Durvalumab: A PD-L1 Blocking Antibody for the Treatment of Adult Patients with Locally Advanced or Metastatic Biliary Tract Cancer

Amit Mahipal,[1,2] Mathias Palmer,[1] Jennifer Gile[1] and Richard Kim[3]

1. Department of Oncology, Mayo Clinic, Rochester, MN, USA; 2. Department of Oncology, University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; 3. Department of Gastrointestinal Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA

Biliary tract cancers (BTCs), comprising intrahepatic, hilar and extrahepatic cholangiocarcinoma and gallbladder cancers, are associated with poor prognoses. The majority of patients present with advanced-stage disease, and systemic treatment remains the mainstay of treatment. Recently, multiple targeted therapies have been approved by the US Food and Drug Administration (FDA), including pemigatinib, infigratinib, futibatinib and ivosidenib for patients whose disease has progressed on first-line systemic therapy. However, there has been no improvement on the first-line systemic therapeutic regimen of gemcitabine and cisplatin chemotherapy in more than a decade. Recently, durvalumab in addition to gemcitabine plus cisplatin was approved by the FDA as a first-line treatment option for patients with advanced BTC based on the TOPAZ-1 trial. The TOPAZ-1 trial was a phase III double-blind, placebo-controlled trial that enrolled 685 patients into a durvalumab plus gemcitabine plus cisplatin arm or a gemcitabine plus cisplatin arm. The trial demonstrated that the addition of durvalumab to standard-of-care chemotherapy was associated with improvement in median overall survival (12.8 versus 11.5 months), progression-free survival (7.2 versus 5.7 months) and response rates (27% versus 19%). The incidence and severity of adverse events were similar in both groups. Durvalumab in addition to gemcitabine plus cisplatin has become the new standard-of-care treatment for patients with advanced BTCs. This article reviews the immunotherapeutic options for patients with BTCs, describes the studies that led to the TOPAZ-1 trial, and summarizes key areas of research that are necessary to inform future drug development and improve patient outcomes.

Biliary tract cancers (BTCs) are a heterogeneous group of adenocarcinomas that originate from the epithelial lining of the biliary tree and are classified into cholangiocarcinoma (CCA) and gallbladder cancer. BTC is an aggressive and rare epithelial malignancy that is usually diagnosed at an advanced stage with few effective therapeutic options.[1] CCA is divided into extrahepatic and intrahepatic cholangiocarcinoma, with the extrahepatic type further classified into perihilar and distal based on relation to the hilum. Incidence rates have recently increased worldwide; 5-year survival is 5–10% for non-resectable advanced disease and approximately 30% for those treated with curative surgical intent.[2,3] The only potentially curative treatment option is surgery; however, only approximately 35% of tumours at diagnosis are amenable to resection.[4]

Advancements in genomic profiling have revealed critical pathophysiological features of BTCs, leading to the discovery of various actionable molecular targets, including alterations in *fibroblast growth factor receptor (FGFR), isocitrate dehydrogenase (IDH), B-Raf proto-oncogene serine/threonine-protein kinase (BRAF), neurotrophic tropomyosin receptor kinase (NTRK)* and *human epidermal growth factor receptor 2 (HER-2),* with development of multiple targeted therapies.[5] Over the past few years, the US Food and Drug Administration (FDA) has approved multiple targeted therapies for patients with BTC that has progressed on first-line chemotherapy, including pemigatinib, infigratinib, futibatinib and ivosidenib. However, these targeted agents benefit only a small subset of patients with BTCs that harbour specific actionable alterations. For the majority of patients, chemotherapy remains the only viable option.

In patients with BTCs who have unresectable or metastatic disease, the combination of gemcitabine and cisplatin chemotherapy serves as first-line therapy based on the ABC-02 trial published in 2010.[6] The ABC-02 trial demonstrated the efficacy of cisplatin plus gemcitabine with an improved overall survival (OS) compared with single-agent gemcitabine (median OS 11.7 months versus 8.1 months).[6] However, progress to improve the first-line therapy options for BTCs remains slow, with gemcitabine plus cisplatin being the standard of care for more than a decade. Only one recently published phase III trial has demonstrated improved outcomes by the addition of durvalumab to gemcitabine plus cisplatin in patients with advanced BTCs (TOPAZ-1, see below). This article reviews the immunotherapeutic options for patients with BTCs, describes the studies that led to the TOPAZ-1 trial, and summarizes key areas of research that are necessary to inform future drug development and improve patient outcomes.

Immune checkpoint inhibitor physiology

In addition to small molecule inhibitors, immune checkpoint inhibitors (ICIs) have emerged as a potential option for patients with BTCs. Preclinical studies demonstrated a promising immune microenvironment for ICI usage.[7] Initial data demonstrated extensive immune cell involvement in CCA, with improved survival, decreased rates of metastasis and better Tumour-Node-Metastasis staging correlating with the presence of CD4 and CD8 T cells, and poor prognosis associated with macrophage and neutrophil involvement.[8,9] Programmed death-ligand 1 (PD-L1) expression is seen in more than 45% of tumours and has been associated with a worse prognosis and poor survival.[10,11] Additionally, in a study by Nakamura et al., 40% of the CCA tumours assessed were determined to have a high mutational load and high immune checkpoint expression.[12] Furthermore, a pathological study of occupational-associated CCA demonstrated higher levels of PD-L1-expressing lymphocytes and infiltrating CD-8 cells, and hypothesized that these tumours demonstrated immune escape via their expression of PD-L1.[13]

Based on work in previous cancers, ICIs are known to produce improved responses with various malignancies, especially in those with increased tumour mutational burden (TMB) and high microsatellite instability (MSI-H). Genetic studies of CCA demonstrated a modest prevalence of MSI-H and high TMB. In one large-scale genetic analysis, 2–3.5% of CCA was classified as high TMB with >17 somatic missense mutations per mega base (Mb) analysed.[14] In several additional studies, CCA was associated with a moderate burden of MSI-H and deficiency in mismatch repair proteins with a prevalence around 5%.[15,16]

Single-agent immunotherapy

Multiple trials have evaluated the use of single-agent immunotherapy in patients with CCA following progression on chemotherapy (*Table 1*).[17–26] Pembrolizumab, a monoclonal antibody that binds to the programmed death 1 (PD-1) receptor has recently been studied in CCA in two trials, KEYNOTE-158 and KEYNOTE-028.[17] These were phase II and phase Ib trials that used pembrolizumab in patients with incurable CCA that progressed after standard treatment regimens. The KEYNOTE-028 trial required patients to have PD-L1-positive tumours, whereas the KEYNOTE-158 trial was open to patients regardless of PD-L1 status. The objective response rate (ORR) was 5.8% in KEYNOTE-158 and 13.0% in KEYNOTE-028. The median OS and PFS were 7.4 months and 2.0 months, respectively, in KEYNOTE-158 compared with 5.7 months and 1.8 months, respectively, in KEYNOTE-028. In a subgroup analysis of KEYNOTE-158, the ORR was 6.6% in PD-L1 expressors compared with 2.9% in non-expressors.[17]

Another PD-1 inhibitor, nivolumab, has been studied as a second-line treatment in patients with CCA. An early phase I trial comparing nivolumab alone versus in combination with gemcitabine plus cisplatin demonstrated improved median OS associated with PD-L1 expression; the single patient with a partial response was found to have deficiency in mismatch repair proteins.[19] Kim et al. evaluated single-agent nivolumab in a phase II trial of 54 patients with advanced, refractory BTCs.[18] The trial demonstrated median progression-free survival (PFS) and OS of 3.7 months (95% confidence interval [CI]: 2.3–5.7) and 14.2 months (95% CI: 5.9–not reached), respectively, with an ORR of 22%. In patients with PD-L1 expression, there was a superior median PFS compared with PD-L1-negative tumours (10.4 months versus 2.3 months; p<0.001).[18] In another phase I trial of 42 patients, treatment with durvalumab, a PD-L1 inhibitor, was associated with median PFS and OS of 2 months and 8.1 months, respectively.[20]

The above studies suggest that single-agent ICIs have modest activity in patients with BTCs who have progressed on prior chemotherapy. Response rates of 5–20% are noted, with median PFS of about 2 months. Currently, there is no good biomarker to predict the efficacy of single-agent immunotherapy. In one retrospective study of 47 patients with BTCs treated with immunotherapy, patients with TMB >5 mutations/Mb had improved PFS and OS compared with patients with TMB <5 mutations/Mb.[27]

Dual-agent immunotherapy

Treatment with dual ICIs has been attempted following at least one line of systemic therapy, but thus far has not demonstrated effective responses

Table 1: Key clinical trials with checkpoint inhibitors

Author	Drug	Trial	N	Line of therapy	ORR	PFS	OS	Phase
	Single-agent immunotherapy							
Piha-Paul[17]	Pembrolizumab	KEYNOTE-158	104	2nd or later	5.8%	2 months	7.4 months	II
Piha-Paul[17]	Pembrolizumab	KEYNOTE-028	24	2nd or later	13%	1.8 months	5.7 months	Ib
Kim[18]	Nivolumab	NCT02829918	54	2nd or later	22%	3.7 months	14.2 months	II
Ueno[19]	Nivolumab	JapicCTI-153098	30	2nd or later	3%	1.4 months	5.2 months	I
Ioka[20]	Durvalumab	NCT01938612	42	2nd or later	4.8%	2 months	8.1 months	I
	Dual-agent immunotherapy							
Klein[21]	Nivolumab/Ipilimumab	CA209-538	39	2nd or later	23%	2.9 months	5.7 months	II
Ioka[20]	Durvalumab/Tremelimumab	NCT01938612	65	2nd or later	10.8%		10.1 months	I
	Chemoimmunotherapy							
Feng[22]	Nivolumab/Gemcitabine/Cisplatin	NCT03311789	32	1st	55.6%	6.1 months	8.5 months	I/II
Oh[23]	Durvalumab/Tremelimumab/Gemcitabine/Cisplatin	NCT03046862	47	1st	70%	12.3 months	18.7 months	II
Oh[23]	Durvalumab/Gemcitabine/Cisplatin	NCT03046862	47	1st	72%	11.8 months	20.2 months	II
Li[24]	Toripalimab/Gemcitabine/S-1	NCT03796429	39	1st	27%	7 months	16 months	II
Oh[25]	Durvalumab/Gemcitabine/Cisplatin	TOPAZ-1	341	1st	26.7%	7.2 months	12.8 months	III
Sahai[26]	Nivolumab/Gemcitabine/Cisplatin versus Nivolumab/Ipilimumab	BilT-01	75	1st	59.4 % versus 21.2%	6.6 versus 3.9 months	10.6 versus 8.2 months	II

ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

compared with single-agent ICIs (*Table 1*).[20,21] In a study by Ioka et al., durvalumab and tremelimumab, a CTLA-4 inhibitor, were used as single agents or in combination, and demonstrated no significant differences between the single agent or combination therapy, with median OS of 8.1 versus 10.1 months, respectively, and duration of response of 9.7 versus 8.5 months, respectively.[20] The ORR with single-agent durvalumab and the combination of durvalumab plus tremelimumab was 4.8% and 10.8%, respectively. Nivolumab plus ipilimumab combination in a phase II trial demonstrated an ORR of 23% and a disease control rate of 44%.[21] Interestingly, there was no evidence of MSI-H in the responding patients and all the responses were seen in patients with intrahepatic CCA, with no response in patients with extrahepatic CCA.[21]

Chemotherapy plus immunotherapy

As only modest activity was observed with single-agent and dual-agent ICIs in advanced BTCs, the combination of immunotherapy and standard-of-care chemotherapy was evaluated (*Table 1*).[22–26] An initial phase II study examining nivolumab in combination with gemcitabine plus cisplatin demonstrated a PFS of 6.1 months (95% CI: 3.4–8.2) and ORR of 55.6%.[22] Treatment-related adverse events were manageable, with only one patient experiencing immune-related adverse events. A phase Ib/II trial evaluated the addition of nivolumab to 5-fluorouracil and liposomal-irinotecan as second-line therapy.[28] Median PFS and OS were 4.2 months (95% CI: 1.9–10.2) and 7.5 months (95% CI: 5.8–21.4), respectively, and, according to the authors' conclusions, this study failed to reject the null hypothesis (H0=PFS of 2.9 months) due to overlapping confidence intervals.

In a phase II trial assessing nivolumab, cisplatin, plus gemcitabine compared with nivolumab plus ipilimumab as first-line treatment for advanced BTCs, there was no statistically significant difference in outcomes between the two arms.[26] The median PFS and OS were 6.6 months (95% CI: 3.4–7.7) and 10.6 months (95% CI: 6.4–24.5), respectively, with chemoimmunotherapy compared with 3.9 (95% CI: 2.3–4.5) and 8.2 months (95% CI: 5.8–16.9), respectively, with dual ICIs.[26] A large single-centre, phase II trial conducted in Asia, enrolled 128 patients to receive durvalumab or combination of durvalumb plus tremelimumab in addition to gemcitabine plus cisplatin.[23] Initially, patients received immunotherapy following the first cycle of chemotherapy but after protocol amendment, all patients received immunotherapy concurrent with the first cycle of chemotherapy. Impressive ORRs were observed, with 72% in the chemotherapy plus durvalumab arm and 70% in the chemotherapy plus durvalumab and tremelimumab arm. The most common adverse events were cytopenias, with no unexpected safety events. The impressive results of this study formed the basis for development of the TOPAZ-1 trial.

TOPAZ-1 trial

The TOPAZ-1 trial evaluated the addition of durvalumab to the standard chemotherapy regimen of gemcitabine and cisplatin as a first-line systemic treatment option for patients with advanced or recurrent BTCs.[25,29] TOPAZ-1 was a phase III, double-blind, randomized and placebo-controlled study in which patients were assigned to receive either durvalumab or placebo with gemcitabine and cisplatin. The primary outcome was OS and secondary outcomes included PFS, response rates and safety. Inclusion criteria required patients to have previously untreated BTC that was either unresectable or metastatic or who developed recurrence more than 6 months after curative intent surgery and completion of adjuvant therapy. Patients with ampullary carcinoma or those with exposure to prior immunotherapy were excluded. In the trial, patients could receive up to eight cycles of

chemotherapy and if they had stable disease or better response, they were switched to maintenance durvalumab every 4 weeks or placebo, which they continued until progression or unacceptable toxicity.

A total of 685 patients were enrolled, with 341 receiving durvalumab with standard chemotherapy and 344 receiving placebo with standard chemotherapy. Baseline characteristics were similar in both groups. The majority of patients were Asian (56%) and had intrahepatic CCA subtype (56%). Only 1% of the patients had MSI-H tumours. The study met its primary endpoint, with median OS of 12.8 months (95% CI: 11.1–14.0) in the durvalumab group and 11.5 months (95% CI: 10.1–12.5) in the placebo group (p=0.021). OS rates at 12, 18 and 24 months were 54.1%, 35.1% and 24.9%%, respectively, compared with 48.0%, 25.6% and 10.4%, respectively, for placebo. Median PFS was 7.2 months (95% CI: 6.7–7.4) in patients who received durvalumab and 5.7 months (95% CI: 5.6–6.7) in those who received placebo (p=0.001). Multiple subgroup analyses for OS and PFS were conducted to examine the effect of features such as sex, age, PD-L1 expression, cancer subtype, race and Eastern Cooperative Oncology Group Performance Status. In all subgroup analyses, there was a trend favouring the durvalumab arm in both OS and PFS. When patients were stratified by PD-L1 positivity, there was no difference in outcomes between those who received durvalumab or placebo, suggesting that PD-L1 status may have limited value in predicting clinical benefit. Finally, ORR was 26.7% in the durvalumab arm and 18.7% in the placebo arm. Treatment-related adverse event rates were similar between the two groups. The incidences of grade 3 or 4 adverse events were 75.7% and 77.8% in the durvalumab and placebo arms, respectively. Only 6% of the patients discontinued durvalumab due to adverse events.

The updated results presented at the 2022 European Society for Medical Oncology congress, with an additional 6.5 months of follow-up, continued to demonstrate OS benefit with durvalumab plus chemotherapy compared with placebo plus chemotherapy (median OS 12.9 months [95% CI: 11.6–14.1] versus 11.3 months [95% CI: 10.1–12.5], respectively; hazard ratio 0.76).[30] The 2-year OS rate was 40.6% among patients achieving response to treatment with chemoimmunotherapy compared with only 20.7% in patients who achieved stable disease. All patient subgroups continued to benefit in the updated analyses as well. Subgroup analysis by genomic alterations could not identify any particular alteration including *KRAS, TP53, CDKN2A, ARID1A, IDH1* and *FGFR* that would predict response or lack of benefit to durvalumab treatment.

This study is the first phase III trial to include chemoimmunotherapy in the treatment of BTC. The addition of durvalumab to chemotherapy led to median OS improvement of 1.3 months. More importantly, there was an improvement in the 2-year OS rate from 10% to 25% with durvalumab, suggesting the possibility of more durable long-term survival in a minority of BTC patients represented in the tail of the survival curve. Given the above findings, the US FDA approved durvalumab in combination with gemcitabine and cisplatin for adult patients with locally advanced or metastatic biliary tract cancer.[31]

One of the major criticisms of the trial design was that patients received a maximum of eight cycles of chemotherapy followed by durvalumab or placebo as maintenance therapy until progression. This trial design was based on the ABC-02 trial, which established gemcitabine plus cisplatin as the standard of care. However, in typical clinical practice in the USA, treatment with gemcitabine plus cisplatin is continued until unacceptable toxicity or progression of disease, especially in patients responding to treatment. Cisplatin is sometimes difficult to continue beyond

eight cycles due to nephrotoxicity and ototoxicity, but gemcitabine is typically continued until progression. The separation in survival curves between the two arms started at 6 months, coinciding with cessation of chemotherapy. Following the results of this trial, it remains unknown whether the current clinical practice should be changed or whether chemotherapy plus immunotherapy could be continued beyond eight cycles. This trial demonstrated an OS benefit of durvalumab in both Asian and Western populations, although the improvement was more pronounced in Asian population. Nonetheless, this was a global study including both Asian and Western populations, suggesting general applicability of trial findings.

The KEYNOTE-966 randomized clinical trial, comparing pembrolizumab with placebo in addition to gemcitabine plus cisplatin in first-line therapy for advanced, non-resectable CCA has finished accrual and is expected to read out in the near future.[32] One key difference from the TOPAZ-1 trial is that gemcitabine can be continued until progression or unacceptable toxicity along with immunotherapy as part of maintenance therapy. The KEYNOTE-966 trial is expected to further address the question of whether immunotherapy adds benefit to chemotherapy as first-line treatment. Hopefully, this trial will also identify markers that could help in selecting patients who would derive maximum benefit from immunotherapy. It remains unknown whether the addition of anti-CTLA-4 would have any incremental benefit to chemotherapy plus anti-PD-1/PD-L1 blockade. In the previous phase II trial, the ORRs were similar when durvalumab or durvalumab plus tremelimumab were added to chemotherapy.[23]

Conclusions

Despite recent advances in the treatment of CCA, survival remains poor. Durvalumab in combination with gemcitabine and cisplatin chemotherapy should be considered as first-line standard-of-care therapy for patients with newly diagnosed locally advanced or metastatic CCA. However, the use of biomarkers including PD-L1 expression and TMB as a marker of response to immunotherapy in patients with CCA remains unclear. Several ongoing trials would further refine the role of immunotherapy in CCA (*Table 2*[28,32–42]). *FGFR2, NTRK, IDH, BRAF* and *HER2* alterations are now recognized as therapeutic targets. Further studies with biomarker-guided treatment strategies assessing novel therapeutic options are fundamental to improving survival in this population. The combination of immunotherapy and targeted therapy remains an active area of research. ❑

Table 2: List of selected on-going clinical trials in biliary tract cancers utilizing immunotherapy

Trial	Regimen	Phase	Line of therapy
NCT03250273[33]	Nivolumab + Entinostat	II	2nd or later
NCT04211168[34]	Toripalimab + lenvatinib	II	2nd or later
NCT04298008[35]	AZD6738+ durvalumab	II	2nd or later
NCT05052099[36]	FOLFOX + bevacizumab + atezolizumab	Ib/II	2nd or later
NCT05451043[37]	Gemcitabine+ cisplatin + durvalumab+ tremelimumab + propranolol	II	1st
NCT04941287[38]	Atezolizumab + varlilumab + cobimetiib	I/II	2nd or later
NCT05327582[39]	Durvalumab + lenvatinib + nab-paclitaxel	I/II	2nd or later
NCT04660929[40]	CT-0508+ pembrolizumab	I	2nd or later
NCT04278144[41]	BDC-1001+ nivolumab	I/II	2nd or later
NCT05239169[42]	Durvaluab + tremelimumab + capecitabine	II	Adjuvant
NCT04003636[32]	Gemcitabine+ cisplatin + /- pembrolizumab	III	1st
Sahai[28]	Nivolumab to 5-fluorouracil + liposomal-irinotecan	I/II	2nd

1. Qiu Z, Ji J, Xu Y, et al. Common DNA methylation changes in biliary tract cancers identify subtypes with different immune characteristics and clinical outcomes. *BMC Med*. 2022;20:64. DOI: 10.1186/s12916-021-02197-w
2. Khan SA, Tavolari S, Brandi G. Cholangiocarcinoma: Epidemiology and risk factors. *Liver Int*. 2019;39(Suppl. 1):19–31. DOI: 10.1111/liv.14095
3. Mavros MN, Economopoulos KP, Alexiou VG, Pawlik TM. Treatment and prognosis for patients with intrahepatic cholangiocarcinoma: Systematic review and meta-analysis. *JAMA Surg*. 2014;149:565–574. DOI: 10.1001/jamasurg.2013.5137
4. Aimar G, Paratore C, Zichi C, et al. A review of molecularly targeted therapy in biliary tract carcinoma: What is the next step? *Explor Target Antitumor Ther*. 2021;2:448–464. DOI: 10.37349/etat.2021.00056
5. Tella SH, Kommalapati A, Borad MJ, Mahipal A. Second-Line therapies in advanced biliary tract cancers. *Lancet Oncol*. 2020;21:e29–e41. DOI: 10.1016/S1470-2045(19)30733-8
6. 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. DOI: 10.1056/NEJMoa0908721
7. Loeuillard E, Conboy CB, Gores GJ, Rizvi S. Immunobiology of cholangiocarcinoma. *JHEP Rep*. 2019;1:297–311. DOI: 10.1016/j.jhepr.2019.06.003
8. Goeppert B, Frauenschuh L, Zucknick M, et al. Prognostic impact of tumour-infiltrating immune cells on biliary tract cancer. *Br J Cancer*. 2013;109:2665–2674. DOI: 10.1038/bjc.2013.610
9. Oshikiri T, Miyamoto M, Shichinohe T, et al. Prognostic value of intratumoral CD8+ T lymphocyte in extrahepatic bile duct carcinoma as essential immune response. *J Surg Oncol*. 2003;84:224–228. DOI: 10.1002/jso.10321
10. 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. DOI: 10.1002/jso.21376
11. Gani F, Nagarajan N, Kim Y, et al. Program death 1 immune checkpoint and tumor microenvironment: Implications for patients with intrahepatic cholangiocarcinoma. *Ann Surg Oncol*. 2016;23:2610–2617. DOI: 10.1245/s10434-016-5101-y
12. Nakamura H, Arai Y, Totoki Y, et al. Genomic spectra of biliary tract cancer. *Nat Genet*. 2015;47:1003–1010. DOI: 10.1038/ng.3375
13. Sato Y, Kinoshita M, Takemura S, et al. The PD-1/PD-L1 axis may be aberrantly activated in occupational cholangiocarcinoma. *Pathol Int*. 2017;67:163–170. DOI: 10.1111/pin.12511
14. Weinberg BA, Xiu J, Lindberg MR, et al. Molecular profiling of biliary cancers reveals distinct molecular alterations and potential therapeutic targets. *J Gastrointest Oncol*. 2019;10:652–62. DOI: 10.21037/jgo.2018.08.18
15. Silva VWK, Askan G, Daniel TD, et al. Biliary carcinomas: Pathology and the role of DNA mismatch repair deficiency. *Chin Clin Oncol*. 2016;5:62. DOI: 10.21037/cco.2016.10.04
16. Kunk PR, Obeid JM, Winters K, et al. Mismatch repair deficiency in cholangiocarcinoma. *J Clin Oncol*. 2018;36(Suppl. 4):269–269. DOI: 10.1200/JCO.2018.36.4_suppl.269
17. Piha-Paul SA, Oh D-Y, Ueno M, et al. Efficacy and safety of pembrolizumab for the treatment of advanced biliary cancer: Results from the KEYNOTE-158 and KEYNOTE-028 studies. *Int J Cancer*. 2020;147:2190–2198. DOI: 10.1002/ijc.33013
18. Kim RD, Chung V, Alese OB, et al. A phase 2 multi-institutional study of nivolumab for patients with advanced refractory biliary tract cancer. *JAMA Oncol*. 2020;6:888–894. DOI: 10.1001/jamaoncol.2020.0930
19. Ueno M, Ikeda M, Morizane C, et al. Nivolumab alone or in combination with cisplatin plus gemcitabine in Japanese patients with unresectable or recurrent biliary tract cancer: A non-randomised, multicentre, open-label, phase 1 study. *Lancet Gastroenterol Hepatol*. 2019;4:611–621. DOI: 10.1016/S2468-1253(19)30086-X
20. Ioka T, Ueno M, Oh D-Y, et al. Evaluation of safety and tolerability of durvalumab (D) with or without tremelimumab (T) in patients (PTS) with biliary tract cancer (BTC). *J Clin Oncol*. 2019;37(Suppl. 4):387–387. DOI: 10.1200/JCO.2019.37.4_suppl.387
21. Klein O, Kee D, Nagrial A, et al. Evaluation of combination nivolumab and ipilimumab immunotherapy in patients with advanced biliary tract cancers: Subgroup analysis of a phase 2 nonrandomized clinical trial. *JAMA Oncol*. 2020;6:1405–1409. DOI: 10.1001/jamaoncol.2020.2814
22. Feng K, Liu Y, Zhao Y, et al. Efficacy and biomarker analysis of nivolumab plus gemcitabine and cisplatin in patients with unresectable or metastatic biliary tract cancers: Results from a phase II study. *J Immunother Cancer*. 2020;8:e000367. DOI: 10.1136/jitc-2019-000367
23. Oh D-Y, Lee K-H, Lee D-W, et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naive patients with advanced biliary tract cancer: An open-label, single-centre, phase 2 study. *Lancet Gastroenterol Hepatol*. 2022;7:522–532. DOI: 10.1016/S2468-1253(22)00043-7

24. Li W, Yu Y, Xu X, et al. Toripalimab with chemotherapy as first-line treatment for advanced biliary tract tumors: Update analytic results of an open-label phase II clinical study (JS001-ZS-BC001). *J Clin Oncol*. 2021;39(Suppl. 15):e16170–e16170. DOI: 10.1200/JCO.2021.39.15_suppl.e16170

25. Oh D-Y, Ruth He A, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. *NEJM Evidence*. 2022;1:EVIDoa2200015.

26. Sahai V, Griffith KA, Beg MS, et al. A randomized phase 2 trial of nivolumab, gemcitabine, and cisplatin or nivolumab and ipilimumab in previously untreated advanced biliary cancer: BilT-01. *Cancer*. 2022;128:3523–3530. DOI: 10.1002/cncr.34394

27. Liddell SS, Chakrabarti S, Wintheiser GA, et al. Tumor mutational burden is a potential predictive biomarker for response to immune checkpoint inhibitors in patients with advanced biliary tract cancer. *JCO Precis Oncol*. 2022;6:e2200003. DOI: 10.1200/PO.22.00003

28. Sahai V, Griffith KA, Lin B-L, et al. A multicenter phase ib/II study of liposomal-irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) with nivolumab as second-line therapy for patients with advanced biliary tract cancer (bilt-03). *J Clin Oncol*. 2022;40(Suppl. 4):438–438. DOI: 10.1200/JCO.2022.40.4_suppl.438

29. Oh D-Y, He AR, Qin S, et al. 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(Suppl. 4):378–378. DOI: 10.1200/JCO.2022.40.4_suppl.378

30. Oh D-Y, He AR, Qin S, et al. 78P updated overall survival (OS) from the phase III TOPAZ-1 study of durvalumab (D) or placebo (PBO) plus gemcitabine and cisplatin (+ GC) in patients (pts) with advanced biliary tract cancer (BTC). *Ann Oncol*. 2022;33:S1462–3. DOI: 10.1016/j.annonc.2022.10.114

31. U.S. Food and Drug Administration. Available at: www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-durvalumab-locally-advanced-or-metastatic-biliary-tract-cancer (accessed date 28 February 2023).

32. ClinicalTrials.gov. Pembrolizumab (MK-3475) plus Gemcitabine/cisplatin Versus Placebo Plus Gemcitabine/cisplatin for First-line Advanced and/or Unresectable Biliary Tract Carcinoma (BTC) (MK-3475-966/KEYNOTE-966) (KEYNOTE-966). ClinicalTrials.gov Identifier: NCT04003636 Available at: https://clinicaltrials.gov/ct2/show/NCT04003636 (accessed date: 28 February 2023).

33. ClinicalTrials.gov. A Clinical Trial of Entinostat in Combination with Nivolumab for Patients with Previously Treated Unresectable or Metastatic Cholangiocarcinoma and Pancreatic Adenocarcinoma. ClinicalTrials.gov Identifier: NCT03250273. Available at: https://clinicaltrials.gov/ct2/show/NCT03250273 (accessed date 28 February 2023).

34. ClinicalTrials.gov. Toripalimab Plus Lenvatinib as Second-line Treatment in Advanced Biliary Tract Cancers. ClinicalTrials.gov Identifier: NCT04211168. Available at: https://clinicaltrials.gov/ct2/show/NCT04211168 (accessed date 28 February 2023).

35. ClinicalTrials.gov. AZD6738 Plus Durvalumab in Biliary Tract Cancer. ClinicalTrials.gov Identifier: NCT04298008. Available at: https://clinicaltrials.gov/ct2/show/NCT04298008 (accessed date 28 February 2023).

36. ClinicalTrials.gov. Phase ib/II Single-arm Study of mFOLFOX6, Bevacizumab and Atezolizumab in Advanced Biliary Tract Cancer (COMBATBIL). ClinicalTrials.gov Identifier: NCT05052099. Available at: https://clinicaltrials.gov/ct2/show/NCT05052099 (accessed date 28 February 2023).

37. ClinicalTrials.gov. Durvalumab and Tremelimumab in Combination with Propranolol and Chemotherapy for Treatment of Advanced Hepatopancreabiliary Tumors (BLOCKED). ClinicalTrials.gov Identifier: NCT05451043. Available at: https://clinicaltrials.gov/ct2/show/NCT05451043 (accessed date 28 February 2023).

38. ClinicalTrials.gov. Testing a New Combination of Anti-cancer Immune Therapies, Atezolizumab and CDX-1127 (varlilumab) with or Without the Addition of a Third Anti-cancer Drug, Cobimetinib, for Advanced-stage Biliary Tract Cancer. ClinicalTrials.gov Identifier: NCT04941287. Available at: https://clinicaltrials.gov/ct2/show/NCT04941287 (accessed date 28 February 2023).

39. ClinicalTrials.gov. An Open-label, Phase I/II Study of PLENA Regimen in Patients with Unresectable Pancreatic Cancer or BTC. ClinicalTrials.gov Identifier: NCT05327582. Available at: https://clinicaltrials.gov/ct2/show/NCT05327582 (accessed date 28 February 2023).

40. ClinicalTrials.gov. CAR-macrophages for the Treatment of HER2 Overexpressing Solid Tumors. ClinicalTrials.gov Identifier: NCT04660929. Available at: https://clinicaltrials.gov/ct2/show/NCT04660929 (accessed date 28 February 2023).

41. ClinicalTrials.gov. A First-in-human Study Using BDC-1001 as a Single Agent and in Combination with Nivolumab in Advanced HER2-expressing Solid Tumors. ClinicalTrials.gov Identifier: NCT04278144. Available at: https://clinicaltrials.gov/ct2/show/NCT04278144 (accessed date 28 February 2023).

42. ClinicalTrials.gov. Immunotherapy with Durva and Treme with or Without Capecitabine in Adjuvant Treatment for Biliary Tract Cancer. ClinicalTrials.gov Identifier: NCT05239169. Available at: https://clinicaltrials.gov/ct2/show/NCT05239169 (accessed date 28 February 2023).