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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Clinical Trial Results

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, and pembrolizumab, an IgG4 PD-1 antagonist, in biomarker-unselected, heavily pretreated patients with advanced or metastatic biliary tract cancer.

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 6.4 months and 16.6 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...
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 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.

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

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**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.

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**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.

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**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

| (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         | 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            | 3 (11.5) | 0       | 0       | 0       | 0       | 3 (11.5) |
| Alanine aminotransferase increased | 0 | 1 (3.8)  | 1 (3.8) | 0 | — | 3 (11.5) |
| 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.

*Consolidated category (fatigue and asthenia).

bConsolidated 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 increased 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 pre-treated 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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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<sup>a</sup>      | 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.

<sup>a</sup>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.

33 assessed for eligibility
7 excluded
4 not meeting inclusion criteria
2 physician decision
1 withdrawal by subject

26 received study treatment
25 discontinued study treatment
20 progressive disease
1 death
1 adverse event
3 physician decision

1 on study treatment at data cutoff

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.

**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

| 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 (%).
*Patients may have received more than one type of therapy.
Abbreviation: IDH, isocitrate dehydrogenase.