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ORIGINAL ARTICLE

Cisplatin-gemcitabine-durvalumab reintroduction in advanced biliary tract cancer: a multinational real-world analysis

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Background: Treatment options for advanced biliary tract cancers (BTCs) progressing after first-line chemoimmunotherapy remain limited. Whether platinum-based chemotherapy reintroduction can restore disease control is unknown. This study evaluates cisplatin-gemcitabine-durvalumab (CGD) reintroduction in patients with advanced BTC progressing during durvalumab maintenance.

Methods: A multinational cohort of patients with BTC received first-line CGD followed by durvalumab maintenance. Those progressing during maintenance and treated with CGD reintroduction or FOLFOX/XELOX were analyzed. Primary endpoints were overall survival (OS) and progression-free survival (PFS) in the CGD reintroduction group; secondary endpoints included survival outcomes from maintenance and second-line initiation, overall response rate, and disease control rate.

Results: Among 1258 patients treated with first-line CGD, 475 received durvalumab maintenance. After disease progression during maintenance ($n = 309$, 65.1%), 31 patients (6.5%) underwent CGD reintroduction, while 114 (24%) received FOLFOX/XELOX. Baseline characteristics were comparable between groups, except for bilirubin levels. After a median follow-up of 22.6 months [95% confidence interval (CI) 20.0-25.1], median OS was not reached in the reintroduction cohort, while median PFS was 13.3 months (95% CI 9.7-15.8) from first-line initiation. From durvalumab maintenance start, median OS remained not reached and median PFS was 7.1 months (95% CI 4.8-11.3). Following reintroduction, median OS and PFS were 10.5 months (95% CI 8.0-10.5) and 9.0 months (95% CI 5.5-10.2). Compared with FOLFOX/XELOX, CGD reintroduction was associated with significantly improved OS [hazard ratio (HR) 0.47; $P = 0.006$] and PFS (HR 0.44; $P < 0.0001$) from first-line therapy start, as well as improved PFS from second-line treatment start (HR 0.60; $P = 0.027$). These findings were confirmed after multivariable and inverse probability of treatment weighting adjustment. Response outcomes were comparable between groups.

Conclusions: This is the first study evaluating CGD reintroduction in patients with BTC progressing during durvalumab maintenance. Although the retrospective design does not allow definitive conclusions, our findings suggest potential benefit in selected patients.

Key words: biliary tract cancer, cholangiocarcinoma, chemoimmunotherapy, durvalumab maintenance, platinum reintroduction, real-world evidence

INTRODUCTION

The therapeutic scenario of advanced biliary tract cancers (BTCs) has undergone profound changes, with the introduction of chemoimmunotherapy in the first-line setting and molecularly targeted agents in subsequent lines for patients with actionable alterations.[1,2] The combinations of cisplatin-gemcitabine-durvalumab (CGD) and cisplatin-gemcitabine-pembrolizumab have been approved based on the TOPAZ-1[3-5] and KEYNOTE-966[6,7] trials, respectively. After completing eight cycles of chemoimmunotherapy, both studies incorporated maintenance treatment (durvalumab in TOPAZ-1 and pembrolizumab plus gemcitabine in KEYNOTE-966); however, neither evaluated the reintroduction of the initial chemotherapy combination in patients progressing during maintenance.

Reintroduction of previously effective first-line chemotherapy is an established strategy in several tumors,[8-18] but evidence in BTC is limited. A study published in 2014, conducted before the adoption of FOLFOX in the second-line and before immunotherapy integration, explored cisplatin—gemcitabine (CG) reintroduction in nine platinum-sensitive patients. Different regimens were used as second line, such as CG reintroduction, 5-fluorouracil/cisplatin, and gemcitabine. Patients were selected for second-line CG reintroduction if they had disease control or objective response to first line and if experienced disease progression at least 12 weeks after the conclusion of first-line CG. Results were encouraging, with a median overall survival (OS) of 26.7 months and a median progression-free survival (PFS) from CG reintroduction of 13.3 months. However, no other studies have further explored these findings.

Based on the hypothesis that platinum reintroduction may restore disease control after a platinum-free interval, the present study evaluates the efficacy of CGD reintroduction in patients with advanced BTC without actionable alterations who had received first-line CGD and progressed during durvalumab maintenance.

MATERIALS AND METHODS

Study cohort

The study cohort consisted of patients with locally advanced, unresectable, or metastatic BTC [including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA), and gallbladder carcinoma (GBC)] without actionable alterations who received first-line CGD followed by durvalumab maintenance, and treated at the time of progression with either CGD reintroduction or second-line FOLFOX/XELOX between December 2020 and April 2025. Data were retrospectively collected from 55 sites across 12 countries (Italy, Germany, Austria, Spain, Portugal, Belgium, United Kingdom, United States, Republic of Korea, China, Hong Kong Special Administrative Region of China, and Japan). CGD was administered intravenously

for up to eight cycles as per the TOPAZ-1 trial. Upon completion of chemoimmunotherapy, durvalumab was continued as maintenance therapy until disease progression or unacceptable toxicity. Patients progressing during durvalumab maintenance were treated, at the discretion of the treating physician, with CGD reintroduction if they had achieved at least disease control during the first-line CGD. CGD reintroduction followed the same regimen used in the first-line setting. The other group analyzed included patients treated with FOLFOX/XELOX as second line after progressive disease (PD) during durvalumab maintenance according to local practice.

Chemotherapy dose reductions were applied according to clinical practice for the management of adverse events (AEs), while no dose modifications were allowed for durvalumab. The study was approved by the local Ethics Committee of each Institutional Hospital, complied with the provisions of the Good Clinical Practice guidelines, 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 concerning the processing of personal data.

Study objectives and statistical analysis

The present study aimed to evaluate the impact on OS and PFS of CGD reintroduction in a large and multinational cohort of patients with advanced or metastatic BTC treated with first-line CGD. We initially assessed outcomes in the overall cohort of patients who received maintenance therapy with durvalumab. Subsequently, we analyzed the subgroups of patients who underwent CGD reintroduction and second-line treatment with FOLFOX/XELOX, followed by a comparative analysis between the two treatment strategies.

Secondary endpoints included OS 2 (OS2), PFS 2 (PFS2), OS 3 (OS3), PFS 3 (PFS3), overall response rate (ORR), and disease control rate (DCR).

OS was defined as the time from the start of first-line therapy with CGD to death from any cause. PFS was defined as the time from first-line initiation to PD, death, or last follow-up. OS2 and PFS2 were defined analogously, starting from the initiation of durvalumab maintenance. OS3 was defined as the time from the start of CGD reintroduction or second-line therapy to death from any cause, and PFS3 as the time from CGD reintroduction or second-line initiation to PD, death, or last follow-up, whichever occurred first.

To better evaluate OS3 and PFS3 in the CGD reintroduction group, patients were initially stratified into long and poor responders using the median PFS2 as a cut-off, and subsequently according to their response to the initial eight cycles of CGD [response group versus stable disease (SD) group]. Treatment response was evaluated by computed tomography (CT) and categorized as complete response (CR), partial response (PR), SD, or PD by local review according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. ORR was defined as the proportion of patients achieving CR or PR, while DCR was defined as the proportion of patients who achieved CR, PR, or SD.

A multivariable Cox proportional hazards model was fitted including covariates with significant association in univariate analysis ($P < 0.05$), together with baseline characteristics that showed relevant imbalance between groups or were considered clinically meaningful.

To reduce confounding and account for baseline imbalances, an inverse probability of treatment weighting (IPTW) approach based on the propensity score was applied.

The propensity score was estimated using a multivariable logistic regression model including clinically relevant baseline covariates, and stabilized weights were used to generate a balanced pseudo-population.

Covariate balance was assessed using standardized mean differences (*d*-values), with values <0.1 indicating negligible imbalance. Weighted Kaplan—Meier curves and Cox models were then used to estimate treatment effects and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs).

Weighted Kaplan—Meier survival curves and weighted Cox proportional hazards models were used to estimate treatment effects on OS and PFS from first-line initiation and from CGD reintroduction, and to derive adjusted HRs with corresponding 95% CIs.

Statistical analyses were carried out using MedCalc software (MedCalc® version 16.8.4) while the IPTW analysis was conducted using R (version 4.3.2).

RESULTS

Patient characteristics

In the overall registry, 1258 patients with advanced BTC were treated with first-line CGD. Among them, 475 patients (37.8%) subsequently received durvalumab maintenance and constituted the study population analyzed in the present study. The remaining 783 patients were excluded because they did not receive durvalumab maintenance: 263 (20.9%) were progression-free during CGD and had not yet started maintenance at data cut-off, whereas 520 (41.3%) experienced progression during CGD. Baseline characteristics of the durvalumab-maintenance cohort ($n = 475$) are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.108248.

Among patients who received durvalumab maintenance, 252 (53.1%) were male and 249 (52.4%) were $\leq$70 years. A total of 263 patients (55.4%) had iCCA, 135 (28.4%) had eCCA, and 77 (16.2%) had GBC. Metastatic disease was present in 358 patients (75.4%), while 117 (24.6%) had locally advanced disease. Elevated CA 19-9 levels were reported in 287 patients (60.4%).

Outcomes in the durvalumab maintenance cohort

Of 475 patients, 360 (75.8%) achieved disease control at the end of the first-line CGD (6 CR, 110 PR, and 244 SD). A small proportion of patients ($n = 16$) initiated durvalumab

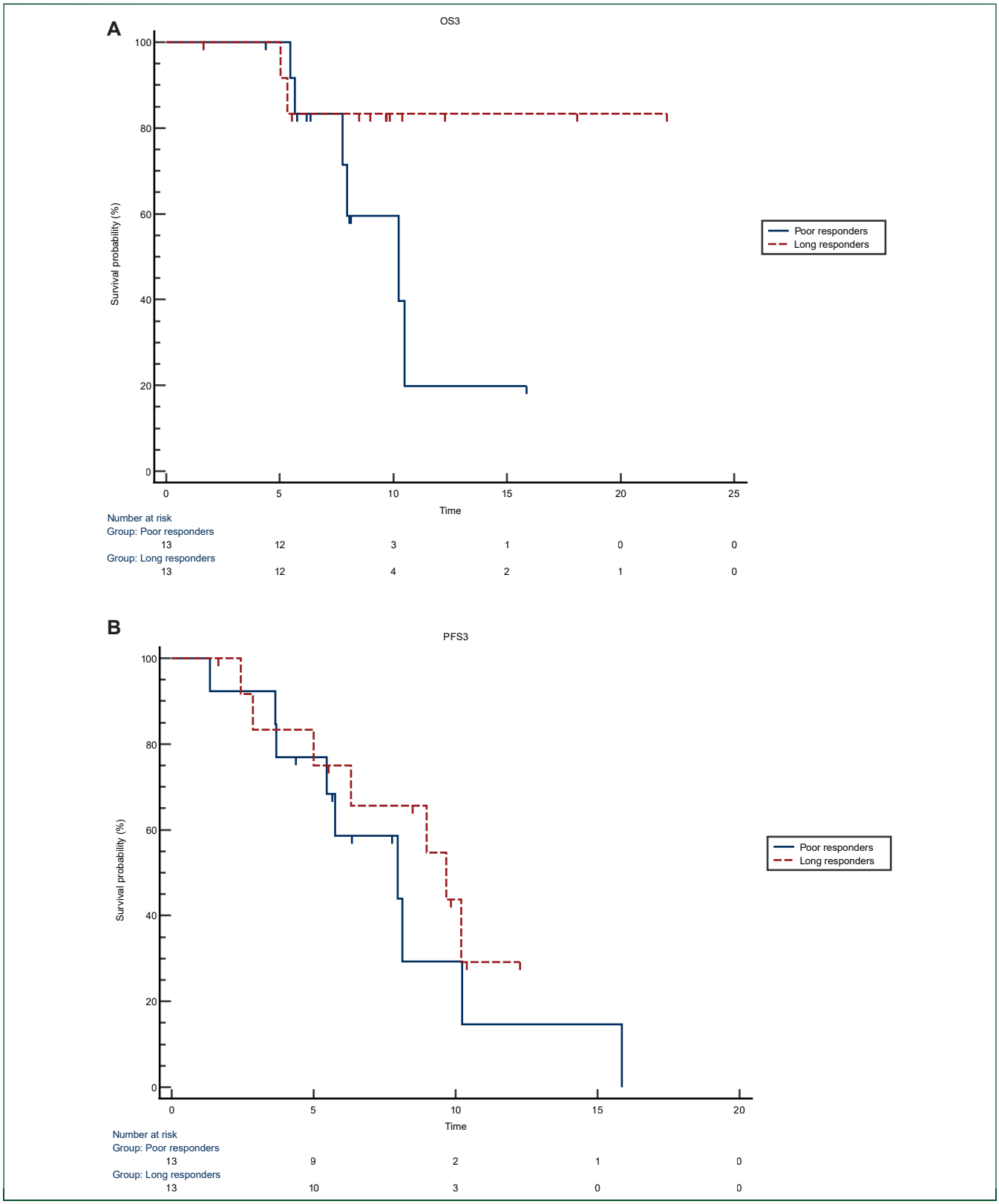
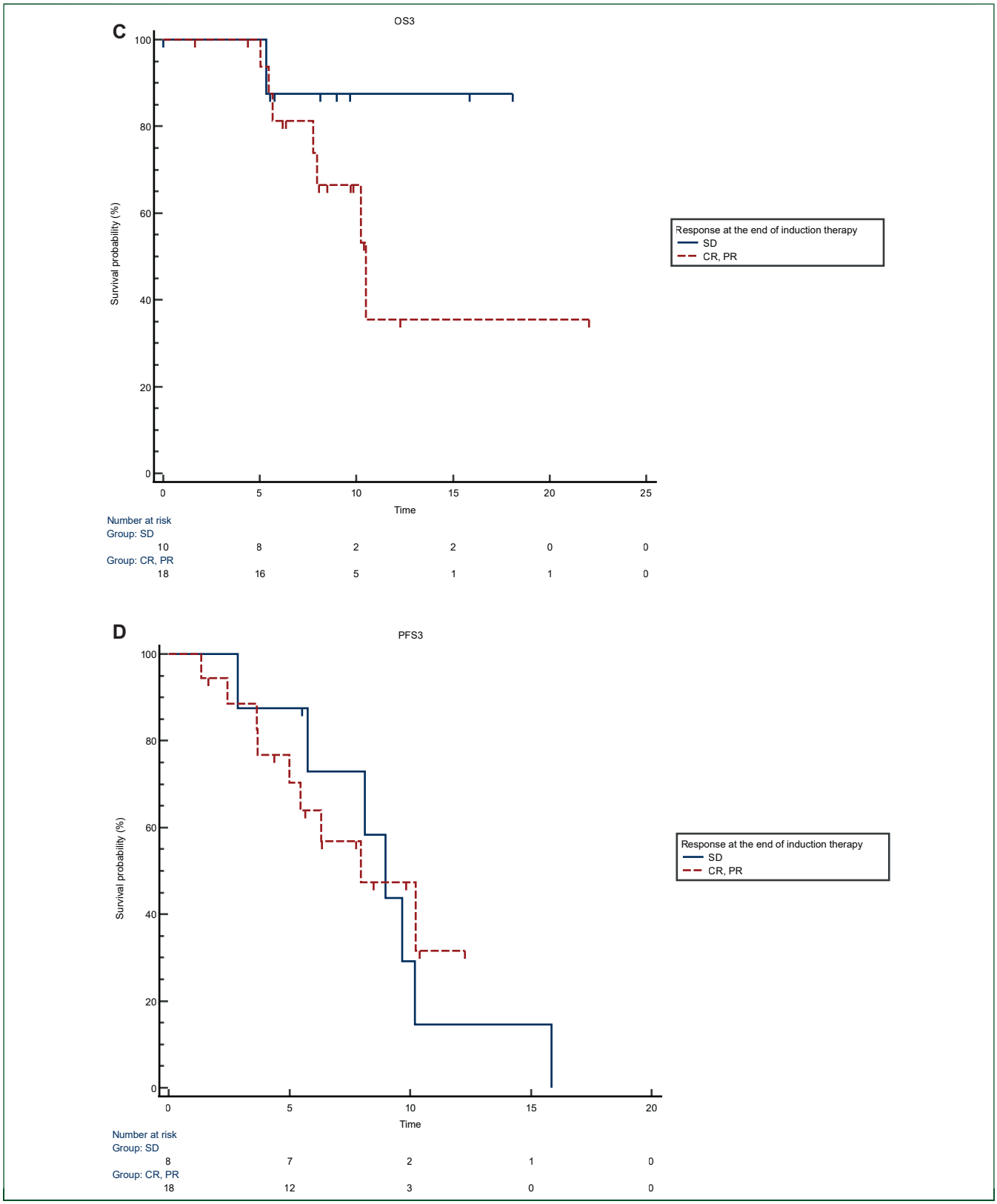


Figure 1. Kaplan–Meier curves of OS3 (A) and PFS3 (B) after patients stratification into long and poor responders using the median PFS2 as a cut-off. Kaplan–Meier curves of OS3 (C) and PFS3 (D) according to response to first line.
CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response; SR, stable response.



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maintenance despite showing PD at the conclusion of the first eight cycles of CGD. For the remaining 99 patients, data on disease status at the end of first-line CGD were not available. The median number of durvalumab maintenance cycles was 4 (range 1-31).

After a median follow-up of 18.1 months (95% CI 16.9-19.3), median OS was 22.8 months (95% CI 20.9-27.1), and median PFS was 10.6 months (95% CI 9.9-11.3).

Median OS2 was 15.7 months (95% CI 13.7-19.8), with estimated OS2 rates at 6, 12, 18, and 24 months of 81.8%, 62.5%, 46.9%, and 32.0%, respectively.

Median PFS2 was 4.1 months (95% CI 3.5-4.8), with estimated PFS2 rates at 3 and 6 months of 62.4% and 37.6%, respectively.

Among the 475 patients who received maintenance therapy, 309 (65.1%) experienced PD. Of these, 31 (10.0%) underwent CGD reintroduction and 114 (36.9%) received FOLFOX/XELOX. Additionally, 9 patients (3.0%) were treated with FOLFIRI (5-fluorouracil, folinic acid, irinotecan), 6 (2.0%) with pemigatinib, 6 (2.0%) with ivosidenib, 12 (4.0%) with 5-FU/capecitabine, 2 (0.7%) with irinotecan, and 20 (6.5%) with other therapies. Data were not available for three patients.

Outcomes in the CGD reintroduction group

Of 475 patients, 31 (6.5%) reintroduced CG during durvalumab maintenance due to PD. Baseline patient characteristics of this cohort are summarized in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.108248. The median number of durvalumab maintenance cycles in this group was 7 (range 1-16). Eleven patients (35.5%) received third-line therapy after CGD reintroduction (four FOLFOX/XELOX, one FOLFIRI, one ivosidenib, three 5FU/capecitabine, one zanidatamab, and one dabrafenib plus trametinib).

After a median follow-up of 22.6 months (95% CI 20.0-25.1), median OS was not reached (95% CI, not estimable), while median PFS was 13.3 months (95% CI 9.7-15.8). Median OS2 was not reached (95% CI, not estimable), and median PFS2 was 7.1 months (95% CI 4.8-11.3) in this cohort. OS3 and PFS3 were 10.5 months (95% CI 8.0-10.5) and 9.0 months (95% CI 5.5-10.2), respectively.

Using the median PFS2 as a cut-off (7.1 months), patients were stratified into two categories: long responders ($n = 16$) and poor responders ($n = 14$). No statistically significant differences were observed in OS3 between the two groups (median OS3 not reached versus 10.2 months; HR 0.32; 95% CI 0.1-1.3; $P = 0.11$; Figure 1A). Similarly, no significant differences were found in PFS3 (median PFS3 9.7 months versus 8.0 months; HR 0.67; 95% CI 0.2-1.9; $P = 0.44$; Figure 1B).

Of 31 patients, 20 (64.5%) completed first-line CGD with an objective response (1 CR, 19 PR; response group), and 11 patients (35.5%) had SD (SD group). Median OS3 in the response group was 10.5 months (95% CI 7.8-10.5), while median PFS3 was 8.0 months (95% CI 3.7-10.2). In contrast, median OS3 was not reached, and median PFS3 was 9.0 months (95% CI 2.9-10.2) in the SD group. No statistically significant differences were observed between the two groups in OS3 (HR 0.40; 95% CI 0.09-1.7; $P = 0.22$; Figure 1C) and PFS3 (HR 0.91; 95% CI 0.3-2.6; $P = 0.87$; Figure 1D).

Among patients who presented objective response at the end of first-line CGD, nine (45%) achieved CR, and three (15%) showed PR as best response during CGD reintroduction. Six patients (30%) experienced PD. In the group of patients with SD on CGD, four patients (36.4%) experienced CR as best response during CGD reintroduction, two patients (18.2%) had PR, and two patients (18.2%) had PD. Data on best response were not available for two patients in the response group and three in the SD group.

Comparison between the CGD reintroduction and the second-line FOLFOX/XELOX group

Of 475, 114 (24%) who experienced PD during durvalumab maintenance were treated with second-line FOLFOX or XELOX. Baseline patient characteristics of this cohort are reported in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.108248. Baseline characteristics were generally comparable between the CGD reintroduction and FOLFOX/XELOX groups, except for bilirubin levels.

The median number of durvalumab maintenance cycles in this group was 3 (range 1-15). A total of 39 patients (34.2%) received third-line therapy after FOLFOX/XELOX (28 FOLFIRI, 2 pemigatinib, 5 ivosidenib, 1 5-FU/capecitabine, 1 irinotecan, 1 gemcitabine, 1 clinical trial).

Median OS and median PFS were 20.7 months (95% CI 18.6-24.4) and 9.0 months (95% CI 8.6-9.6), respectively. Median OS2 was 14.3 (95% CI 12.4-18.3) and median PFS2 was 2.9 (95% CI 2.3-3.3).

Median OS3 was 10.4 months (95% CI 8.3-13.2), while median PFS3 was 4.9 months (95% CI 3.4-6.1).

A statistically significant improvement in OS was observed in favor of the CGD reintroduction group compared with the FOLFOX/XELOX group (HR 0.47, 95% CI 0.3-0.8; $P = 0.006$; Figure 2A). Similarly, PFS was significantly longer in the CGD reintroduction group (HR 0.44, 95% CI 0.3-0.6; $P < 0.0001$; Figure 2B).

No statistically significant differences were observed in OS3 between the two groups, although a trend toward improved OS3 was detected in the CGD reintroduction cohort (HR 0.57, 95% CI 0.3-1.0; $P = 0.06$; Figure 2C). Finally, a statistically significant difference in terms of PFS3 was observed between the two groups (HR 0.58, 95% CI 0.4-0.9; $P = 0.02$; Figure 2D).

At univariate analysis, the only parameter associated with a statistically significantly longer OS was Eastern Cooperative Oncology Group performance status (ECOG PS) 0 versus >0 (HR 0.59, 95% CI 0.34-1.00; $P = 0.05$). To evaluate potential bias related to the selection of patients with more favorable disease biology, our cohort was dichotomized using the median PFS from first-line initiation (9.4 months) as cut-off. In the CGD reintroduction group

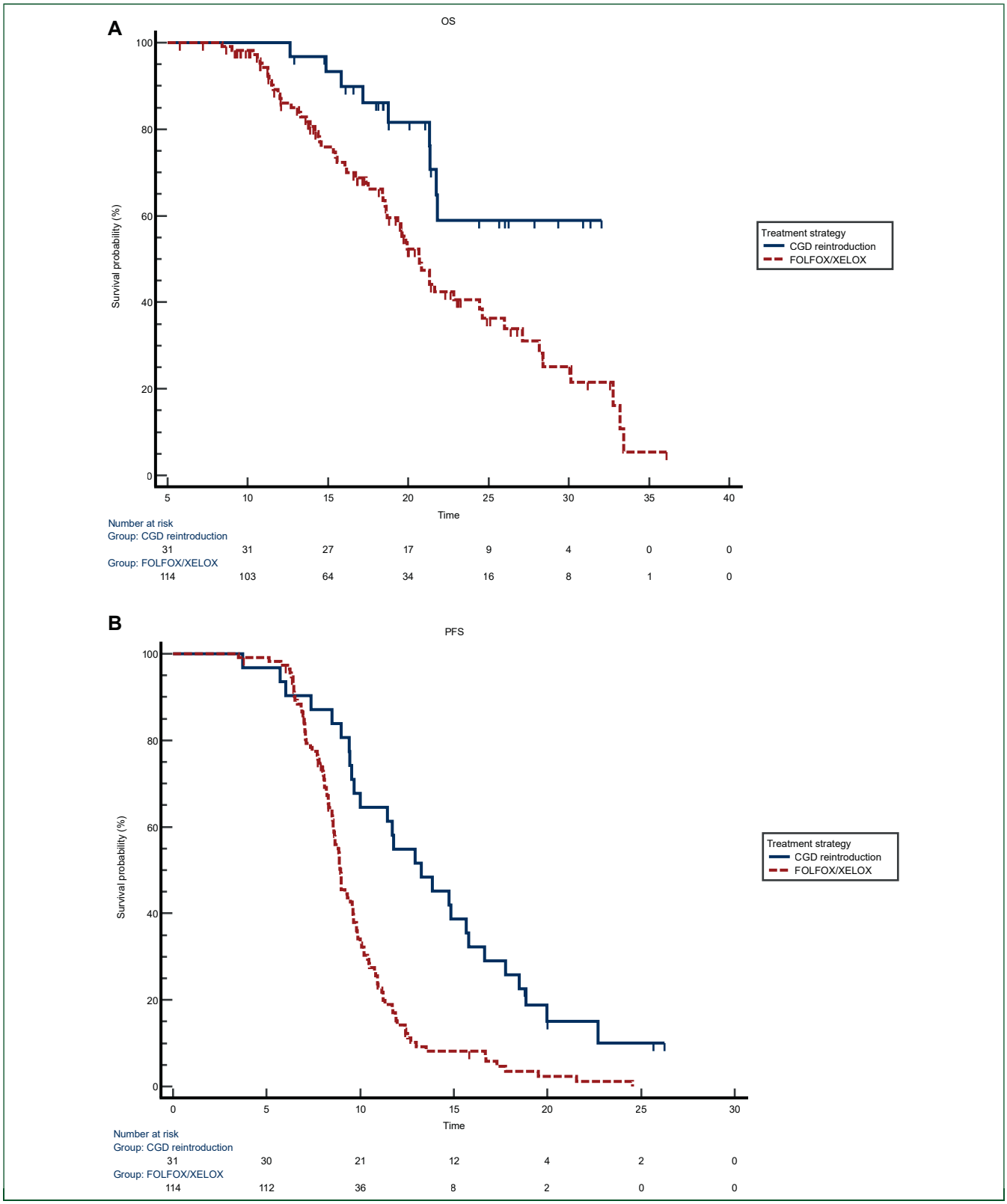
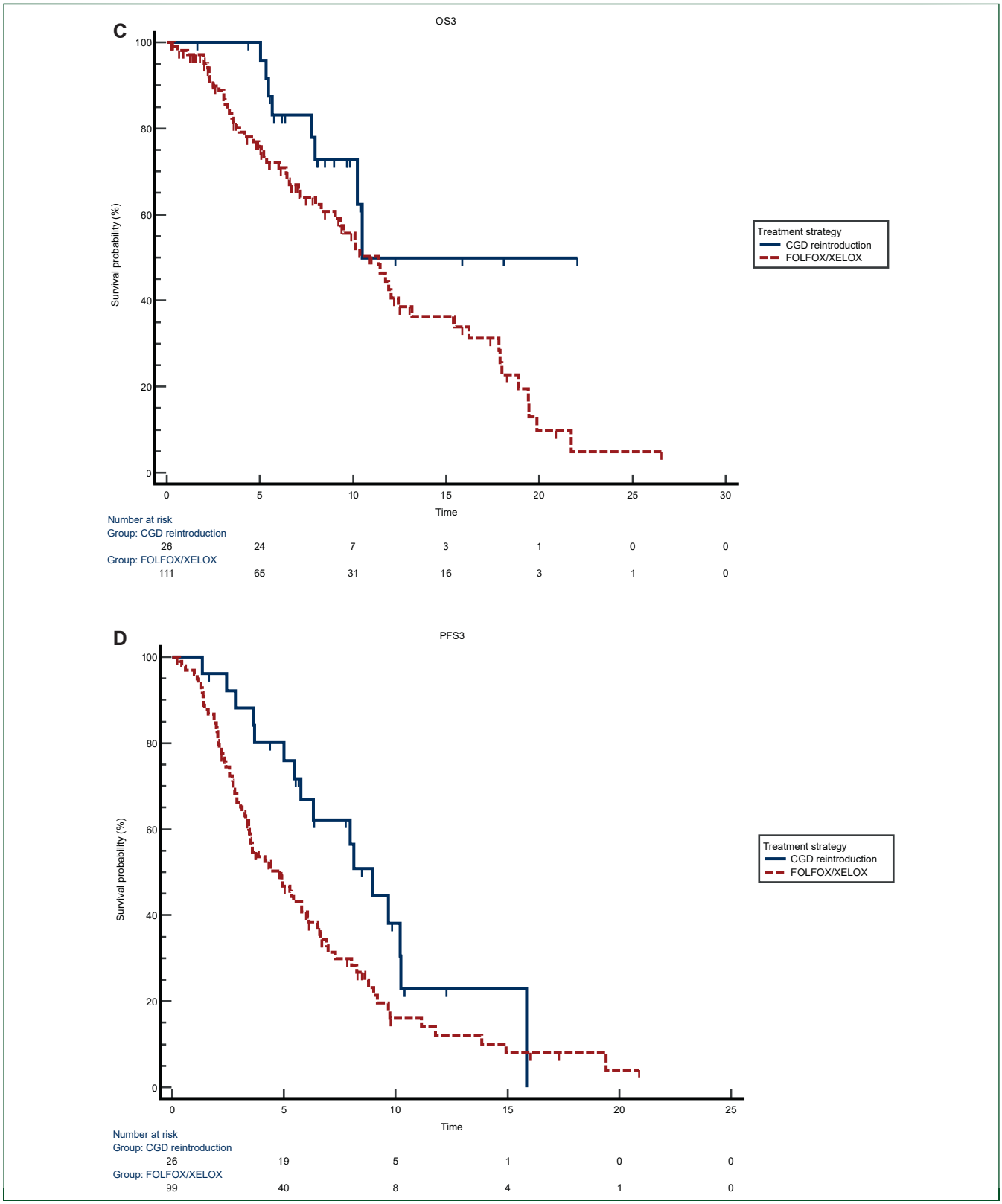


Figure 2. Kaplan–Meier curves of OS (A), PFS (B), OS3 (C), and PFS3 (D) according to treatment strategy.
CGD, cisplatin-gemcitabine-durvalumab; OS, overall survival; PFS, progression-free survival.



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31.2% of patients had a PFS above the median, whereas in the FOLFOX/XELOX group this proportion was 19.4%. At univariate analysis, PFS $\geq$ 9.4 months was associated with significantly longer OS (HR 0.37, 95% CI 0.22-0.62; $P = 0.0002$). After adjustment for clinical covariates positive at univariate analysis (ECOG PS 0 and PFS $\geq$ 9.4 months), unbalanced baseline characteristics (bilirubin), and treatment strategy (CGD reintroduction versus FOLFOX/XELOX), CGD reintroduction confirmed its impact in terms of OS (HR 0.36, 95% CI 0.15-0.85; $P = 0.02$; Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2026.108248).

In an additional exploratory analysis, we evaluated whether the duration of disease control during durvalumab maintenance could better capture treatment sensitivity. Patients were dichotomized according to PFS from the start of maintenance therapy (PFS2), using a clinically meaningful threshold of 6 months. After adjustment for the same clinical covariates included in the previous multivariable model, CGD reintroduction remained significantly associated with improved OS (HR 0.42, 95% CI 0.20-0.95; $P = 0.034$).

Concerning PFS, locally advanced disease (HR 0.64, 95% CI 0.42-0.96; $P = 0.03$) and the presence of biliary drainage (HR 0.66, 95% CI 0.45-0.96; $P = 0.03$) were associated with a statistically significant reduction in the risk of progression at univariate analysis. After adjustment for clinical covariates positive at univariate analysis and unbalanced baseline characteristics, the only parameter associated with a decreased risk of progression at multivariate analysis was CGD reintroduction (HR 0.43, 95% CI 0.27-0.70; $P = 0.0006$; Supplementary Table S2 available at https://doi.org/10.1016/j.esmoop.2026.108248). Similarly to the analysis performed for OS, patients were dichotomized according to PFS2 using a 6-month threshold. After adjustment for the same clinical covariates included in the previous multivariable model, CGD reintroduction remained associated with a reduced risk of progression (HR 0.52, 95% CI 0.33-0.87; $P = 0.0075$).

Similarly to the analysis conducted for OS from first-line initiation, and to minimize bias related to patient selection, the survival analysis from CGD reintroduction or FOLFOX/XELOX initiation (OS3) was carried out after stratifying patients using the median first-line PFS of 9.4 months. At univariate analysis, the only parameter associated with OS3 was PFS $\geq$ 9.4 months (HR 0.18, 95% CI 0.10-0.31; $P < 0.0001$).

After adjustment for clinical covariates positive at univariate analysis (PFS $\geq$ 9.4 months), unbalanced baseline characteristics (bilirubin), and treatment strategy (CGD reintroduction versus FOLFOX/XELOX), CGD reintroduction remained the only parameter associated with improved OS3 at multivariate analysis (HR 0.34, 95% CI 0.14-0.84; $P = 0.02$; Table 1).

In an additional exploratory analysis, patients were dichotomized according to PFS2 using a 6-month threshold. After adjustment for the same clinical covariates included in the previous multivariable model, CGD reintroduction remained associated with a decreased risk of progression (HR 0.41, 95% CI 0.22-0.94; $P = 0.026$).

Regarding PFS from CGD reintroduction or FOLFOX/XELOX initiation (PFS3), primary tumor location (eCCA + GBC; HR 0.59, 95% CI 0.39-0.89; $P = 0.01$), neutrophil to lymphocyte ratio (NLR) <3 (HR 0.51, 95% CI 0.32-0.81; $P = 0.004$), presence of biliary drainage (HR 0.57, 95% CI 0.36-0.89; $P = 0.01$), and CGD reintroduction (HR 0.60, 95% CI 0.37-0.92; $P = 0.02$) were associated with a significantly reduced risk of progression at univariate analysis. At multivariate analysis, the parameters that remained significant were NLR <3 (HR 0.55, 95% CI 0.34-0.88; $P = 0.01$), presence of a biliary drainage (HR 0.54, 95% CI 0.30-0.96; $P = 0.04$), and CGD reintroduction (HR 0.55, 95% CI 0.30-1.00; $P = 0.05$; Table 1). In an additional analysis, patients were dichotomized according to PFS2 using a 6-month threshold. After adjustment for the same clinical covariates included in the previous multivariable model, CGD reintroduction remained associated with a decreased risk of progression (HR 0.49, 95% CI 0.28-0.92; $P = 0.03$).

To reduce potential confounding and account for imbalances in baseline characteristics between treatment groups, an IPTW approach based on the propensity score was applied.

After IPTW adjustment, baseline clinical and tumoral characteristics were very similar between the two groups, as indicated by a d-value <0.10 in all cases (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.108248).

The IPTW procedure generated a pseudo-population of 144 patients, of whom 31 (21.5%) were included in the CGD reintroduction cohort and 113 (78.5%) in the FOLFOX/XELOX cohort (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.108248).

In this weighted population, the median OS (Figure 3A) was 37.5 months (95% CI 20.9-38.4) in the CGD reintroduction group, whereas it was 21.4 months (95% CI 17.7-24.1) in the FOLFOX/XELOX group, corresponding to a HR of 0.55 (95% CI 0.31-0.97; $P = 0.04$).

In term of OS3 after IPTW, the median OS3 was of 13.0 months (95% CI 10.2-13.0) in the CGD reintroduction group, and a median OS3 of 8.0 months (95% CI 6.6-16.2) in the FOLFOX/XELOX group (HR 0.51; 95% CI 0.29-0.89; $P = 0.018$; Figure 3B).

In the FOLFOX/XELOX group, 13 of 114 patients (11.4%) had an objective response (1 CR, 12 PR), 36 patients (31.6%) achieved SD, and 47 patients (41.2%) had PD.

No statistically significant differences in ORR or DCR were observed between the CGD reintroduction and the FOLFOX/XELOX groups (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2026.108248).

In the FOLFOX/XELOX group, 24 of 114 patients (21.1%) completed the first line with an objective response (all PR). Median OS3 and median PFS3 in this subgroup were 10.1 months (95% CI 3.1-16.2) and 2.8 months (95% CI 2.2-5.3), respectively. No statistically significant differences in OS3 were observed between this subgroup and the response group of the CGD reintroduction cohort (HR 0.57, 95% CI

Table 1. Univariate and multivariate analyses for OS3 and PFS3 according to baseline characteristics and treatment strategy

Parameters	CGD reintroduction group	FOLFOX/XELOX group	OS3			OS3			PFS3			PFS3		
	N = 31 (%)	*N* = 114 (%)	Univariate			Multivariate			Univariate			Multivariate		
			HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Gender														
Male	17 (54.8)	62 (54.4)	0.89	0.55-1.46	0.66				0.85	0.56-1.29	0.44			
Female	14 (45.2)	52 (45.6)	1						1					
Age (years)														
>70	16 (51.6)	49 (43.0)	1						1					
≤70	15 (48.4)	65 (57.0)	0.7	0.42-1.13	0.14				0.87	0.58-1.31	0.51			
Not reported														
ECOG PS														
>0	12 (38.7)	46 (40.4)	1						1					
0	19 (61.3)	68 (59.6)	0.84	0.51-1.40	0.5				0.66	0.44-1.05	0.08			
Not reported														
Primary tumor location														
iCCA	16 (51.6)	64 (56.1)	1						1					
eCCA + GBC	15 (48.4)	50 (43.9)	0.96	0.58-1.57	0.86				0.59	0.39-0.89	0.01	0.7	0.44-1.12	0.13
Stage														
Locally advanced	7 (22.6)	20 (17.5)	0.94	0.51-1.74	0.84				0.83	0.50-1.37	0.47			
Metastatic	24 (77.4)	94 (82.5)	1						1					
Surgery														
Yes	9 (29.0)	31 (27.2)	0.69	0.41-1.15	0.16				0.68	0.44-1.05	0.09			
No	22 (71.0)	83 (72.8)	1						1					
CA 19-9 UI/mL														
>Normal levels	17 (54.8)	69 (61.0)	1						1					
Normal levels	10 (32.3)	38 (33.0)	0.89	0.52-1.51	0.66				0.96	0.61-1.50	0.86			
Not reported	4 (12.9)	7 (6.0)												
NLR														
≥3	11 (35.5)	49 (43.0)	1						1					
<3	15 (48.4)	55 (48.2)	0.65	0.38-1.12	0.12				0.51	0.32-0.81	**0.004**	0.55	0.34-0.88	**0.01**
Not reported	5 (16.1)	10 (8.8)												
Bilirubin (mg/dL)														
>Normal levels	10 (32.3)	17 (14.9)	1						0.96	0.54-1.72	0.89	0.71	0.37-1.38	0.31
Normal levels	18 (58.0)	95 (83.3)	0.69	0.33-1.43	0.31	0.53	0.27-1.04	0.07	1					
Not reported	3 (9.7)	2 (1.8)												
Biliary drainage														
Yes	11 (35.5)	24 (21.0)	0.85	0.48-1.50	0.58				0.57	0.36-0.89	0.01	0.54	0.30-0.96	**0.04**
No	19 (61.3)	84 (73.7)	1						1					
Not reported	1 (3.2)	6 (5.3)												
PFS (median PFS 9.4 months)														
<9.4 months			1											
≥9.4 months			0.18	0.10-0.31	**<0.0001**	0.93	0.56-1.57	0.8						
Maximum response during induction														
Complete response plus partial response	18 (58.1)	51 (44.7)	0.63	0.38-1.04	0.0735				0.7	0.46-1.09	0.1145			
Stable disease	13 (41.9)	63 (55.3)	1						1					
Treatment strategy														
CGD Reintroduction			0.57	0.31-1.01	0.06	0.34	0.14-0.84	**0.02**	0.58	0.37-0.92	**0.02**	0.55	0.30-1.00	**0.05**
FOLFOX/XELOX			1						1					

Significant results are in bold.

Multivariable Cox regression analysis included 134 and 110 patients with complete data for all covariates included in the OS3 and PFS3 models, respectively.

CA 19.9, carbohydrate antigen 19-9; CGD, cisplatin, gemcitabine, durvalumab; CI, confidence interval; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder carcinoma; HR, hazard ratio; iCCA, intrahepatic cholangiocarcinoma; NLR, neutrophil to lymphocyte ratio; OS, overall survival; PFS, progression-free survival.

0.2-1.4, $P = 0.21$; Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.108248), while a statistically significant difference in PFS3 was observed (HR 0.38, 95% CI 0.2-0.8; $P = 0.016$; Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2026.108248).

To further explore whether the benefit of CGD reintroduction differed according to the depth of response during first-line therapy, we carried out a subgroup analysis restricted to patients who achieved SD as best response. In this subgroup, CGD reintroduction was associated with a significantly improved OS compared with FOLFOX/XELOX (HR 2.76, 95% CI 1.24-6.16; $P = 0.013$). However, no statistically significant difference was observed in terms of OS3 between treatment strategies (HR 1.09, 95% CI 0.80-5.43; $P = 0.13$).

We carried out a post-progression analysis restricted to patients who remained progression free for $\geq$3 months during maintenance, in order to exclude cases with early progression and to obtain a more homogeneous population with at least a minimal benefit from maintenance therapy. After this correction, the new population included 19 patients in the CGD reintroduction group and 46 patients in the FOLFOX/XELOX group. Median OS3 was not reached in the CGD reintroduction group, and 11.4 months (95% CI 7.1-16.2) in the FOLFOX/XELOX group (HR 0.32, 95% CI 1.15-0.69; $P = 0.003$; Figure 4A). Median PFS3 was 9.7 months (95% CI 5.0-15.9) in the CGD reintroduction group, and 5.8 months (95% CI 2.9-8.2) in the FOLFOX/XELOX group (HR 0.65, 95% CI 0.35-1.22; $P = 0.18$; Figure 4B).

To further explore whether the duration of disease control during durvalumab maintenance could identify patients more likely to benefit from chemotherapy reintroduction compared with FOLFOX/XELOX, we carried out an exploratory analysis evaluating different PFS2 thresholds. Using a data-driven approach, the optimal cut-off of PFS2 for discriminating PFS3 between treatment strategies was identified at 4.5 months, with an area under the curve of 0.64 (95% CI 0.55-0.73; $P = 0.008$).

DISCUSSION

The therapeutic landscape of advanced BTC has significantly changed, driven primarily by the introduction of immunotherapy in the first-line and targeted therapies in later lines. For patients without actionable alterations, FOLFOX represents the standard second-line regimen, as established by the ABC-06 trial.[19] Conversely, the reintroduction of a previously effective first-line therapy remains largely unexplored.

To the best of our knowledge, this is the first study evaluating the reintroduction strategy with CGD after PD during maintenance therapy with durvalumab in a large and worldwide population of patients with advanced BTC.

In TOPAZ-1, durvalumab improved long-term survival (3-year OS 14.6% versus 6.9%; HR 0.74), but no subgroup analyses of patients receiving maintenance were reported.[5] Updated results showed that 20% of patients in the durvalumab arm and 40% of long survivors underwent cisplatin or gemcitabine reintroduction, although outcomes were not provided and the role of continuing durvalumab was not explored.[4] In KEYNOTE-966, cisplatin reintroduction during gemcitabine plus pembrolizumab maintenance was not allowed.[6] In our population, selected patients who received durvalumab maintenance showed remarkable outcomes, with a median OS from the start of first-line CGD of 22.8 months, which is longer than in all-comer cohorts, including the intention-to-treat population of TOPAZ-1 trial (12.9 months).[5] Furthermore, 32% of patients were alive at 24 months from maintenance initiation, and nearly 38% remained progression free at 6 months. These findings are consistent with a previous real-world analysis conducted by our group.[20] Notably, our study showed interesting results in the CGD reintroduction group, with median OS from first-line initiation not reached and median PFS of 13.3 months after a median follow-up of 22.6 months.

Patients who underwent CGD reintroduction showed a median PFS from reintroduction initiation of 9.0 months, which is highly relevant in a palliative setting. Since durvalumab was continued during CG reintroduction, the observed clinical benefit may reflect not only chemotherapy reintroduction but also the effect of re-adding chemotherapy to ongoing immune checkpoint inhibition. When patients were stratified into long and poor responders using median PFS from maintenance initiation as a cut-off, no significant differences were observed in PFS or OS calculated from CGD reintroduction. Although limited by the small sample size, these findings may suggest that maintenance-related PFS might not be an appropriate criterion to select patients for CGD reintroduction in clinical practice, whereas objective response or disease control during CGD could potentially represent a more reliable indicator. However, these findings are speculative and need further investigation. Consistent with the findings reported by Adhikaree et al.,[21] all patients in our CGD reintroduction group had experienced objective response or disease control during the first line. Furthermore, more than half of those with disease control at the end of first line achieved an objective response during reintroduction, supporting the hypothesis of underlying platinum sensitivity in this group. However, this remains speculative and requires validation.

Finally, we compared the CGD reintroduction group with the FOLFOX/XELOX group. A statistically significant difference in OS and PFS from the start of first line favored the reintroduction strategy; however, this should be interpreted with caution, as treatment allocation was not randomized and patients selected for CGD reintroduction may have had more favorable disease characteristics and prior treatment sensitivity. A significant difference in PFS from the CGD reintroduction/second-line initiation was also observed. Baseline characteristics were mostly comparable between groups, and following adjustment using both multivariate and IPTW analyses, an advantage of CGD reintroduction arm was confirmed in terms of OS and PFS

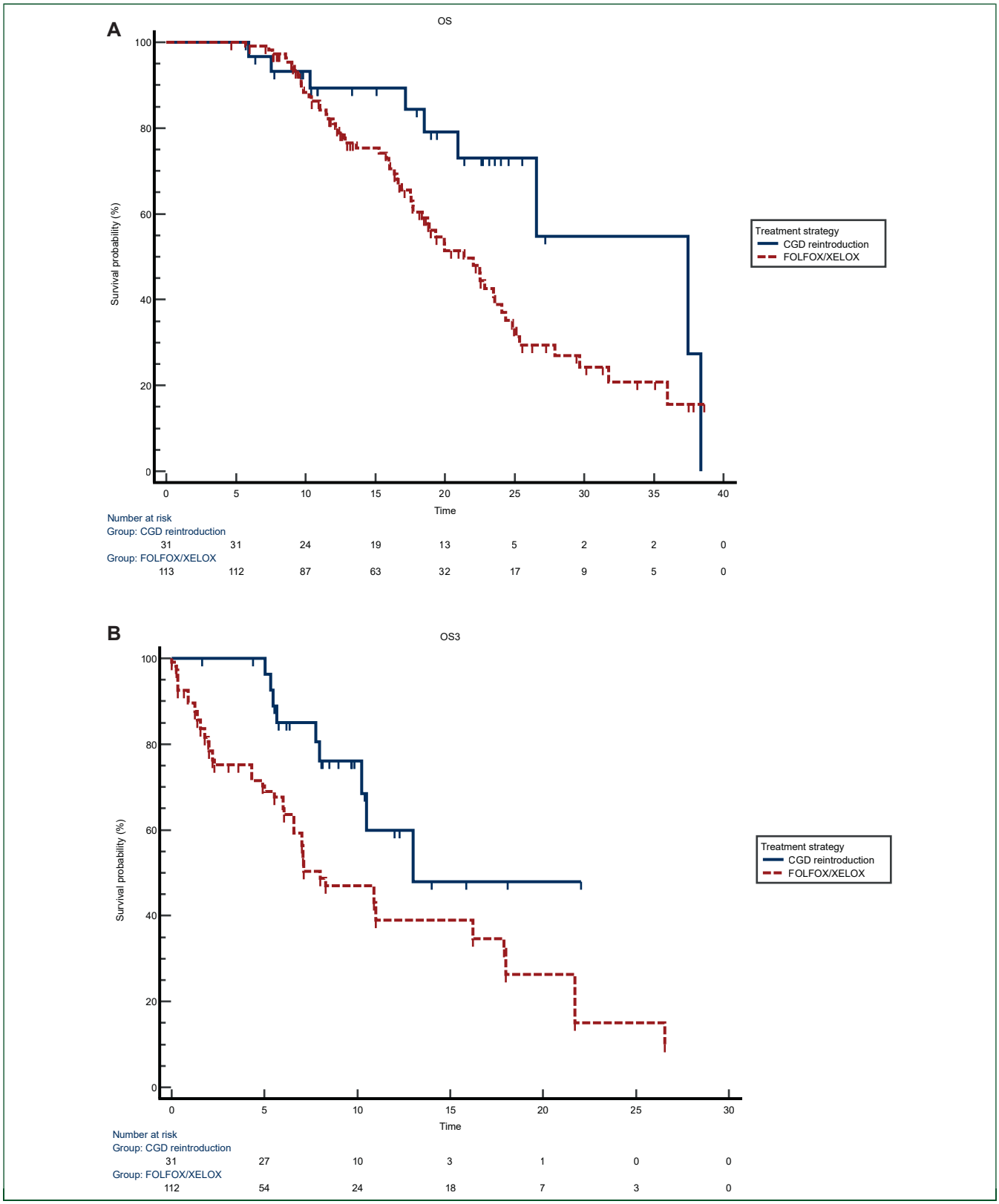

Figure 3. Kaplan–Meier curves of OS (A), and OS3 (B) according to treatment strategy after inverse probability of treatment weighting analysis.
CGD, cisplatin-gemcitabine-durvalumab; OS, overall survival.

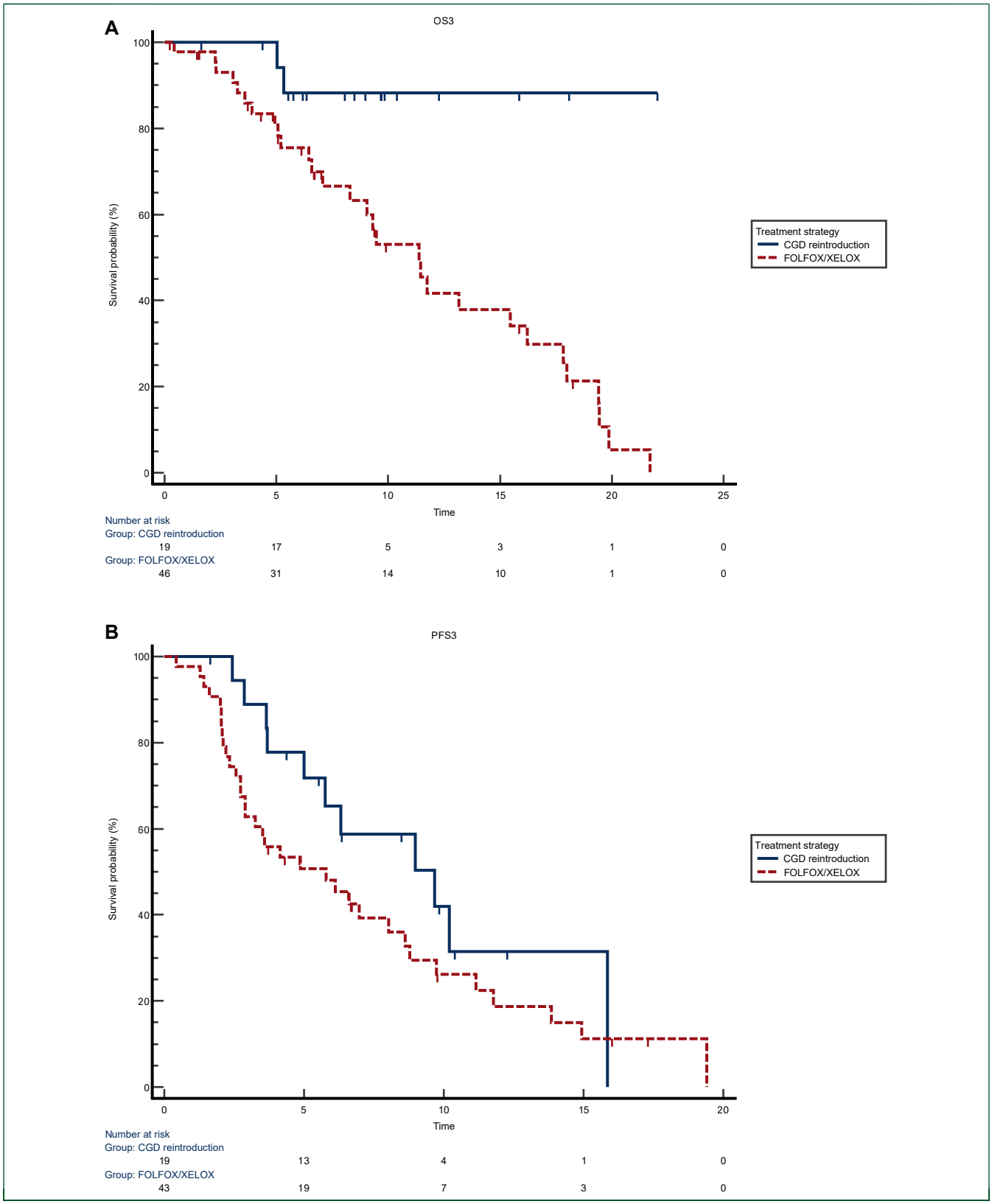

Figure 4. Kaplan–Meier curves of OS3 (A) and PFS3 (B) according to treatment strategy after post-progression analysis restricted to patients with PFS2 ≥3 months during durvalumab maintenance.

CGD, cisplatin-gemcitabine-durvalumab; OS, overall survival; PFS, progression-free survival.

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from both the start of first-line CGD and the start of CGD reintroduction or second-line initiation. Although a direct comparison is not feasible, outcomes of the FOLFOX/XELOX group exceeded those reported in the ABC-06 trial,[19] likely reflecting a more favorable population, as all patients in our cohort had completed first-line CGD and initiated maintenance. In contrast, ABC-06 enrolled patients at progression to first-line therapy, resulting in a less selected and poorer-prognosis population.[19] Among patients with an objective response at the end of CGD, a statistically significant difference in PFS from reintroduction or second line initiation was observed between the CGD reintroduction and FOLFOX/XELOX groups. This suggests that patients who experienced an objective response to first line may derive greater benefit from reintroducing CG during durvalumab maintenance rather than switching to second-line FOLFOX at progression. However, no biomarkers or clinical characteristics are currently available to identify which patients are more likely to benefit from a reintroduction strategy compared with second-line treatment and further studies are needed. A subgroup analysis of the ABC-06 trial showed a negative prognostic role for pathogenic mutations in DNA damage response genes. However, their predictive value was not confirmed for either first-line CG or second-line FOLFOX.[22]

Regarding the generalizability of our findings to chemotherapy backbone reintroduction after progression during maintenance in patients initially treated with pembrolizumab plus CG, applicability remains uncertain. In KEYNOTE-966, maintenance therapy included not only immunotherapy but also gemcitabine, which could potentially influence chemotherapy sensitivity and reduce the benefit of reintroducing cisplatin.

This study has several important limitations. Firstly, its retrospective design inherently introduces potential selection and reporting biases, which cannot be fully excluded despite the large multinational cohort. Treatment choice, CGD reintroduction versus second-line FOLFOX/XELOX, was not randomized but based on clinician judgment and patient fitness, possibly affecting outcome comparability. In addition, the small sample size of the CGD reintroduction group limits statistical power and the precision of HR estimates, particularly in subgroup analyses. Secondly, the lack of uniform data collection across centers may have introduced heterogeneity in baseline assessments, radiologic evaluations, and timing of follow-up. Clinical and laboratory parameters at the start of maintenance, CGD reintroduction, and second-line therapy were inconsistently available, preventing comprehensive adjustment for potential confounders. This limitation may have constrained the ability to account for patient fitness and disease dynamics at these key treatment decision points. Thirdly, data on AEs and on the exact number of CGD reintroduction cycles were incomplete, precluding safety assessment or evaluation of cumulative toxicity. Moreover, because of the multicenter nature of the dataset, the assessment of PFS, ORR, and DCR relied on investigator evaluation rather than centralized radiologic review. Finally, no molecular data were available, limiting our ability to assess whether specific tumor genomic profiles may modulate responsiveness to CGD reintroduction or help refine patient selection. An additional limitation is that a minimum duration of durvalumab maintenance before CGD reintroduction was not predefined a priori. Although analyses were restricted to patients remaining progression free for at least 3 months during maintenance, treatment selection may still have been influenced by clinical judgment, introducing potential selection bias. For these reasons, the present findings should be regarded as hypothesis generating. Despite its retrospective nature and the above-mentioned limitations, this study represents the first analysis investigating the efficacy of CGD reintroduction in a large, international cohort of patients with advanced BTC previously treated with first-line CGD. While these findings do not support routine implementation of this strategy, they suggest that CGD reintroduction may represent a potential treatment option in carefully selected patients without actionable alterations who previously derived meaningful benefit from first-line chemoimmunotherapy.

INFORMED CONSENT

Written informed consent for treatment was obtained for all patients.

ETHICAL APPROVAL

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.

DATA AVAILABILITY

Data available on request from the authors.

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DISCLOSURE

The authors have declared no conflicts of interest.

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