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Evaluation of Combination Nivolumab and Ipilimumab Immunotherapy in Patients With Advanced Biliary Tract Cancers

Subgroup Analysis of a Phase 2 Nonrandomized Clinical Trial

Oliver Klein, MD; Damien Kee, MD; Adnan Nagrial, MD; Ben Markman, MD; Craig Underhill, MD; Michael Michael, MD; Louise Jackett, MD; Caroline Lum, MD; Andreas Behren, PhD; Jodie Palmer, PhD; Niall C. Tebbutt, MD; Matteo S. Carlino, PhD; Jonathan Cebon, PhD

IMPORTANCE Biliary tract cancers represent a rare group of malignant conditions with very limited treatment options. Patients with advanced disease have a poor outcome with current therapies.

OBJECTIVE To evaluate the efficacy and safety of combination immunotherapy with nivolumab and ipilimumab in patients with advanced biliary tract cancers.

DESIGN, SETTING, AND PARTICIPANTS The CA209-538 prospective multicenter phase 2 nonrandomized clinical trial included patients with advanced rare cancers including patients with biliary tract cancers. This subgroup analysis evaluated 39 patients from CA209-538 with biliary tract cancers who were enrolled from December 2017 to December 2019. Most of the patients (n = 33) had experienced disease progression after 1 or more lines of therapy and had tumor tissue available for biomarker research.

INTERVENTIONS Patients received treatment with nivolumab at a dose of 3 mg/kg and ipilimumab at 1 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks and continued for up to 96 weeks until disease progression or the development of unacceptable toxic events.

MAIN OUTCOMES AND MEASURES The primary end point was disease control rate (complete remission, partial remission, or stable disease) as assessed by RECIST 1.1.

RESULTS Among the 39 patients included in this subgroup analysis of a phase 2 clinical trial (20 men, 19 women; mean [range] age, 65 [37-81] years), the objective response rate was 23% (n = 9) with a disease control rate of 44% (n = 17); all responders had received prior chemotherapy, and none had a microsatellite unstable tumor. Responses were exclusively observed in patients with intrahepatic cholangiocarcinoma and gallbladder carcinoma. The median duration of response was not reached (range, 2.5 to ≥23 months). The median progression-free survival was 2.9 months (95% CI, 2.2-4.6 months), and overall survival was 5.7 months (95% CI, 2.7-11.9 months). Immune-related toxic events were reported in 49% of patients (n = 19), with 15% (n = 6) experiencing grade 3 or 4 events.

CONCLUSIONS AND RELEVANCE This subgroup analysis of a phase 2 clinical trial found that combination immunotherapy with nivolumab and ipilimumab was associated with substantial positive outcomes patients with advanced biliary tract cancers. This treatment compares favorably to single-agent anti–programmed cell death protein 1 (anti–PD-1) therapy and warrants further investigation. Ongoing translational research is focused on identifying biomarkers that can predict treatment response.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Oliver Klein, FRACP, MD, Olivia Newton-John Cancer Centre, Austin Hospital, 145 Studley Rd, Heidelberg VIC 3084, Australia (oliver.klein@onjcri.org.au).

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Biliary tract cancers (BTCs) represent a heterogeneous group of cancers with limited treatment options for patients with advanced disease.[1] Despite better molecular characterization,[2,3] chemotherapy is still the standard treatment for all patients with advanced BTCs, resulting in only modest survival benefits in the first- and second-line setting.[4,5] In addition, targeted therapy using isocitrate dehydrogenase 1 (IDH1) and fibroblast growth factor receptor inhibitors has shown clinical activity in subgroups of patients.[6,7] Immunotherapy using anti-programmed cell death protein 1 (PD-1) blockade has shown limited activity in patients with advanced BTCs in early clinical trials.[8,9] Immunotherapy using combined anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blockade with nivolumab and ipilimumab has demonstrated superior efficacy compared with single-agent anti-PD-1 therapy across several tumor types[10-12] and has, to our knowledge, not been investigated in patients with BTC.

Key Points

Question Is combination immunotherapy with nivolumab and ipilimumab associated with positive outcomes in patients with advanced biliary tract cancers?

Findings In this subgroup analysis of a phase 2 nonrandomized clinical trial of 39 patients with advanced biliary tract cancers, 33 of whom had undergone previous systemic therapy, an objective response rate of 23% and a disease control rate of 44% was observed. Most of the responses were durable and limited to patients with intrahepatic cholangiocarcinoma and gallbladder carcinoma.

Meaning These data indicate that nivolumab and ipilimumab combination treatment has significant activity in a subset of patients with advanced biliary tract cancers.

Methods

Study Design, Treatment, and Participants

The CA209-538 trial is a multicenter, nonrandomized open-label phase 2 study for rare cancers conducted at 5 Australia sites (Olivia Newton-John Cancer Centre at Austin Health, Peter McCallum Cancer Centre and Monash Health, Melbourne; Blacktown Hospital, Sydney; and Albury Wodonga Health). The trial enrolled patients in 3 tumor cohorts (rare upper gastrointestinal cancers, rare gynecological cancers, and neuroendocrine neoplasms) with each cohort being limited to 40 patients. Patients with advanced BTC were enrolled into the upper gastrointestinal cohort and are reported in this subgroup analysis. The clinical trial protocol (Supplement 1) was reviewed and approved by the institutional review board at Austin Health (Melbourne, Australia) and was undertaken in accordance with the Declaration of Helsinki and the guidelines of Good Clinical Practice. Written informed consent was obtained from all participants prior to enrollment into the study.

Nivolumab and ipilimumab were administered intravenously at a dose of 3 mg/kg and 1 mg/kg, respectively, every 3 weeks for 4 doses, followed by nivolumab monotherapy at a dose of 3 mg/kg every 2 weeks until disease progression, unacceptable toxic events, or a maximum of 2 years after enrollment. Tumor assessments were performed by radiological assessment (computed tomography of brain, chest, abdomen, pelvis) at baseline and then every 12 weeks during treatment or follow-up. The primary end point was the proportion of patients with disease control at week 12 (complete response, partial response, or stable disease) according to RECIST version 1.1. Safety analyses were performed on all patients who received at least 1 dose of study treatment. Microsatellite status of responders was determined by examining the expression of mismatch repair proteins by immunohistochemical analysis.

Statistical Analysis

Given the heterogeneous nature of the rare cancer trial patient population, statistics were descriptive, and no sample size calculation was undertaken. The survival curves were generated using Graphpad Prism, version 8.3.0, software, using the Kaplan-Meier product limit method. Descriptive statistics (medians and CIs) were also performed using this software.

Table 1. Patient Demographic and Disease Characteristics

Characteristic	No. (%)
Sex	
Male	20 (51)
Female	19 (49)
Mean age (range), y	65 (37-81)
ECOG performance score	
0	16 (41)
1	23 (59)
Lines of previous systemic therapy	
0	6 (15)
1	25 (64)
2	8 (21)
Tumor location	
Intrahepatic	16 (41)
Extrahepatic	10 (26)
Gallbladder	13 (33)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Results

Between December 2017 and December 2019, 39 patients with advanced BTC were enrolled into the CA209-538 clinical trial. The patients' demographic and disease characteristics are outlined in **Table 1**.

Twenty-two (56%) patients completed the induction treatment with 4 doses of nivolumab and ipilimumab; 8 patients (21%) experienced disease progression clinically during the induction phase, with 7 patients receiving only 1 treatment dose. Two patients (5%) discontinued treatment during the induction period due to grade 3 or 4 immune-related adverse events, and 1 patient had to cease treatment after 2 doses for severe infusion reactions to nivolumab. One patient died after only 1

Table 2. Antitumor Activity of Ipilimumab and Nivolumab

Best overall response	No. (%)			
			Cholangiocarcinoma	
	Total cohort (n = 39)	Gallbladder (n = 13)	Intrahepatic (n = 16)	Extrahepatic (n = 10)
Objective response rate (CR or PR)	9 (23)	4 (31)	5 (31)	0
Disease control rate (CR, PR, or SD)	17 (44)	9 (70)	7 (44)	1 (10)
CR	0	0	0	0
PR	9 (23)	4 (31)	5 (31)	0
SD	8 (21)	5 (39)	2 (13)	1 (10)
No assessment[a]	9 (23)	2 (15)	3 (19)	4 (40)
Progressive disease	13 (33)	2 (15)	6 (37)	5 (50)
Duration of response, median (range), mo[b]	Not reached (2.5-23+)	2.5+, 5.7, 11.8+, and 23+ mo	3, 4.2, 9, 10.8, and 14.8 mo	NA

Abbreviations: CR, complete response; NA, not applicable; PR, partial response; SD, stable disease.

[a] No assessment includes patients who did not undergo a postbaseline assessment because the patient experienced disease progression or died before their first assessment.

[b] Response duration of individual responders; (+) marks ongoing response.

treatment dose due to a polymicrobial sepsis that was unrelated to study treatment. Fifteen patients (38%) entered the maintenance phase with nivolumab infusions every 2 weeks.

The objective response rate (ORR) of the entire cohort was 23% (9 of 39 patients) (**Table 2**). Eight patients had stable disease as their best radiological response, leading to a disease control rate of 44% (17 patients). Thirteen patients (33%) had progressive disease at their first restaging scan. The median progression-free and overall survival times were 2.9 (95% CI, 2.2-4.6) months and 5.7 (95% CI, 2.7-11.9) months, respectively (**Figure**). The ORR was 27% (9 patients) in the 33 patients who received prior therapy, with the median progression-free survival being 2.9 (95% CI, 1.9-4.5) months; median overall survival, 5.4 (95% CI, 2.7-12.1) months. Two patients with an ongoing response subsequently underwent surgical resection of their residual disease and were relapse free at last follow-up. There were no responses seen in the 6 treatment-naive patients; 1 patient with gallbladder carcinoma experienced delayed tumor regression after leaving the trial that had fallen short for an objective response, according to RECIST 1.1.

The ORR was 31% (4 of 13) among patients with gallbladder carcinoma and 31% (5 of 16) among patients with intrahepatic cholangiocarcinoma; no responses were observed in 10 patients with extrahepatic cholangiocarcinoma. The median duration of response was not reached (range, 2.5 to ≥23 months; top of the range indicates no progressive disease by the time of last assessment). None of the responding patients had a microsatellite unstable tumor.

Twelve patients received subsequent treatment after coming off trial, with 10 patients receiving further chemotherapy. One patient with an IDH1-mutated intrahepatic cholangiocarcinoma and an ongoing treatment response withdrew consent and enrolled in a trial with an IDH1 inhibitor; a responding patient who had to discontinue study treatment owing to severe autoimmune hepatitis was successfully retreated at the time of disease progression with nivolumab in combination with regorafenib.

Nineteen (49%) of 39 patients experienced immune-related adverse events of any grade (eTable 1 in Supplement 2). A grade 3 or higher immune-related toxic event occurred in 6 patients (15%). There were no treatment-related deaths.

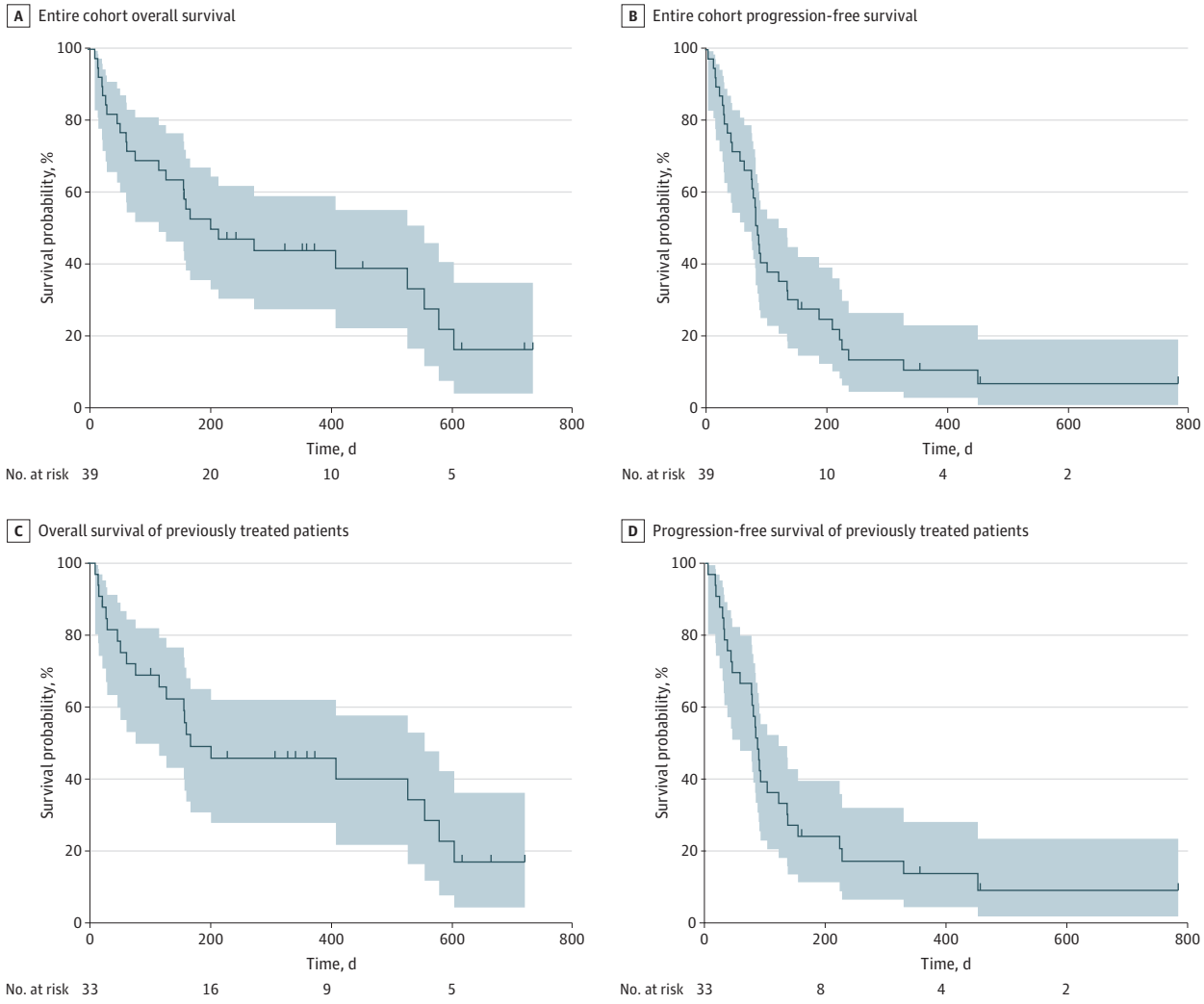
Discussion

Patients with advanced BTC have limited treatment options and an overall poor prognosis, so new treatment approaches are needed. In this subgroup analysis of a phase 2 clinical trial, to our knowledge, we report the first cohort of patients with BTC treated with immunotherapy using combined anti-PD-1/CTLA-4 blockade; we observed an ORR of 23% and a disease control rate of 44%, with all responding patients being treated in the second-line setting. Responses were prolonged in most patients; none of the responding patients had a tumor with a microsatellite unstable phenotype, which accounts for 0.5%-2.5% of all BTCs and is known to have a high likelihood of response to anti-PD-1 therapy.[13] The response rate in the present study trial compares favorably with the modest activity that has been observed with single-agent anti-PD-1 therapy in patients with advanced BTC in early clinical trials.[8,9]

A recently reported clinical trial using single-agent nivolumab in 54 patients with BTC[14] demonstrated a similar response rate to that reported in the present study and showed a favorable overall survival. Interpretation of treatment response in that trial[14] is made difficult by the significant difference in response between investigator-based assessment and central review. In addition, patients who received study treatment and experienced disease progression prior to their first radiological restaging were not accounted for in the response assessment. Both studies, however, indicate that there is clinically significant activity with checkpoint inhibition in a subset of patients with microsatellite-stable BTC, and further translational research is required to identify biomarkers to help with better patient selection. Additional clinical trials will be required to determine if combined anti-CTLA-4/PD-1 blockade is superior to single-agent anti-PD-1 therapy in patients with advanced BTC, as demonstrated in other malignant conditions.[10-12]

Interestingly, all responding patients in the present study had either gallbladder carcinoma or intrahepatic cholangiocarcinoma, suggesting that response to dual checkpoint inhibitor therapy in BTC may differ by anatomical site. This may

Figure. Kaplan-Meier Curve of Overall Survival and Progression Free Survival for the Entire Cohort (A, B) and Previously Treated Patients (C, D)



be explained by a different frequency of genomic alterations in genes of the SWI/SNF chromatin remodeling complex between anatomical subtypes[2] that are known to sensitize tumor cells to T-cell mediated killing.[15]

A fifth of patients experienced rapid disease progression after enrollment in the trial and received only 1 or 2 treatment doses, which may reflect the aggressive biology and poor prognosis of patients with advanced BTC at later stages of their disease[5] and the delayed response kinetics of immunotherapy. However, a negative impact of checkpoint inhibition leading to accelerated tumor growth in this patient population, as has been recognized in other cancers, cannot be excluded.[16]

The rate of grades 3 and 4 immune-related toxic events in the present study population is slightly lower than that seen in other clinical trials using the same dosing regimen, which may be due to the limited drug exposure of the subgroup of patients who experienced rapid disease progression.[11,12]

Limitations

This subgroup analysis evaluates anti-tumor activity of anti-CTLA-4/PD-1 combination immunotherapy in a single-arm, nonrandomized study with a limited number of patients, and further investigation will be required in a larger patient population.

Conclusions

This subgroup analysis of the CA209-538 trial is the first, to our knowledge, to assess combination immunotherapy with nivolumab and ipilimumab in patients with advanced biliary tract cancers. This regimen was associated with significantly improved clinical outcomes in patients with gallbladder carcinoma and intrahepatic cholangiocarcinoma, leading to durable responses; this contrasts with the generally short-lived responses obtained with chemotherapy. The promising activity suggests that this combination may be the preferred immunotherapy regimen for further study in biliary tract cancers.

ARTICLE INFORMATION

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Author Affiliations: Department of Medical Oncology, Austin Health, Melbourne, Australia (Klein, Kee, Tebbutt, Cebon); Olivia Newton-John Cancer Research Institute, Melbourne, Australia (Klein, Behren, Palmer, Cebon); Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia (Kee, Michael); Blacktown Hospital and the University of Sydney, Sydney, Australia (Nagrial, Carlino); Department of Medical Oncology, Monash Health, Melbourne, Australia (Markman, Lum); Monash University, Melbourne, Australia (Markman); Albury-Wodonga Regional Cancer Centre, Albury-Wodonga, Australia (Underhill); Department of Anatomical Pathology, Austin Health, Melbourne, Australia (Jackett); School of Cancer Medicine, La Trobe University, Australia (Behren, Palmer, Cebon); Department of Surgery, University of Melbourne, Melbourne, Australia (Tebbutt).

Author Contributions: Drs Klein and Cebon had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Klein, Kee, Michael, Cebon.
Acquisition, analysis, or interpretation of data: Klein, Kee, Nagrial, Markman, Underhill, Michael, Jackett, Lum, Behren, Palmer, Tebbutt, Carlino.
Drafting of the manuscript: Klein, Kee, Markman, Underhill, Michael, Lum, Behren, Palmer, Tebbutt.
Critical revision of the manuscript for important intellectual content: Klein, Kee, Nagrial, Markman, Underhill, Michael, Jackett, Behren, Palmer, Tebbutt, Carlino, Cebon.
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