VIA MEDICA

EXPERTS' OPINION

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Experts' position on durvalumab treatment for cholangiocarcinoma patients

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ABSTRACT

In the Polish population, biliary tract cancers account for about 1% of the incidence and 2.5% of deaths due to all cancers, with 85% of all cases diagnosed in patients over the age of 60. Biliary tract cancer is a neoplasm that originates from intrahepatic or extrahepatic biliary epithelial cells and shows features of cholangiocyte differentiation. It can also develop from perihilar glands and hepatocytes. It is characterized by a poor prognosis, while the use of exclusive chemotherapy in the treatment leads to a slight improvement in the treatment effect. The paper presents current guidelines for imaging and endoscopic diagnosis in patients with biliary tract cancer and summarizes data on the efficacy and safety of durvalumab from clinical trials as well as everyday clinical practice.

Keywords: cholangiocrcinoma, immunotherapy, durvalumab

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Epidemiology of biliary tract cancers

Introduction and subtypes of biliary tract cancer

Biliary tract cancer is an epithelial cell-derived neoplasm that can occur anywhere along the biliary tract. It shows features of cholangiocyte differentiation and is likely derived primarily from epithelial cells lining the bile ducts, known as cholangiocytes. These tumors can also develop from perihilar glands and hepatocytes, depending on the location and underlying liver disease [1, 2] The majority (up to 99%) of biliary tract cancers are adenocarcinomas, with other histological subtypes such as adenosquamous carcinoma or clear cell carcinoma being rare [3]. These tumors are highly desmoplastic, surrounded by a dense network of inflammatory cells and matrix [4].

The most common anatomical division includes intrahepatic, perihilar, and distal subtypes (Fig. 1) [5]. Intrahepatic biliary tract cancer is in the liver parenchyma proximal to the second-order bile ducts, perihilar occurs between the second-order bile ducts and the junction of the cystic duct with the common bile duct, while distal biliary tract cancer is limited to the common bile duct below the junction with the cystic duct. Each anatomical subtype is characterized by distinct genetic abnormalities, clinical presentation, and treatment options [6, 7].

The most common subtype is perihilar cancer (50–60%), with its own anatomical classification, the Bismuth classification (Fig. 2) [8]. Intrahepatic cancer accounts for

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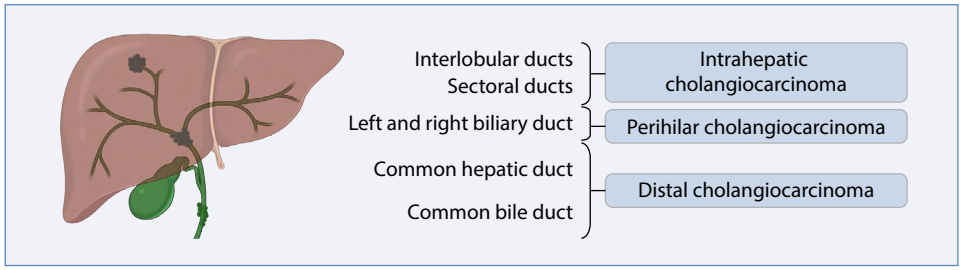

Figure 1. Anatomical subtypes of bile duct cancer

about 20% of all subtypes, and extrahepatic/distal cancer for about 10%. The rarest subtype is cancer developing multifocally in the bile ducts (about 5% of cases) [9]. Recent studies suggest that the intrahepatic type may be more common than previously estimated [10].

Biliary tract cancer is the second most common primary malignant liver tumor after hepatocellular carcinoma. In developed countries, since the mid-1990s, there has been a systematic increase in the incidence of this cancer. Analyzing data worldwide, a rapid, steady increase in the incidence of intrahepatic bile duct cancer has been observed, with a simultaneous decrease in the incidence of extrahepatic bile duct cancers. Some researchers point out that this phenomenon may be, at least partially, due to the misclassification of perihilar extrahepatic cancers (Klatskin tumors) as intrahepatic cancers.

Epidemiology worldwide and in Poland

Approximately two-thirds of biliary tract cancers occur in patients aged from 50 to 70 years, with a slight male predominance [7]. The reported incidence of bile duct tumors has increased in recent years; however, this increase is likely due to improved data collection and analysis.

The epidemiology of these tumors varies worldwide. It is believed that the global variability in the incidence of biliary tract cancer results from a complex interaction between host-specific genetic predisposition and geographical distribution of related risk factors (Tab. 1). The highest rates of CCA in the world occur in northeastern Thailand and surrounding areas, where the main risk factor is chronic liver fluke infection. The disease secondary to fluke invasion can appear anywhere in the bile ducts and occur as any of the three anatomical variants. Despite specific pathogenesis, especially genetic aberrations, diagnosis, and treatment do not differ from bile duct cancer unrelated to liver fluke infection. In the Western world, the most known risk factor for bile duct cancer is primary sclerosing cholangitis (PSC) [6, 7, 11].

In Poland, biliary tract cancers account for about 1% of the incidence of all cancers and 2.5% of deaths [12]. In 2019, the National Cancer Registry recorded 1720 cases and 1750 deaths due to these cancers. The incidence and mortality in both sexes increase with age, with 85% of these cancers occurring after the age of 60 [13].

Risk factors

Analysis of the incidence of individual subtypes of biliary tract cancer in different geographic regions suggests the presence of various risk factors. A summary of available data on the potential association of factors with the risk of developing bile duct cancer is presented in Table 2. It should be noted that some risk factors are common to both intrahepatic and extrahepatic bile duct cancers, while others appear to be more specific to individual subtypes [6, 14, 15]. Most known major risk factors are associated with chronic inflammation of the bile duct epithelium and bile stasis. In the case of Western European countries, sporadic forms predominate without the presence of any identifiable risk factors. Recent data indicate that obesity and metabolic syndrome may be significant risk factors for intrahepatic bile duct cancer [9].

Host gene polymorphisms encoding enzymes involved in xenobiotic detoxification, DNA repair, multidrug resistance, immune response, and folate metabolism have also been associated with cholangiocarcinogenesis, although no genome-wide association studies have been published [7, 16].

Diagnosis of biliary tract cancer

The type of presented symptoms results from the location and advancement of bile duct cancer, while clinical symptoms determine the choice of diagnostic methods, including laboratory tests, imaging studies, and interventional procedures. Obtaining a histopathological diagnosis may be difficult depending on the location of the lesion, which is particularly problematic in the case of perihilar lesions. Methods for obtaining material for studies include brush cytology, fine-needle aspiration biopsy, and biopsy under radiological imaging or cholangioscopic.

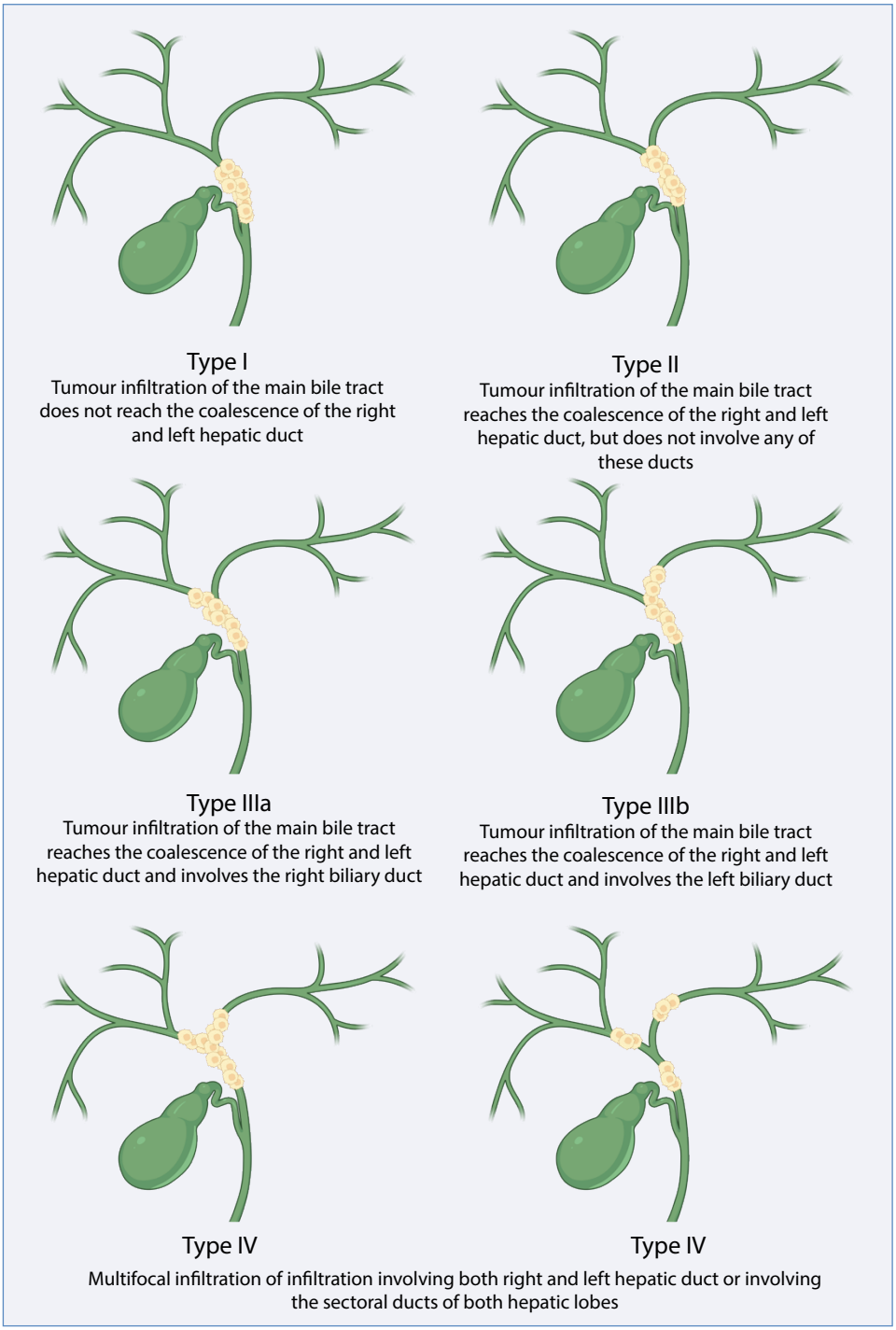

Figure 2. Bismuth Classification [8]

Intrahepatic bile duct cancer often presents as an intrahepatic mass and is detected incidentally during liver imaging in 25–30% of patients. Patients with intrahepatic bile duct cancer remain asymptomatic in the early stages, and nonspecific symptoms such as abdominal pain or, less frequently, jaundice, appear only as the disease progresses to an advanced stage where bile flow is significantly impaired by the tumor mass within the liver [11].

Patients with perihilar and distal bile duct cancer usually present with painless jaundice resulting from bile duct obstruction occurring at an earlier stage of the disease compared to intrahepatic bile duct cancer.

Table 1. Global incidence of bile duct cancer

Geographical region	Incidence rate per 100,000 people (age-standardized)
Thailand — Northeast	85.0
South Korea	8.8
China, Shanghai	7.6
Thailand —South	5.7
Taiwan	4.7
Japan	3.5
Italy	3.4
Germany	3.0
Austria	2.7
United Kingdom	2.2
United States	1.6
France	1.3
Poland	0.7
Spain	0.5
Switzerland	0.5
Australia	0.4
Canada	0.4
Israel	0.3

Table 2. Most common risk factors and their association with the development of bile duct cancer [7, 14, 15]

Risk factor	Association with the risk of intrahepatic cholangiocarcinoma (OR)	Association with the risk of perihilar and distal cholangiocarcinoma (OR)	Level of evidence regarding reported epidemiology
Caroli's disease	38	97	Population study
Primary sclerosing cholangitis	22	41	Population study
Bile duct stones	10.1	18.6	Meta-analysis
Liver cirrhosis	15.3	3.8	Meta-analysis
Hepatitis B virus infection	5	5	Meta-analysis
Chronic pancreatitis	2.7	6.6	Population study
Chronic hepatitis B	4.6	2.1	Meta-analysis
Chronic hepatitis C	4.3	2	Meta-analysis
Inflammatory bowel disease	2.7	2.4	Meta-analysis
Alcohol consumption	3.2	1.8	Meta-analysis
Non-alcoholic fatty fiver disease	2.2	1.5	Meta-analysis
Hemochromatosis	2.1	2.1	Population study
Type 2 diabetes	1.7	1.5	Meta-analysis
Smoking	1.3	1.7	Meta-analysis
Obesity	1.1	1.2	Meta-analysis

OR — odds ratio is a statistic that measures the strength of association between two events, comparing the likelihood of one event occurring (in this case, bile duct cancer) in the presence of another event (the risk factor) with the likelihood of the same event occurring in the absence of the second event

Histopathological analysis of tumor biopsy remains the main method of confirming the diagnosis of bile duct cancer; however, if the patient qualifies for resection, a biopsy may not be necessary [17].

Role of individual diagnostic tests in diagnosing biliary tract cancers

Imaging methods used in the diagnosis of bile duct cancer include conventional ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and contrast-enhanced ultrasound (CEUS). MRI can provide a better assessment of the primary mass in the intrahepatic location, while CT is more accurate in imaging vascular enhancement, making it an essential examination in determining resectability [2]. In cases of suspected perihilar or distal bile duct cancer, magnetic resonance cholangiopancreatography (MRCP) is used [17]. The sensitivity and specificity of MRCP in distinguishing benign and malignant causes of bile duct obstruction in the hilar region are 87% and 85%, respectively [18]. Magnetic resonance cholangiopancreatography can also accurately visualize bile duct anatomy before endoscopic intervention using endoscopic retrograde cholangiopancreatography (ECPW). Endoscopic retrograde cholangiopancreatography serves a diagnostic and therapeutic role, allowing the detection of malignant strictures in case of diagnostic uncertainty and the collection of bile duct samples for cytological and fluorescent *in situ* hybridization (FISH) analysis. A positive cytology result from the bile ducts or biopsy sample for adenocarcinoma is diagnostic for bile duct cancer [19].

Contrast-enhanced computed tomography

Contrast-enhanced computed tomography, including the chest, abdomen, and pelvis, should be performed in all cases of suspected bile duct cancer as the initial standard imaging method. The main advantage of this method is very high spatial resolution, allowing comprehensive assessment of the primary tumor, its local vascular relationships (including potential vascular anomalies), and overall resectability [20, 21]. Computed tomography also allows the detection of local lymphadenopathy and metastatic disease, although sensitivity is lower than for positron emission tomography (PET) [22]. A meta-analysis involving 448 patients from 16 studies provided data mainly on CT, with an estimated accuracy of tumor staging of 86%; estimated sensitivity and specificity were 89% and 92%, respectively, for portal vein involvement, 83% and 93%, respectively, for hepatic artery involvement, and 61% and 88%, respectively, for lymph node involvement [23]. Assessing the extent of bile duct involvement with CT can also be challenging, especially in perihilar tumors.

Magnetic resonance imaging and magnetic resonance cholangiopancreatography

A meta-analysis of 32 studies involving 1626 patients showed that the sensitivity and specificity of MRI for local tumor staging were 90% and 84%, respectively, while for lymph node metastasis assessment, they were 64% and 69%, respectively [24].

The choice of contrast agent depends on the type and location of the tumor. In the case of intrahepatic tumors, MRI with hepatobiliary contrast is considered the most accurate method for identifying satellite lesions and intrahepatic metastases [25]. In the case of perihilar tumors, especially in the presence of bile duct obstruction, the use of extracellular contrast agents is recommended [21].

Diffusion imaging should be routinely included in the examination as it helps characterize intrahepatic bile duct lesions and detect extrahepatic lesions. For perihilar tumors, MRCP combined with contrast-enhanced MRI helps determine the local extent of bile duct involvement, which is important for assessing resectability and planning bile drainage [26]. In the case of tumors involving the distal part of the common bile duct, it is unlikely that MRI will provide additional information beyond that obtained with CT [17].

Positron emission tomography with ^{18}F-fluorodeoxyglucose

Positron emission tomography with ^{18}F-fluorodeoxyglucose (^{18}FDG-PET) combined with CT (^{18}FDG-PET-CT) is recommended as part of the staging studies to detect lymph node and distant metastases [17].

A meta-analysis evaluating the diagnostic value of ^{18}FDG-PET-CT showed a 15% (95% CI 11–20) rate of treatment changes based on ^{18}FDG-PET-CT results, with most changes resulting from upstaging the disease [27]. The meta-analysis results do not support the use of ^{18}FDG-PET-CT for diagnosing the primary tumor in the absence of other disease foci or pathological confirmation due to low specificity.

Interventional radiology

Percutaneous liver biopsy under image guidance (mainly in the form of transabdominal ultrasound) is used for diagnosing intrahepatic bile duct cancer and, if possible, non-resectable extrahepatic bile duct cancer. Biopsy under transabdominal ultrasound or CT guidance for diagnostic purposes can also be performed in the case of metastatic bile duct cancer, targeting the most accessible site [17].

There is no evidence to support and justify the routine use of CEUS in biopsies conducted under transabdominal ultrasound guidance for focal liver lesions due to cost and time. CEUS may be useful when a second biopsy is necessary due to insufficient material in the initial biopsy with necrotic material or insufficient

visualization of the focal liver lesion, which may be relevant in a small percentage of cases [28].

Endoscopy

Endoscopy in the treatment of patients with bile duct cancer includes three goals: 1) establishing histological/cytological diagnosis; 2) facilitating surgery and chemotherapy; 3) alleviating symptoms of cholestasis and improving quality of life. This is particularly true for tumors located distally and in a perihilar position.

Considering that endoscopic procedures can cause complications that may affect the interpretation, sensitivity, and specificity of radiological staging, it is recommended that basic diagnostic and staging studies be performed before endoscopy. This will also facilitate the planning of the endoscopic procedure by the operator [17].

In practice, after analyzing radiological images, distinguishing potential causes of malignant distal bile duct strictures is not always possible (e.g., differentiation between distal bile duct cancer, pancreatic cancer, ampullary cancer, and perivascular cancer).

In cases of suspected ampullary lesions, diagnosis should begin with duodenoscopy with surface biopsy if indicated by primary imaging.

Patients with malignant distal common bile duct strictures potentially eligible for surgery should undergo a combination of endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ECPW) to maximize the possibility of histological diagnosis before surgery.

In patients without jaundice with distal common bile duct strictures potentially eligible for surgical treatment, EUS should be performed first to avoid ECPW complications that may delay or prevent surgery.

In the presence of jaundice and distal common bile duct stricture where EUS is not available, patients may undergo ECPW with brush cytology or fluoroscopy-guided biopsy to confirm the diagnosis of bile duct cancer [17].

In ECPW, the simplest method for tissue collection (available in most centers) is to obtain cytological diagnosis using bile duct brushings and cytological examination [29]. However, the diagnostic value of brush cytology is low. Recent meta-analyses suggest that brush cytology provides a correct cytological diagnosis with a sensitivity of 45% and specificity close to 99% [30]. It is recommended to brush the stricture more than five times with one brush to increase the number of collected cells [17].

To improve the low sensitivity of brush cytology, additional techniques such as FISH and digital image analysis are suggested. Fluorescent *in situ* hybridization uses a combination of molecular probes to detect the presence of polysomy (defined as more than 5 cells expressing two or more molecular markers) [31]. However, these techniques are not routinely available in most centers.

Another method of performing bile duct biopsies during ECPW is to obtain tissue from the stricture using intraductal forceps under leader or fluoroscopy guidance. These biopsies are placed directly in formalin and, similar to brushings, offer a sensitivity of about 50%, but by combining them with brushings, higher sensitivity can be achieved [32].

In selected cases (especially with proximal bile duct strictures), direct cholangioscopy is an additional method for making histological diagnosis by combining direct visualization and intraductal biopsies. Most centers use a single-use cholangioscope operated by one operator. In a meta-analysis of eight studies involving 335 patients, diagnostic sensitivity of cholangioscopy was 90%, and specificity was 80% [33]. For targeted tissue biopsies, a meta-analysis of 10 studies involving 456 patients showed that the sensitivity of cholangioscopy was 60% and specificity was 98% [34].

Biomarkers present in bile and blood

In the near future, an increasing number of molecular bile markers may contribute to better differentiation of malignant and benign bile duct strictures. However, none of them can be currently recommended as they often rely on different pathologies (and different clinical stages) and are limited to single-center studies. Additionally, none of them provide nearly 100% sensitivity or specificity, so molecular bile markers should still be considered a still-researched tool. However, recent publications on bile sample sequencing indicate its great potential [35], but until validated and standardized, this technique cannot be recommended.

The CA19-9 antigen is the main serum marker used in diagnosis of bile duct cancer, but its specificity is low, and its levels can be elevated in various conditions. It is considered that a CA19-9 level > 1000 U/mL in blood serum raises suspicion of advanced bile duct cancer [36].

It should be emphasized that obtaining cytological/histological confirmation of the diagnosis of bile duct cancer is a significant challenge in current clinical practice, and in cases where doubts remain, the decision to undertake surveillance or surgery to obtain a definitive diagnosis should be made only after thorough discussion between the patient and the clinician. International guidelines allow recommending surgery when histologically the diagnosis cannot be excluded, and surgery can provide a cure and certain diagnosis [17].

Durvalumab in patients with biliary tract cancer

First-line palliative treatment — the role of conventional chemotherapy

For patients diagnosed with unresectable or metastatic biliary tract cancer, systemic treatment is palliative in nature [37]. For over a decade, standard chemotherapy

for these patients has been combination therapy based on gemcitabine and cisplatin. This approach was established in 2010 based on the results of the phase III randomized clinical trial ABC-02 (Advanced Biliary Cancer–02 trial) [38]. The study included 410 patients with histopathologically confirmed advanced biliary tract cancers in all anatomical locations (including gallbladder cancer and ampulla of Vater cancer). The study planned systemic treatment for up to 24 weeks in 3-week cycles (a total of 8 treatment cycles). Median OS (primary endpoint) in the group receiving gemcitabine monotherapy was 8.1 months, while in the combination therapy group, it was 11.7 months [hazard ratio (HR) = 0.64; 95% confidence interval (CI) 0.52–0.80; $p < 0.001$]. Additional benefits were observed in other parameters, such as PFS (8 *vs.* 5 months; HR = 0.63; $p < 0.01$) and disease control rate (DCR; 81.4% *vs.* 71.8%; $p = 0.049$). Toxicity of the treatment, particularly enhanced myelosuppression, was mainly associated with neutropenia. There were no significant differences between the study groups in the frequency of severe infections [38].

Since the publication of the ABC-02 study results, the combination therapy of gemcitabine and cisplatin has become an internationally recognized standard treatment for patients with biliary tract cancer who are in good or very good general condition [Eastern Cooperative Oncology Group (ECOG) 0 or 1] and have normal renal function. For patients in poorer condition (ECOG 2) or with significant clinically relevant comorbidities and/or contraindications to cisplatin, gemcitabine monotherapy should be considered [37, 39].

Durvalumab combined with chemotherapy — a new standard of therapy

In 2022, a breakthrough occurred in the standard of systemic therapy for advanced and/or metastatic biliary tract cancer, with the confirmation of the benefit of adding durvalumab (a human anti-PD-L1 monoclonal antibody) to standard chemotherapy. This change was based on the published results of the phase III randomized, double-blind clinical trial, TOPAZ-1 [40]. Recruitment for this study took place between April 2019 and December 2020 in 105 clinical centers across 17 countries, including Poland. A total of 685 patients with histologically confirmed locally advanced, unresectable, or metastatic biliary tract adenocarcinoma who were previously untreated or had a recurrence of the disease at least 6 months after primary radical surgery were enrolled and randomized. During randomization, patients were stratified by disease status (unresectable or recurrent) and primary tumor location (intrahepatic *vs.* extrahepatic *vs.* gallbladder cancer). The study administered intravenous infusions of durvalumab at a dose of 1500 mg or placebo in combination with gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2. Durvalumab and placebo were given on day 1, and gemcitabine and cisplatin on days 1 and 8 of each 21-day cycle for 8 cycles. Patients then continued durvalumab 1500 mg or placebo once every 4 weeks (28 days) until disease progression or other predefined criteria for treatment discontinuation (e.g., unacceptable toxicity). Treatment response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 The primary endpoint was OS (defined as the time from randomization to death from any cause). Secondary endpoints included PFS, overall response rate (ORR), DCR, and treatment efficacy depending on PD-L1 expression.

The statistically significant impact of this treatment on OS was demonstrated (median OS — 12.8 *vs.* 11.5 months; HR = 0.80; 95% CI 0.66–0.97; $p = 0.021$). Statistically significant differences in favor of adding durvalumab compared to placebo were also observed in secondary endpoints (PFS 7.2 *vs.* 5.7 months; ORR 26.7% *vs.* 18.7%). No predictive factors for treatment response were identified. Therefore, contemporary immunochemotherapy is recommended for all patients regardless of the primary anatomical site within the biliary tract or the PD-L1 expression status in tumor tissue. Regarding reported treatment toxicities, no significant differences in the incidence of grade 3 and 4 adverse events were noted between the study groups (75.7% and 77.8% for durvalumab and placebo, respectively). The most common grade 3 or 4 treatment toxicities are presented in Figure 3 [40].

Analyses of the therapy's impact on quality of life, conducted using European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EORTC QLQ-BIL21 assessment questionnaires, did not show a significant decrease in the quality of life in any of the studied functional areas. Adjusted mean changes compared to baseline values suggested an improvement in quality of life in the case of durvalumab in combination with chemotherapy. The median time to patient-reported deterioration in overall health/quality of life was slightly longer for durvalumab in combination with chemotherapy (7.4 months) compared to placebo in combination with chemotherapy (6.7 months), although this difference was not statistically significant [40].

Durvalumab is currently (December 2024) registered for systemic treatment, in addition to biliary tract cancer, in other indications such as locally advanced and metastatic non-small cell lung cancer, small cell lung cancer, and advanced hepatocellular carcinoma. Durvalumab for biliary tract cancer treatment is administered as an intravenous infusion (60 minutes) once every 3 weeks, in combination with gemcitabine and cisplatin for 8 cycles, followed by monotherapy once every 4 weeks. Treatment should be continued

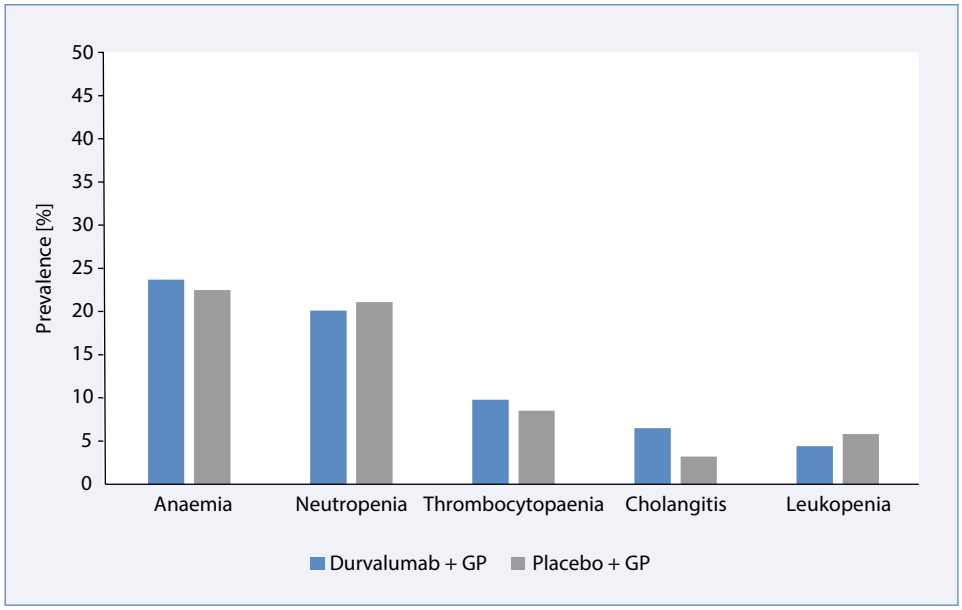

Figure 3. The most common adverse events (reported in > 5% of patients) in grade 3 or 4 in the study and control groups [40]; GP — gemcitabine + cisplatin

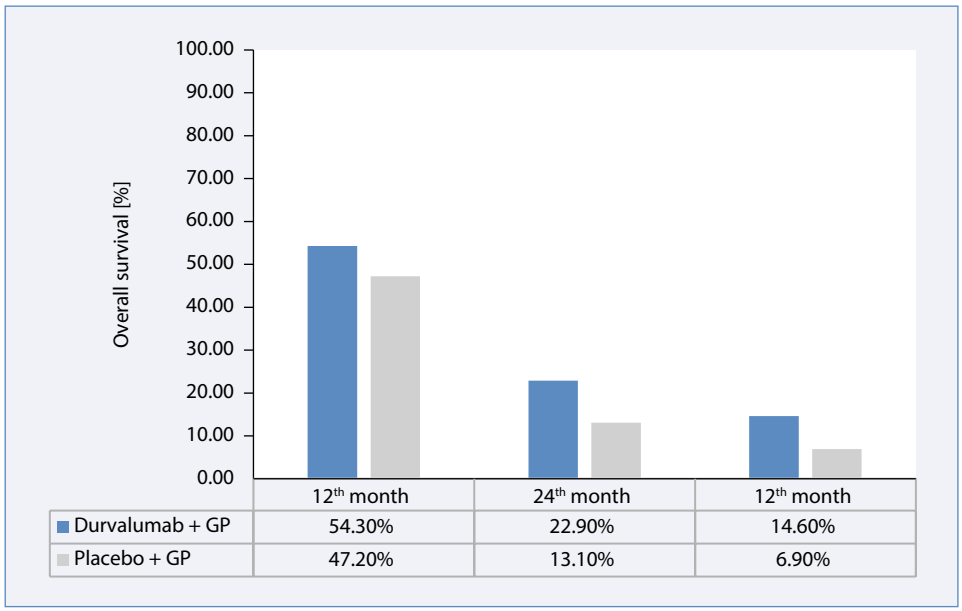

Figure 4. Percentages of overall survival of study groups at 12, 24 and 36 months in the TOPAZ-1 study [42, 43]; GP — gemcitabine + cisplatin

until disease progression or occurrence of unacceptable toxicity. The recommended dose of durvalumab is 1500 mg. Patients with a body weight of 36 kg or less should receive a weight-adjusted dose of durvalumab at 20 mg/kg of body weight. Durvalumab, used in combination with chemotherapy, is administered before chemotherapy on the same day [see current Summary of Product Characteristics (SmPC)] [41].

Recently updated results from the TOPAZ-1 study confirm that durvalumab, in combination with chemotherapy, improves survival in patients with advanced biliary tract cancer, increasing the chances of long-term treatment responses and survival rates at 12, 24, or 36 months (Fig. 4) [6]. After a median follow-up time of 41.3 months (the longest published for immunotherapy in this indication), durvalumab in combination

with chemotherapy reduced the risk of death by 26% compared to chemotherapy alone (HR = 0.74; 95% CI 0.63–0.87), representing a numerical increase compared to the primary analysis (HR = 0.80; 95% CI 0.66–0.97). In this analysis, the median OS rate was 12.9 months for the treatment group compared to 11.3 months for the chemotherapy-only group. It is worth noting that the three-year survival rate was twice as high in the treatment group, at 14.6%, compared to 6.9% in the placebo group. Analyzing the results of patients with radiologically confirmed disease control during the systemic treatment, three-year OS for the durvalumab in combination with the chemotherapy group was also more than twice as common as in the placebo in combination with the chemotherapy group (14.6% *vs*. 6.9%) [42, 43].

In the safety analysis, serious adverse events considered to be treatment-related by the researchers occurred in 15.4% of patients who received durvalumab in combination with chemotherapy and in 17.3% of patients who received placebo in combination with chemotherapy. The most frequently reported adverse events, regardless of cause or toxicity grade, were anemia, nausea, constipation, and neutropenia in the durvalumab group and anemia, nausea, and neutropenia in the placebo with the chemotherapy group. The frequency of adverse events defined by researchers as having an immunological basis was higher in the durvalumab group (14%) than in the placebo group (5%). However, these complications of grade 3 or 4 intensity were observed in only 2% of patients receiving durvalumab and in 1% of patients receiving placebo. No new, unusual adverse events related to this therapy were reported in patients with biliary tract cancer [42, 43].

In summary, the long-term results of the TOPAZ-1 study confirm the efficacy of combining durvalumab with chemotherapy, reinforcing its position as the standard therapeutic option in this difficult disease entity with unfavorable prognosis. The safety profile of durvalumab in combination with chemotherapy was consistent with previously published analyses and is associated with low risk of adverse events related to immunotherapy.

The use of durvalumab in the treatment of patients with biliary tract cancer in the context of "real-world evidence"

Data obtained from clinical trials form the foundation for evaluating the effectiveness and safety of new therapies. Clinical trials are designed to create tightly controlled conditions, similar to studies conducted in laboratory settings, allowing for a more precise assessment of the effect of the intervention being evaluated. This includes population selection and treatment administration according to a strict protocol, leading to differences between the clinical trial population and patients treated in everyday clinical practice, as well as differences in the way treatments are conducted between the study and actual practice. Consequently, the results of clinical trials may not be fully representative of the broader patient population in real clinical conditions [44].

The assessment of real-world clinical data, referred to as "real-world evidence" (RWE), helps to understand the actual effectiveness of treatment beyond the conditions of clinical trials. RWE data include information collected from routine medical practice, such as medical registries, hospital databases, or insurance records. Analyzing such aggregated data, especially from multiple centers, helps evaluate the effectiveness and safety of new therapies in a broader patient population and the context of everyday clinical practice. It is important to consider that data from clinical practice are not collected under controlled conditions and may vary in terms of detail depending on their origin and degree of aggregation. From this perspective, it is important to emphasize that RWE cannot replace clinical trials but rather aids in their interpretation in the context of everyday clinical practice.

Data from RWE analyses provide valuable insights into the effectiveness of treatments for patients with biliary tract cancer. An example of such analysis comes from administrative databases in Ontario, presented by Seung et al. [45]. The analysis included 2142 patients with advanced biliary tract cancer, the majority of whom experienced disease recurrence after radical treatment, with only a minority diagnosed *de novo* with advanced/metastatic biliary tract cancers. A subset of the patients received first-line systemic treatment, most commonly gemcitabine with cisplatin, and a smaller percentage received second-line systemic treatment. The median OS rate from diagnosis to death for the entire group was 11.0 months, with a significant difference observed between patients who received any systemic treatment (14.1 months) and those who did not (3.3 months). The median OS rate from the start of first-line treatment for all patients, regardless of chemotherapy regimen, was 7.4 months and was significantly better in the group treated in the first line with gemcitabine and cisplatin, reaching 9.3 months.

We already have the first RWE data evaluating the efficacy of the combined treatment of gemcitabine, cisplatin, and durvalumab in the first-line treatment of locally advanced or metastatic biliary tract cancer. The first published study is a multicenter analysis of data from 17 centers in Italy, published by Rimini et al. in 2023 [46]. This analysis included 145 patients with locally advanced or metastatic biliary tract cancer, of whom 60% had intrahepatic biliary tract cancer, 24.8% had extrahepatic

biliary tract cancer, and 15.2% had gallbladder cancer. Previous surgical treatment was received by 28.3% of the patients. All patients were treated identically to the TOPAZ-1 study — they received up to 8 cycles of gemcitabine and cisplatin chemotherapy, as well as durvalumab, after which they continued maintenance treatment with durvalumab until disease progression. After a median follow-up of 8.5 months, median PFS of 8.9 months and median OS from the start of systemic treatment of 12.9 months were achieved, which was consistent with the results of the TOPAZ-1 study. The ORR was 34.5%, with 4.8% complete responses (CR) and 29.6% partial responses (PR). The safety profile was also similar to the results of the TOPAZ-1 study, with 94.5% of patients experiencing any grade of adverse events and 35.2% experiencing grade 3–4 adverse events. There were no deaths related to durvalumab treatment, and the percentage of patients who discontinued durvalumab due to adverse events was 4.1%. More than half (55.3%) of patients with disease progression received subsequent-line treatment.

The second available analysis is a 2024 study published by Rimini et al. [47]. The similarity in author names is not coincidental, as this is an extensive RWE analysis from the same 17 centers in Italy as the 2023 study. In this retrospective study, both patients treated with gemcitabine, cisplatin, and durvalumab, as well as a control group treated exclusively with gemcitabine and cisplatin, were included. A total of 563 patients were evaluated – 350 in the combination chemotherapy group with durvalumab and 213 in the group receiving chemotherapy alone. Both groups did not significantly differ in terms of demographic and clinical data, except for a higher percentage of patients over 70 years of age in the combination treatment group. It is worth noting that, similar to the previous analysis, the majority of patients had intrahepatic biliary tract cancer (approximately 56% in both groups), and a minority had undergone prior surgical treatment for biliary tract cancer (slightly over 30% in both groups). The median follow-up was 11.5 months in the combination treatment group and 30.1 months in the chemotherapy-only group. The median OS rate was 14.8 months in the combination treatment group compared to 11.2 months in the chemotherapy-only group. The median PFS rate was 8.3 months in the combination treatment group and 6 months in chemotherapy-only group. Survival differences in favor of the combination treatment were evident in all subgroups, with the greatest benefit seen in patients with locally advanced biliary tract cancer without distant metastases and in patients over 70 years of age. In the propensity score matching analysis, which included 213 patients from each group, significant differences in favor of the combination treatment were also obtained in terms of median OS (13.2 months in the combination treatment group compared to 11.2 months in the chemotherapy group; HR = 0.61; 95% CI 0.53–0.94; p = 0.01), as well as median PFS (7.4 months compared to 6 months; HR = 0.63; 95% CI 0.51–0.97; p = 0.002). Safety profiles of both treatment regimens were not compared in this study. The analysis indicated greater benefit from the combination treatment versus chemotherapy alone in patients with neutrophil-to-lymphocyte ratio (NLR) < 3, ECOG 0, and locally advanced disease without distant metastases. The overall findings were in line with the TOPAZ-1 study results.

The last of the currently available RWE studies, at this moment, is a retrospective, collective analysis from a total of 39 centers in 11 countries in Europe, Asia, and the United States, published by Rimini et al. once again [48]. This largest RWE analysis of durvalumab's effectiveness in combination with gemcitabine and cisplatin involved a total of 666 patients. The study demonstrated an ORR of 32.7%, with a DCR [percentage of patients with CR, PR and stable disease (SD) according to RECIST] of 77.9%. The median PFS rate was 8.2 months, and the median OS rate was 15.1 months. Subgroup analyses showed poorer prognoses in patients with high baseline carcinoembryonic antygen (CEA) values, ECOG performance status > 0, the presence of distant metastases, and NLR > 3. The percentage of all adverse events > G2 was 46.6%, with adverse events associated with durvalumab > G2 at 2.5%. Immunological adverse events led to discontinuation of durvalumab in only 1.5% of patients. The study also assessed the impact of selected genetic disorders (such as *FGFR2* fusions, *IDH1* mutations, *BRAF V600E* mutations, *KRAS G12C* mutations, or HER2 amplifications) on patient prognosis, finding no statistically significant differences in any of the analyzed molecular subgroups. However, significantly better survival was observed in patients who received molecularly targeted drugs in the second line (median OS after progression not reached) compared to those who received second-line chemotherapy (median OS after progression 6.2 months) (HR = 0.40; 95% CI 0.20–0.83; p = 0.00133). Similar to previous analyses, the effectiveness indicators of combination therapy with gemcitabine, cisplatin, and durvalumab appear to be consistent with the results achieved in the TOPAZ-1 study.

The available RWE data evaluating the value of combining gemcitabine-cisplatin chemotherapy with durvalumab are in line with the results obtained in the TOPAZ-1 registration study, and they are also better than the results achieved with gemcitabine and cisplatin in earlier RWE analyses. The confirmation of the benefits arising from adding durvalumab to gemcitabine-cisplatin chemotherapy in data derived from real-world clinical practice justifies the recognition of this treatment regimen as the standard of care for first-line treatment of patients with locally advanced or metastatic biliary tract cancer.

Possibilities of treatment with durvalumab in the drug program "Treatment of patients with hepatocellular carcinoma or biliary tract cancer"

Currently (as of December 2024), the use of chemotherapy combining gemcitabine with cisplatin and durvalumab in the first-line treatment of patients with biliary tract cancer is the standard of care included in the recommendations of the ESMO, NCCN, and PTOK. For a long time, this treatment in Poland was limited by the lack of reimbursement for durvalumab in this indication. Fortunately, after the recent changes, we have the drug program "Treatment of patients with hepatocellular carcinoma or biliary tract cancer," allowing the treatment of patients with biliary tract cancer in Poland in accordance with current standards.

The mentioned drug program regarding biliary tract cancer may include patients with microscopically confirmed (histopathologically or cytologically) biliary tract cancer, including those with intrahepatic and extrahepatic biliary tract cancer, as well as those with gallbladder cancer. The possibility of qualification includes patients not previously subjected to systemic treatment for advanced biliary tract cancer, regardless of prior surgical treatment and any adjuvant chemotherapy, provided that the treatment was radical. Other significant qualification criteria include an appropriate performance status (ECOG 0–1), ability to assess treatment response according to RECIST criteria, adequate organ function as assessed by the treating physician, as well as no contraindications to durvalumab, cisplatin, and gemcitabine, and no presence of concomitant conditions preventing the implementation of treatment, as determined based on the current SmPC of the program components. Similar to other treatment regimens containing immunotherapy, the drug program excludes patients with active autoimmune diseases, except type 1 diabetes, hypothyroidism, psoriasis, and vitiligo. It also requires the absence of symptomatic metastases in the central nervous system (inclusion of patients is permissible after previous radical surgical treatment or stereotactic radiotherapy with no evidence of changes on imaging studies and no neurological symptoms); pregnant and breastfeeding women are also excluded. In the case of concomitant active tumors, qualification for the drug program requires consideration of the prognosis resulting from the presence of the concomitant tumor. Treatment under the program is conducted routinely until disease progression, according to RECIST, significant deterioration in quality of life due to complications or worsening of ECOG performance status to ≥ 2, as well as occurrence of pregnancy/breastfeeding, hypersensitivity reactions, or any other condition that, in the physician's opinion, prevents the continuation of treatment.

The current (December 2024) version of the drug program "Treatment of patients with hepatocellular carcinoma or biliary tract cancer" allows the qualification for treatment with gemcitabine and cisplatin in combination with durvalumab for patients diagnosed with C24.1, defined according to ICD-10 classification as "Malignant neoplasm: Ampulla of Vater." Patients with Vater's ampulla cancer were not qualified for the TOPAZ-1 study, and there is lack of data in this subgroup regarding the activity of the combination of gemcitabine and cisplatin with durvalumab. At the same time, it is known from clinical practice that the C24.1 group often includes patients with classic ampulla of Vater cancer, as well as cancer of the duodenum, cancer of the distal biliary tract, or pancreatic cancer, due to diagnostic difficulties and the frequent inability to precisely specify the location of the primary lesion. In our opinion, the qualification of patients diagnosed with C24.1 for the current drug program "Treatment of patients with hepatocellular carcinoma or biliary tract cancer" requires special attention and careful consideration of whether, in a specific case, we are indeed dealing with a tumor originating from the distal segment of the biliary tract, i.e., the group of patients with C24.1 diagnosis who will actually benefit from the addition of durvalumab to cisplatin and gemcitabine.

The drug program "Treatment of patients with hepatocellular carcinoma or biliary tract cancer" for biliary tract cancer involves the use of chemotherapy with gemcitabine (at a dose of 1000 mg/m^2) and cisplatin (at a dose of 25 mg/m^2) administered on days 1 and 8 of the cycle in combination with durvalumab (at a fixed dose of 1500 mg) administered on day 1 of the cycle, with cycles repeated every 21 days (3 weeks; Tab. 3). The duration of treatment with the combined chemotherapy and durvalumab is 8 cycles, followed by maintenance treatment with durvalumab at a dose of 1500 mg every 4 weeks. Treatment modifications and dose reductions are in accordance with the appropriate SmPC. It is important to note that in the case of adverse events with durvalumab, it is possible to delay the administration of the next dose, but there is no possibility of reducing the dose of this drug [49].

Including a patient in the drug program requires performance of appropriate tests as described in the program, which are not significantly different from those typically conducted at the initiation of treatment containing chemotherapy and immunotherapy. Most monitoring tests are performed before each subsequent cycle of treatment during the use of the combination of chemotherapy and immunotherapy and then no less frequently than every 3 months during the maintenance treatment with durvalumab. Imaging studies

Table 3. Dosing schedule of durvalumab with gemcitabine and cisplatin [41]

Cycle	Day	Durvalumab	Cisplatin	Gemcitabine
C1–8 (every 3 weeks)	D1	1500 mg	25 mg/m^2	1000 mg/m^2
C1–8 (every 3 weeks)	D8	–	25 mg/m^2	1000 mg/m^2
> C8 (every 4 weeks)	D1	1500 mg	–	–

*Unless dose reduction is indicated or the dose has been previously reduced

for monitoring treatment effectiveness should be conducted at least every 3 months, using the same imagining method as in the qualification assessment [49].

The aforementioned changes in the drug program "Treatment of patients with hepatocellular carcinoma or biliary tract cancer" aim to align the first-line treatment of biliary tract cancer in Poland with European and global standards. The broad eligibility criteria and the scope of required procedures appear to be consistent with standard treatment protocols and facilitate the practical implementation of the program, which, in our opinion, should bring tangible benefits to patients and provide satisfaction from effective treatment for healthcare professionals.

Article Information and Declarations

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Conflict of Interest
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Supplementary material
None.

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