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Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Meng Zhou, PhD, Professor, School of Biomedical Engineering, Wenzhou Medical University, Wenzhou 325027, Zhejiang Province, China. zhoumeng@wmu.edu.cn

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WJGO mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including liver cell adenoma, gastric neoplasms, appendiceal neoplasms, biliary tract neoplasms, hepatocellular carcinoma, pancreatic carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, *etc.*

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Immunotherapy in biliary tract cancers: Current evidence and future perspectives

Pedro Luiz Serrano Uson Junior, Raphael LC Araujo

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Pedro Luiz Serrano Uson Junior, Center for Personalized Medicine, Hospital Israelita Albert Einstein, São Paulo 05652-900, Brazil

Raphael LC Araujo, Department of Surgery, Universidade Federal de São Paulo, São Paulo 04039-002, Brazil

Raphael LC Araujo, Department of Oncology, Hospital Israelita Albert Einstein, São Paulo 05652-900, Brazil

Corresponding author: Raphael LC Araujo, MD, PhD, Adjunct Professor, Surgical Oncologist, Department of Surgery, Universidade Federal de São Paulo, Rua Napoleão de Barros, 715, São Paulo 04039-002, Brazil. raphael.l.c.araujo@gmail.com

Abstract

Bile duct tumors are comprised of tumors that originate from both intrahepatic and extrahepatic bile ducts and gallbladder tumors. These are aggressive tumors and chemotherapy is still the main treatment for advanced-stage disease and most of these cases have a poor overall survival. Strategies are aimed at treatments with better outcomes and less toxicity which makes immunotherapy an area of significant importance. Recent Food and Drug Administration approvals of immune checkpoint inhibitors (ICI) for agnostic tumors based on biomarkers such as microsatellite instability-high and tumor mutation burden-high are important steps in the treatment of patients with advanced bile duct tumors. Despite limited responses with isolated checkpoint inhibitors in later lines of systemic treatment in advanced disease, drug combination strategies have been demonstrating encouraging results to enhance ICI efficacy.

Key Words: Biliary tract cancer; Cholangiocarcinoma; Anti-programmed cell death protein-1; Anti-programmed death ligand-1; Microsatellite instability high; Tumor mutational burden high

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Core Tip: Chemotherapy remains the main treatment for advanced bile duct tumors regardless of tumor aggressiveness and poor overall survival rates. The Food and Drug Administration has approved immune checkpoint inhibitors for agnostic tumors based on biomarkers such as microsatellite instability-high and tumor mutation burden-high. They are important steps in combined treatment with systemic chemotherapy for patients with advanced disease and show encouraging results.

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INTRODUCTION

More than 905677 new cases of hepatobiliary cancer were estimated worldwide including hepatocellular carcinoma (HCC) in 2020. In addition, more than 115949 new cases of gallbladder cancer (GC) were reported in the same period[1]. In the United States, the incidence of patients diagnosed with liver and intra-hepatic tumors was estimated to be 42810 cases in 2020. Additionally, around 11980 patients were diagnosed with gallbladder and other biliary cancers[2,3]. The overall survival remains dismal with less than 10% of patients diagnosed with cholangiocarcinoma surviving 5 years after diagnosis[4,5]. Biliary tract cancers (BTC) comprise of a set of malignant tumors that can arise from any part of the bile ducts. BTC can be divided in intra-hepatic cholangiocarcinoma (ICC), peri-hilar cholangiocarcinoma, extra-hepatic cholangiocarcinoma (EHC) and GC.

In the last few years, several advances have been made in the management of BTC particularly in relation to ICC. Furthermore, the personalized medicine aligned with new molecules have brought about new hope for patients with advanced disease. For patients with tumors harboring isocitrate dehydrogenase 1 (IDH-1) mutations, reported in about 25% of ICC, the IDH-1 mutant inhibitor ivosidenib was evaluated in a randomized phase 3 trial including patients with disease in progress after at least one previous treatment. Ivosidenib delayed progression of the disease compared to placebo[6, 7]. For tumors harboring fibroblast growth factor receptor 2 (FGFR2) fusions, United States Food and Drug Administration (FDA) has just approved the inhibitor pemigatinib that showed an objective response rate of 36% in a single arm cohort of 107 patients whom disease had progressed from previous chemotherapy treatment and of these patients, 3 patients had a complete response[8]. Multiple other FGFR inhibitors are under development and new agents will be incorporated into the landscape in the next few years[9,10].

Biliary cancers are desmoplastic tumors with an immunoresistant tumor microenvironment[4,11]. The liver has a great capacity of immunotolerance related to a continuous exposure to antigens derived from intestinal flora and a large population of macrophages. This microenvironment actively contributes to the limited effect of checkpoint inhibitors in these tumors[4,12]. Hepatobiliary cancers have unique characteristics and components related to immune evasion. Tumor-associated macrophages were associated with higher tumor recurrence in a retrospective analysis in a small group of surgically resected hilar cholangiocarcinoma specimens which also showed a worse overall survival[13]. However, more precise and comprehensive evaluation of cellular components, including myeloid-derived suppressor cells and natural-killer cells, are necessary to drive conclusions of the impact of targeting to these cells in biliary cancers[4]. Immune checkpoint inhibitors (ICI), particularly anti-programmed cell death protein-1/programmed death ligand-1 (PD1/PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA4) antibodies have shown excellent results in HCC[14,15]. For this reason, most of the recent clinical trials in biliary cancers have been conducted with single ICI or combinations[16,17]. More recently, durvalumab also was evaluated along with chemotherapy and exhibited exciting results in a randomized phase 3 trial in advanced biliary cancers[18,19]. The aim of this review is to cover the main studies of immunotherapy in biliary cancers, biomarkers of efficacy, future combinations and strategies in advanced-stage disease.

TUMOR-AGNOSTIC BIOMARKERS

Microsatellite instability high

Microsatellite-instability is a phenotype presented in cells with defective mismatch repair genes that result in a hypermutation state and the prevalence of microsatellite instability is high (MSI-H) in biliary tract cancers (BTC) ranging between 5%-10%[20]. The MSI-H phenotype can be a germline (Lynch syndrome) or somatic[21,22]. Multiples studies have evaluated the effect of ICI in patients harboring

MSI-H tumors. Recently, a randomized phase III trial demonstrated better outcomes in MSI-H metastatic colorectal cancer treated with upfront front-line therapy with pembrolizumab compared with the standard chemotherapy regimen[23]. Pembrolizumab is an anti PD-1 antibody. PD-1 is a cell surface protein presented in most activated T cells. When PD-L1 bound to the PD-1, this binding facilitates apoptosis and dysfunction of activated T cells and mediates an immune suppressive microenvironment [24,25]. Therefore, binding PD-1 with an antibody may promote functional enhancement of activated T cells repairing anti-tumor immunity[24].

In BTC, the efficacy of pembrolizumab in MSI-H was evaluated in different cohorts. In one study including 11 patients with advanced BTC MSI-H, the response rate (RR) was 27% (3/11) with response duration ranging between 11.6 to 19.6 mo[26]. Data from microsatellite instability in high BTC patients treated with the Keynote-158 with pembrolizumab showed better response rates. In a cohort of 22 patients, the objective response rate (ORR) was 40.9% (20.7-63.6) with a complete response in 2 patients. The median progression-free survival (PFS) was 4.2 mo with a median overall survival (OS) of 24.3 mo; however, the median duration of response was not reached[27]. A report of 4 BTC MSI-H patients was also included in a cohort of solid tumors treated with pembrolizumab. Of these patients, one had a complete response and the remaining three had stable disease[28]. Based on this evidence, immunotherapy should be considered for the treatment of advanced BTC patients with the microsatellite instability high phenotype. All of these studies included patients previously exposed to chemotherapy regimens and evaluation of ICI in previous lines of systemic treatment in MSI-H BTC should be prospectively evaluated. Currently, pembrolizumab is approved by the FDA to treat MSI-H BTC in cases that progressed following prior treatment and those with no satisfactory alternative treatment options.

Tumor mutational burden high

Tumor mutational burden (TMB) is a biomarker that measures and quantifies the total mutation load in tumors. In biliary tract cancers, the TMB was evaluated retrospectively in a group of 156 patients. Of these, 133 tumoral tissues were assessed for the TMB with next-generating sequencing. Forty-eight cases were GC, 58 were ICC and 50 were EHC. The mean TMB value was high among patients with GC, followed by EHC and ICC [7.1 vs 5.5 vs 3.9 mutations/megabase (mut/Mb), $P < 0.05$]. The proportion of the TMB high (TMB-H), is defined in the study as 9.0 muts/Mb and was higher in GC than in ICC and EHC[29]. In another cohort including 803 BTC patients, 160 patients were evaluated with whole-exome sequencing and 643 patients with hybrid capture-based comprehensive genomic profiling. The mean TMB was 3.0 (IQR: 0.8-6.1) mut/Mb. In this cohort, 4 of 6 patients with MSI-H phenotype had a response to the disease after immunotherapy of the PD1 inhibitor[30].

In Keynote-158, a phase II basket study of pembrolizumab monotherapy for patients with advanced solid tumors, the relationship between activity of pembrolizumab and TMB was an exploratory endpoint. TMB-H was considered ≥ 10 mut/Mb. In the study, 790 patients had evaluable TMB included for efficacy analysis and 102 patients (13%) were TMB-H. The ORR observed was 29% (21-39) for TMB-H and 6% (5-8) for TMB-low. In addition, median duration of response in months was not reached for TMB-H and was 33 mo in TMB-low. The median OS for TMB-H and low was 11.7 mo (9.1-19.1) and 12.8 mo (11.1-14.1), respectively[31]. Based on these results, on June 16th, 2020, the FDA approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H (≥ 10 mut/Mb) solid tumors that showed progression following the prior treatment and for those who have no satisfactory alternative treatment options. Despite being an important approval and option in the management of patients with advanced BTC, no BTC patients were evaluated in the TMB-H cohort. With the approval and clinical utilization in practice, future cohorts will bring insights about response rate and efficacy for this group of patients.

IMMUNE CHECKPOINT INHIBITORS CLINICAL TRIALS

ICI were first evaluated in metastatic BTC patients whose disease had progressed on chemotherapy and the pembrolizumab was evaluated in two cohorts[32,33]. In the Keynote-028 PD-L1-positivity (membranous PD-L1 expression in $\geq 1\%$ of tumor and associated inflammatory cells or positive staining in stroma) was required for eligibility and at the median follow-up time of 6.5 mo, the ORR was 13% in 23 patients. The median OS was 6.2 mo (3.8-10.3) with a 12-mo OS rate of 27.6%. The grade ≥ 3 adverse events (AE) occurred in 16.7% of the patients[33]. In the Keynote-158, a total of 104 patients with advanced BTC whose disease progressed on any lines of systemic treatment were treated with pembrolizumab. In that study, PD-L1 positivity was not mandatory and 61 patients had PD-L1 combined positive scores (CPS) ≥ 1 . The overall RR was 5.8% (2.1-12.1) with six partial responses. Among patients with tumors with PD-L1 CPS ≥ 1 ($n = 61$) the ORR was 6.6% (1.8-15.9) and in patients with tumors with PD-L1 CPS < 1 ($n = 34$), the ORR was 2.9% (0.1-15.3). The median OS was compared in patients with PD-L1 CPS ≥ 1 vs < 1 , 7.2 mo (5.3-11.0) vs 9.6 mo (5.4-12.8), respectively. Overall, 13% of patients had a Grade ≥ 3 AE[32].

Equivalent results were obtained in another single center cohort including 40 patients. In this prospective cohort pembrolizumab was evaluated in advanced PD-L1 $\geq 1\%$ BTC patients who radiologically progressed after receiving first-line gemcitabine plus cisplatin. In the study, 47.5% of the patients included had ECOG performance status ≥ 2 . The ORR by Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 was 10% and by immune-modified RECIST was 12.5%, and the median OS was 4.3 mo (3.5-5.1). OS did not statistically differ between groups in different biomarker analyses, including CPS or tumor proportion score[34]. Anti-PD-1 nivolumab was evaluated in a multi-site phase II study including 54 advanced BTC patients whose disease progressed while undergoing treatment with at least 1 Line but no more than 3 Lines of systemic therapy. Central independent review RR was 11% (5/46), and investigator-assessed (IA) review response rate was 22% (10/46). Among the intention-to-treat population, median PFS was 3.68 mo (2.3-5.69) and median OS was 14.24 mo (5.98 to not reached). In this study, samples with 1% or more tumor cells for PD-L1 and any tumor infiltrating lymphocytes (TILs) for PD-1 exhibiting membranous staining were considered biomarker positive. PD-L1 expression was associated with prolonged PFS ($P < 0.001$). The PD-1 expression on TILs in this study had no correlation with clinical outcomes[35]. Although some responses were seen in these studies, immunotherapy with anti-PD-1 alone in unselected biomarker patients did not show great efficacy.

IMMUNE CHECKPOINT INHIBITORS COMBINED WITH CHEMOTHERAPY

Combination of chemotherapy with ICI in BTCs are the subject of study. A phase II study conducted in China evaluated the anti-PD-1 camrelizumab with FOLFOX4 (fluorouracil plus oxaliplatin) in 47 chemotherapy naïve advanced BTC patients. In 43 patients available for RR analysis, the confirmed response was achieved in 7%, with a disease control rate of 67.4%. Median PFS and OS were not reached. A Grade ≥ 3 AE occurred in 57.4% of the patients, the most commonly occurring AE was hematological count decreases[36]. Another study conducted in China evaluated the addition of anti-PD-1 antibodies to nab-paclitaxel and S1 in 32 patients with advanced BTC who were treated with anti-PD-1 inhibitors (pembrolizumab, nivolumab, sintilimab or toripalimab) plus nab-paclitaxel and S1, and in 26 patients who were treated with the combination chemotherapy alone. ORR were higher in the PD-1 inhibitors combination group (25%) compared with chemotherapy alone (15.3%). The median PFS was 5.4 mo in the group treated with anti-PD-1 compared to 2.82 mo in the group with chemotherapy alone ($P = 0.01$). The median OS is not mature[37].

Multiple mechanisms related to the synergism between chemotherapy and immunotherapy have been established. Chemotherapy can induce PD-L1 expression in cancer cells, facilitates infiltration of cytotoxic T cells in the tumor microenvironment and increases neoantigens and antigen-presenting cells. All of these effects can enhance the PD-1 inhibition[38]. Further evaluation of this synergism, preliminary safety and efficacy results of toripalimab and gemcitabine plus S-1 were presented[39]. In this phase II study, 34 patients were treated with the combination. Overall RR was 20.6% with a disease control rate (DCR) of 85.3%. In this study, patients with a mutation on TP53 or ATM had shorter PFS than the wild type[39].

The TOPAZ-1 trial is a randomized phase 3 trial that evaluated the combination of durvalumab, an anti-PD-L1, with chemotherapy against chemotherapy alone in advanced BTC. The study presented at the 2022 ASCO Gastrointestinal Cancers Symposium met its primary endpoint by improving OS in this subgroup of patients. Median OS was 12.8 mo with the combination *vs* 11.6 mo with gemcitabine and cisplatin alone (HR 0.8, $P = 0.021$). Furthermore, the addition of durvalumab to gemcitabine and cisplatin also improved PFS, 7.2 mo *vs* 5.7 mo (HR 0.75, $P = 0.001$) and tumor responses, 26.7% *vs* 18.7% [19].

IMMUNE CHECKPOINT INHIBITORS COMBINATIONS

Another strategy to enhance anti-PD1/PD-L1 efficacy is combination with CTLA-4 inhibitors. This strategy has proposed that these combinations can enhance the activity and infiltration of cytotoxic T cells in tumor microenvironment in BTC[4]. Nivolumab plus ipilimumab was evaluated in a group of 39 metastatic BTC patients included in the CA 209-538 clinical trial for rare cancers. The primary endpoint was clinical benefit rate, exploratory endpoints included correlation of efficacy with biomarkers including PD-L1 expression and TMB. A total of thirty-three patients (85%) received at least one prior line of systemic treatment (0-2 Lines). The ORR was 24% and the clinical benefit rate was 45%. Responses were observed in all subgroups of BTC. The median OS and PFS were 6.1 and 3.1 mo, respectively. The other twenty-two (56%) patients experienced an immune-related adverse event of grade ≥ 3 AE were observed in 8 (20%) patients[40].

The combination was further evaluated in a multi-institutional phase 2 trial with patients who had advanced BTC but without previous systemic therapy. Patients were distributed into two groups of treatment, the arm A was treated with gemcitabine, cisplatin and nivolumab and patients received this combination every 3 wk for 6 mo, followed by nivolumab monotherapy that patients received every 2

wk for a total duration of 2 years. The arm B consisted of nivolumab given for patients every 2 wk and ipilimumab every 6 wk for 2 years in case of no disease progression. The primary endpoint was a PFS rate at 6 mo, and of all the patients, 35 were treated in arm A and 36 patients treated in arm B. Progression-free survival rate at 6 mo was 70% in arm A and 18.6% in arm B. In addition, the observed PFS rates at 6 mo were insufficient to reject the null hypothesis in both arms[41].

In another phase II study, combination of durvalumab, an anti-PD-L1 antibody, with tremelimumab, an anti-CTLA-4 antibody, with chemotherapy were evaluated in 121 chemotherapy naïve metastatic BTC patients[42]. In this study, patients were allocated in three groups of treatment. The first group, biomarker cohort (BMC) in which thirty patients were treated with cisplatin and gemcitabine for one cycle, following the next cycles with gemcitabine plus cisplatin, and durvalumab plus tremelimumab every 3 wk until the disease progression. The second group, three combo cohort (3C), a total of 45 patients were treated with gemcitabine, cisplatin and durvalumab. The latter group, in the four-combo cohort (4C) including 46 patients, were treated with all the four drugs, chemotherapy with gemcitabine and cisplatin plus durvalumab and tremelimumab until disease progression or unacceptable toxicity. Overall, the addition of immunotherapy associated with chemotherapy on the first-line therapy was well tolerated and demonstrated to be a promising activity. The ORR was 50% (32.1-67.9) in the BMC group, 73.4% (60.5-86.3) in the 3C group and 73.3% (60.4-86.2) in the 4C group. In addition, the DCR ranged between 96.7%-100%. The median PFS was 13 mo in the BMC group, 11 mo in the 3C group and 11.9 mo in the 4C group. Median OS in the 4C group was 20.7 mo, 18.1 mo in the 3C group, and 15 mo in the BMC group. PD-L1 analysis before treatment did not show any association with PFS or OS. Interestingly, in the BMC group, a trend in higher PFS was observed after gemcitabine and cisplatin first cycle, in patients whose tumor had high expression of PD-L1 compared with patients with lower PD-L1. The main studies described are included on Table 1.

IMMUNE CHECKPOINT INHIBITORS COMBINED WITH ANTIANGIOGENICS

Combination with antiangiogenics can enhance the immunotherapy effect, contributing to cytotoxic effect of lymphocytes on the tumor microenvironment. After promising results in HCC, studies combining these agents are another option for refractory patients. In a non-randomized phase II study, 31 patients with chemotherapy refractory BTC were treated with Lenvatinib, a tyrosine kinase inhibitor (TKI) with antiangiogenics properties, associated with pembrolizumab[43]. The combination showed an ORR of 10% (2-26). These patients had a median PFS of 6.1 mo and a median OS of 8.6 mo. The most frequent treatment-related AEs, as expected, included hypertension and immune mediated adverse events[43]. Similar results were observed with the combination of regorafenib, another TKI, with anti-PD-L1 avelumab[44]. In this phase II study, 34 heavily pretreated patients with advanced BTC were treated. Four (13.8%) achieved partial response. Hypertension and fatigue were the most common grade 3/4 AE.

FUTURE DIRECTIONS

Most of the recruiting studies in advanced BTC tend to combine ICI with chemotherapy in first-line systemic treatment or later lines. This combination has additional effects in enhancing ICI efficacy, as previously discussed[40,19]. Local ablative therapies and liver directed therapies are also strategies focused in enhancing neoantigens presentation and/or developing abscopal effect[45,46]. The main ongoing recruiting studies with different strategies and combinations with ICI are summarized in Table 2. In October 2021, interim analysis of the randomized phase III study TOPAZ-1, evaluated cisplatin, gemcitabine and durvalumab, against standard-of-care chemotherapy, and demonstrated a significant OS benefit as a 1st-line treatment for patients with advanced biliary tract cancer[47]. Recently, a final report confirmed that the addition of durvalumab to cisplatin and gemcitabine improved progression-free survival and overall survival compared to chemotherapy alone with no safety concerns.

Based on the results of the TOPAZ-1 trial, upfront combination of chemotherapy with durvalumab could be considered a standard of care however some concerns need to be further evaluated. First, it is clear that based on the curves of overall survival they began to separate around 6 mo. We need to consider that after 6 mo, the control arm is placebo not chemotherapy, the HR was 0.91 for up to 6 mo and 0.74 thereafter. We don't know if continuing chemotherapy with the same regimen or a maintenance strategy would affect the results of the study. Second, more than half of patients included in the study had intrahepatic cholangiocarcinoma and more than half had a PD-L1 score TAP (tumor are positivity) above 1. It is unclear if the study would have different results with more patients with PD-L1 score 0 or other underrepresented sites including extrahepatic cholangiocarcinoma or gallbladder. Third, in the subgroup analysis it seems that Asian patients derived more benefit from the combination than non-Asian patients. Asian patients comprised half of the patients included in the study. Lastly, no molecular analysis was presented, nether evaluation of underlying liver diseases including viral

Table 1 Immunotherapy studies including biliary cancer patients, biomarkers, response rate and Food and Drug Administration approvals

Ref.	Patients	n	Biomarker	RR	Drug	FDA approval
Lemery <i>et al</i> [26], 2017	Previously treated	11	MSI-H	27%	Pembrolizumab	5/23/2017
Marabelle <i>et al</i> [27], 2020 (KN158)	Previously treated	22	MSI-H	40.9%	Pembrolizumab	5/23/2017
Marabelle <i>et al</i> [31], 2020 (KN158)	No TMB-H in cholangiocarcinoma cohort	0	TMB-H (≥ 10 mut/Mb)	?	Pembrolizumab	6/16/2020
Ueno <i>et al</i> [32], 2018 (KN158)	Previously treated	104	PD-L1 (CPS ≥ 1)	CPS ≥ 1 : 6.6% CPS < 1 : 2.9%	Pembrolizumab	-
Bang <i>et al</i> [33], 2019 (KN028)	Previously treated	24	PD-L1 ≥ 1	13%	Pembrolizumab	-
Kim <i>et al</i> [35], 2020	Previously treated	54	-	IA: 22% CIR: 11%	Nivolumab	-
Klein <i>et al</i> [40], 2020 (CA 209-538)	Previously treated	39	-	24%	Nivolumab + Ipilimumab	-
Oh <i>et al</i> [42], 2020	Chemo-naïve	121	-	50%-73%	Gem + Cis + Durvalumab \pm Tremelimumab	-
Oh <i>et al</i> [19], 2022 (TOPAZ-1)	Chemo-naïve	344	PD-L1 (TAP)	18.7%	Gem + Cis	-
		341		26.7%	Gem + Cis + Durvalumab	

KN: Keynote; RR: Response rate; MSI-H: Microsatellite instability-high; TMB-H: Tumor mutational burden-high; mut/Mb: Mutations/megabase; PD-L1: Programmed death-ligand 1; CPS: Combined positive score; IA: Investigator-assessed; CIR: Central independent review; Gem: Gemcitabine; Cis: Cisplatin; TAP: Tumor area positivity.

Table 2 Recruiting trials with checkpoint inhibitors in biliary tract cancers

ClinicalTrials.gov identifier	Study	Intervention	Patients included	State
Immune checkpoint inhibitors combined with chemotherapy				
NCT03796429	Phase II	Gemcitabine + S1 + Toripalimab	Chemo naïve	Recruiting
NCT04172402	Phase II	Gemcitabine + TS-1 + Nivolumab	Chemo naïve	Recruiting
NCT04027764	Phase II	Nab-paclitaxel + S1 + Toripalimab	Chemo naïve	Recruiting
NCT04300959	Phase II	Gemcitabine + Cisplatin + Anlotinib + Sintilimab	Chemo naïve	Recruiting
NCT03785873	Phase Ib/II	Nanoliposomal-irinotecan + 5-Fluorouracil + Nivolumab	Advanced disease	Recruiting
NCT04066491	Phase II/III	Gemcitabine + Cisplatin + Bintrafusp alfa	Chemo naïve	Recruiting
NCT04004234	Phase I/II	Gemcitabine + Nab-paclitaxel + Manganese primed anti-PD-1 antibody	Advanced disease	Recruiting
NCT04308174	Phase II	Gemcitabine + Cisplatin + Durvalumab	Resectable disease	Recruiting
NCT03875235	Phase III	Gemcitabine + Cisplatin + Durvalumab	Chemo naïve	Recruiting
NCT03046862	Phase II	Gemcitabine + Cisplatin + Durvalumab + Tremelimumab	Chemo naïve	Recruiting
NCT03478488	Phase III	Gemcitabine + Cisplatin + KN035	Chemo naïve	Recruiting
NCT04191343	Phase II	Gemcitabine + Oxaliplatin + Toripalimab	Chemo naïve	Recruiting
NCT03111732	Phase II	Capecitabine + Oxaliplatin + Pembrolizumab	Advanced disease	Recruiting
NCT03704480	Phase II	Durvalumab + Tremelimumab + Paclitaxel	Second-line systemic treatment	Recruiting
NCT03260712	Phase II	Gemcitabine + Cisplatin + Pembrolizumab	Chemo naïve	Recruiting
Immune checkpoint inhibitors combined with targeted therapy				

NCT03639935	Phase II	Rucaparib + Nivolumab	Advanced disease	Recruiting
NCT04211168	Phase II	Toripalimab + Lenvatinib	Second-line systemic treatment	Not yet recruiting
NCT04057365	Phase II	Nivolumab + DKN-01	Advanced disease	Recruiting
NCT04298008	Phase II	Durvalumab + AZD6738	Advanced disease	Recruiting
NCT04298021	Phase II	Durvalumab + AZD6738 + Olaparib	Second-line systemic treatment	Recruiting
NCT03475953	Phase I/II	Regorafenib + Avelumab	Advanced disease	Recruiting
NCT04234113	Phase I	SO-C101 + Pembrolizumab	Advanced disease	Recruiting
NCT04010071	Phase II	Toripalimab + Axitinib	Advanced disease	Not yet recruiting
NCT03829436	Phase I	TPST-1120 + Nivolumab	Advanced disease	Recruiting
NCT03095781	Phase I	Pembrolizumab + XL888	Advanced disease	Recruiting
NCT03250273	Phase II	Entinostat + Pembrolizumab	Advanced disease	Recruiting
NCT03895970	Phase II	Lenvatinib + Pembrolizumab	Advanced disease	Recruiting
NCT03825705	Phase Ib/II	Anlotinib + TQB2450	Advanced disease	Recruiting
Immune checkpoint inhibitors combined with local therapy				
NCT03482102	Phase II	Durvalumab + Tremelimumab + Radiotherapy	Advanced disease	Recruiting
NCT02866383	Phase II	Nivolumab + Ipilimumab + Radiotherapy	Second-line systemic treatment	Recruiting
NCT04238637	Phase II	Durvalumab + Tremelimumab + Y-90 SIRT	Intrahepatic biliary cancer	Recruiting
NCT02821754	Phase II	Durvalumab + Tremelimumab + Ablative therapies	Advanced disease	Recruiting
NCT03898895	Phase II	Camrelizumab + Radiotherapy	Unresectable disease	Recruiting
Immune checkpoint inhibitors combined with cell therapy				
NCT03937895	Phase I/IIa	Allogeneic NK cell (SMT-NK) + Pembrolizumab	Advanced disease	Recruiting

Ongoing clinical trials identified in ClinicalTrials.gov using the term “Biliar”.

hepatitis or NASH[19]. This question opens up future strategies of research to improve the care and understanding of immunotherapy in advanced biliary cancer patients.

CONCLUSION

Immune checkpoint agnostic approvals for advanced-stage cancer with biomarkers such as MSI-H and TMB-H are important treatment options for patients with advanced BTC who currently have limited options for treatment of refractory disease. Drug combinations such as anti-PD-1/PD-L1 with anti-CTLA-4 and/or chemotherapy have the potential to establish the standard of care for these patients and benefit a larger proportion of individuals if adopted in earlier lines of systemic treatment, however, more studies are necessary to better identify subgroups of patients that will most benefit from these strategies and treatments.

FOOTNOTES

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Country/Territory of origin: Brazil

ORCID number: Pedro Luiz Serrano Uson Junior 0000-0001-6122-1374; Raphael LC Araujo 0000-0002-7834-5944.

S-Editor: Gong ZM

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REFERENCES

- 1 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
- 2 **NCCN**. Hepatobiliary Cancers, NCCN guidelines version 2. 2021. [Accessed 1 May 2021] Available from: https://www.nccn.org/professionals/physician_gls/pdf/hepatobiliary.pdf
- 3 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]
- 4 **Arora M**, Bogenberger JM, Abdelrahman A, Leiting JL, Chen X, Egan JB, Kasimsetty A, Lenkiewicz E, Malasi S, Uson PLS, Nagalo BM, Zhou Y, Salomao MA, Kosiorek HE, Braggio E, Barrett MT, Truty MJ, Borad MJ. Evaluation of NUC-1031: a first-in-class ProTide in biliary tract cancer. *Cancer Chemother Pharmacol* 2020; **85**: 1063-1078 [PMID: 32440762 DOI: 10.1007/s00280-020-04079-z]
- 5 **Uson Junior PLS**, Bogenberger J, Borad MJ. Advances in the treatment of biliary tract cancers. *Curr Opin Gastroenterol* 2020; **36**: 85-89 [PMID: 31972599 DOI: 10.1097/MOG.0000000000000606]
- 6 **Lowery MA**, Abou-Alfa GK, Burris HA, Janku F, Shroff RT, Cleary GM, Azad NS, Goyal L, Maher EA, Gore L, Hollebecque A, Beeram M, Trent JC, Jiang L, Ishii Y, Auer J, Gliser C, Agresta SV, Pandya SS, Zhu A. Phase 1 study of AG-120, an IDH1 mutant enzyme inhibitor: results from the cholangiocarcinoma dose escalation and expansion cohorts. *J Clin Oncol* 2017; **35**: 4015 [DOI: 10.1200/JCO.2017.35.15_suppl.4015]
- 7 **Abou-Alfa GK**, Macarulla T, Javle MM, Kelley RK, Lubner SJ, Adeva J, Cleary JM, Catenacci DV, Borad MJ, Bridgewater J, Harris WP, Murphy AG, Oh DY, Whisenant J, Lowery MA, Goyal L, Shroff RT, El-Khoueiry AB, Fan B, Wu B, Chamberlain CX, Jiang L, Gliser C, Pandya SS, Valle JW, Zhu AX. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 796-807 [PMID: 32416072 DOI: 10.1016/S1470-2045(20)30157-1]
- 8 **Abou-Alfa GK**, Sahai V, Hollebecque A, Vaccaro G, Melisi D, Al-Rajabi R, Paulson AS, Borad MJ, Gallinson D, Murphy AG, Oh DY, Dotan E, Catenacci DV, Van Cutsem E, Ji T, Lihou CF, Zhen H, Félez L, Vogel A. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol* 2020; **21**: 671-684 [PMID: 32203698 DOI: 10.1016/S1470-2045(20)30109-1]
- 9 **Ahn DH**, Uson Junior PLS, Masci P, Kosiorek H, Halfdanarson TR, Mody K, Babiker H, DeLeon T, Sonbol MB, Gores G, Smoot R, Bekaii-Saab T, Mahipal A, Mansfield A, Tran NH, Hubbard JM, Borad MJ. A pilot study of Pan-FGFR inhibitor ponatinib in patients with FGFR-altered advanced cholangiocarcinoma. *Invest New Drugs* 2022; **40**: 134-141 [PMID: 34463891 DOI: 10.1007/s10637-021-01170-x]
- 10 **Zugman M**, Botrus G, Pestana RC, Uson Junior PLS. Precision Medicine Targeting *FGFR2* Genomic Alterations in Advanced Cholangiocarcinoma: Current State and Future Perspectives. *Front Oncol* 2022; **12**: 860453 [PMID: 35444941 DOI: 10.3389/fonc.2022.860453]
- 11 **Razumilava N**, Gores GJ. Cholangiocarcinoma. *Lancet* 2014; **383**: 2168-2179 [PMID: 24581682 DOI: 10.1016/S0140-6736(13)61903-0]
- 12 **Havel JJ**, Chowell D, Chan TA. The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy. *Nat Rev Cancer* 2019; **19**: 133-150 [PMID: 30755690 DOI: 10.1038/s41568-019-0116-x]
- 13 **Atanasov G**, Hau HM, Dietel C, Benzing C, Krenzien F, Brandl A, Wiltberger G, Matia I, Prager I, Schierle K, Robson SC, Reutzel-Selke A, Pratschke J, Schmelzle M, Jonas S. Prognostic significance of macrophage invasion in hilar cholangiocarcinoma. *BMC Cancer* 2015; **15**: 790 [PMID: 26497197 DOI: 10.1186/s12885-015-1795-7]
- 14 **Finn RS**, Qin S, Ikeda M, Galle PR, Ducreux M, Kim TY, Kudo M, Breder V, Merle P, Kaseb AO, Li D, Verret W, Xu DZ, Hernandez S, Liu J, Huang C, Mulla S, Wang Y, Lim HY, Zhu AX, Cheng AL; IMbrave150 Investigators. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. *N Engl J Med* 2020; **382**: 1894-1905 [PMID: 32402160 DOI: 10.1056/NEJMoa1915745]
- 15 **Yau T**, Kang YK, Kim TY, El-Khoueiry AB, Santoro A, Sangro B, Melero I, Kudo M, Hou MM, Matilla A, Tovoli F, Knox JJ, He AR, El-Rayes BF, Acosta-Rivera M, Neely J, Shen Y, Baccan C, Dela Cruz CM, Hsu C. Nivolumab (NIVO) + ipilimumab (IPI) combination therapy in patients (pts) with advanced hepatocellular carcinoma (aHCC): Results from CheckMate 040. *J Clin Oncol* 2019; **37**: 4012-4012 [DOI: 10.1200/JCO.2019.37.15_suppl.4012]
- 16 **Rizzo A**, Ricci AD, Brandi G. Recent advances of immunotherapy for biliary tract cancer. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 527-536 [PMID: 33215952 DOI: 10.1080/17474124.2021.1853527]
- 17 **Ricci AD**, Rizzo A, Brandi G. Immunotherapy in Biliary Tract Cancer: Worthy of a Second Look. *Cancer Control* 2020; **27**: 1073274820948047 [PMID: 32806956 DOI: 10.1177/1073274820948047]
- 18 **Rizzo A**, Ricci AD, Brandi G. Durvalumab: an investigational anti-PD-L1 antibody for the treatment of biliary tract cancer.

- Expert Opin Investig Drugs* 2021; **30**: 343-350 [PMID: [33645367](#) DOI: [10.1080/13543784.2021.1897102](#)]
- 19 **Oh DY**, He AR, Qin S, Chen LT, Okusaka T, Vogel A, Kim JW, Suksombooncharoen T, Lee MA, Kitano M, Burris III HA, Bouattour M, Tanasanvimon S, Zaucha R, Avallone A, Cundom J, Rokutanda N, Xiong J, Cohen G, Valle JW. A phase 3 randomized, double-blind, placebo-controlled study of durvalumab in combination with gemcitabine plus cisplatin (GemCis) in patients (pts) with advanced biliary tract cancer (BTC): TOPAZ-1. *J Clin Oncol* 2022; **40**: 378 [DOI: [10.1200/JCO.2022.40.4_suppl.378](#)]
 - 20 **Silva VW**, Askan G, Daniel TD, Lowery M, Klimstra DS, Abou-Alfa GK, Shia J. Biliary carcinomas: pathology and the role of DNA mismatch repair deficiency. *Chin Clin Oncol* 2016; **5**: 62 [PMID: [27829276](#) DOI: [10.21037/cco.2016.10.04](#)]
 - 21 **Cortes-Ciriano I**, Lee S, Park WY, Kim TM, Park PJ. A molecular portrait of microsatellite instability across multiple cancers. *Nat Commun* 2017; **8**: 15180 [PMID: [28585546](#) DOI: [10.1038/ncomms15180](#)]
 - 22 **Bogenberger JM**, DeLeon TT, Arora M, Ahn DH, Borad MJ. Emerging role of precision medicine in biliary tract cancers. *NPJ Precis Oncol* 2018; **2**: 21 [PMID: [30302397](#) DOI: [10.1038/s41698-018-0064-z](#)]
 - 23 **André T**, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Diaz LA Jr; KEYNOTE-177 Investigators. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med* 2020; **383**: 2207-2218 [PMID: [33264544](#) DOI: [10.1056/NEJMoa2017699](#)]
 - 24 **Chen L**, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J Clin Invest* 2015; **125**: 3384-3391 [PMID: [26325035](#) DOI: [10.1172/JCI80011](#)]
 - 25 **Oliveira AF**, Bretes L, Furtado I. Review of PD-1/PD-L1 Inhibitors in Metastatic dMMR/MSI-H Colorectal Cancer. *Front Oncol* 2019; **9**: 396 [PMID: [31139574](#) DOI: [10.3389/fonc.2019.00396](#)]
 - 26 **Lemery S**, Keegan P, Pazdur R. First FDA Approval Agnostic of Cancer Site - When a Biomarker Defines the Indication. *N Engl J Med* 2017; **377**: 1409-1412 [PMID: [29020592](#) DOI: [10.1056/NEJMp1709968](#)]
 - 27 **Marabelle A**, Le DT, Ascierto PA, Di Giacomo AM, De Jesus-Acosta A, Delord JP, Geva R, Gottfried M, Penel N, Hansen AR, Piha-Paul SA, Doi T, Gao B, Chung HC, Lopez-Martin J, Bang YJ, Frommer RS, Shah M, Ghori R, Joe AK, Pruitt SK, Diaz LA Jr. Efficacy of Pembrolizumab in Patients With Noncolorectal High Microsatellite Instability/Mismatch Repair-Deficient Cancer: Results From the Phase II KEYNOTE-158 Study. *J Clin Oncol* 2020; **38**: 1-10 [PMID: [31682550](#) DOI: [10.3410/E.736855157.793571317](#)]
 - 28 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science* 2017; **357**: 409-413 [PMID: [28596308](#) DOI: [10.1126/science.aan6733](#)]
 - 29 **Yi B**, Liu L, Song J, Huang Y, Zhang M, Chen R, Xia X, Jiang X. Mutational landscape and tumor mutation burden (TMB) feature of biliary cancer. *J Clin Oncol* 2020; **38**: e16670 [DOI: [10.1200/JCO.2020.38.15_suppl.e16670](#)]
 - 30 **Lin J**, Yang X, Cao Y, Li G, Zhao S, Shi J, Pan J, Hu K, Zhao L, Guan M, Sang X, Javle MM, Wang K, Wang X, Zhao HT. Genomics and translational precision oncology for 803 patients with biliary tract cancer. *J Clin Oncol* 2020; **38**: 4589 [DOI: [10.1200/JCO.2020.38.15_suppl.4589](#)]
 - 31 **Marabelle A**, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, Chung HC, Kindler HL, Lopez-Martin JA, Miller WH Jr, Italiano A, Kao S, Piha-Paul SA, Delord JP, McWilliams RR, Fabrizio DA, Aurora-Garg D, Xu L, Jin F, Norwood K, Bang YJ. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol* 2020; **21**: 1353-1365 [PMID: [32919526](#) DOI: [10.1016/S1470-2045\(20\)30445-9](#)]
 - 32 **Ueno M**, Chung HC, Nagrial A, Marabelle A, Kelley RK, Xu L, Mahoney J, Pruitt SK, Oh DY. 625PD Pembrolizumab for advanced biliary adenocarcinoma: Results from the multicohort, phase II KEYNOTE-158 study. *Ann Oncol* 2018; **29**: mdy282-009 [DOI: [10.1093/annonc/mdy282.009](#)]
 - 33 **Bang YJ**, Ueno M, Malka D, Chung HC, Nagrial A, Kelley RK, Piha-Paul SA, Ros W, Italiano A, Nakagawa K, Rugo HS, De Braud FG, Varga AI, Hansen AR, Gao C, Krishnan S, Norwood K, Doi T. Pembrolizumab (pembro) for advanced biliary adenocarcinoma: Results from the KEYNOTE-028 (KN028) and KEYNOTE-158 (KN158) basket studies. *J Clin Oncol* 2019; **37**: 4079 [DOI: [10.1200/JCO.2019.37.15_suppl.4079](#)]
 - 34 **Kang J**, Jeong JH, Hwang HS, Lee SS, Park DH, Oh DW, Song TJ, Kim KH, Hwang S, Hwang DW, Kim SC, Park JH, Hong SM, Kim KP, Ryoo BY, Yoo C. Efficacy and Safety of Pembrolizumab in Patients with Refractory Advanced Biliary Tract Cancer: Tumor Proportion Score as a Potential Biomarker for Response. *Cancer Res Treat* 2020; **52**: 594-603 [PMID: [32019287](#) DOI: [10.4143/crt.2019.493](#)]
 - 35 **Kim RD**, Chung V, Alese OB, El-Rayes BF, Li D, Al-Toubah TE, Schell MJ, Zhou JM, Mahipal A, Kim BH, Kim DW. A Phase 2 Multi-institutional Study of Nivolumab for Patients With Advanced Refractory Biliary Tract Cancer. *JAMA Oncol* 2020; **6**: 888-894 [PMID: [32352498](#) DOI: [10.1001/jamaoncol.2020.0930](#)]
 - 36 **Qin S**, Chen Z, Liu Y, Xiong J, Ren Z, Meng Z, Gu S, Wang L, Zou J. A phase II study of anti-PD-1 antibody camrelizumab plus FOLFOX4 or GEMOX systemic chemotherapy as first-line therapy for advanced hepatocellular carcinoma or biliary tract cancer. *J Clin Oncol* 2019; **37**: 4074 [DOI: [10.1200/JCO.2019.37.15_suppl.4074](#)]
 - 37 **Gou M**, Liu TE, Yan H, Si H, Wang Z, Qian N, Dai G. Pd-1 inhibitors plus nab-paclitaxel with S1 (AS) as first line in patients with advanced biliary tract cancer. *J Clin Oncol* 2020; **38**: e15195 [DOI: [10.1200/JCO.2020.38.15_suppl.e15195](#)]
 - 38 **Bailly C**, Thuru X, Quesnel B. Combined cytotoxic chemotherapy and immunotherapy of cancer: modern times. *NAR Cancer* 2020; **2**: zcaa002 [PMID: [34316682](#) DOI: [10.1093/narcan/zcaa002](#)]
 - 39 **Liu T**, Li W, Yu Y, Guo X, Xu X, Wang Y, Li Q, Cui Y, Liu H, Zhang S, Wang F, Yao M, Zhang L. 53P Toripalimab with chemotherapy as first-line treatment for advanced biliary tract tumors: A preliminary analysis of safety and efficacy of an open-label phase II clinical study. *Ann Oncol* 2020; **31**: S261 [DOI: [10.1016/j.annonc.2020.08.031](#)]
 - 40 **Klein O**, Kee D, Nagrial A, Markman B, Underhill C, Michael M, Lum C, Behren A, Palmer J, Tebbutt N, Carlino M,

- Cebon J. Combination immunotherapy with ipilimumab and nivolumab in patients with advanced biliary tract cancers. *J Clin Oncol* 2020; **38**: 4588 [DOI: [10.1200/JCO.2020.38.15_suppl.4588](https://doi.org/10.1200/JCO.2020.38.15_suppl.4588)]
- 41 **Sahai V**, Griffith KA, Beg MS, Shaib WL, Mahalingam D, Zhen DB, Deming DA, Dey S, Mendiratta-Lala M, Zalupski M. A multicenter randomized phase II study of nivolumab in combination with gemcitabine/cisplatin or ipilimumab as first-line therapy for patients with advanced unresectable biliary tract cancer (BiT-01). *J Clin Oncol* 2020; **38**: 4582 [DOI: [10.1200/JCO.2020.38.15_suppl.4582](https://doi.org/10.1200/JCO.2020.38.15_suppl.4582)]
- 42 **Oh DY**, Lee KH, Lee DW, Kim TY, Bang JH, Nam AR, Lee Y, Zhang Q, Rebelatto M, Li W, Kim JW. Phase II study assessing tolerability, efficacy, and biomarkers for durvalumab (D)±tremelimumab (T) and gemcitabine/cisplatin (GemCis) in chemo-naïve advanced biliary tract cancer (aBTC). *J Clin Oncol* 2020; **38**: 4520 [DOI: [10.1200/JCO.2020.38.15_suppl.4520](https://doi.org/10.1200/JCO.2020.38.15_suppl.4520)]
- 43 **Villanueva L**, Lwin Z, Chung HC, Gomez-Roca C, Longo F, Yanez E, Senellart H, Doherty M, Garcia-Corbacho J, Hendifar AE, Maurice-Dror C, Gill SS, Kim TW, Heudobler D, Penel N, Ghorri R, Kubiak P, Jin F, Norwood KG, Graham D. Lenvatinib plus pembrolizumab for patients with previously treated biliary tract cancers in the multicohort phase II LEAP-005 study. *J Clin Oncol* 2021; **39**: 321 [DOI: [10.1200/JCO.2021.39.3_suppl.321](https://doi.org/10.1200/JCO.2021.39.3_suppl.321)]
- 44 **Cousin S**, Bellera CA, Guégan JP, Mazard T, Gomez-Roca CA, Metges JP, Cantarel C, Adenis A, Korakis I, Poureau P, Spalato-Ceruso M, Bourcier K, Kind M, Soubeyran I, Bessede A, Italiano A. Regomune: A phase II study of regorafenib+avelumab in solid tumors-Results of the biliary tract cancer (BTC) cohort. *J Clin Oncol* 2021; **39**: 4096 [DOI: [10.1200/JCO.2021.39.15_suppl.4096](https://doi.org/10.1200/JCO.2021.39.15_suppl.4096)]
- 45 **Shi L**, Chen L, Wu C, Zhu Y, Xu B, Zheng X, Sun M, Wen W, Dai X, Yang M, Lv Q, Lu B, Jiang J. PD-1 Blockade Boosts Radiofrequency Ablation-Elicited Adaptive Immune Responses against Tumor. *Clin Cancer Res* 2016; **22**: 1173-1184 [PMID: [26933175](https://pubmed.ncbi.nlm.nih.gov/26933175/) DOI: [10.1158/1078-0432.CCR-15-1352](https://doi.org/10.1158/1078-0432.CCR-15-1352)]
- 46 **Wehrenberg-Klee E**, Goyal L, Dugan M, Zhu AX, Ganguli S. Y-90 Radioembolization Combined with a PD-1 Inhibitor for Advanced Hepatocellular Carcinoma. *Cardiovasc Intervent Radiol* 2018; **41**: 1799-1802 [PMID: [29845347](https://pubmed.ncbi.nlm.nih.gov/29845347/) DOI: [10.1007/s00270-018-1993-1](https://doi.org/10.1007/s00270-018-1993-1)]
- 47 **AstraZeneca**. Imfinzi plus chemotherapy significantly improved overall survival in 1st-line advanced biliary tract cancer in TOPAZ-1 Phase III trial at interim analysis. 2021. [Accessed on November 23, 2021] Available from: <https://www.astrazeneca.com/media-centre/press-releases/2021/imfinzi-improved-survival-in-biliary-tract-cancer.html>



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