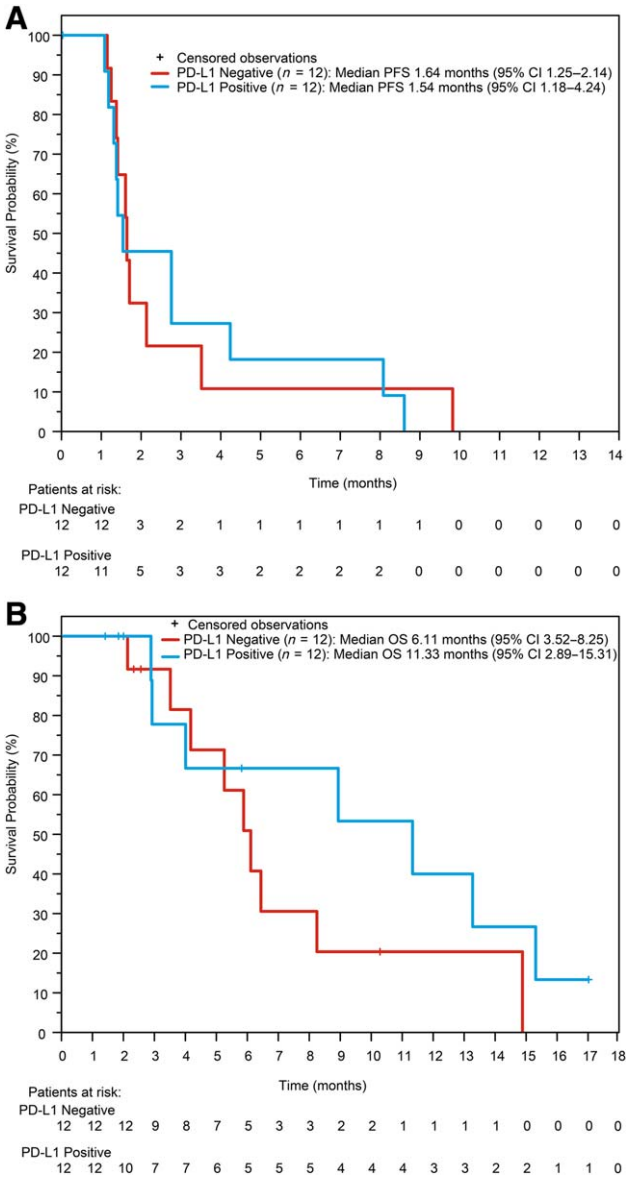

Figure 5. Kaplan-Meier plot. Progression-free survival **(A)** and overall survival **(B)** by PD-L1 status.

Abbreviations: CI, confidence interval; PD-L1, programmed death-ligand 1.

Table 5. Prior systemic anticancer therapy[a]

Therapy	Ramucirumab + pembrolizumab, *n* = 26
Gemcitabine	26 (100)
Cisplatin	24 (92.3)
Oxaliplatin	8 (30.8)
Fluorouracil	6 (23.1)
Folinic acid	6 (23.1)
Capecitabine	3 (11.5)
Carboplatin	2 (7.7)
Irinotecan	1 (3.8)
Investigational antineoplastic drugs	2 (7.7)
IDH inhibitor (IDH305)	1 (3.8)
Lurbinectedin (PM1183)	1 (3.8)

Data are *n* (%).
[a]Patients may have received more than one type of therapy.
Abbreviation: IDH, isocitrate dehydrogenase.