Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

The Oncologist®

Clinical Trial Results

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

Hendrik-Tobias Arkenau,[a,b] Juan Martin-Liberal,[c,d] Emiliano Calvo,[e] Nicolas Penel,[f] Matthew G. Krebs,[g] Roy S. Herbst,[h] Richard A. Walgren,[i] Ryan C. Widau,[i] Gu Mi,[i] Jin Jin,[j] David Ferry,[j] Ian Chau[k]

[a]Drug Development Unit, Sarah Cannon Research Institute UK, London, United Kingdom; [b]Cancer Institute, University College London, London, United Kingdom; [c]Vall d'Hebron Institute of Oncology, Barcelona, Spain; [d]Catalan Institute of Oncology (ICO), Barcelona, Spain; [e]Early Clinical Drug Development Program, START Madrid-HM CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; [f]Centre Oscar Lambret, Lille, France; [g]The Christie NHS Foundation Trust and The University of Manchester, Manchester, United Kingdom; [h]Yale University School of Medicine, Yale Cancer Center, New Haven, Connecticut, USA; [i]Eli Lilly and Company, Indianapolis, Indiana, USA; [j]Eli Lilly and Company, New York, New York, USA; [k]Royal Marsden Hospital, Sutton, United Kingdom

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;23:1–10

Discussion

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

Correspondence: Hendrik-Tobias Arkenau, M.D., Ph.D., Drug Development Unit, Sarah Cannon Research Institute, 93 Harley St., London, England W1G6AD, United Kingdom. Telephone: 020-3219-5200; e-mail: tobias.arkenau@hcahealthcare.co.uk Received April 6, 2018; accepted for publication May 14, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0044

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

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

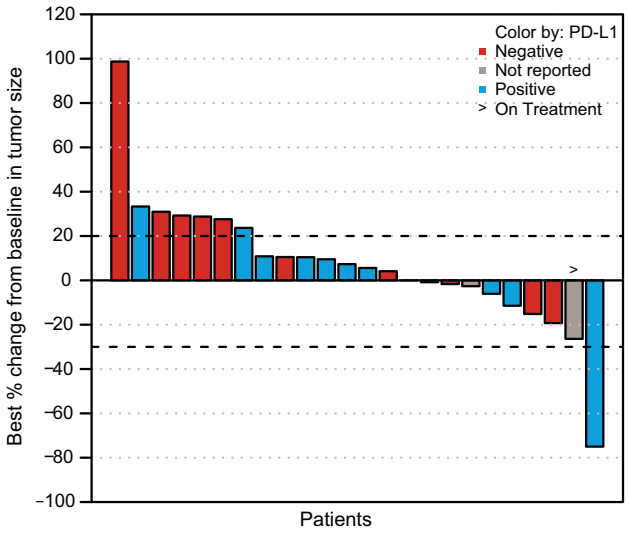

Figure 1. Maximum change in tumor size from baseline.
Abbreviation: PD-L1, programmed death-ligand 1.

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

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

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%)

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

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

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

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 $\geq$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 $\geq$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].

Acknowledgments

This study was sponsored by Eli Lilly and Company, in collaboration with Merck & Co., Inc. We thank the patients, their families, and the study personnel across all sites for participating in this study. Writing assistance was provided by Eli Lilly and Company. Editorial assistance was funded by Eli Lilly and Company and provided by Teri Tucker (Syneos Health, Raleigh, NC).

Disclosures

Roy S. Herbst: Merck, Eli Lilly & Co. (RF, H); **Richard A Walgren**: Eli Lilly & Co. (E, OI); Ryan C Widau: Eli Lilly & Co. (E, OI); **Gu Mi**: Eli Lilly & Co. (E, OI); **Jin Jin**: Eli Lilly & Co. (E, OI); **David Ferry**: Eli Lilly & Co. (E, OI); **Ian Chau**: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, MSD, Bayer, Merck-Serono, Roche, Five Prime Therapeutics (C/A), Janssen-Cilag, Sanofi Oncology, Merck-Serono (RF), Taiho, Pfizer, Amgen, Eli-Lilly (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

References

1. Motz GT, Coukos G. The parallel lives of angiogenesis and immunosuppression: Cancer and other tales. Nat Rev Immunol 2011;11:702–711.

2. Huang Y, Chen X, Dikov MM et al. Distinct roles of VEGFR-1 and VEGFR-2 in the aberrant hematopoiesis associated with elevated levels of VEGF. Blood 2007;110:624–631.

3. Schaer D. The effect of VEGFR-2 inhibition on tumor blood vessels and immune landscape: Keystone Symposia. #2015. 2017; Keystone, CO.

4. Kulangara K, Hanks DA, Waldroup S et al. Development of the combined positive score (CPS) for the evaluation of PD-L1 in solid tumors with the immunohistochemistry assay PD-L1 IHC 22C3 pharmDx. J Clin Oncol 2017;35:e14589–e14589.

5. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Dicker D et al. The global burden of cancer 2013. JAMA Oncol 2015;1:505–527.

6. Saha SK, Zhu AX, Fuchs CS et al. Forty-year trends in cholangiocarcinoma incidence in the U.S.: Intrahepatic disease on the rise. ***The Oncologist*** 2016;21:594–599.

7. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet 2014;383:2168–2179.

8. Zhu AX, Hezel AF. Development of molecularly targeted therapies in biliary tract cancers: Reassessing the challenges and opportunities. Hepatology 2011;53:695–704.

9. Okusaka T, Nakachi K, Fukutomi A et al. Gemcitabine alone or in combination with cisplatin in patients with biliary tract cancer: A comparative multicentre study in Japan. Br J Cancer 2010;103:469–474.

10. Valle J, Wasan H, Palmer DH et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362:1273–1281.

11. Lamarca A, Hubner RA, David Ryder W et al. Second-line chemotherapy in advanced biliary cancer: A systematic review. Ann Oncol 2014;25:2328–2338.

12. Finke JH, Rini B, Ireland J et al. Sunitinib reverses type-1 immune suppression and decreases T-regulatory cells in renal cell carcinoma patients. Clin Cancer Res 2008;14:6674–6682.

13. Motz GT, Santoro SP, Wang LP et al. Tumor endothelium FasL establishes a selective immune barrier promoting tolerance in tumors. Nat Med 2014;20:607–615.

14. Terme M, Pernot S, Marcheteau E et al. VEGFA-VEGFR pathway blockade inhibits tumor-induced regulatory T-cell proliferation in colorectal cancer. Cancer Res 2013;73:539–549.

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

16. Mobius C, Demuth C, Aigner T et al. Evaluation of VEGF A expression and microvascular density as prognostic factors in extrahepatic cholangiocarcinoma. Eur J Surg Oncol 2007;33:1025–1029.

17. Park BK, Paik YH, Park JY et al. The clinicopathologic significance of the expression of vascular endothelial growth factor-C in intrahepatic cholangiocarcinoma. Am J Clin Oncol 2006;29:138–142.

18. Giatromanolaki A, Koukourakis MI, Simopoulos C et al. Vascular endothelial growth factor (VEGF) expression in operable gallbladder carcinomas. Eur J Surg Oncol 2003;29:879–883.

19. Yoshikawa D, Ojima H, Iwasaki M et al. Clinicopathological and prognostic significance of EGFR, VEGF, and HER2 expression in cholangiocarcinoma. Br J Cancer 2008;98:418–425.

20. Valle JW, Wasan H, Lopes A et al. Cediranib or placebo in combination with cisplatin and gemcitabine chemotherapy for patients with advanced biliary tract cancer (ABC-03): A randomised phase 2 trial. Lancet Oncol 2015;16:967–978.

21. Zhu AX, Meyerhardt JA, Blaszkowsky LS et al. Efficacy and safety of gemcitabine, oxaliplatin, and bevacizumab in advanced biliary-tract cancers and correlation of changes in 18-fluorodeoxyglucose PET with clinical outcome: A phase 2 study. Lancet Oncol 2010;11:48–54.

22. Lubner SJ, Mahoney MR, Kolesar JL et al. Report of a multicenter phase II trial testing a combination of biweekly bevacizumab and daily erlotinib in patients with unresectable biliary cancer: A phase II consortium study. J Clin Oncol 2010;28:3491–3497.

23. Herbst RS, Martin-Liberal J, Calvo E et al. 90PDPreviously treated advanced NSCLC cohort from a multi-disease phase 1 study of ramucirumab (R) plus pembrolizumab (P): Efficacy and safety data. Ann Oncol 2017;28:mdx091.010.

24. Petrylak DP, Arkenau HT, Perez-Gracia JL et al. A multicohort phase I study of ramucirumab (R) plus pembrolizumab (P): Interim safety and clinical activity in patients with urothelial carcinoma. J Clin Oncol 2017;35(suppl 6):349.

25. Chau I, Bendell JC, Calvo E et al. Interim safety and clinical activity in patients (pts) with advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma from a multicohort phase 1 study of ramucirumab (R) plus pembrolizumab (P). J Clin Oncol 2017;35(suppl 4):102.

26. Topalian SL, Hodi FS, Brahmer JR et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443–2454.

27. Herbst RS, Soria JC, Kowanetz M et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature 2014;515:563–567.

28. Ye Y, Zhou L, Xie X et al. Interaction of B7-H1 on intrahepatic cholangiocarcinoma cells with PD-1 on tumor-infiltrating T cells as a mechanism of immune evasion. J Surg Oncol 2009;100:500–504.

29. Chau I. Clinical development of PD-1/PD-L1 immunotherapy for gastrointestinal cancers: Facts and hopes. Clin Cancer Res 2017;23:6002–6011.

30. Bang YJ, Doi T, Braud FD et al. 525 Safety and efficacy of pembrolizumab (MK-3475) in patients (pts) with advanced biliary tract cancer: Interim results of KEYNOTE-028. Eur J Cancer 2015;51:S112.

31. Czink E, Kloor M, Goeppert B et al. Successful immune checkpoint blockade in a patient with advanced stage microsatellite-unstable biliary tract cancer. Cold Spring Harb Mol Case Stud 2017;3.

32. Rizvi NA, Hellmann MD, Snyder A et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124–128.

33. Le DT, Uram JN, Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–2520.

34. Silva VW, Askan G, Daniel TD et al. Biliary carcinomas: Pathology and the role of DNA mismatch repair deficiency. Chin Clin Oncol 2016;5:62.

35. Bonneville R, Krook MA, Kautto EA et al. Landscape of microsatellite instability across 39 cancer types. JCO Precis Oncol 2017:1–15.

36. Valle JW, Bousmans N, Zhang W et al. Cisplatin and gemcitabine plus ramucirumab or merestinib or placebo in first-line treatment for advanced or metastatic biliary tract cancer: A double-blind, randomized phase 2 trial. Ann Oncol 2016;27:712TiP.

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

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.

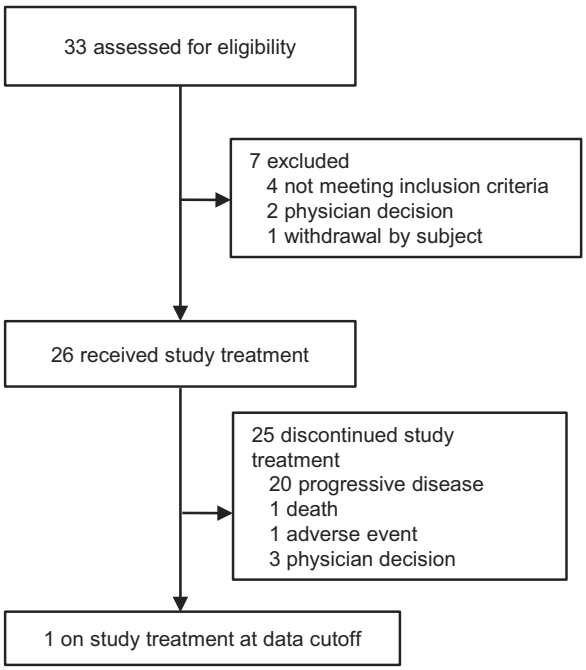

Figure 2. Consolidated Standards of Reporting Trials diagram.

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.

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

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.

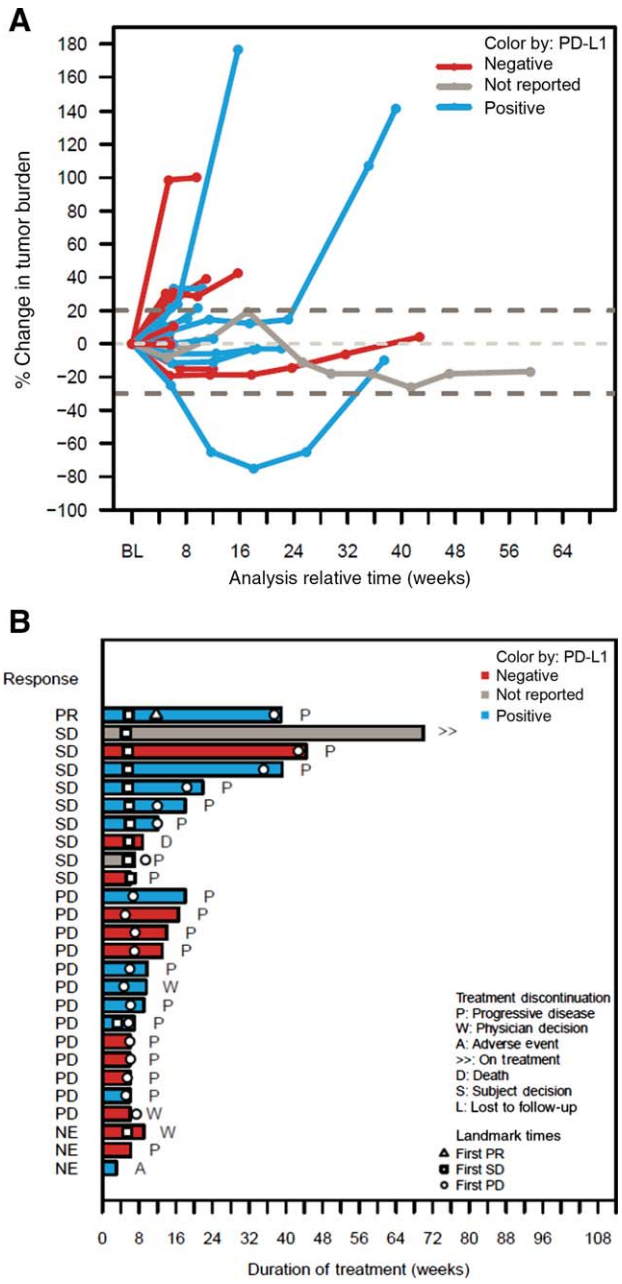

Figure 3. Tumor response assessment per RECIST v1.1 by investigator review. **(A)**: Change in tumor size over time. **(B)**: Treatment duration and response.

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)

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

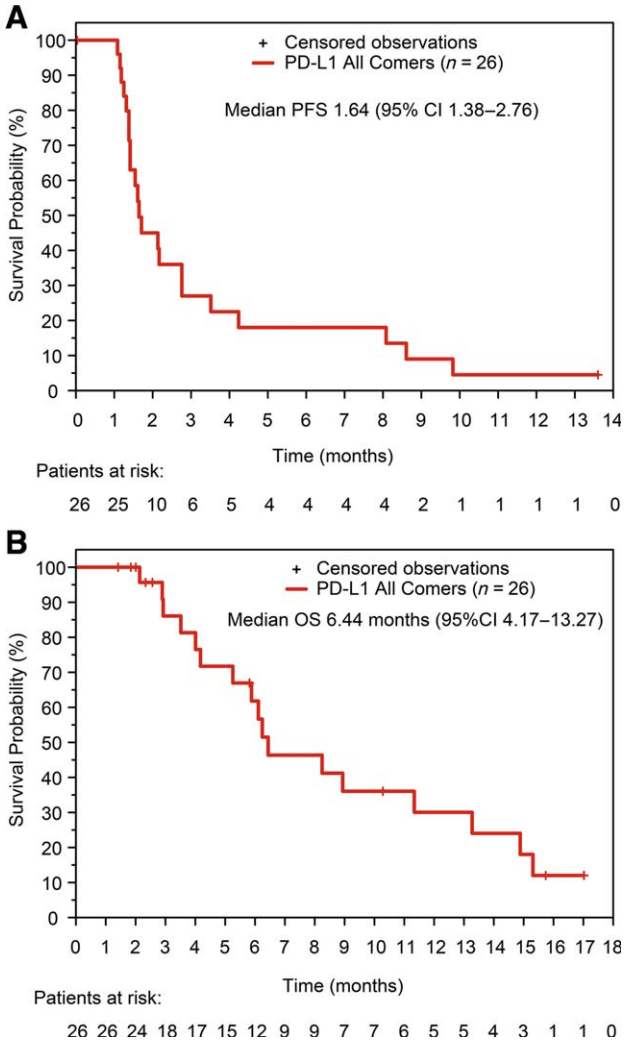

Figure 4. Kaplan-Meier plot. **(A)**: Progression-free survival. **(B)**: Overall survival.

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

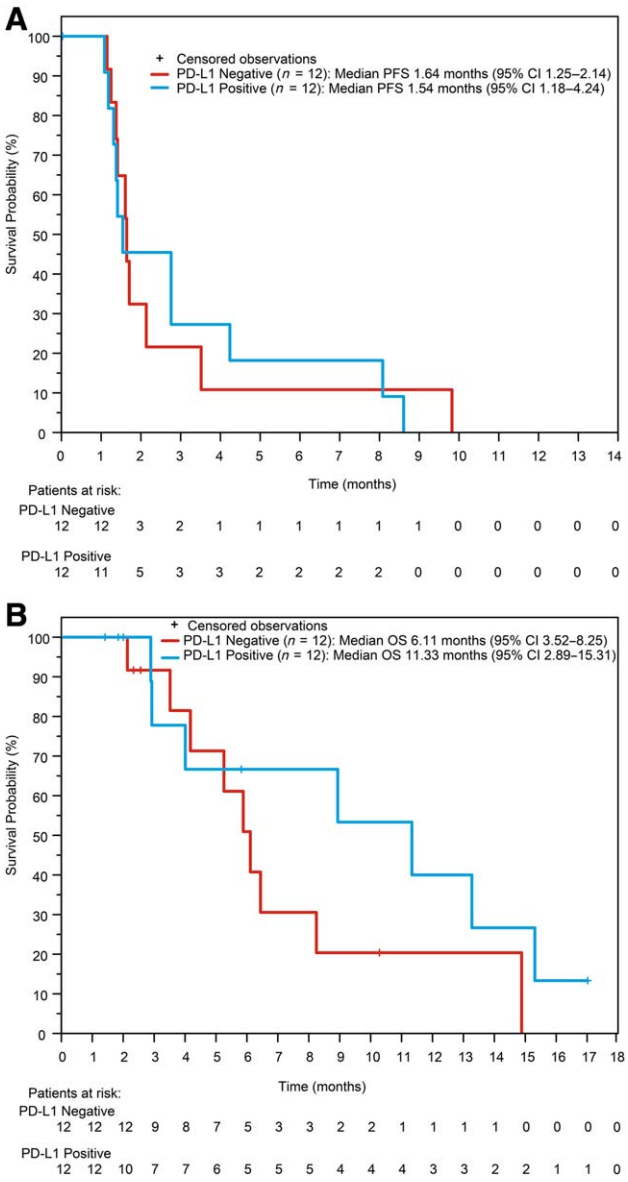

Figure 5. Kaplan-Meier plot. Progression-free survival **(A)** and overall survival **(B)** by PD-L1 status.

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

Published Ahead of Print on May 31, 2018 as 10.1634/theoncologist.2018-0044.

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.