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ORIGINAL RESEARCH ARTICLE

Durvalumab Plus Gemcitabine and Cisplatin Versus Gemcitabine and Cisplatin in Biliary Tract Cancer: a Real-World Retrospective, Multicenter Study

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Abstract

Background The TOPAZ-1 phase III trial reported a survival benefit with the anti-programmed cell death ligand 1 (anti-PD-L1) durvalumab in combination with gemcitabine and cisplatin in patients with advanced biliary tract cancer (BTC).

Objective The present study investigated for the first time the impact on survival of adding durvalumab to cisplatin/gemcitabine compared with cisplatin/gemcitabine in a real-world setting.

Patients and Methods The analyzed population included patients with unresectable, locally advanced, or metastatic BTC treated with durvalumab in combination with cisplatin/gemcitabine or with cisplatin/gemcitabine alone. The impact of adding durvalumab to chemotherapy in terms of overall survival (OS) and progression free survival (PFS) was investigated with univariate and multivariate analysis.

Results Overall, 563 patients were included in the analysis: 213 received cisplatin/gemcitabine alone, 350 received cisplatin/gemcitabine plus durvalumab. At the univariate analysis, the addition of durvalumab was found to have an impact on survival, with a median OS of 14.8 months versus 11.2 months [hazard ratio (HR) 0.63, 95% confidence interval (CI) 0.50–0.80, $p = 0.0002$] in patients who received cisplatin/gemcitabine plus durvalumab compared to those who received cisplatin/gemcitabine alone. At the univariate analysis for PFS, the addition of durvalumab to cisplatin/gemcitabine demonstrated a survival impact, with a median PFS of 8.3 months and 6.0 months (HR 0.57, 95% CI 0.47–0.70, $p < 0.0001$) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively. The multivariate analysis confirmed that adding durvalumab to cisplatin/gemcitabine is an independent prognostic factor for OS and PFS, with patients > 70 years old and those affected by locally advanced disease experiencing the highest survival benefit. Finally, an exploratory analysis of prognostic factors was performed in the cohort of patients who received durvalumab: neutrophil–lymphocyte ratio (NLR) and disease stage were to be independent prognostic factors in terms of OS. The interaction test highlighted NLR ≤ 3, Eastern Cooperative Oncology Group Performance Status (ECOG PS) = 0, and locally advanced disease as positive predictive factors for OS on cisplatin/gemcitabine plus durvalumab.

Conclusion In line with the results of the TOPAZ-1 trial, adding durvalumab to cisplatin/gemcitabine has been confirmed to confer a survival benefit in terms of OS and PFS in a real-world setting of patients with advanced BTC.

1 Introduction

Advanced biliary tract cancer (BTC) remains a big clinical challenge in the oncology field, due to the dismal prognosis and suboptimal response to systemic treatments [1–4]. However, in recent years, there has been a significant improvement in the therapeutic armamentarium available against this heterogeneous group of diseases, above all thanks to the growing knowledge of its biological landscape. Molecular insights have revealed a number of targetable genomic alterations, including *IDH1* mutations and *FGFR2* gene fusions, with important therapeutic implications and positive results from prospective trials investigating targeted therapies in molecularly selected subgroups of patients with advanced BTC [5–12]. Moreover, in 2022 another class of compounds has been introduced in the BTC treatment: immunotherapy. The phase III randomized, double-blind, placebo-controlled TOPAZ-1 trial investigated the

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Key Points

The present study investigated for the first time the impact on survival of adding durvalumab to cisplatin/gemcitabine compared with cisplatin/gemcitabine in patients with advanced biliary tract cancer (BTC) in a real-world setting.

Durvalumab was found to have an impact on survival, with a median OS of 14.8 months versus 11.2 months (HR 0.63, 95% CI 0.50–0.80, $p = 0.0002$) and median PFS of 8.3 months and 6.0 months (HR 0.57, 95% CI 0.47–0.70, $p < 0.0001$) in patients who received cisplatin/gemcitabine plus durvalumab compared to those who received cisplatin/gemcitabine alone.

Adding durvalumab to cisplatin/gemcitabine has been confirmed to confer a survival benefit in terms of OS and PFS in a real-world setting of patients with advanced BTC.

role of the anti-programmed cell death ligand 1 (PD-L1) durvalumab in addition to the chemotherapy backbone cisplatin/gemcitabine as a first-line systemic treatment in patients with advanced BTC [9]. This study demonstrated a survival benefit in favor of the combination of durvalumab plus chemotherapy compared with chemotherapy alone, with a median overall survival (OS) of 12.8 months compared with 11.5 months [hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.66–0.97; $p = 0.021$] [13]. Following the TOPAZ-1 trial, the combination of durvalumab and cisplatin/gemcitabine has been approved by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA) as new first-line standard of care for patients with previously untreated, unresectable or metastatic BTC. Another immune checkpoint inhibitor (ICI) has recently received the FDA approval for the treatment of the advanced BTC: the anti-programmed cell death 1 (anti-PD1) pembrolizumab. In the randomized, double-blind, placebo-controlled phase III KEYNOTE-966 study, the authors demonstrated a significantly improved OS in patients who received the combination of pembrolizumab plus cisplatin/gemcitabine compared with cisplatin/gemcitabine alone (12.7 versus 10.9 months respectively, hazard ratio of 0.83 [95% CI 0.72–0.95], $p = 0.0034$), whereas no statistically significant differences in terms of progression free survival (PFS) were shown [14].

Outside the clinical trial framework, our research group recently evaluated the efficacy and safety outcomes of durvalumab plus cisplatin/gemcitabine in patients with advanced BTC treated at 17 Italian institutions. We retrospectively assessed 145 patients who received durvalumab in combination with cisplatin/gemcitabine for unresectable or metastatic BTC in a real-world setting, showing survival outcomes which were consistent with those of the TOPAZ-1 trial [15]. In addition, the incidence of any grade adverse events in our cohort of patients was in line with those reported in the TOPAZ-1 trial, thus confirming the safety profile and the good tolerance of the combination [15]. If results from randomized, prospective trials are the only ones that could change the clinical practice, real-world data are crucial to confirm the trials' results in a more heterogeneous and less selected population.

In the present work we retrospectively compared two cohorts of patients, the first one receiving the previous standard of care (cisplatin/gemcitabine) and the second one receiving the new combination (durvalumab plus cisplatin/gemcitabine), with the aim to evaluate the survival impact derived by the addition of durvalumab to chemotherapy. Furthermore, we performed an exploratory analysis of prognostic and predictive factors of response to durvalumab plus cisplatin/gemcitabine, to identify potential prognostic factors.

2 Materials and Methods

2.1 Study Population

The study population included consecutive patients with unresectable, locally advanced, or metastatic adenocarcinoma of the biliary tract, including intrahepatic or extrahepatic cholangiocarcinoma and gallbladder carcinoma. Data were collected from 17 centers in Italy from March 2006 to December 2023. Patients who received treatment before the publication of the TOPAZ-1 results received the previous standard combination of cisplatin 25 mg/m^2 plus gemcitabine 1000 mg/m^2 on days 1 and 8 of each 21-day cycle for up to eight cycles, according to the ABC-02 trial [16]. Patients who received treatment after the publication of the TOPAZ-1 results received durvalumab 1500 mg administered on day 1 of each cycle in combination with cisplatin/gemcitabine; after completion of eight cycles, patients received maintenance therapy with durvalumab 1500 mg monotherapy administered every 4 weeks until clinical or imaging disease progression or unacceptable toxicity [13]. Since durvalumab was not approved by the EMA until 21 December 2022, and it has been reimbursed only starting from March 2024 by the Italian Medicines Agency (AIFA), durvalumab was provided free of charge at the request of the treating physician for each individual patient by AstraZeneca Italy as part of an early access program. AstraZeneca Italy had no role in planning this study, collecting, or analyzing patient data.

The present study was approved by local Ethics Committee at each center, complied with the provisions of the Good Clinical Practice guidelines and the Declaration of Helsinki

and local laws, and fulfilled the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data.

2.2 Statistical Analysis

The primary endpoint of the study was to evaluate the OS of patients who received the combination of durvalumab plus cisplatin/gemcitabine compared with cisplatin/gemcitabine in two cohorts of patients treated outside of clinical trials. Secondary endpoints of the study were PFS, objective response rate (ORR), and disease control rate (DCR) in the two cohorts of patients. OS was defined as the time from the date of treatment initiation to the date of death; PFS was defined as the time from the date of treatment initiation to the date of disease progression or death, whichever occurred first. ORR was assessed by the investigator and defined as the proportion of patients who achieved a complete response (CR) or partial response (PR); disease control rate (DCR) was defined as the proportion of patients who achieved ORR or stable disease (SD). Treatment response was evaluated by computed tomography (CT) and categorized as CR, PR, SD or progressive disease (PD) by local review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Categorical variables were compared using Fisher exact test.

Finally, an exploratory analysis on potential prognostic and predictive factors in the cohort of patients who received durvalumab in combination with cisplatin/gemcitabine was performed.

Survival curves were estimated using the product-limit method of Kaplan–Meier. The role of stratification factors was analyzed with log-rank tests. Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics were calculated using the Cox proportional hazards model. A propensity score matching analysis was performed. A propensity score model was developed to control the results for baseline variable imbalances between the treatment groups. A multivariate logistic regression analysis was applied to calculate the propensity score. A p value < 0.05 was considered statistically significant. The predictive role of baseline characteristics was evaluated through the interaction test. A MedCalc package (MedCalc® version 20.2) was used for statistical analysis.

3 Results

3.1 Study Population

Overall, 563 patients were enrolled at 17 Italian sites and included in the analysis: 213 patients received cisplatin/gemcitabine alone, and 350 received durvalumab in combination with cisplatin/gemcitabine. The two cohorts of patients were quite homogeneous in terms of demographic and disease characteristics, except for the age and disease status. Patient demographics and disease characteristics are reported in Table 1. At data cutoff (31 December 2023), the median duration of follow-up was 11.5 months (95% CI 10.2–29.0) for patients who received durvalumab in combination with cisplatin/gemcitabine compared with 30.1 months (95% CI 22.1–44.9) for patients who received cisplatin/gemcitabine alone.

3.2 Survival Analysis

Overall, 299 patients died during treatment: 80.7% in the cisplatin/gemcitabine group, and 36.3% in the cisplatin/gemcitabine plus durvalumab group. At the univariate analysis for OS, the addition of durvalumab to cisplatin/gemcitabine was found to have a prognostic impact, with median OS of 14.8 versus 11.2 months (HR 0.63, 95% CI 0.50–0.80, $p = 0.0002$) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Fig. 1A). In addition, locally advanced disease, previous surgery, carcinoembryonic antigen (CEA) baseline normal levels versus greater than normal levels, carbohydrate antigen (CA) 19-9 baseline normal levels versus greater than normal levels, neutrophil–lymphocyte ratio (NLR) ≤ 3 versus > 3, and Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0 versus > 0 had a positive prognostic impact at univariate analysis. After adjustment for unbalanced clinical covariates and for all the variables with a prognostic impact at the univariate analysis, the multivariate analysis for OS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared to cisplatin/gemcitabine alone (HR 0.68, 95% CI 0.45–0.87, $p = 0.0001$) (Table 2).

At the univariate analysis for PFS, the addition of durvalumab to cisplatin/gemcitabine had a prognostic impact, with median PFS of 8.3 months compared with 6.0 months (HR 0.57, 95% CI 0.47–0.70, $p < 0.0001$) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Fig. 1B). In addition, baseline CEA and CA 19-9 levels, NLR, and ECOG PS resulted to have a prognostic impact at univariate analysis. After adjustment for unbalanced clinical covariates and for all variables with a prognostic impact at the univariate analysis, the multivariate analysis for PFS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared to cisplatin/gemcitabine alone (HR 0.64, 95% CI 0.44–0.76, $p < 0.0001$) (Table 3).

Subgroup analysis showed a survival benefit in term of overall survival for all subgroups of patients, with patients

Table 1 Patient demographics and disease characteristics

Characteristics	Total population *N* (%) *N* = 563	Cisplatin/gemcitabine *N* (%) *N* = 213	Cisplatin/gemcitabine + durvalumab *N* (%) *N* = 350	*P*
Gender				
Male	286 (50.8)	98 (46)	188 (53.8)	0.08
Female	277 (49.2)	115 (54)	162 (46.2)	
Age				
≥ 70	189 (33.6)	47 (22.1)	142 (40.6)	**0.000006**
< 70	374 (66.4)	166 (77.9)	208 (59.4)	
Primary tumor site				
Intrahepatic	317 (56.3)	119 (56)	198 (60)	0.6878
Extrahepatic	149 (26.5)	54 (24.5)	95 (23.5)	
Gallbladder	95 (16.9)	38 (17.5)	57 (15)	
Unknown	2 (0.3)	2 (1)		
Previous surgery				
Yes	185 (32.8)	77 (36.1)	108 (30.8)	0.19
No	378 (67.2)	136 (63.9)	242 (69.2)	
Drainage or stent				
Yes	142 (25.2)	52 (24.5)	90 (25.7)	0.76
No	241 (74.8)	161 (75.5)	260 (74.3)	
Disease status				
Locally advanced	112 (19.9)	32 (15)	80 (22.8)	0.029
Metastatic	451 (80.1)	181 (85)	270 (77.2)	
ECOG PS				
0	291 (51.7)	108 (50.5)	183 (52.3)	0.93
> 0	268 (47.6)	101 (47.5)	167 (47.7)	
Unknown	4 (0.7)	4 (2.0)	0 (0)	
CA 19-9				
Normal value	162 (28.8)	51 (24)	111 (31.7)	0.42
Greater than normal value	337 (59.8)	119 (56)	218 (62.3)	
Unknown	64 (11.4)	43 (29)	21 (6.0)	
CEA				
Normal value	272 (48.3)	92 (43.5)	180 (51.4)	1.0
Greater than normal value	217 (38.5)	74 (34.5)	143 (40.8)	
Unknown	74 (13.2)	47 (22)	27 (7.8)	
NLR				
< 3	267 (47.4)	105 (49.5)	162 (46.3)	0.28
> 3	278 (49.4)	97 (45.5)	181 (51.7)	
Unknown	18 (3.2)	11 (5.0)	7 (2.0)	

Bold value is positive data

> 70 years and those with locally advanced disease having the best survival (Fig. 2).

The interaction test highlighted NLR ≤ 3, ECOG PS of 0, and locally advanced disease as positive predictive factors for OS on cisplatin/gemcitabine plus durvalumab.

The combination of cisplatin/gemcitabine plus durvalumab showed a tendency toward a higher ORR, which did not reach the statistical significance ($p = 0.08$), whereas DCR was significantly higher for the combination of chemo-immunotherapy compared with cisplatin/gemcitabine alone ($p = 0.000003$) (Supplementary Table 1, Supplementary Fig. 1).

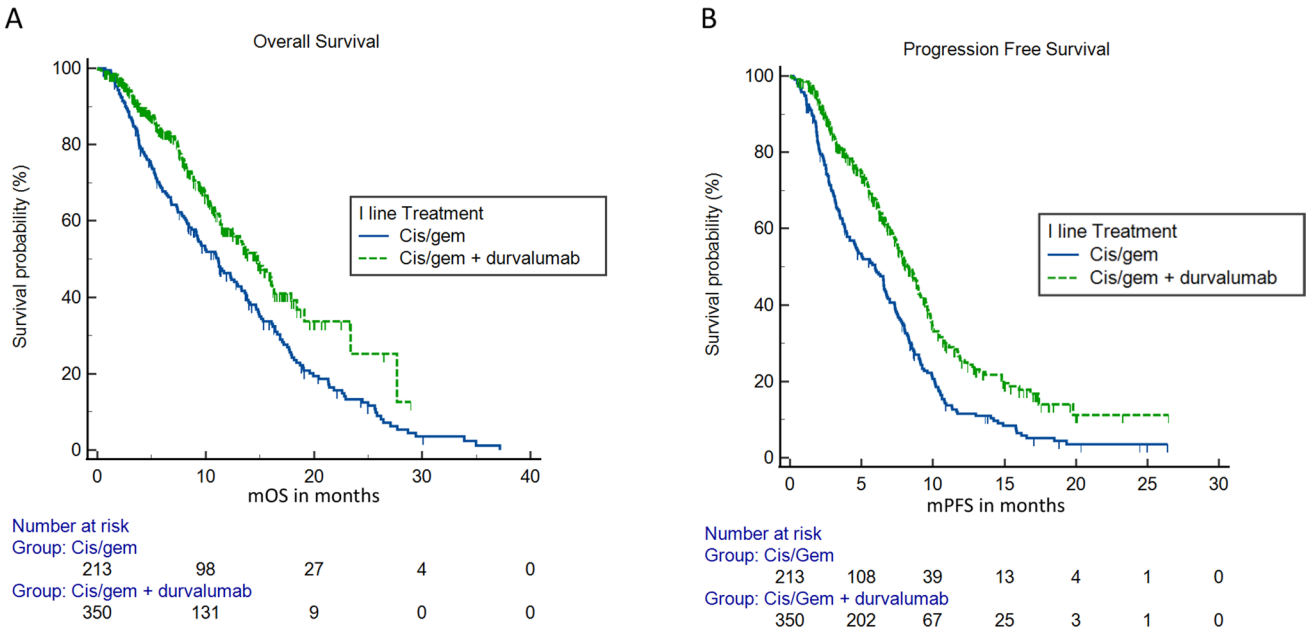

Fig. 1 Kaplan–Meier curves for OS (A) and PFS (B)

3.3 Survival Analysis after Propensity Score Matching

After propensity score matching, 213 patients were treated with cisplatin/gemcitabine and 213 patients were treated with cisplatin/gemcitabine and durvalumab. Baseline patient characteristics were well balanced between the groups (Supplementary Table 2).

At the univariate analysis for OS, patients who received cisplatin/gemcitabine plus durvalumab had better median OS compared with those who received cisplatin/gemcitabine alone (13.2 versus 11.2 months, respectively, HR 0.71, 95% CI 0.55–0.92, $p = 0.009$) (Supplementary Fig. 2A). In addition, CEA baseline levels, disease status, CA 19-9 baseline levels, NLR, and ECOG PS had a prognostic impact at univariate analysis. After adjustment for the variables with a prognostic impact at the univariate analysis, the multivariate analysis for OS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared with cisplatin/gemcitabine alone (HR 0.61, 95% CI 0.53–0.94, $p = 0.01$) (Supplementary Table 3).

At the univariate analysis for PFS, patients who received cisplatin/gemcitabine plus durvalumab had a better median PFS compared with those who received cisplatin/gemcitabine alone (7.4 versus 6.0 months, respectively, HR 0.68, 95% CI 0.54–0.84, $p = 0.0006$) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Supplementary Fig. 2B). In addition, baseline NLR, and ECOG PS had a prognostic impact at univariate analysis. After adjustment for the variables with a prognostic impact at the univariate analysis, the multivariate analysis for PFS confirmed the positive prognostic role of the treatment with durvalumab in combination to cisplatin/gemcitabine compared with cisplatin/gemcitabine alone (HR 0.63, 95% CI 0.51–0.97, $p = 0.002$) (Supplementary Table 4).

3.4 Exploratory Analysis in the Durvalumab Cohort

An exploratory analysis of prognostic factors in the cohort of patients who received durvalumab was performed. At univariate analysis, disease stage (locally advanced versus metastatic), NLR (≤ 3 versus > 3), ECOG PS (0 versus > 0), CEA, CA19-9, and previous surgery were found to have an impact on OS. The multivariate analysis confirmed NLR and disease stage as prognostic factors for OS (Table 4).

4 Discussion

In the present analysis the positive survival impact of first-line durvalumab in combination with cisplatin/gemcitabine compared with cisplatin/gemcitabine alone has been confirmed in a real-world cohort of patients with locally advanced or metastatic BTC. Significantly, after the propensity score-matching analysis, the results have been confirmed. The survival outcomes observed in the present analysis are consistent with those of the phase III TOPAZ-1 trial, thus reinforcing the benefit derived by the addition of immunotherapy to platinum-based chemotherapy [13].

Table 2 Univariate and multivariate analysis for OS according to baseline characteristics in the whole cohort

Parameters	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
> 70	1			0.96	0.74–1.26	0.79
≤ 70	0.99	0.77–1.26	0.92			
Gender						
Male	1					
Female	1.17	0.93–1.47	0.17			
Primary tumor site						
iCCA	1					
eCCA	1.01	0.80–1.28	0.92			
Disease stage						
Locally						
Advanced	1			1		
Metastatic	1.59	1.21–2.10	0.0009	1.68	1.14–1.68	0.02
Previous surgery						
Yes	1			1		
No	1.34	1.05–1.69	0.016	1.22	0.92–1.62	0.41
First-line treatment						
Cisplatin/gemcitabine	1					
Cisplatin/gemcitabine + durvalumab	0.63	0.50–0.80	**0.0002**	0.68	0.45–0.87	**0.0001**
CEA						
Nv	1					
> nv	1.72	1.33–2.23	**< 0.0001**	1.40	1.10–1.79	0.0052
CA 19-9						
Nv	1					
> nv	1.68	1.30–2.17	**0.0001**	1.58	1.14–1.94	0.0705
NLR						
> 3	1					
≤ 3	0.49	0.38–0.62	**< 0.0001**	0.52	0.41–0.67	**<0.0001**
ECOG PS						
0	1					
> 0	1.88	1.48–2.38	**< 0.0001**	1.74	1.36–2.22	**< 0.0001**

Bold values are positive data

ECOG PS, Eastern Cooperative Oncology Group performance status; *NLR*, neutrophil to lymphocyte ratio; *AST*, aspartate aminotransferase; *ALT*, alanine transaminase

Moreover, survival results in the cisplatin/gemcitabine cohort are very similar to those reported in the ABC-02, TOPAZ-1, and KEYNOTE-966 studies, thus suggesting that no significant underestimation of survival outcomes was done for the control group of patients. A similar consideration could be done for ORR and DCR: the results achieved in both our cohorts, durvalumab plus cisplatin/gemcitabine and cisplatin/gemcitabine alone, are comparable with those reported in the phase III trials.

Although a direct comparison between the present retrospective analysis and the TOPAZ-1 and ABC-02 prospective, randomized trials cannot be done, results confirm the survival benefit of combining immunotherapy with chemotherapy in this setting [13, 16]. Our research team recently published the first real-world experience of durvalumab in combination with cisplatin/gemcitabine [15]. Differently from our previous work, the present paper evaluated both patients receiving durvalumab and patients receiving chemotherapy alone and highlighted the survival benefit provided by immunotherapy compared to a cohort of patients who received the previous first-line standard of care represented by cisplatin/gemcitabine.

Interestingly, we observed a particular benefit of durvalumab in older patients and in patients with locally

Table 3 Univariate and multivariate analysis for PFS according to baseline characteristics in the whole cohort

	Univariate			Multivariate		
Parameters	HR	95% CI	*P*	HR	95% CI	*P*
Age						
> 70	1			0.91	0.74– 1.25	0.63
≤ 70	0.84	0.65–1.23	0.25			
Gender						
Male	1					
Female	0.94	0.72–1.14	0.57			
Primary tumor site						
iCCA	1					
eCCA	0.92	0.75–1.22	0.62			
Disease stage						
Locally advanced	1					
Metastatic	0.92	0.74–1.23	0.24			
Previous surgery						
Yes	1					
No	0.97	0.83–1.23	0.94			
First-line treatment						
Cisplatin/gemcitabine	1					
Cisplatin/gemcitabine + durvalumab	0.57	0.47–0.70	**< 0.0001**	0.64	0.44–0.76	**< 0.0001**
CEA						
> nv	1					
Nv	0.79	0.62–1.04	0.06			
CA 19-9						
> nv	1					
Nv	0.64	0.52–0.93	**0.03**	0.81	0.66–1.18	0.25
NLR						
> 3	1					
≤ 3	0.53	0.47–0.75	**< 0.0001**	0.55	0.34–0.76	**< 0.0001**
ECOG PS						
> 0	1					
0	0.63	0.52–0.84	**0.01**	0.72	0.53–0.95	**0.01**

Bold values are positive data

ECOG PS, Eastern Cooperative Oncology Group performance status; *NLR*, neutrophil to lymphocyte ratio; *AST*, aspartate aminotransferase; *ALT*, alanine transaminase

advanced disease. The link between cancer, response to treatments, and aging is complex and not yet completely understood. Immune response has been highlighted to decrease in elderly patients in the so-called immunosenescence process, thus leading to the increased risk of cancer onset. Starting from the immunosenescence concept, a lower benefit from immunotherapy in elderly patients has been hypothesized. Nevertheless, available data are controversial. A number of previous papers reported good survival results in elderly patients who received immunotherapy in several cancer settings, including advanced hepatocellular carcinoma [17–20]. Even more, Kugel and colleagues previously reported a high rate of response to ICI in elderly patients with melanoma. Moreover, they observed a higher population of regulatory T cells (T_{regs}) in older mouse models, which could be associated with an increased response to immunotherapy [21]. Further investigations focused on the complex interplay between cancer and immune microenvironment are needed to define the impact of aging on immunotherapy-related survival outcomes.

The second subgroup of patients who showed more benefit from the combined treatment in our analysis are patients with locally advanced disease, in line with the findings of the TOPAZ-1 trial. Similar results have been achieved in other oncology settings, where immunotherapy has been shown to work better in earlier tumor stages

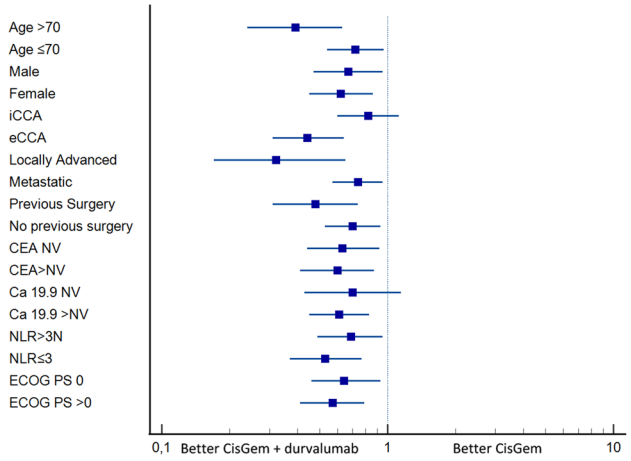

Fig. 2 Forest plot analysis for OS

compared with metastatic stages in both preclinical and clinical studies [22–29]. In BTC, this result deserves attention. The survival benefit observed in patients with locally advanced disease, together with the high ORR, paves the way for future research focused on potential neoadjuvant strategies or conversion treatments. To date, the only published trial on the role of systemic therapy in the neoadjuvant setting for patients with resectable intrahepatic cholangiocarcinoma (iCCA) is the NEO-GAP, which demonstrated the feasibility and safety of the chemotherapy combination of gemcitabine, cisplatin, and nab-paclitaxel prior to resection for iCCA [30]. In addition, no data about the role of immunotherapy for BTC in the neoadjuvant setting are available. The good survival results obtained in the present analysis in patients with locally advanced disease might suggest a potential benefit in reducing the risk of recurrence after surgery. Furthermore, the high

Table 4 Univariate and multivariate analysis for OS in the durvalumab plus cisplatin/gemcitabine cohort

Parameters	Univariate			Multivariate		
	HR	95% CI	*P*	HR	95% CI	*P*
Age						
> 70	1					
≤ 70	1.21	0.72–2.01	0.46			
Gender						
Male	1					
Female	0.87	0.57–1.32	0.51			
Primary tumor site						
iCCA	1					
eCCA	0.83	0.54–1.27	0.39			
Disease stage						
Locally Advanced	1			1		
Metastatic	2.03	1.27–3.23	0.0029	2.16	1.42–3.57	0.0068
Previous surgery						
Yes	1			1		
No	1.62	1.03–2.53	0.03	1.52	0.87–2.12	0.18
CEA						
Nv	1			1		
> nv	1.65	1.06–2.58	0.027	1.21	0.78–1.90	0.38
CA 19-9						
Nv	1					
> nv	1.45	0.92–2.29	0.1037	1.42	0.85–2.04	0.36
NLR						
> 3	1					
≤ 3	0.42	0.27–0.64	**0.0001**	0.41	0.25–0.64	**0.0001**
ECOG PS						
0	1					
> 0	1.58	1.02–2.44	**0.037**	1.47	0.92–2.26	**0.10**

Bold values are positive data

ECOG PS, Eastern Cooperative Oncology Group performance status; *NLR*, neutrophil to lymphocyte ratio; *AST*, aspartate aminotransferase; *ALT*, alanine transaminase

response rate leads to the hypothesis that investigations on the role of this combination could be interesting in terms of conversion treatment in patients with unresectable disease. Future investigations are needed to explore the role of chemo-immunotherapy in the preoperative setting. In the second part of our work, we performed an exploratory analysis of potential prognostic and predictive factors for response in patients who received durvalumab in combination with cisplatin/gemcitabine, since no clinical factors that could guide treatment choice have been validated in clinical practice.

Our analysis highlighted NLR ≤ 3 and ECOG PS of 0 to be both positive prognostic factors and predictive factors for response to durvalumab and cisplatin/gemcitabine. NLR has previously been defined as a potential surrogate of the systemic inflammatory status, since it considers two populations of immune cells with antithetical functions: neutrophils involved in the proinflammatory and carcinogenic process and lymphocytes with mainly cytotoxic and anti-cancer functions [31–38]. A high value of NLR could reflect an immune system characterized by a proinflammatory and carcinogenic status, thus possibly interfering with the response to the treatment with durvalumab combined to cisplatin/gemcitabine. Deeper insights into the biological pathways underlying the interaction between cancer, immune microenvironment, and immune checkpoint inhibition are crucial to verify this hypothesis.

Concerning the prognostic and predictive role of ECOG PS, few considerations could be made. In other oncology setting, ECOG PS has been demonstrated to be a prognostic factor in patients receiving immunotherapy alone and immunotherapy combined with chemotherapy [39–41]. A disrupted balance of immune response due to advanced disease and/or comorbidities could explain a scarce or reduced response to ICI. Further studies are needed to investigate this topic.

Recently, Olkus et al. published a small case series of patients treated with CisGem plus durvalumab. They investigated survival and treatment response within the context of the inclusion and exclusion criteria of TOPAZ-1. No significant differences were found in the subgroups, reinforcing the use of this treatment as a standard of care in the first line [42].

Several limitations could be ascribed to the present analysis. First of all, the retrospective nature of the work could not exclude possible selection biases, despite the adjustment in multivariate analysis and the propensity score-matching analysis that cannot replace level I evidence derived from a prospective, randomized trial. Secondly, due to the multicenter nature of the study, the PFS data have to be contextualized and a slight difference in tumor assessment modalities and timepoints between the institutes have to be considered. Moreover, information regarding side effects could have added more value to the analysis, strengthening the feasibility of chemotherapy plus immunotherapy combination in clinical practice. However, an accurate comparison in terms of safety profile was not possible, due to the lack of data in the cohort of patients who received cisplatin and gemcitabine. Indeed, despite the high importance to make investigations in the real-world setting, some data could be missing thus making the analysis difficult and affected by bias. Finally, results of the TOPAZ-1 trial have been recently published, and durvalumab is available from January 2022, thus the median follow-up of patients on durvalumab plus cisplatin/gemcitabine is significantly shorter compared with that of patients who received cisplatin/gemcitabine. Nevertheless, even considering the differences between prospective randomized trials and retrospective studies in the real-world setting, our results are consistent with those reported in the registration trials. Future updates after longer follow-up will be helpful to confirm the present results. Moreover, a comparative genomic analysis between patients who received cisplatin/gemcitabine alone compared with cisplatin/gemcitabine plus durvalumab would be of special interest with the aim to identify potential molecular prognostic and predictive biomarkers of response. Unfortunately, in past years, molecular testing was not performed routinely, so the molecular profiling is available only for few patients who received cisplatin/gemcitabine alone.

In conclusion, the present analysis adds a piece to our previously published data on the use of durvalumab in combination with cisplatin/gemcitabine in patients with advanced BTC, highlighting the survival benefit of adding immunotherapy to chemotherapy. Thus, the use of durvalumab in this setting confirmed to provide a survival benefit, mainly in patients older than 70 years and with locally advanced disease.

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Declarations

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Conflict of Interest L.R. reports consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, BMS, Eisai, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, and Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Merck Serono, Roche, and Servier; travel expenses from AstraZeneca; research grants (to institution) from Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, and Zymeworks. T.P. received consulting fees from Bayer, Ipsen, and AstraZeneca; institutional research funding from Roche, Bayer, and AstraZeneca; travel expenses from Roche. A.C.G. reports consulting fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, and Servier; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Roche, and

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Ethics Approval and Consent to Participate The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the ethics committee of each institution involved in the project. Under the condition of retrospective archival tissue collection and patient data anonymization, our study was exempt from the acquisition of informed consent from patients by the institutional review board.

Consent to Publish Not applicable.

Data Availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability Not applicable.

Authors' Contributions Conception and design: A. Casadei-Gardini, M. Rimini, Lorenza Rimassa, Lorenzo Fornaro, Sara Lonardi, Lorenzo Antonuzzo. Acquisition of data (acquired and managed patients): All authors. Analysis and interpretation of data: A. Casadei-Gardini, M. Rimini, Lorenza Rimassa, Lorenzo Fornaro, Sara Lonardi, Lorenzo Antonuzzo. Writing, review, and/or revision of the manuscript: A. Casadei-Gardini, M. Rimini, Lorenza Rimassa, Lorenzo Fornaro, Sara Lonardi, Lorenzo Antonuzzo. Final approval of manuscript: All authors.

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