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# Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: A large real-life worldwide population

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ABSTRACT

*Background:* The TOPAZ-1 phase III trial showed a survival benefit with durvalumab plus gemcitabine and cisplatin in patients with advanced biliary tract cancer (BTC). To understand this combination's real-world efficacy and tolerability, we conducted a global multicenter retrospective analysis of its first-line treatment outcomes.

*Methods:* We included patients with unresectable, locally advanced, or metastatic BTC treated with durvalumab, gemcitabine, and cisplatin at 39 sites in 11 countries (Europe, the United States, and Asia). The primary endpoint was overall survival (OS).

*Results:* 666 patients were enrolled. Median OS was 15.1 months and median PFS was 8.2 months. The investigator-assessed overall response rate was 32.7 %, with stable disease in 45.2 % of patients. High baseline CEA levels, ECOG PS > 0, metastatic disease, and NLR > 3 were associated with poor survival. Any grade adverse events (AEs) occurred in 92.9 % of patients (grade >2: 46.6 %). Immune-related AEs (irAEs) occurred in 20.0 % (grade >2: 2.5 %). Three deaths (0.5 %) were deemed treatment-related, none linked to immunotherapy. Common irAEs were rash (8.2 % all grades; 0.3 % grade >2), itching (10.3 % all grades; 0.2 % grade >2), and hypothyroidism (5.1 % all grades; 0.3 % grade >2). Durvalumab discontinuation rate due to AEs was 1.5 %. ESMO-recommended genes were analyzed and no outcome differences were found. A comparative analysis with a historical cohort of patients treated with chemotherapy alone confirmed the positive survival impact of durvalumab in combination with cisplatin/gemcitabine.

*Conclusion:* This first global real-world analysis largely confirmed the TOPAZ-1 findings, supporting gemcitabine, cisplatin, and durvalumab as a first-line standard of care for patients with advanced BTC.

## 1. Introduction

Biliary tract cancer (BTC) has a poor prognosis and scarce therapeutic possibilities [1–4]. The only curative option is surgery followed by adjuvant chemotherapy [2], but only one patient out of five with BTC is eligible for surgery at the time of presentation [5]. Systemic platinum-based chemotherapy was the sole treatment available for patients with locally advance or metastatic disease for almost 15 years [2]. The results from the ABC-02 trial led to establish cisplatin plus gemcitabine as first-line standard of care in 2010, since the combination conferred a survival benefit compared to gemcitabine monotherapy [6]. Nevertheless, the predicted 24-month survival rate was only 15 % [6], and the median overall survival (OS) remained less than a year. Consequently, the need to investigate novel and more effective therapeutic options became an urgent need for these patients. Recently, interesting new insights in the molecular profile of BTC have emerged, including the description of multiple targetable genomic alterations that carry significant therapeutic implications [1,7–10]. Furthermore, immune checkpoint inhibitors (ICIs) have been introduced in the BTC therapeutic armamentarium. Preclinical data demonstrated a link between persistent inflammation and a higher risk of BTC, and the tumor microenvironment has been highlighted to expresses higher levels of immune checkpoints, including cytokine T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death ligand 1 (PD-L1) in this disease [11–13].

In patients with BTC who had previously received systemic treatment, early-phase trials reported conflicting results with ICI in unselected population [14]. Additionally, a growing body of evidence has shown that cytotoxic chemotherapy, such as the combination of gemcitabine and cisplatin, has an immunomodulatory effect, thus, providing a rationale for combining immunotherapy with chemotherapy to improve survival outcomes [15,16]. Based on this rationale, the phase III randomized placebo-controlled TOPAZ-1 study was designed. 658 patients with unresectable or metastatic BTC were randomized to receive the anti-PD-L1 durvalumab or placebo in combination with cisplatin plus gemcitabine for a maximum of eight cycles. Durvalumab or placebo was then given as a maintenance treatment until disease progression or unacceptable toxicity. Patients receiving chemotherapy plus durvalumab had a median OS of 12.8 months, while patients receiving chemotherapy plus a placebo had a median OS of 11.5 months,

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corresponding to a 20 % lower risk of death [17]. Based on these results, the European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA) approved durvalumab in addition to gemcitabine and cisplatin as the new first-line standard of care for patients with untreated, metastatic, or unresectable BTC. Moreover, the survival benefit of combining chemotherapy and immunotherapy in this setting has been confirmed by the KEYNOTE-966 phase III study of pembrolizumab plus cisplatin and gemcitabine [18].

In a previous Italian analysis on 145 patients with BTC treated with durvalumab in combination to cisplatin and gemcitabine in clinical practice, a median progression free survival (PFS) of 8.9 months and a median OS of 12.9 months were highlighted, consistently with the results of the randomized phase III trial [19]. Real-world evidence (RWE) is gaining momentum in clinical oncology in recent years [20], and it is being increasingly used as supportive data for regulatory approval of targeted therapies. However, international collaboration in this field is still limited, thus lowering the representativeness of the populations in published RWE studies. For this reason, we present the results achieved with durvalumab plus chemotherapy as first-line treatment of advanced or metastatic BTC in a larger patient population treated in different countries worldwide.

## 2. Matherial and methods

### 2.1. Study Population

The study population included patients with unresectable, locally advanced, or metastatic BTC, including intrahepatic (iCCA) or extrahepatic cholangiocarcinoma (eCCA) and gallbladder carcinoma (GBC). Patients were prospectively treated and data were retrospectively collected from 39 sites in 11 countries (Italy, Germany, Austria, Spain, United Kingdom, US, Republic of Korea, China, Hong Kong Special Administrative Region of China, Japan and Belgium). Patients were treated with durvalumab combined with gemcitabine and cisplatin administered intravenously on a 21-day cycle for up to eight cycles. Durvalumab (1500 mg) was administered on day 1 of each cycle, in combination with gemcitabine (1000 mg/m2) and cisplatin (25 mg/m2), which were administered on days 1 and 8 of each cycle. After completion of gemcitabine and cisplatin, durvalumab monotherapy (1500 mg) was administered every 4 weeks until clinical or imaging disease progression or unacceptable toxicity.

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 endpoints of the study were PFS and OS achieved with the combination of durvalumab plus cisplatin and gemcitabine in a cohort of patients treated outside of clinical trials. Secondary endpoints were overall response rate (ORR) and safety of the combination of durvalumab plus cisplatin and gemcitabine.

PFS was defined as the time from the date of treatment initiation to the date of disease progression or death or last follow-up whichever occurred first. OS was defined as the time from the date of treatment initiation to the date of death. Survival curves were estimated using the product-limit method of Kaplan-Meier. PFS and OS were reported as median values expressed in months, with 95 % confidence interval (CI).

ORR was assessed by the investigator and defined as the proportion of patients who achieved 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.

Adverse events (AEs) were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics were calculated using the Cox proportional hazards model. Categorical variables were compared using Fisher exact test. A p value $< 0.05$ was considered statistically significant.

A MedCalc package (MedCalc® version 20.2) was used for statistical analysis.

## 3. Results in the cisplatin, gemcitabine, durvalumab cohort

### 3.1. Outcome

From February 2022 to January 2024, 666 patients were enrolled at 39 sites in 11 countries (Italy, Germany, Austria, Spain, United Kingdom, US, South Korea, China, Hong Kong Special Administrative Region of China, Japan and Belgium). Patient demographics and disease characteristics are reported in Table 1. At data cutoff (April 1, 2024), the median duration of follow-up was 8.5 months (95 % CI: 7.9–9.5), 350 patients (52.5 %) discontinued the treatment due to disease progression, and 200 patients (30.0 %) died.

**Table 1**
Patient demographics and disease characteristics.

| Characteristic | N (%)N = 666 |
|---|---|
| **Gender** | |
| Male | 355 (53.3) |
| Female | 311 (46.7) |
| **Age at first-line therapy** years | 67 (range 29-89) |
| **Primary tumor Site** | |
| Intrahepatic | 363 (54.5) |
| Extrahepatic | 168 (25.2) |
| Gallbladder | 135 (20.3) |
| **Hepatitis** | |
| Hepatitis B positiveHepatitis C positiveNegative | 38 (5.7)21 (3.1)607 (91.2) |
| **Previous surgery** | |
| YesNo | 178 (26.7)488 (73.3) |
| **Previous adjuvant therapy** | |
| YesNo | 109 (61.2)69 (38.8) |
| **Drainage or stent** | |
| YesNo | 175 (26.3)491 (73.7) |
| **Disease Status** | |
| Locally Advanced | 157 (23.6) |
| Metastatic | 509 (76.4) |
| **ECOG PS** | |
| 0 | 328 (49.2) |
| > 0 | 338 (50.8) |
| **CA 19-9** median (range) UI/mL | 105 (0.6-628400) |
| Within Normal Levels | 203 (30.5) |
| >Normal Levels | 427 (64.1) |
| Not reported | 36 (5.4) |
| **CEA** median (range) ng/mL | 3.1 (0.2-30340) |
| Within Normal Levels | 333 (50.0) |
| >Normal Levels | 263 (39.5) |
| Not reported | 70 (10.5) |
| **NLR** | |
| < 3 | 252 (37.8) |
| ≥ 3 | 331 (49.7) |
| Not reported | 83 (12.5) |
| **AST U/L** | |
| Within Normal Levels | 340 (51.1) |
| >Normal Levels | 255 (38.3) |
| Not reported | 71 (10.6) |
| **ALT U/L** | |
| Within Normal Levels | 509 (76.4) |
| >Normal Levels | 124 (18.6) |
| Not reported | 33 (5.0) |

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

Median PFS was 8.2 months (95 % CI: 7.5–8.9), and median OS 15.1 months (95 % CI: 13.4–29.1) (Fig. 1A).

The investigator-assessed ORR was 32.6 %. The percentage of patients achieving a CR was 2.6 %, while PR was 30.0 % and SD was 45.2 %, leading to a DCR of 77.8 % (Fig. 1B).

By considering chemo-immuno cycles and maintenance cycles with single-agent durvalumab, the median number of administered cycles was 9 with a range of 1–26 cycles. 222 (36.1 %) patients were free from disease progression after 8 cycles of chemotherapy plus durvalumab, receiving subsequent maintenance therapy with durvalumab monotherapy.

### 3.2. Safety

Safety data were available for 650 patients (one center did not gather any safety information). Any grade AEs occurred in 604 patients (92.9 %). Grade 3 or 4 AEs occurred in 303 patients (46.6 %) (Fig. 2A). The most common AEs were fatigue (55.0 %), neutropenia (47.7 %), anemia (46.8 %), and thrombocytopenia (39.2 %) (Figure 2B). The number of deaths due to treatment-related AEs (TRAEs) was 3 (0.5 %) (two cholangitis and one febrile neutropenia): none of these events was related to immunotherapy. The rate of immune-related AEs (irAE) was 20.0 %. Grade 3 or 4 irAE occurred in 2.5 % of patients (Fig. 2A). The most common AEs were rash (8.2 % all grade; 0.3 % grade >2), itching (10.3 % all grade; 0.2 % grade >2), hypothyroidism (5.1 % all grade; 0.3 % grade >2), hyperthyroidism (1.8 % all grade; 0 % grade >2), colitis (1.4 % all grade; 0 % grade >2), immune-mediated pneumonia (0.01 % all grade; 0 % grade >2) and hypophysitis (0.01 % all grade; 0 % grade >2). The rate of discontinuation of durvalumab due to AEs was 1.5 %.

### 3.3. Gene alterations and clinical outcome

414 patients (62.2 %) underwent ESCAT I/II gene alteration analysis on tumor tissue samples according to ESMO recommendations (*FGFR2* fusion, *IDH1* mutation, *KRAS* (G12C) mutation, *BRAF* V600E mutation, *HER2* amplification.

In the whole population, *FGFR2* fusion was found in 3.6 % of patients, *IDH1* mutation in 8.5 %, *KRAS* G12C mutation in 0.05 %, BRAF V600E mutation in 1.2 %, and *HER2* amplification in 4.8 %. In patients with iCCA, *FGFR2* fusion was found in 5.1 %, *IDH1* mutation in 14.5 %, *KRAS* G12C mutation in 0.8 %, *BRAF* V600E mutation in 2.1 %, and *HER2* amplification in 4.2 %. In the eCCA group, *FGFR2* fusion was found in 1.7 % of subjects, *IDH1* mutation in 0.5 %, *KRAS* G12C mutation in 0 %, *BRAF* 600E mutation in 0 %, and *HER2* overexpression/mutation in 5.6 %.

In the whole population, at univariate analysis for PFS no gene alteration was found to be associated with prognosis compared to the wild-type counterpart. *FGFR2* fusion (9.6 vs. 8.6 months, HR 0.79; 95 % CI 0.38–1.63; p = 0.53), *IDH1* mutation (8.3 vs. 8.7 months, HR 0.87; 95 % CI 0.54–1.41; p = 0.58), *KRAS* G12C mutation (3.1 vs. 8.6 months, HR 1.08; 95 % CI 0.14–8.32; p = 0.94), *BRAF* V600E (15.7 vs. 8.6 months, HR 0.54; 95 % CI 0.22–1.36; p = 0.19), *HER2* overexpression/mutation (7.8 vs. 8.9 months, HR 1.31; 95 % CI 0.69–2.53; p = 0.41).

In the whole population, at univariate analysis for OS no gene alteration was found to be associated with prognosis compared to the wild-type counterpart. *FGFR2* fusion (not reach vs. 15.9 months, HR 0.60; 95 % CI 0.22–1.67; p = 0.33), *IDH1* mutation (11.6 vs. 15.9 months, HR 0.97; 95 % CI 0.49–1.90; p = 0.93), *KRAS* G12C mutation (not reach vs. 15.9 months, HR 0.44; 95 % CI 0.12–2.343; p = 0.54), *BRAF* V600E (29.1 vs. 15.9 months, HR 0.32; 95 % CI 0.09–1.11; p = 0.07), *HER2* overexpression/mutation (9.9 vs. 16.1 months, HR 2.10; 95 % CI 0.83–5.30; p = 0.12).

### 3.4. Subgroup analysis

In the univariate analysis for PFS, baseline high levels of alanine transaminase (p = 0.011, HR 1.64, 95 % CI: 1.18–2.01), aspartate transaminase (p = 0.012, HR: 1.66, 95 % CI: 1.32–1.96), bilirubin (p = 0.0023, HR: 1.78, 95 % CI: 1.34–2.10), CA 19–9 (p = 0.0064, HR: 1.66, 95 % CI: 1.26–1.94), CEA (p = 0.0004, HR: 1.72, 95 % CI: 1.18–2.00), ECOG PS > 0 (p < 0.0001, HR: 1.82, 95 % CI: 1.52–2.06), metastatic disease (p = 0.0001, HR: 1.84, 95 % CI: 1.52–2.12), eCCA (vs iCCA HR: 1.62, 95 % CI: 1.26–1.96; vs GBC HR 1.78, 95 % CI: 1.30–2.12), and NLR > 3 (p = 0.0004, HR: 1.72, 95 % CI: 1.36–1.98) correlated with shorter PFS (supplementary table 1).

After adjustment for the variables with a prognostic impact at the univariate analysis, the multivariate analysis for PFS confirmed the negative prognostic role of high baseline CA 19–9 (p = 0.03, HR: 1.54, 95 % CI: 1.08–1.90), high baseline CEA (p = 0.02, HR: 1.34, 95 % CI: 1.10–1.38), ECOG-PS>0 (p < 0.0001, HR: 1.54, 95 % CI: 1.26–1.94), and metastatic disease (p = 0.0001, HR: 1.86, 95 % CI: 1.40–2.16) (supplementary table 1).

In the univariate analysis for OS, baseline high levels of alanine transaminase (p = 0.0075, HR 1.76, 95 % CI: 1.17–2.65), aspartate transaminase (p = 0.0016, HR: 1.78, 95 % CI: 1.25–2.54), bilirubin (p = 0.0007, HR: 1.74, 95 % CI: 1.15–2.63), CEA (p = 0.0001, HR: 2.04, 95 % CI: 1.43–2.90), ECOG PS > 0 (p < 0.0001, HR: 1.92, 95 % CI: 1.37–2.70), metastatic disease (p < 0.0001, HR: 2.77, 95 % CI: 1.74–4.40), and NLR > 3 (p < 0.0001, HR: 2.09, 95 % CI: 1.45–3.01)

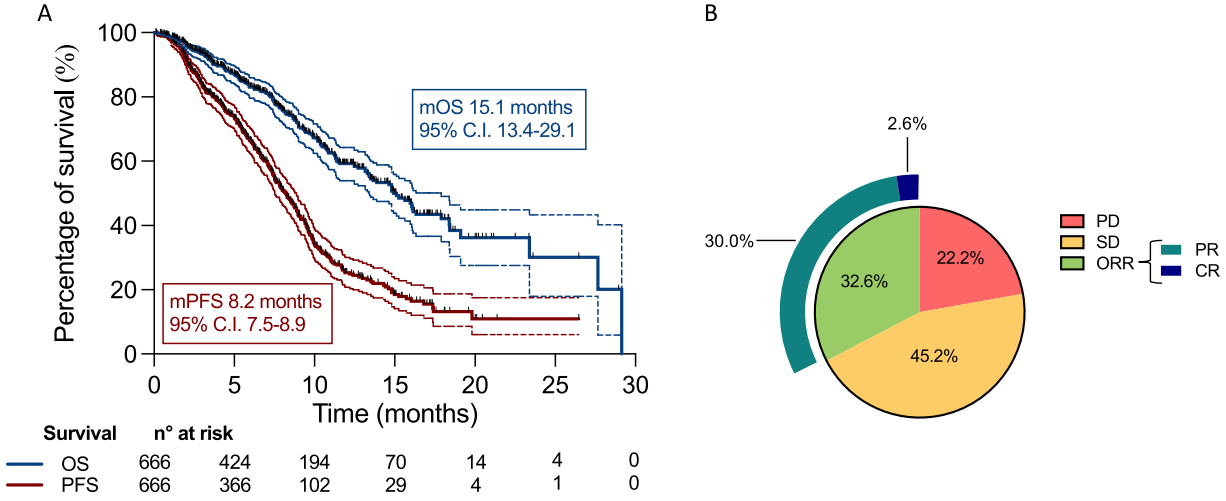


**Fig. 1.** A: Kaplan Meier curves for OS and PFS; B: Graphical representation of response to treatment in the cisplatin, gemcitabine, durvalumab cohort.

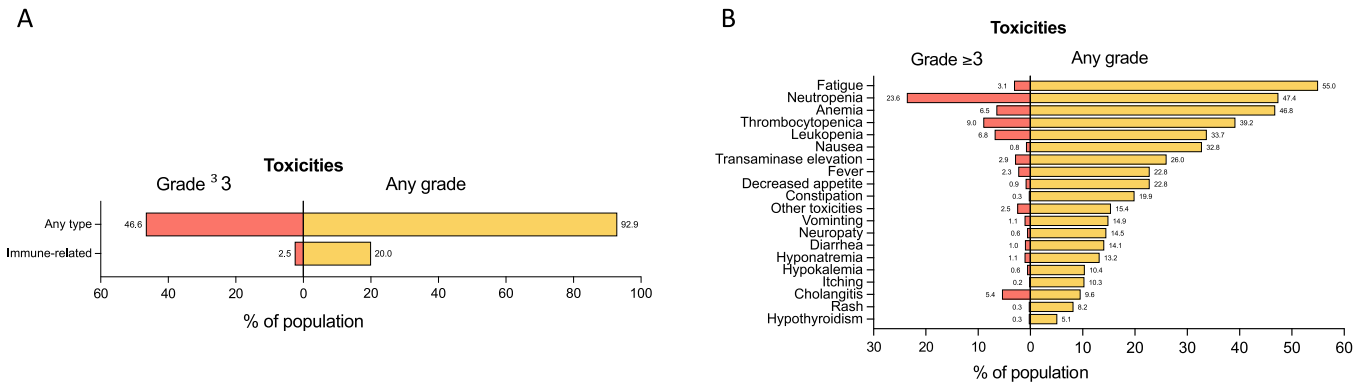


**Fig. 2.** A: Incidence of grade ≥ 3 and any grade adverse events; B: Incidence of most frequent adverse events in the cisplatin, gemcitabine, durvalumab cohort.

correlated with shorter OS (Fig. 4 and Supplementary table 2).

After adjustment for the variables with a prognostic impact at the univariate analysis, the multivariate analysis for OS confirmed the negative prognostic role of high baseline CEA levels (p = 0.0004, HR: 1.99, 95 % CI: 1.33–2.80), ECOG PS > 0 (p = 0.0001, HR: 1.82, 95 % CI: 1.25–2.55), metastatic disease (p < 0.0001, HR: 2.54, 95 % CI: 1.57–4.17), and NLR > 3 (p = 0.0002, HR: 2.07, 95 % CI: 1.43–2.99) (Supplementary table 2).

ECOG PS, disease status and absence or drainage or stent were associated with higher objective response to treatment (Table 2). Patients with ECOG PS 0 had an ORR of 39.2 % versus 25.6 % in patients with ECOG PS> 0; patients with locally advanced disease had an ORR of 39.2 % versus 31.8 % in patients with metastatic disease and patients with absence of drainage or stent had an ORR of 35.2 % versus 29,9 % in patients with drainage or stent.

### 3.5. *Further-line therapies*

179 patients (51.1 %) with disease progression received subsequent treatments. Of these, 135 patients (75.4 %) received 5-fluorouracil or capecitabine plus oxaliplatin, 21 patients (11.7 %) received targeted therapy according to their tumor molecular profile (8 patients ivosidenib, 7 patients anti-HER2 drugs, 5 patients pemigatinib and 1 patient dabrafenib plus trametinib), 11 patients (6.1 %) received 5-fluorouracil or capecitabine monotherapy, and 12 patients (6.8 %) received other treatments. Post-progression median OS was 3.8 months (95 % CI: 2.9–5.0), and was longer in patients who received any treatment compared to best supportive care (7.4 months vs 1.4 months). Median OS was not reached in patients treated with any targeted therapy versus 6.2 months (95 % CI 4.7–9.6) in patients treated with chemotherapy, corresponding to a reduction in the risk of death of 60 % with targeted therapy (HR 0.40, 95 % CI 0.20–0.83, p = 0.00133) (Figure 3).

**Table 2**
Overall response rate based on baseline patients' characteristics.

| Characteristic | ORR | P-value |
|---|---|---|
| **Gender** | | |
| Male | 40.6 % | |
| Female | 34.6 % | 0.17 |
| **Primary tumor Site** | | |
| Intrahepatic | 34.9 % | |
| Extrahepatic | 31.4 % | |
| Gallbladder | 28.2 % | 0.203 |
| **Drainage or stent** | | |
| **Yes** | **29.9 %** | |
| **No** | **35.2 %** | **0.01** |
| **Disease Status** | | |
| **Locally Advanced** | **39.2 %** | |
| **Metastatic** | **31.8 %** | **0.006** |
| **ECOG PS** | | |
| **0** | **39.2 %** | |
| **>0** | **25.6 %** | **0.0009** |
| **CA 19-9** median (range) UI/mL | | |
| Within Normal Levels | 32.7 % | |
| >Normal Levels | 30.3 % | 0.57 |
| **CEA** median (range) ng/mL | | |
| Within Normal Levels | 31.1 % | |
| >Normal Levels | 33.8 % | 0.51 |
| **NLR** | | |
| <3 | 34.1 % | |
| ≥3 | 32.0 % | 0.38 |

## 4. Durvalumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin

Overall, 879 patients were enrolled and included in the analysis: 213 patients received cisplatin/gemcitabine alone, and 666 received durvalumab in combination to cisplatin/gemcitabine. .

Patients treated with cisplatin plus gemcitabine, were enrolled from the centers in Italy from March 2016 to December 2022. Patients who received treatment before the publication of the TOPAZ-1 results received the previous standard combination of cisplatin 25 mg/m2 plus gemcitabine 1000 mg/m2 on days 1 and 8 of each 21-day cycle for up to 8 cycles, according to the ABC-02 trial.

The two cohorts of patients were homogeneous in terms of demographic and disease characteristics.

At the univariate analysis for OS, the addition of durvalumab to cisplatin/gemcitabine was found to have a prognostic impact, with median OS of 15.1 versus 11.1 months (HR 0.59, 95 % CI 0.47–0.74, p < 0.0001) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Fig. 5A).

At the univariate analysis for PFS, the addition of durvalumab to

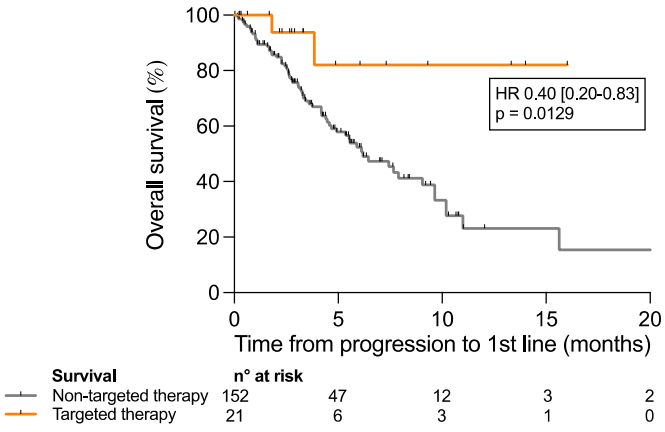


**Fig. 3.** Kaplan Meier curves for OS in patients treated with any targeted therapy and patients treated with chemotherapy in second line.

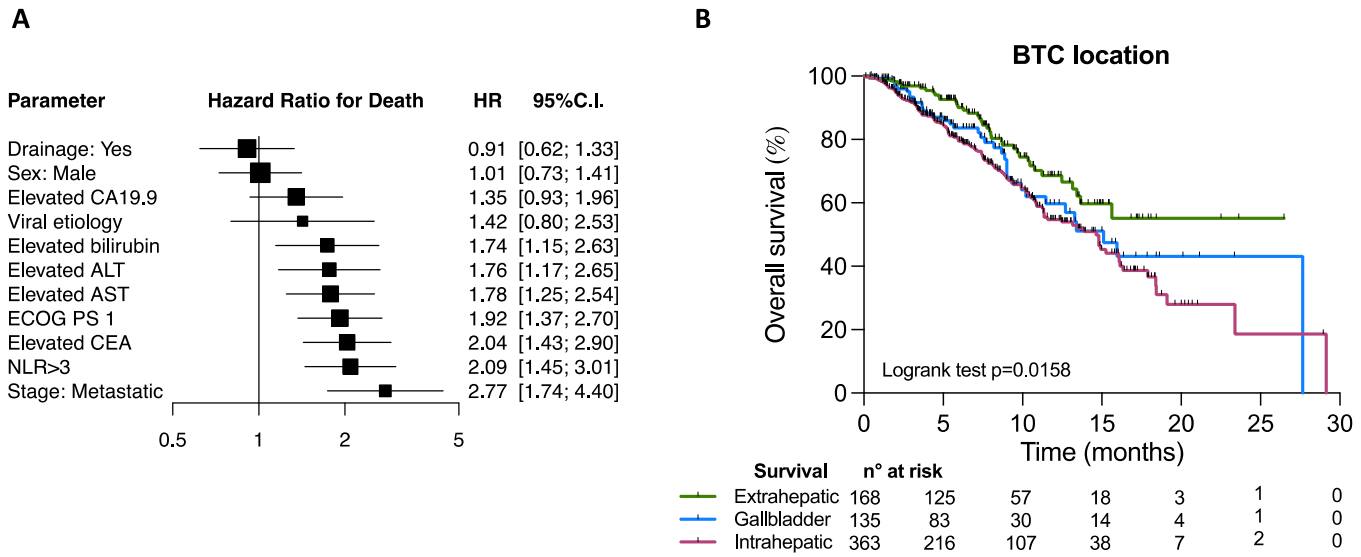


**Fig. 4.** A: Forest plot for OS according to baseline characteristics; B: Kaplan Meier curves for OS based on primary tumor site.

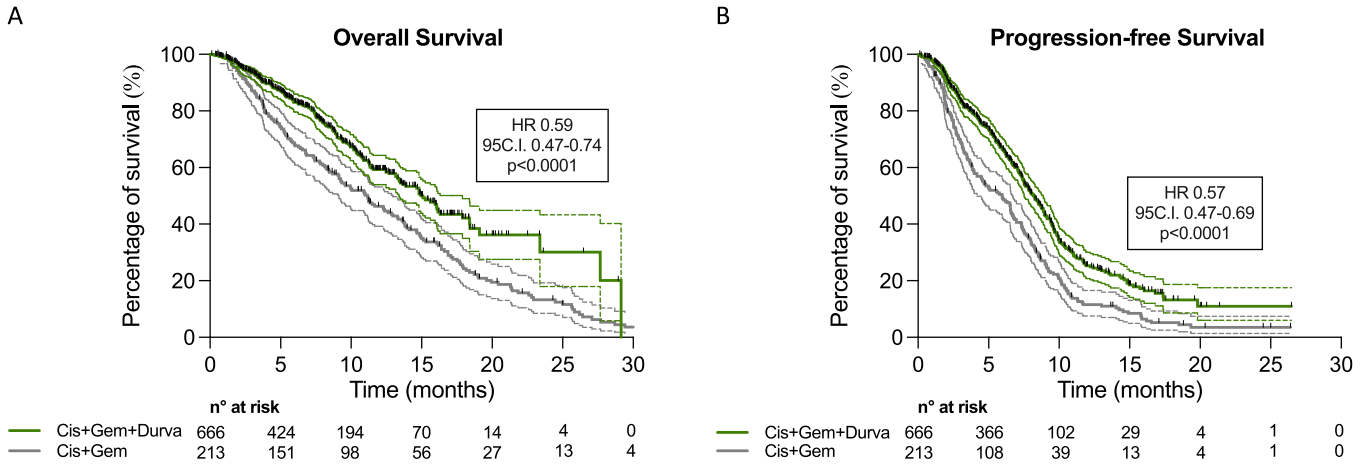


**Fig. 5.** (A) Kaplan Meier curves for OS and (B) for PFS in the cisplatin, gemcitabine, durvalumab cohort and in the cisplatin, gemcitabine cohort.

cisplatin/gemcitabine resulted to have a prognostic impact, with median PFS of 8.2 months compared to 6.0 months (HR 0.57, 95 % CI 0.47–0.69, $p \leq 0.0001$) in patients who received cisplatin/gemcitabine plus durvalumab and cisplatin/gemcitabine alone, respectively (Fig. 5B).

The combination of cisplatin/gemcitabine plus durvalumab showed a tendence toward a higher ORR which did not reach the statistical significance (32.7 % vs 25.6 %, $p = 0.057$), whereas DCR was significantly higher for the combination of chemo-immunotherapy compared to cisplatin/gemcitabine alone (76.0 % vs 59.2 %, $p < 0.000001$).

## 5. Discussion

The positive results of the phase III TOPAZ-1 trial have changed the treatment paradigm for advanced BTC [17]. In fact, for the first time, a palliative treatment reached a median survival of more than one year in this setting, thus leading to the approval of durvalumab plus cisplatin and gemcitabine as the new standard of care for patients with unresectable BTC. The unfavorable prognosis of patients with BTC and the high percentage of patients diagnosed with advanced disease, making them ineligible for curative therapy, make these results even more relevant.

To the best of our knowledge, the current research represents the first, largest, worldwide RWE with durvalumab in combination to cisplatin and gemcitabine as first-line therapy in patients with advanced BTC. The results reported in this real-world analysis mostly confirmed the results achieved in the TOPAZ-1 trial. In our analysis, the combination of durvalumab with standard chemotherapy achieved a median PFS of 8.2 months, which is consistent with the median PFS of 7.2 months reported in the TOPAZ-1 trial. Interestingly, considering the differences in the populations included in RWE and prospective randomized studies, OS seems to be even longer in a real-world setting compared to the registrational trial (15.1 months versus 12.8 months). In addition, in our analysis the ORR was comparable to the pivotal study (32.6 % versus 26.7 %). Moreover, the results of the present work are consistent with those reported in the previous RWE study conducted at 17 Italian institutions [19]. Differently from our previous research, this study was conducted globally and included patients from both Eastern and Western Countries, supporting the use of cisplatin and gemcitabine plus durvalumab as standard of care in clinical practice for patients with unresectable, locally advanced, or metastatic BTC, independently from ethnicity.

Furthermore, the positive survival impact of durvalumab in combination with cisplatin/gemcitabine compared to cisplatin/gemcitabine alone has been confirmed in a real-world cohort of patients.

Regarding the safety profile, our findings indicate that the overall incidence of any grade AEs was 92.9 %, in line with the findings of the

TOPAZ-1 study. In contrast, the incidence of grade 3–4 AEs was 46.6 % in our work, compared to 75.7 % in the TOPAZ trial [17]. The lower incidence of grade 3–4 AEs, primarily in relation to bone marrow toxicities that may manifest later during treatment, may be explained by the shorter median follow-up of our analysis when compared to the pivotal study.

Furthermore, we observed a slightly different safety profile than that of the phase III study, with fatigue, neutropenia, anemia, and thrombocytopenia being the most common AEs as opposed to anemia, nausea, constipation, and neutropenia highlighted as main toxicities in the TOPAZ-1 trial. Interestingly, when analyzing only grade 3–4 irAE, our reported incidence matched the TOPAZ-1 data. Notably, treatment-related deaths were not correlated with immunotherapy (two cholangitis and one febrile neutropenia). Moreover, the rate of durvalumab discontinuation was very low (1.7 %), confirming the overall safety of this agent in BTC also in the RWE, as most TRAEs were represented by typical chemotherapy-related toxicities.

Similarly to our previous results, multivariate analysis showed that normal baseline CA 19–9 and CEA levels and locally advanced disease correlated with better outcome in terms of PFS. CEA, ECOG PS 0, locally advanced disease, and NLR $< 3$ were indeed associated with OS. These baseline characteristics are recognized to have an impact on prognosis and our results are not surprising. With regard to disease extent, phase III data also reported longer PFS and higher response rate among patients with locally advanced (compared to metastatic) disease. Future, prospectively collected series should explore the possibility of achieving secondary, curative-intent surgery among patients experiencing objective response to chemotherapy plus immunotherapy, thus opening up a new therapeutic scenario for patients with locally advanced disease.

ECOG PS$>$ 0 is a well-known negative prognostic factor, similarly to baseline high CEA and CA 19–9 levels. In fact, in various contexts, it has been shown that CEA and CA 19–9 levels, particularly when both are elevated, are associated with a worse prognosis in patients with BTC.

Prior research has indicated that NLR has a prognostic role in several solid tumors undergoing systemic therapy, primarily ICIs [21,22]. Indeed, it incorporates the status of two immune populations (neutrophils and lymphocytes) with opposing functions—the former with proinflammatory and carcinogenic properties, and the latter with cytotoxic and antitumoral properties. Recently, Tanaka et al showed a negative correlation between NLR and CD8 +T cells that infiltrate tumors. These cells have been shown to directly kill tumor cells, which means they are essential for the anti-tumoral immune response [23–25]. The link between the tumor microenvironment and the systemic immune response, as well as the interaction between cancer cells and host immunological populations, remain unclear in BTC and require further research to shed light on potential biomarkers of benefit from ICIs. Indeed, with the introduction of ICIs in this setting, the research of biomarkers able to select patients who could benefit more from immunotherapy has become an urgent need, and the identification of the patients who are more likely to benefit from immunotherapy will be a crucial point.

In the new era of precision medicine, genetic alterations, such as mutations, gene fusions, and copy number variations, have been identified in BTC. Pemigatinib [26], futibatinib [27], ivosidenib [28–30], larotrectinib [31], entrectinib [32], dabrafenib-trametinib [33] and trastuzumab-pertuzumab [34] are available treatments for patients with previously treated BTC with *FGFR2* gene fusion or rearrangements, *IDH1* mutations, *BRAF* mutations, and *HER2* overexpression or amplification, respectively.

Regarding molecular profiling, we analyzed the genes recommended by the ESMO guidelines. However, we have to highlight that molecular profiling was performed only in 62.2 % of the patients, despite the centers involved in this study had a high expertise in the management of patients with BTC. In terms of the percentage of gene alterations, our data are in line with previously published studies. Finally, in terms of outcome, we found no difference based on the genetic alterations observed.

However, our data showed a reduction in the risk of death of 60 % in favor of patients who received any subsequent targeted therapy, reinforcing the importance of molecular profiling for all patients with advanced BTC. Of note, our series is the first reporting the outcome with targeted agents after the failure of cisplatin and gemcitabine plus durvalumab.

Our research has several limitations. The retrospective nature of the dataset makes it at risk of selection bias. Also, this is a multicenter study, in which response evaluation and timing of assessment were performed at individual physician's discretion, leading to variability that may have impacted on PFS estimate. Additionally, due to the relatively short median follow-up, future update is needed after a longer period of observation to confirm the observed results.

In conclusion, we presented the first worldwide RWE with durvalumab in combination with gemcitabine and cisplatin. Our data support the use of this combination in clinical practice by largely corroborating the efficacy and safety outcomes obtained in the phase III TOPAZ-1 trial.

## Ethics statement

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 patients' data anonymization, our study was exempted from the acquisition of informed consent from patients by the institutional review board.

## Funding

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## Institutional Review Board Statement

The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki.

## Informed consent statement

Written informed consent for treatment was obtained for all patients.

## CRediT authorship contribution statement

**Mario Scartozzi:** Investigation. **Marta Schirripa:** Investigation. **Il Hwan Kim:** Investigation. **Gerald W. Prager:** Investigation. **Antonio Avallone:** Investigation. **Monica Verrico:** Investigation. **Jorge Adeva:** Investigation. **Lukas Perkhofer:** Investigation. **Ester Oneda:** Investigation. **Stephen L. Chan:** Investigation. **Gianluca Masi:** Investigation. **Anna Diana:** Investigation. **Sara Lonardi:** Investigation. **Selma Ahcene Djaballah:** Investigation. **Changhoon Yoo:** Investigation. **Valentina Zanuso:** Investigation. **Alessandro Parisi:** Investigation. **Lorenza Rimassa:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Andrea Casadei Gardini:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Federico Nichetti:** Investigation. **Hong Jae Chon:** Investigation. **Guido Giordano:** Investigation. **Florian Castet:** Investigation. **Emiliano Tamburini:** Investigation. **Chiara Braconi:** Investigation. **Chiara Pirrone:** Investigation. **Monica Niger:** Investigation. **Stefano Tamberi:** Investigation. **Rita Balsano:** Investigation. **Fabian Finkelmeier:** Investigation. **Oluseyi Abidoye:** Investigation. **Jeroen Dekervel:** Investigation. **Ilario Giovanni Rapposelli:** Investigation. **Tanios Bekaii-Saab:** Investigation. **Luca Esposito:** Investigation. **Giuseppe Tonini:** Investigation. **Minsu Kang:** Investigation. **Matteo Landriscina:** Investigation. **Alessandra Boccaccino:**

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## Declaration of Competing Interest

LR reports consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Incyte, Ipsen, Roche, 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, Zymeworks.

ACG reports consulting fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, Servier; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Roche, Servier; travel expenses from AstraZeneca; research grants (to Institution) from AstraZeneca, Eisai. SLC serves an advisory member for AstraZeneca, MSD, Eisai, BMS, Ipsen, and Hengrui, received research funds from MSD, Eisai, Ipsen, SIRTEX, and Zailab, and honoraria from AstraZeneca, Eisai, Roche, Ipsen, and MSD.

TP received consulting fees from Bayer, Ipsen, and AstraZeneca; institutional research funding from Roche, Bayer, and AstraZeneca; travel expenses from Roche.

CB received honoraria as speaker (Astrazeneca, Incyte, Servier) and consultant (Incyte, Servier, Boehringer Ingelheim, Astrazeneca), received research funds (Avacta, Medannex, Servier) and her spouse is an employee of Astrazeneca.

M. Ikeda reports honoraria from AstraZeneca, Chugai Pharma, Eisai, Incyte, Lilly Japan, MSD, Novartis, Ono Pharmaceutical, Takeda, Teijin Pharma, Nihon Servier, Taiho and research funding from AstraZeneca, Bayer, Bristol-Myers Squibb, Chiome Bioscience, Chugai, Eisai, Eli Lilly Japan, Delta-Fly Pharma, Invitae, J-Pharma, Merck biopharma, Merus N.V., MSD, Novartis, Nihon Servier, Ono, Syneos Health, and Rakuten Medical.

GWP: Advisories and/or Speaker fees: Servier, Bayer, Roche Amgen, Merck, MSD, BMS, Sanofi, Lilly, Astra Zeneca, Astellas, Pierre-Fabre, Incyte, Arcus, CECOG.

F. F. has received travel support from Ipsen, Abbvie, Astrazeneca and speaker's fees from AbbVie, MSD, Ipsen, Astrazeneca.

LP: Advisory role: AstraZeneca, Servier, Travel expenses: AstraZeneca, Ipsen.

GG: Consulting Fees: Astra Zeneca, MSD, Servier, Seagen, Bayer, Amgen, Novartis, Ipsen, BMS.

Travel Expenses: Astra Zeneca, Servier, Bayer, Novartis.

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JD received consulting fees and/or speaker honoraria from Amgen, AstraZeneca, Bayer, BMS, Eisai, Need Inc., Ipsen, Lilly, MediMix, Merck, MSD, Novartis, Roche and Servier.

All remaining authors have declared no conflicts of interest.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114199.

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