Cancer Immunology, Immunotherapy (2024) 73:251
https://doi.org/10.1007/s00262-024-03842-y

RESEARCH

Exploring the impact of durvalumab on biliary tract cancer: insights from real-world clinical data

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Received: 1 August 2024 / Accepted: 20 September 2024 / Published online: 3 October 2024

Abstract

Introduction This study assesses the effectiveness of durvalumab with platinum and gemcitabine for biliary tract cancers (BTC). It aims to confirm the TOPAZ-1 trial results in a real-world context and explore the link between BTC molecular profiles and patient outcomes.

Methods A retrospective analysis was conducted on 102 BTC patients treated with durvalumab, platinum, and gemcitabine at five cancer centers in Austria and one in Germany from 2022 to 2024. Molecular profiling used targeted DNA and RNA assays. Clinical endpoints, including progression-free survival (PFS) and overall survival (OS), were assessed using log-rank tests and Cox regression, with correlations to second-line molecular-targeted therapies.

Results Among 102 patients, 60.8% had intrahepatic cholangiocarcinoma. The treatment achieved a disease control rate of 71.57% and an overall response rate of 35.11%. Median PFS was 6.51 months, and OS was 13.61 months. Patients under 65 had significantly better OS. Alterations in chromatin remodeling or homologous recombination repair genes were not predictive of survival benefit (HR: 0.45; $p = 0.851$ and HR: 1.63; $p = 0.26$, respectively). Patients with molecular-informed second-line therapy showed a trend toward survival benefit (HR: 0.23; $p = 0.052$).

Conclusion This study confirms the phase 3 trial results of durvalumab with platinum and gemcitabine, providing a substantial real-world dataset with detailed molecular characterization. No specific patient subgroup showed a markedly better response to durvalumab based on conventional NGS panels. Further research is needed to explore the link between immunotherapy responses and molecular subgroups.

Keywords Durvalumab · Homologous recombination repair (HRR) · Chromatin remodeling · Biliary tract cancer · Molecular-informed therapy · Precision oncology

Introduction

Biliary tract cancer (BTC) constitutes a heterogeneous group of malignancies arising from various parts of the biliary system. This collective term includes carcinomas of the gallbladder/cystic duct (GBC) and cholangiocarcinomas (CCA). CCAs can be further divided into three subtypes: intrahepatic (iCCA), perihilar (pCCA) and distal (dCCA), depending on their exact anatomical origin [1, 2].

Although, BTCs are quite rare, accounting for less than 1% of all malignant tumors, recent data have shown an increase in global incidence [2–4]. Prognosis remains poor with 5-year overall survival rates of approximately 5–15% [5, 6]. This is attributed to several reasons, primarily: 1) about two thirds of all patients are diagnosed with advanced/metastatic disease and 2) patients undergoing potentially curative resection for localized tumors suffer from a high relapse rate [7].

Palliative treatment in advanced BTCs was studied intensely over the past decades. However, after gemcitabine was first established as a valid treatment option in 1996, many subsequent trials with different treatment approaches yielded disappointing results [7, 8]. Progress was not achieved until the ABC-02 trial in 2010. This phase

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III study investigated gemcitabine in combination with cisplatin against gemcitabine alone and showed a statistically significant advantage in median overall survival (OS) of 11.7 vs. 8.1 months, thereby establishing a new standard of care for advanced/metastatic BTCs [9]. The next milestone in BTC treatment was reached when the results of TOPAZ-1 trial were published, reporting improved OS (12.8 vs. 11.5 months; HR 0.80; $p = 0.021$) and median progression-free survival (PFS) in patients treated with durvalumab plus gemcitabine and cisplatin over gemcitabine and cisplatin [10]. Thus, this combined chemoimmunotherapy is currently considered standard of care as first-line treatment in patients with BTCs [2].

Specifically, BTCs seem to be excellent candidates for molecularly guided treatment strategies. Notably, nearly half of the patients with BTC might be eligible for therapies based on molecular diagnostics [20, 21]. Molecular informed therapies have been introduced as second-line treatments, strongly recommended by the ESMO guidelines, as they provide an overall survival advantage [20, 21]. For some of these alterations, approved therapies are already available.

Recently ClarIDHy led to the approval of Ivosidenib in isocitrate dehydrogenase 1 (*IDH1*) mutant BTCs showing an improvement in PFS [11].

Further studies on targetable alterations such as *FGFR2* fusions (FIGHT-202 trial), HER2 amplification/overexpression (MyPathway trial), *BRAF* mutations (ROAR trial) and *NTRK* fusions (ALKA-372–001, STARTRK-1, and STARTRK-2 trial) opened up new second-line treatment options and are validated by multiple real-world cohorts [12–21].

However, despite recent progress in palliative treatment many questions remain unanswered: 1) There is paucity of real-world clinical data on the efficacy of first-line gemcitabine/cisplatin/durvalumab. 2) Predictive biomarkers highlighting patients, who benefit most from the addition of durvalumab are currently pending. 3) The majority of previously mentioned studies on targeted therapies in second line did not employ gemcitabine and cisplatin plus durvalumab as first-line therapy. Current clinical data are therefore urgently needed to address this gap.

Materials and methods

Patients

We conducted a retrospective analysis involving 102 patients with histologically confirmed biliary tract cancer treated with durvalumab, platin and gemcitabine at five cancer centers in Austria and one comprehensive cancer center in Germany. The initial diagnoses were made between April 2022 and January 2024.

Written informed consent for molecular analysis was obtained from all patients as part of routine clinical workflow. The study protocol received approval from local committees on human research (21–10239-BO, Essen, Germany; Ethics Committee, Land Oberoesterreich, 1100/2023; and Ethics Committee of the City of Vienna, EK-1099/2021), ensuring compliance with the ethical guidelines of the 1975 Declaration of Helsinki.

Clinical data were retrieved from the patients' electronic records system, encompassing demographics, clinical history, surgical interventions, chemotherapy, molecular-informed therapies, response to treatment, molecular pathology diagnostics, and survival status up to March 29th 2024. Decisions regarding individual molecular-matched therapeutic options were based on contemporary scientific and clinical knowledge, the availability of clinical trials, and approved agents at the time. Disease stages were defined according to the TNM 8th edition [22–25]. Patients with distal CCAs, perihilar CCAs and carcinomas of the Ampulla Vateri were pooled under the term extrahepatic cholangiocarcinoma (eCCA).

Molecular profiling and classification of mutations

DNA and RNA were extracted from formalin-fixed, paraffin-embedded (FFPE) samples from core tumor biopsies or surgical samples. Sequencing was conducted using customized NGS panels: TruSight Tumor 170, TruSight Oncology 500 (Illumina Inc., San Diego, CA, USA), GeneRead DNAseq Custom Panel V2 (QIAgen, Hilden, Germany), Oncomine Comprehensive V3, Ion AmpliSeq Cancer Hotspot Panel v2 (Thermo Fisher Scientific, Waltham, MA, USA) and FoundationOne CDx hybrid-capture NGS service platform (324 genes for both mutations and fusions) Foundation Medicine, Inc, Cambridge, MA in the Austrian centers, and PACAP Panel (DNA-based customized NGS panel, 20 genes), CCP3 Panel (DNA-based customized NGS panel, 20 genes)(MiSeq platform, Illumina Inc., San Diego, CA, USA)- in the German center. All platforms were used according to the manufacturers´ instructions. For RNA sequencing FusionPlex CTL Panel, Archer (Illumina Inc., San Diego, CA, USA) was used.

Additionally, data on defective mismatch repair (dMMR)/microsatellite instability (MSI) status, PD-1 or PDL-1 and *HER2neu* (IHC) were collected when reported. Genes associated directly or indirectly with homologous recombination repair (HRR) were the following: *ARID1A, BRCA1, BRCA2, PALB2, BARD1, ATR, ATRX, ATM, BAP1, RAD51C, RAD51D, BRIP1, NBN, CHEK1, CHEK2, FANCA, FANCC,* and *MRE11* [26, 27]. Genes thought to be associated with chromatin remodeling comprised: *ARID1A/B, ARID2,*

ASXL1, ATRX, CREBBP, DAXX, DNMT1, DNMT3A, EP300, EZH2, H3F3A, HIST1H3B, IDH1/2, KDM5C, KDM6A, MEN1, MLL2/3, NCOR1, PAX5, PBRM1, PRDM1, SETBP1, SETD2, SMARCA4, SPOP, TET2, WT1 [28, 29].

Identification of pathogenic mutations was based on the effect of the gene alterations (including nonsense, frameshift, start/stop codon alterations and splice site mutations) on the function of the corresponding proteins. These gene changes were then verified for their clinical relevance by querying the following databases: ClinVar, Catalogue of Somatic Mutations in Cancer (COSMIC), Varsome and Alamut Visual Plus (Sophia Genetics) [30–33].

For annotation of targetable mutations, two variant classification systems were implemented: ESCAT, as a framework for the actionability of molecular targets, and the National Center for Tumor Diseases (NCT) Heidelberg variant classifier [34, 35]. Both were used to rank the clinical evidence for the matched molecular-informed therapies. The pathogenicity of mutations was evaluated according to ACMG-AMP (American College of Medical Genetics and Genomics the Association for Molecular Pathology) criteria [36].

Study end points

Our primary objectives were to assess the time to progression on first-line therapy and overall survival of patients treated with platinum plus gemcitabine in combination with durvalumab in first-line therapy. PFS was defined as the time from the start of the first-line chemotherapy until radiologically proven progression, untreatable toxicities or death from any cause, whichever occurred first. The response to treatment was assessed for each therapy line using a combination of clinical response and imaging findings, including computed tomography and magnetic resonance tomography. Radiological response was classified in accordance with the RECIST V1.1 criteria. The Disease Control Rate (DCR) was defined as the proportion of patients who achieved either a complete response (CR), partial response (PR), or stable disease (SD). The Overall Response Rate (ORR) was defined as the proportion of patients who achieved either a CR or PR.

OS was defined as the time from the starting date of first-line palliative chemotherapy to the date of death; patients without documented death on the cut-off date were censored on the date the patient was last known to be alive. Median follow-up was calculated by reverse Kaplan–Meier method.

Statistics

Descriptive statistics were used to summarize the baseline clinical data of all patients and molecular testing results. Differences in baseline characteristics and response rate were calculated using Fisher's exact test.

Survival analysis was conducted for patients who received a first-line platinum-based chemotherapy doublet consisting of platinum and gemcitabine combined with durvalumab.

Time-to-event endpoints were estimated using the Kaplan–Meier method and log-rank test for statistical comparison. The proportional hazards assumption was based on Schoenfeld residuals with a significance threshold of $p = 0.05$. Cox proportional hazards models were used to obtain hazard ratios with 95% confidence intervals. The association between clinical variables and OS was evaluated using univariate Cox regression analysis. The most clinically prominent factors were included in a multivariate Cox model. To address the violation of the rule of 10 events per variable (EPV), a stepwise selection was employed to reduce the number of covariates and enhance the stability of the final model. The stepwise procedure used a p-value threshold of 0.10 for variable inclusion or removal. This approach ensures that only variables contributing significantly to the model are retained, helping to prevent overfitting due to the limited number of events relative to the number of covariates.

Statistical significance was determined by two-sided p-values, with a threshold of $p < 0.05$. All statistical analyses were performed using Stata software package (Stata. version 18.5) and R (version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

Between April 2022 and January 2024 we identified 104 patients with a histologically confirmed diagnosis of biliary tract cancer treated with platinum and gemcitabine plus durvalumab. The allocation of these patients is depicted in Fig. 1.

The study enrolled 102 eligible patients, of whom 43.1% were female and 56.9% were male. The participants had a median age of 65.18 years, with a range from 25.57 to 83.84 years. More than half (52%) of the patients were older than 65 years. The majority (92.2%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. The subtypes of biliary tract cancer included intrahepatic cholangiocarcinoma (iCCA) in 60.8% of patients, distal cholangiocarcinoma (dCCA) in 13.7%, gallbladder cancer in 12.7%, perihilar cholangiocarcinoma in 10.8%, and carcinoma of the Ampulla Vateri in 2.0%. At the time of diagnosis, 76.5% had stage IV disease. A total of 23.5% of patients had metachronous metastatic disease following initial curative surgical resection, and 75% of these patients had received adjuvant therapy. The median body mass index (BMI) was

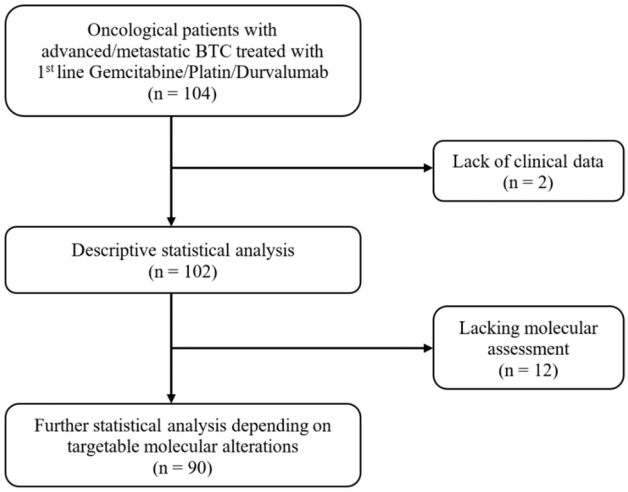

Fig. 1 Study profile. The number of patients (n) at key target points is indicated; BTC, biliary tract cancer

26.2 kg/m^2. Metabolic liver disease was present in 15.7% of patients, and 2.9% had a history of viral hepatitis. A detailed summary of patient characteristics can be found in Table 1.

Molecular characterization

Comprehensive molecular profiling was completed for 90 patients (Fig. 2), with no detectable genetic alterations found in 20% of the cohort. Tumor mutational burden (TMB) was evaluated in 23 patients, showing a median value of 2.61 mutations per megabase (mut/Mb), with a 95% confidence interval (CI) of 2.4–4.62. Microsatellite status was assessed in 75.6% of the patients characterized, with only one patient exhibiting microsatellite instability (MSI). The most frequently mutated genes were *TP53* (29%), *KRAS* (18%), and *CDKN2A* (11%). Alterations in chromatin remodeling genes were identified in 18 patients, with *ARID1A/B* altered in 9% and *IDH1/2* in 10%. Additionally, homologous recombination repair (HRR) gene alterations were observed in 26 patients, with *BAP1* and *BRCA1/2* being the most commonly affected, each in 9% of the cohort, and *ARID1A* in 8%.

In terms of therapeutic relevance, ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) Level I/II alterations were identified in 20 patients, while Level III/IV alterations were seen in 15 patients. The most prevalent actionable alterations were observed in *BRCA1/2* (9%), *IDH1* (8%), *ERBB2* (6%), and *PIK3CA* (5%). *FGFR2* alterations were noted in 4% of patients, including three cases of *FGFR2* fusion.

Table 1 Patient characteristics

Number of patients	102
Gender, n (%)	
Female	44 (43.1)
Male	58 (56.9)
Age, years, median (min, max)	65.18 (25.57, 83.84)
Age < 65 years, n (%)	49 (48.0)
Age ≥ 65 years, n (%)	53 (52.0)
Eastern cooperative oncology group-performance status (ECOG-PS), n (%)	
0	61 (59.8)
1	33 (32.4)
2	8 (7.8)
Tumor location, n (%)	
Intrahepatic CCA	62 (60.8)
Perihilar CCA	11 (10.8)
Distal CCA	14 (13.7)
Ampulla Vateri Carcinoma	2 (2.0)
Gallbladder Carcinoma	13 (12.7)
Stage at diagnosis	
I	1 (1.0)
II	8 (7.8)
III	15 (14.7)
IV	78 (76.5)
Resection of primary tumor, n (%)	
Yes	24 (23.5)
No	78 (76.5)
Adjuvant therapy, n (%)	
Yes	18 (17.6)
No	84 (82.4)
Metabolic liver disease, n (%)	
Yes	16 (15.7)
No	86 (82.4)
History of hepatitis, n (%)	
Hepatitis C	2 (2.0)
Hepatitis B	1 (1.0)
No	99 (97.1)
BMI at diagnosis, kg/m^2, median (IQR)	26.2 (23.0 – 29.0)
Microsatellite instability status, n (%)	
MSS	67 (65.7)
MSI	1 (1.0)
Unknown	34 (33.3)
Tumor mutational burden, mut/Mb	
Median (IQR) §	2.61 (2.0 – 4.7)
First-line regimen, n (%)	
Cisplatin/Gemcitabine/Durvalumab	96 (94.1)
Carboplatin/Gemcitabine/Durvalumab	5 (4.9)
Oxaliplatin/Gemcitabine/Durvalumab	1 (1.0)
ongoing first-line treatment	36 (35.3)
Second-line regimen, n (%)	
FOLFOX	12 (11.8)
FOLFIRI	12 (11.8)

Table 1 (continued)

Number of patients	102
Molecular-informed therapy	12 (11.8)
Third-line regimen, n (%)	
FOLFOX	2 (2.0)
FOLFIRI	5 (4.9)
Capecitabin mono	1 (1.0)
Molecular-informed therapy	2 (2.0)
Fourth-line regimen, n (%)	
Molecular-informed therapy	1 (1.0)
Actionable targets, n (%)	
ESCAT I/II	20 (19.6)
BRAF V600E mutation	1 (1.0)
IDH1 mutation	8 (7.8)
FGFR2 fusion	3 (2.9)
HER2/neu amplification	5 (4.9)
ESCAT III/IV	15 (14.7)

IQR, interquartile range; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; CCA, Cholangiocarcinoma; BMI, Body Mass Index; MSS, Microsatellite Stable; MSI, Microsatellite Instability; mut, Mutations; Mb, megabase; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; ESMO, European Society For Medical Oncology; BRAF, B-raf Proto-Oncogene; IDH1, Isocitrate Dehydrogenase 1; FGFR2, Fibroblast Growth Factor Receptor 2; HER2/neu, Human Epidermal Growth Factor Receptor 2; [§]This group only includes 23 patients

Efficacy of durvalumab + platinum-based doublet regarding PFS in first line and OS

For the survival analysis, data were collected from a cohort of 102 patients undergoing first-line treatment with a combination of platinum-based chemotherapy and gemcitabine, plus durvalumab. The majority of patients (94.1%) received cisplatin as the chemotherapeutic backbone, with a smaller number receiving carboplatin (4.9%) and one patient treated with oxaliplatin. The median follow-up period was 9.34 months, with a 95% CI of 6.58 to 11.18 months. At the data cut-off (end of March 2024), 35.3% of patients were still receiving their first-line treatment.

The disease control rate (DCR) was 71.57%, with an overall response rate (ORR) of 35.11%. The median progression-free survival (PFS) reached 6.51 months (95%CI: 4.77–7.27), while median overall survival (OS) was 13.61 months (95%CI: 11.28–21.63, Fig. 3).

In patients who achieved at least a partial response (PR), median overall survival was 14.14 months (95%CI: 13.55–NR). For those with stable disease (SD), median overall survival was 12.20 months (95%CI: 10.52–NR), and for patients with progressive disease (PD), it was 8.52 months (95%CI: 5.46–NR). Patients who responded to durvalumab and the platinum-based doublet (CR or PR) demonstrated significantly better overall survival compared to non-responders (HR: 0.29; 95%CI: 0.12–0.72; $p = 0.007$).

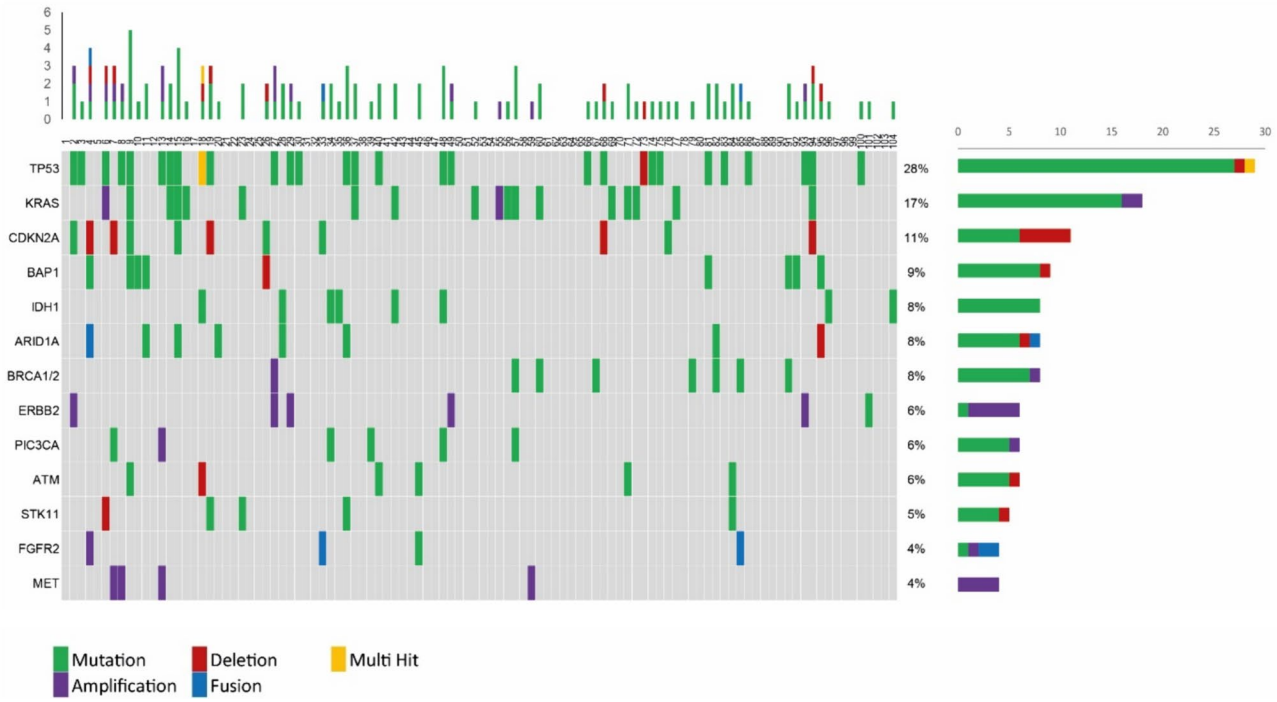

Fig. 2 Oncoplot diagram of all patients. All types of detected mutations are indicated, including insertions, deletions, frameshift alterations, splice site, nonsense and missense mutations. Each column represents an individual patient and each row an individual gene. The right column displays the number of patients carrying mutations in these genes along with the corresponding percentage

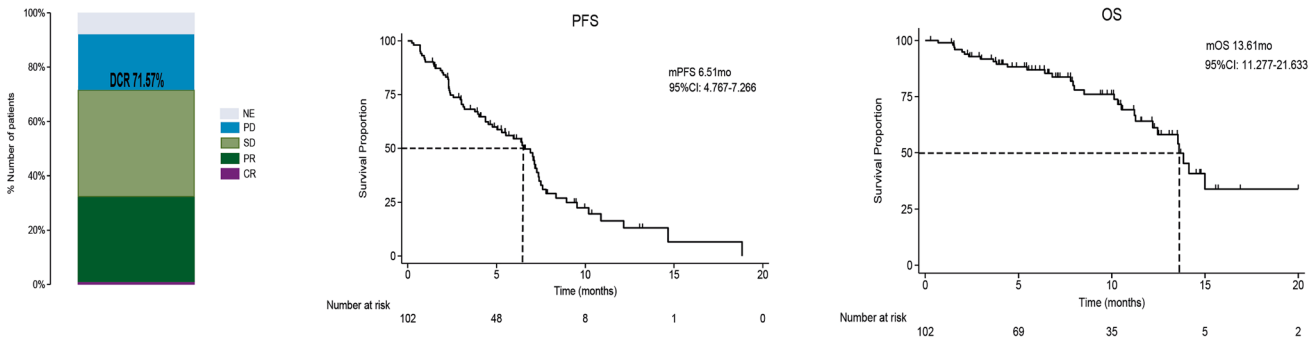

Fig. 3 Response Rates and Kaplan–Meier curves illustrating progression-free survival (PFS) and overall survival (OS) of the total cohort

In a comparison of cisplatin-based versus other platinum-based chemotherapeutic regimens, there was no statistically significant difference in OS. The cisplatin group had an OS of 13.84 months (95%CI: 12.20–21.63), compared to 10.32 months (95%CI: 2.96–NR) for the non-cisplatin group ($p = 0.3$).

The univariate Cox regression analysis evaluated the association between several clinically relevant factors and OS. No significant relationship was found for localization, sex, Eastern Cooperative Oncology Group (ECOG) performance status, tumor stage at diagnosis, resection of the primary tumor, or adjuvant therapy. However, age below 65 years was significantly associated with improved OS. (Fig. 4).

In the multivariate Cox regression analysis, the initial model included age below 65 years, localization, resection of the primary tumor, ECOG performance status, and sex. Tumor stage and adjuvant therapy were excluded due to multicollinearity with resection of the primary tumor (Supplementary Table 1). However, due to a violation of the

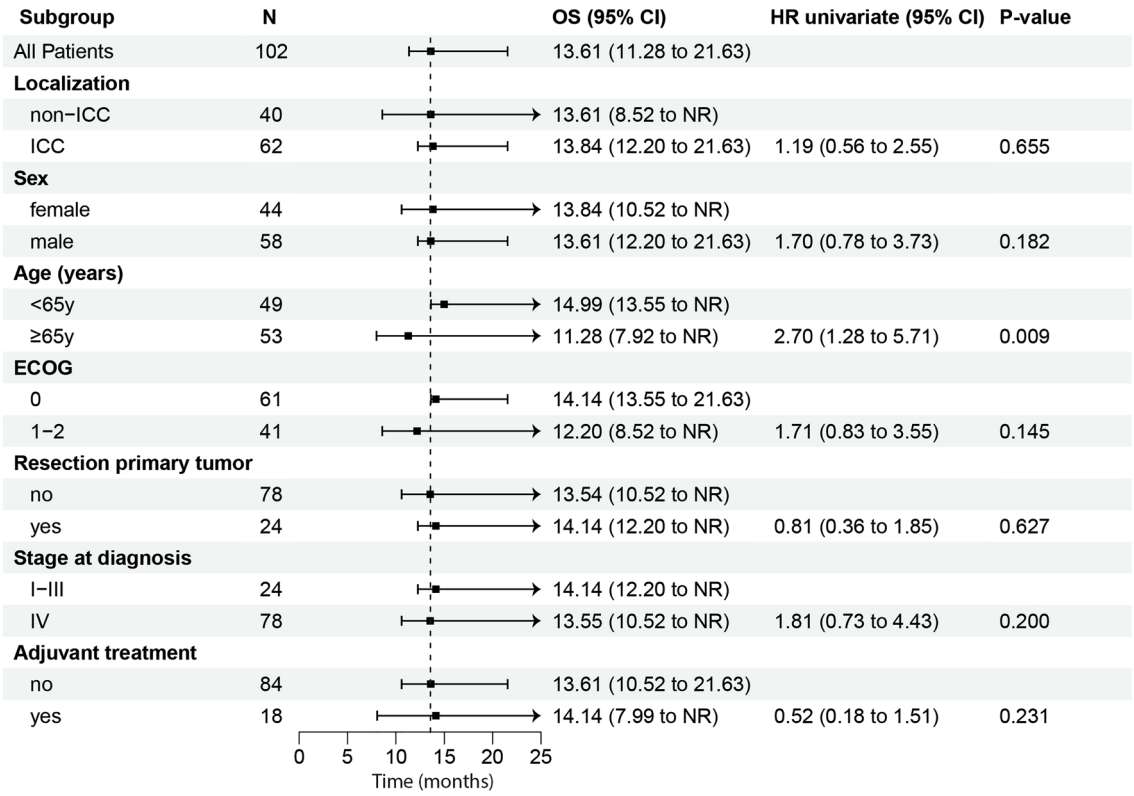

Fig. 4 Univariate analysis of OS across clinical subgroups. The plot shows median OS (months) with 95% confidence intervals (CI), hazard ratios (HR) from univariate Cox regression, and associated *p*-values. Age < 65 years was significantly associated with improved OS; other factors, including tumor localization, sex, ECOG status, resection, stage, and adjuvant treatment, were not significant

events per variable (EPV) rule, which recommends at least 10 events per covariate, a stepwise selection process was performed to reduce the number of variables and improve model stability.

The stepwise selection process removed localization, resection of the primary tumor, ECOG performance status, and sex, as these variables did not meet the significance threshold for inclusion ($p < 0.10$). The final model identified age below 65 years as the only significant predictor of overall survival (OS). Patients younger than 65 years had a hazard ratio of 0.370 (95%CI: 0.175–0.783; $p = 0.009$), indicating a significantly lower risk of death compared to those aged 65 or older.

Clinical outcome of distinct molecular subgroups

Comprehensive molecular profiling was conducted in 90 patients to explore whether mutations in specific genes or pathways influenced the response to and efficacy of the combined therapy. The distribution of clinically relevant pathogenic variants associated with tumor response and survival outcomes is shown in Supplementary Table 2. No individual gene demonstrated a significant association with improved outcome (Supplementary Table 2).

Alterations in genes associated with homologous recombination repair (HRRm) were observed in 26 patients. The ORR for these patients was 30.77% compared to 32.81% in those without HRRm (non-HRRm) ($p = 0.851$). The DCR was 71.88% in HRRm patients versus 76.92% in non-HRRm patients ($p = 0.624$). Median PFS was 6.44 months (95%CI: 2.96–7.50) in the HRRm group and 7.13 months (95%CI: 4.77–7.60) in the non-HRRm group, corresponding to a HR of 1.33 (95%CI: 0.74–2.39; $p = 0.343$). Median OS was 13.55 months (95%CI: 6.81-NR) in HRRm patients and 13.84 months (95%CI: 11.28–21.63) in non-HRRm patients (HR: 1.63; 95%CI: 0.70–3.81; $p = 0.26$, Fig. 5).

In line with findings from a recent study suggesting that loss-of-function mutations in chromatin remodeling genes may be linked to longer survival in patients with biliary tract cancers receiving chemoimmunotherapy, we evaluated this potential predictive biomarker within our cohort [28, 29]. Patients with alterations in genes involved in chromatin modification had a DCR of 77.78% compared to 72.22% in patients without these alterations ($p = 0.634$). ORR was 50% in patients with chromatin modifications, while those without had an ORR of 27.78% ($p = 0.71$). There was no statistically significant difference in PFS between these groups, with a median PFS of 6.44 months versus 7.04 months (HR 1.21; 95%CI: 0.67–2.18; $p = 0.533$). Median OS was 14.14 months for patients with chromatin gene alterations and 13.61 months for those without (HR: 0.45; 95%CI: 0.17–1.22; $p = 0.851$, Fig. 6).

A total of 20 patients were identified with ESCAT I/II alterations. The DCR was 75.00% in patients with ESCAT I/II alterations compared to 72.86% in those without ($p = 0.848$). No statistically significant difference was observed in ORR (35% vs 31.43%; $p = 0.763$) and median PFS (7.17 months vs 6.38 months, HR: 0.88; 95%CI: 0.49-1.61; $p = 0.684$), nor in median OS (14.99 months vs 13.55 months, HR: 0.45; 95%CI: 0.17-1.22; $p = 0.116$) between these groups.

In accordance with ESCAT I/II alterations, 15 patients received matched molecular therapy in 2nd or later lines. Median OS was not reached (NR) in this patient group (95%CI: 14.99-NR). In contrast, patients who did not receive molecular-informed therapy for ESCAT I/II alterations had a median OS of 13.55 months (95%CI: 11.21-21.63) resulting in an HR of 0.23 (95%CI: 0.05–1.01; $p = 0.052$, Fig. 7). The most frequently targeted alterations were *IDH1* ($N = 5$), *ERBB2* Amplification ($N = 2$), *FGFR2* Fusion ($N = 2$) and *MET* Amplification ($N = 2$).

Among the 24 patients without targetable alterations who received second-line chemotherapy, half were treated with FOLFOX ($N = 12$), and the other half with FOLFIRI ($N = 12$). Median OS from the start of second-line treatment was 8.52 months (95%CI: 3.42–NR) for those receiving FOLFOX and 4.18 months (95%CI: 2.63–NR) for patients receiving FOLFIRI (HR: 0.47; 95%CI: 0.14–1.55; $p = 0.213$, Fig. 7).

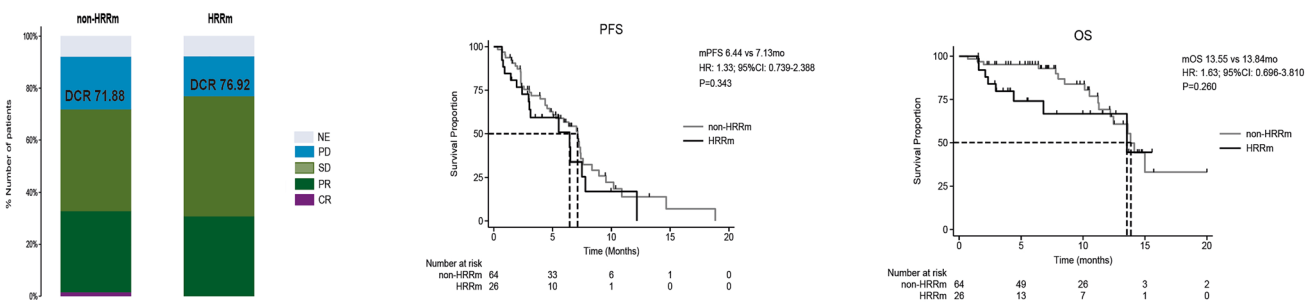

Fig. 5 Response rates and Kaplan Meier curves comparing HRRm and non-HRRm patients exposed to durvalumab + platinum doublet

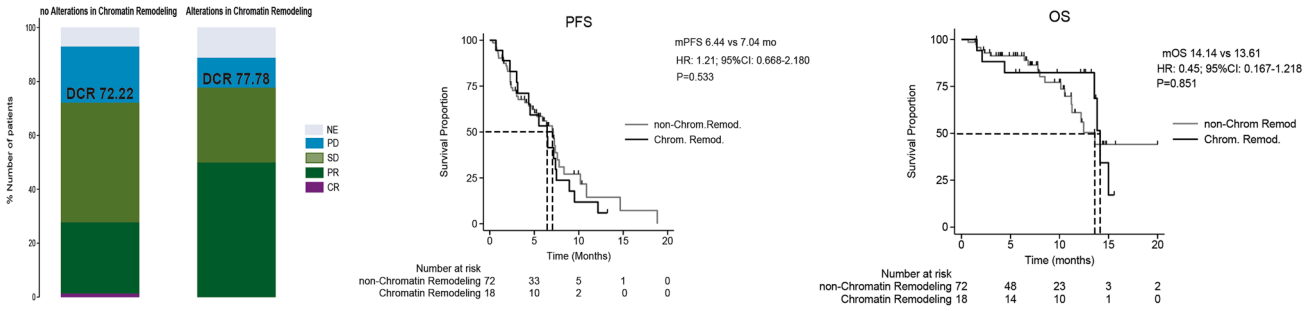

Fig. 6 Response rates and Kaplan Meier curves comparing patients with alterations in chromatin remodeling genes exposed to durvalumab + platinum doublet

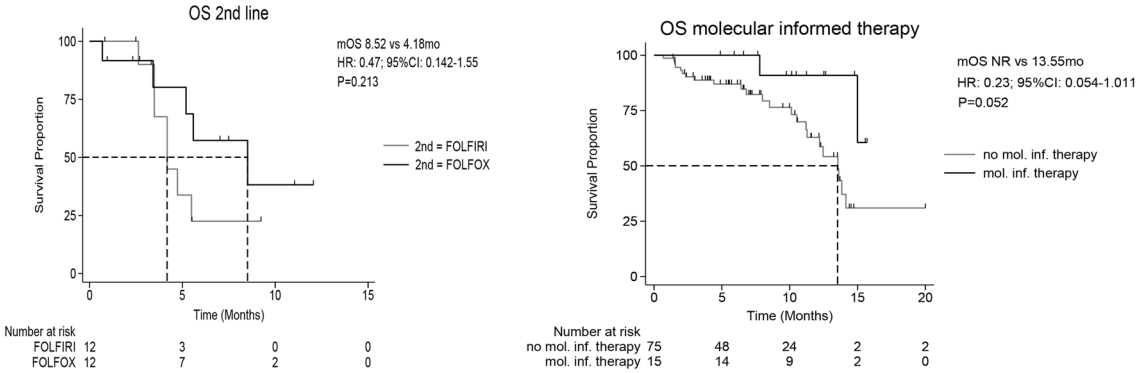

Fig. 7 Kaplan Meier curves comparing FOLFOX vs FOLFIRI in 2nd line after durvalumab + platinum-based doublet (left). Application of molecular-matched therapies in 2nd line and beyond post-progression on durvalumab + platinum-based doublet (right)

Discussion

This real-world analysis investigating durvalumab in combination with platinum-based chemotherapy doublet in 102 patients with BTC confirmed the positive outcomes observed in the TOPAZ-1 trial. In our cohort, the median OS was 13.6 months which aligns with the median OS of 12.8 months reported by the TOPAZ-1 trial. Similarly, median PFS (6.5 vs 7.2 months), DCR (71.6% vs 85.3%) and ORR (35.1% vs 26.7%) were comparable across the two studies [10, 37, 38]. These findings are also consistent with the recently published KeyNote-966 study which tested pembrolizumab as checkpoint inhibitor [39].

A retrospective analysis from Italy previously reported a prolonged PFS in patients with underlying viral hepatitis B and/or hepatitis C infection treated with gemcitabine and cisplatin plus durvalumab [40]. While the TOPAZ-1 trial registered approximately 20% of patients with a history of viral hepatitis, our cohort comprised only 3 patients with this diagnosis. The difference in prevalence may explain the slightly lower PFS observed in our study. Additionally, the shorter follow-up time (9 vs 16.8 months) and the higher proportion of Caucasian patients in our cohort may account for the worse PFS as the Asian population in the registration trial demonstrated prolonged PFS [10]. The potential for a slight overestimation of PFS in our trial should be acknowledged when interpreting the results. While the timing of imaging assessments followed the ESMO guidelines for BTC, they were conducted at longer intervals compared to the TOPAZ-1 trial.

Additionally, 4.9% of our patients received carboplatin and 1% of patients received oxaliplatin instead of cisplatin. No statistically significant difference in overall survival was observed between the non-cisplatin and cisplatin groups. Therefore, in certain cases where renal function is compromised, cisplatin may be substituted with other platinum-based agents without a notable loss in efficacy.

The univariate analysis, the stepwise variable selection method, and the full multivariate model all identified age below 65 years as the only significant predictor of overall survival (OS) in our cohort. This contrasts with the findings from the TOPAZ-1 trial. We hypothesize that one reason for this discrepancy may be that, in our cohort, twice as many patients under the age of 65 received palliative second-line chemotherapy compared to older patients.

A smaller study by Rimini et al. clustered patients based on molecular and genomic alterations, finding that those with alterations in the RTK/RAS pathway and cell-cycle apoptosis had worse outcomes compared to patients with chromatin modification pathway alterations [41]. In our cohort patients with alterations in chromatin remodeling genes ($N = 18$) ORR, PFS and OS did not differ significantly and results need to be interpreted with care due to the small sample size.

Deficiency in homologous recombination repair (HRR) is associated with increased sensitivity to DNA damaging agents, such as platinum-based therapies. Although BTCs are not typically classified as HRD-associated cancers (unlike breast, prostate, pancreatic, or ovarian cancers), trials have shown inconsistent sensitivity to cisplatin in first-line therapy when HRR gene alterations are present. Our data is first to explore the impact of adding checkpoint inhibitors to standard platinum doublet on HRRm BTCs. We found no evidence of enhanced sensitivity in HRRm patients compared to non-HRRm patients. Therefore, HRD in BTC still needs more refinement particularly when it comes to the choice of maintenance therapy, including mono-immunotherapy or chemotherapy [26, 27].

NGS testing has become mandatory in the treatment landscape of BTCs, especially when it comes to selection of 2nd line therapy. Molecular-informed therapies have gained importance, with multiple options now available for second-line treatment [7]. However, available studies on molecular-informed therapies in BTC were performed primarily in immunotherapy-naïve patients, and data on targeted therapies following chemoimmunotherapy are lacking [11, 12, 14, 17]. In our cohort, 88.2% of patients underwent molecular profiling and actionable targets were identified in 22.2%. In line with previous research, most targetable alterations were quite rare [20]. Therefore, we pooled all patients with ESCAT level I/II alterations, as addressing these targets provided the greatest benefit as recently shown by Verdaguer et al. [20]. Although no statistically significant differences in OS, PFS, ORR, or DCR were found between patients with and without ESCAT I/II alterations, among the 15 patients who received targeted therapies in second or later lines, there was a trend toward prolonged OS (NR vs. 13.6 months), approaching statistical significance (HR 0.23; $p = 0.052$). No single genetic alteration predicted an enhanced benefit from the addition of durvalumab, a finding consistent with biomarker analyses from the TOPAZ-1 trial and real-world cohorts. [42, 43]. Nevertheless we observed one long-term responder, who had an MSI background. Therefore, further research with larger cohorts is required to identify new predictive biomarkers.

Our data is first in investigating efficacy of 2nd line after failure of durvalumab + platinum-based doublet. In our trials in non-targetable BTCs re-challenge with a platinum compound (FOLFOX) showed a numerically better outcome compared to FOLFIRI, though statistical significance was not reached.

This study has several limitations. Due to the limited number of patients and small sample sizes within certain subgroups, the *p*-values may not be statistically robust. Additionally, the wide confidence intervals reflect the uncertainty in the estimates. Therefore, caution is needed when interpreting these findings, which should be considered exploratory rather than definitive. Future studies with larger cohorts are required to better assess potential clinical predictors and to explore interactions between age and other clinical variables. Moreover, since this study was conducted as a retrospective analysis, subsequent therapies were not pre-defined and a few participants received targeted therapy only after the second line. Furthermore, the characterization of potential long-term responders is limited by the incomplete analysis of MSI status and tumor mutational burden (TMB) within our cohort. A slight overestimation of PFS should be noted, as imaging assessments, while adhering to ESMO guidelines for BTC, were conducted less frequently than in the TOPAZ-1 trial. This discrepancy is a common challenge in real-world settings and may have impacted the accuracy of PFS estimates.

In conclusion, treatment with platinum-based chemoimmunotherapy showed promising results in our analysis of a real-world cohort, supporting the results from the TOPAZ-1 trial and establishing durvalumab + platinum doublet as a new first-line standard with efficacy across prominent subgroups. Our data further support the early integration of molecularly informed therapies, at least in the second line, which resulted in numerical OS prolongation compared to chemotherapy, and reinforce FOLFOX as the preferred second-line treatment for patients without targetable alterations.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00262-024-03842-y.

Author contributions All authors of this research paper have directly participated in the planning, execution, or analysis of the study. P.R. and B.D.: writing original draft B.D., P.R., T.W., H.R.: Conceptualization B.D., P.R.: Data curation and formal analysis IM.A, H.T., G.S., D.M., M.B., EM.S., S.M., A.D., G.W.P: Data curation. All authors: review and editing.

Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committees Essen (21–10239-BO, Essen, Germany), Land Oberoester-

reich (1100/2023, Upper Austria, Austria), and Vienna (EK-1099/2021, Vienna, Austria).

Consent to participate Informed consent was obtained from all individual participants included in the study.

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