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ORIGINAL ARTICLE

Silmitasertib plus gemcitabine and cisplatin first-line therapy in locally advanced/metastatic cholangiocarcinoma: A Phase 1b/2 study

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Abstract

Background and Aims: This study aimed to investigate safety and efficacy of silmitasertib, an oral small molecule casein kinase 2 inhibitor, plus gemcitabine and cisplatin (G+C) versus G+C in locally advanced/metastatic cholangiocarcinoma.

Approach and Results: This work is a Phase 1b/2 study (S4-13-001). In Phase 2, patients received silmitasertib 1000 mg twice daily for 10 days with G+C on Days 1 and 8 of a 21-day cycle. Primary efficacy endpoint was progression-free survival (PFS) in the modified intent-to-treat population (defined as patients who completed at least one cycle of silmitasertib without dose interruption/reduction) from both phases (silmitasertib/G+C $n = 55$, G+C

Abbreviations: CA 19-9, carbohydrate antigen 19-9; CK2, casein kinase 2; CI, confidence interval; CSNK2A, CK2 alpha; CSNK2B, CK2 beta; DCR, disease control rate; G+C, gemcitabine plus cisplatin; ITT, intent-to-treat; mITT, modified intent-to-treat; MTD, maximum tolerated dose; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; TCGA, The Cancer Genome Atlas; TEAE, treatment emergent adverse event.

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n = 29). The response was assessed by Response Evaluation Criteria in Solid Tumors v1.1. The median PFS was 11.2 months (95% confidence interval [CI], 7.6, 14.7) versus 5.8 months (95% CI, 3.1, not evaluable [NE]) (p = 0.0496); 10-month PFS was 56.1% (95% CI, 38.8%, 70.2%) versus 22.2% (95% CI, 1.8%, 56.7%); and median overall survival was 17.4 months (95% CI, 13.4, 25.7) versus 14.9 months (95% CI, 9.9, NE) with silmitasertib/G+C versus G+C. Overall response rate was 34.0% versus 30.8%; the disease control rate was 86.0% versus 88.5% with silmitasertib/G+C versus G+C. Almost all silmitasertib/G+C (99%) and G+C (93%) patients reported at least one treatment emergent adverse event (TEAE). The most common TEAEs (all grades) with silmitasertib/G+C versus G+C were diarrhea (70% versus 13%), nausea (59% vs. 30%), fatigue (47% vs. 47%), vomiting (39% vs. 7%), and anemia (39% vs. 30%). Twelve patients (10%) discontinued treatment because of TEAEs during the study.

Conclusions: Silmitasertib/G+C demonstrated promising preliminary evidence of efficacy for the first-line treatment of patients with locally advanced/metastatic cholangiocarcinoma.

INTRODUCTION

Cholangiocarcinoma accounts for approximately 3% of gastrointestinal tumors,[1] and intrahepatic cholangiocarcinoma comprises approximately 10%–15% of primary liver cancers.[2] In most countries, cholangiocarcinoma is an uncommon cancer, with an incidence of fewer than six cases per 100,000 people,[3] but in some regions, such as Southeast Asia, it is more common, even endemic.[4] The majority of patients with cholangiocarcinoma present with advanced disease because of the difficulties of diagnosing cholangiocarcinoma at an early stage.[3,5,6] Advanced/metastatic cholangiocarcinoma is therefore associated with a poor prognosis, with a 5-year overall survival (OS) rate of 7%–20%, and tumor recurrence rates after resection remain discouraging.[7–9]

Surgery or liver transplantation after neoadjuvant chemoradiotherapy are potentially curative treatment options for patients with early-stage disease.[3,5] For advanced cholangiocarcinoma and other biliary tract cancers, the standard first-line treatment is gemcitabine plus cisplatin (G+C) combination chemotherapy .[3,5,10–14] However, chemotherapy is largely palliative because of the substantial resistance of cholangiocarcinoma to chemotherapy, and most patients experience disease progression and ultimately die from the disease.[3,15–17] As such, there is a need for more effective therapies to treat advanced disease.[18–20] Because of the high heterogeneity of cholangiocarcinomas, tumor profiling is considered an indispensable approach for personalized molecular medicine. Newer approved treatments, such as the neurotrophic tyrosine receptor kinase inhibitors larotrectinib[21,22] and entrectinib[22,23] and the anti–programmed cell death-1 monoclonal antibody pembrolizumab,[22,24] are beneficial in subsets of patients with the relevant genomic aberrations.

Casein kinase 2 (CK2), a protein serine/threonine kinase that plays an important role in cell growth, death, and survival, is frequently overexpressed in many cancer types and is being investigated as a potential therapeutic target in patients with cholangiocarcinoma.[25–27] CK2 is thought to be involved in the progression and invasion of cholangiocarcinoma[25] and has been shown to contribute to the malignant phenotype of cholangiocarcinoma cells,[28] making it an attractive therapeutic target for patients with biliary tract cancer. Silmitasertib (CX-4945, Senhwa Biosciences Inc.) is a first-in-class, orally bioavailable small molecule inhibitor of CK2 being evaluated in patients with cancer. In preclinical studies, silmitasertib demonstrated potent and selective inhibition of CK2, causing cell-cycle arrest and apoptosis in cancer cells versus normal cells and antitumor activity in murine xenograft models[29] and enhanced the antiproliferative activity of G+C in ovarian cancer cells[30] and cholangiocarcinoma cell lines.[31]

Based on the promising preclinical activity of silmitasertib, a Phase 1b/2 study (S4-13-001) was conducted to assess the safety and tolerability of silmitasertib in combination with standard-of-care G+C as first-line treatment for patients with locally advanced or metastatic cholangiocarcinoma. In addition, the expression levels of the CK2 components CK2 alpha (CSNK2A)

1, CSNK2A2, and CK2 beta (CSNK2B) in cholangiocarcinoma tumors were assessed and compared with normal liver tissue in samples available in The Cancer Genome Atlas (TCGA).

PATIENTS AND METHODS

Study design

This multicenter, open-label, Phase 1b/2, dose-escalation, safety, and pharmacokinetic (PK) study was conducted at centers in the United States (n = 6), South Korea (n = 4), and Taiwan (n = 6). The Phase 1b study comprised three sets of cohorts: dose escalation, dose expansion, and exploratory (Figure 1 and Table S1). The dose-escalation cohorts were used to determine the maximum tolerated dose (MTD) of silmitasertib, which was the starting dose for the expansion cohort. The dose-expansion cohort was used to assess and optimize the tumor imaging strategy for determining antitumor activity in patients to be enrolled to the Phase 2 study. The exploratory cohort, which investigated two dose schedules (10-day and 21-day dosing), was used to determine the recommended Phase 2 dosage from the perspective of schedule optimization of dosing of silmitasertib in combination with G+C.

In the Phase 2 study, patients were randomized to receive either G+C alone or silmitasertib plus G+C until disease progression. Randomization was stratified based on cancer stage (locally advanced or metastatic), tumor location (intrahepatic or extrahepatic), and geographical region (United States or non–United States). Permuted block randomization (random allocation within the block) was used to assign patients to treatments within each stratum.

Patients

Eligible patients were ≥18 years of age with intrahepatic or extrahepatic unresectable or metastatic cholangiocarcinoma for which treatment with G+C was intended; Eastern Cooperative Oncology Group (ECOG) Performance Status 0–1; and adequate bone marrow (absolute neutrophil count >1500 cells/mm^3, platelet count >100,000 cells/mm^3, and hemoglobin >9 g/dl), liver (bilirubin <1.5 × upper limit of normal [ULN], alkaline phosphatase, alanine aminotransferase, or aspartate aminotransferase <5.0 × ULN), and renal function (serum creatinine within normal limits).

Exclusion criteria included pregnant or breastfeeding women; prior systemic chemotherapy or chemoradiotherapy treatment; radiotherapy or surgery within 1

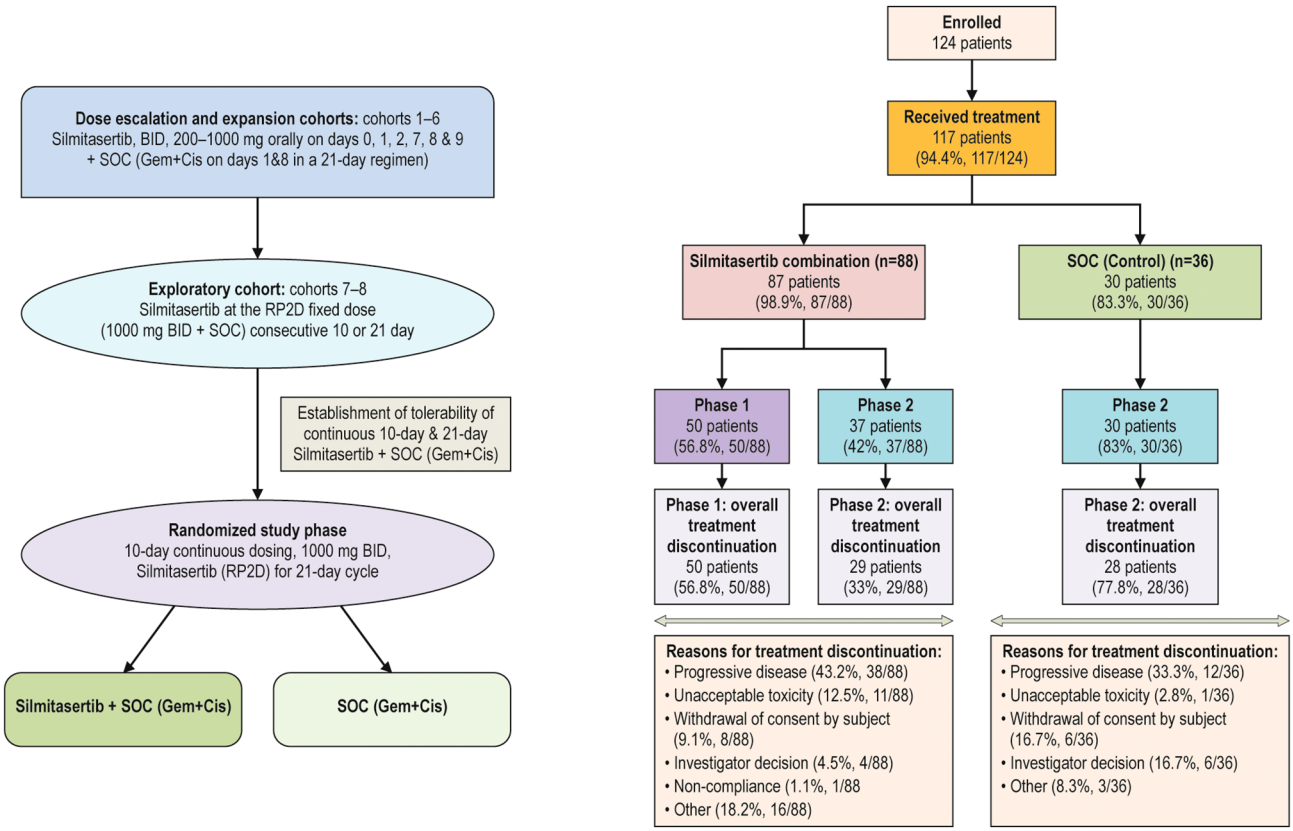

FIGURE 1 Study design and patient disposition. BID, twice daily; Cis, cisplatin; Gem, gemcitabine; RP2D, recommended phase 2 dose; SOC, standard of care

month prior to study entry; treatment with chemotherapy or investigational drugs within 21 days prior to the screening visit; known brain metastases; seizure disorders requiring anticonvulsant therapy; history of another malignancy within 3 years of the baseline visit; concurrent severe or uncontrolled medical disease; active symptomatic fungal, bacterial, and/or viral infection; difficulty with swallowing or an active malabsorption syndrome; chronic diarrhea; gastrointestinal disease; and any clinically significant bleeding event within the last 3 months.

The study was approved by the institutional review board or independent ethics committee at each study site and by the appropriate regulatory authorities. The study was conducted in accordance with the Declaration of Helsinki, the Declaration of Istanbul, and Good Clinical Practice guidelines. All patients provided written, informed consent before study entry.

Procedures

In the dose-escalation and dose-expansion cohorts, oral silmitasertib was administered twice daily on Days 0, 1, 2, 7, 8, and 9, and intravenous cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 were administered on Days 1 and 8 of a 21-day cycle (Table S1). On Days 1 and 8, the morning dose of silmitasertib was administered first, followed 30 min later by cisplatin and gemcitabine. Treatment cycles were repeated in the absence of disease progression or unacceptable toxicity. In the dose-escalation cohort, the starting dose of silmitasertib was 200 mg twice daily, which was escalated in 200-mg, twice-daily increments to a maximum permitted dosage of 1000 mg twice daily. In the exploratory cohorts, oral silmitasertib was administered twice daily for 10 days on Days 0–9 or for 21 days on Days 0–20; intravenous cisplatin 25 mg/m^2 and gemcitabine 1000 mg/m^2 were administered on Days 1 and 8.

In the dose-escalation phase, concentrations of silmitasertib at predose in Cycle 1 on Days 0, 1, 7, and 8 and at 2-h postdose of silmitasertib dosing in Cycle 1 on Days 0, 1, and 8 were compared across silmitasertib dose cohorts. The concentrations of G+C at the end of infusion (peak concentrations) in Cycle 1 on Days 1 and 8 were compared across silmitasertib dose cohorts. In the expansion cohort, blood samples for PK analysis were collected by serial sampling over 6 h postdose on Day 8 in Cycle 1. Plasma was analyzed for silmitasertib, gemcitabine, and cisplatin by validated high performance liquid chromatography mass spectrometry assays. For the 10-day continuous dosing exploratory cohort, predose and serial blood samples over 6 h on Day 1 and Day 8 plus 24-, 48-, and 72-h after the last dose of silmitasertib were collected for silmitasertib PK analysis. For the 21-day continuous dosing exploratory cohort, blood samples were collected predose on Day 1 and Day 8 of Cycle 1 and Day 0 of Cycle 2 for silmitasertib PK analysis.

In the Phase 2 study, oral silmitasertib was administered at a dosage of 1000 mg twice daily on a 10-day continuous dosing schedule from Day 0 to Day 9. Intravenous gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 and were administered on Days 1 and 8 of a 21-day cycle in both phases. On Days 1 and 8, the morning dose of silmitasertib was administered first, followed 30 min later by G+C.

Outcomes

The primary endpoint of the Phase 1b study was to determine the safety and MTD of silmitasertib in combination with G+C. The secondary endpoint was to determine the PK of silmitasertib. The PK parameters calculated were maximum concentration (C_{max}), time $(T)_{max}$, area under the curve $(AUC)_{(0-6\ h)}$/$AUC_{(0-72\ h)}$, $AUC_{(0-T)}$ (from Time 0 to the last measurable plasma concentration), and terminal half-life ($T_{1/2}$). In the Phase 2 study, the primary efficacy endpoint was progression-free survival (PFS) in the modified intent-to-treat (mITT) population, which included only patients who completed at least one cycle of silmitasertib without dose interruption/reduction. Time to PFS was calculated as the date of objective disease progression or death due to any cause, whichever occurred earlier, minus the date of consent plus one. Secondary efficacy endpoints were PFS at 10 months, OS, objective response rate (ORR), and disease control rate (DCR; stable disease plus ORR) in the mITT population. OS was calculated as the date of death due to any cause minus the date of consent plus one. If there was no evidence of death, OS was censored at last known alive date in the clinical database. Tumor assessments were conducted at screening and approximately every 6 weeks thereafter. Responses were assessed by the principal investigator using Response Evaluation Criteria in Solid Tumors version 1.1.

An exploratory outcome was the tumor marker carbohydrate antigen 19-9 (CA 19-9) response. CA 19-9 is a validated and commonly used serum tumor marker that adds diagnostic value for gastrointestinal tumors such as cholangiocarcinoma[32–34] and pancreatic cancer[35]. CA 19-9 has a high prognostic value and acts as a biomarker for surveillance, diagnosing symptomatic patients, and monitoring patient's responses with therapy. CA 19-9 assessments were considered exploratory in nature, as they can be confounded by concomitant cholangitis, biliary obstruction, or lithiasis in this patient population. Evaluable patients included those with elevated CA 19-9 levels at baseline. Safety was assessed by treatment-emergent adverse events (TEAEs) recorded and graded according to the Common Terminology Criteria for Adverse Events Version 4.0.

Expression of CSNK2A1, CSNK2A2, and CSNK2B

The Genomic Data Commons log2 fragments per kilobase million (FPKM)–normalized expression values from the TCGA cholangiocarcinoma cohort (https://gdc-hub.s3.us-east-1.amazonaws.com/download/TCGA-CHOL.htseq_fpkm.tsv.gz) were analyzed to complement the results of this study. These values were used to generate box plots in the University of California Santa Cruz Xena browser and, with Welch's t-test, calculated by the Xena browser application, were all shown to be below 0.05 for the tumor versus normal comparisons for the CSNK2A1, CSNK2A2, and CSNK2B genes. Samples with a log2 FPKM value higher than 1 SD from the mean for this cohort were defined as having high expression for each of the evaluated genes. Those samples with high expression were than compared with the rest of the cohort within cBioPortal to evaluate other clinical and omic features enriched in that grouping. A Kruskal–Wallis test and Chi-squared test[36] were used for statistical analysis. Custom group comparisons were also performed in cBioPortal[37] to investigate various omic subgroups.

Statistical analysis

Two predefined populations analyzed for efficacy were the intent-to-treat (ITT), and mITT populations. The ITT population, which was defined as all patients who were enrolled in the Phase 1 portion and all patients who are randomized to treatment in the Phase 2 portion, was used for analysis of baseline demographics and efficacy. The mITT population, defined as any patient who completed at least one cycle of silmitasertib treatment without dose interruption or dose reduction, was used as the primary analysis population for the evaluation of efficacy. The mITT was employed in an effort to avoid underestimating efficacy in those patients who discontinued therapy early because of intolerance at dose levels other than the recommended Phase 2 dosing schedule. The safety population was defined as patients who received any part of a dose of study drug in Phase 1 and Phase 2.

The survival analysis for PFS and OS was conducted using the SAS procedure Proc Lifetest to calculate estimates of the survival function using the Kaplan–Meier method. A Cox proportional hazards model was used to estimate the hazard ratio (HR) along with 95% confidence intervals (CIs). The *p* value was calculated using the log-rank test, and the HR was estimated from a Cox proportional hazard model. All statistical analyses were conducted using SAS statistical software (Version 9.4) and validated by SAS programs. Plasma pharmacokinetic (PK) analyses were performed using Phoenix WinNonlin Professional 7.0. Univariate and multivariate analyses of PFS and OS were performed to investigate potential confounding factors. Factors analyzed were age (>60 vs. ≤60 years), sex (male vs. female), race (Asian vs. non-Asian), region (United States vs. non–United States), primary tumor site (intrahepatic vs. extrahepatic), ECOG performance status (0 vs. 1), and treatment group.

RESULTS

Patients

The study was initiated in April 2014, and efficacy data were collected up to the data cutoff (February 20, 2020). All 124 patients who were enrolled were included in the ITT population (Phase 1b, *n* = 50; Phase 2, *n* = 74), of whom 84 were included in the mITT population (Phase 1b, *n* = 35; Phase 2, *n* = 49), and 117 in the safety population (Figure 1). Baseline demographics and clinical characteristics are shown in Table 1. The majority of patients were male and Asian, and the median age was 60 years. The Phase 1b dose cohorts are shown in Table S1. In the dose-escalation cohort, the MTD of silmitasertib was 1000 mg twice daily, which was then used in the expansion and exploratory cohorts. Overall, 107 patients (86%) discontinued the study, with disease progression being the main reason (*n* = 50, 40%). Other reasons included withdrawal of consent (*n* = 14, 11%), TEAEs (*n* = 12, 10%), and investigator's decision (*n* = 10, 8%).

Efficacy

Efficacy results are shown in Table 2. In the mITT population, median PFS was 11.2 months (95% CI, 7.6, 14.7) with silmitasertib plus G+C and 5.8 months (95% CI, 3.1, not evaluable [NE]) with G+C (*p* = 0.0496; HR, 0.546) (Figure 2A). Ten-month PFS was 56.1% (95% CI, 38.8%, 70.2%) with silmitasertib plus G+C and 22.2% (95% CI, 1.8%, 56.7%) with G+C in the mITT population (Figure 2B). In the ITT population, median PFS was 8.8 months (95% CI, 4.3, 11.1) with silmitasertib plus G+C and 5.8 months (95% CI, 3.1, NE) with G+C (*p* = 0.3190; HR, 0.857). Ten-month PFS was 40.3% (95% CI, 26.9%, 53.2%) with silmitasertib plus G+C and 22.2% (95% CI, 1.8%, 56.7%) with G+C in the ITT population.

In the mITT population, median OS was 17.4 months (95% CI, 13.4, 25.7) with silmitasertib plus G+C and 14.9 months (95% CI, 9.9, NE) with G+C (*p* = 0.3867; HR, 0.878). The ORR and DCR were 34.0% (*n* = 17) and 86.0% (*n* = 43), respectively, with silmitasertib plus G+C and 30.8% (*n* = 8) and 88.5% (*n* = 23), respectively, with G+C. In the ITT population, median OS was 13.6 months (95% CI, 10.6, 18.9) with silmitasertib and

TABLE 1 Patient demographics and clinical characteristics in the Phase 1, Phase 2, ITT, and mITT populations

	Phase 1	Phase 2		ITT (Phase 1b/2)		mITT (Phase 1b/2)	
	Silmitasertib/ G+C (*n* = 50)	Silmitasertib/ G+C (*n* = 38)	G+C (*n* = 36)	Silmitasertib/ G+C (*n* = 88)	G+C (*n* = 36)	Silmitasertib/ G+C (*n* = 55)	G+C (*n* = 29)
Median age (years)	60 (38–84)	60 (44–78)	60 (25–75)	60 (38–84)	60 (25–75)	60 (38–84)	59 (25–75)
Male, *n* (%)	27 (54)	21 (55)	21 (58)	48 (55)	21 (58)	34 (62)	16 (55)
Race, *n* (%)							
Asian	18 (36)	26 (68)	25 (69)	44 (50)	25 (69)	22 (40)	21 (72)
Black or African American	0	1 (3)	1 (3)	1 (1)	1 (3)	1 (2)	1 (3)
White	32 (64)	10 (26)	10 (28)	42 (48)	10 (28)	32 (58)	7 (24)
Other/not reported	0	1 (3)	0	1 (1)	0	0	0
Ethnicity, *n* (%)							
Non-Hispanic or non-Latino	49 (98)	37 (97)	35 (97)	86 (98)	35 (97)	54 (98)	28 (97)
Hispanic or Latino	1 (2)	1 (3)	1 (3)	2 (2)	1 (3)	1 (2)	1 (3)
Country, *n* (%)							
United States	32 (64)	12 (32)	11 (31)	44 (50)	11 (31)	33 (60)	8 (28)
Korea	9 (18)	4 (10)	8 (22)	13 (15)	8 (22)	6 (11)	6 (21)
Taiwan	9 (18)	22 (58)	17 (47)	31 (35)	17 (47)	16 (29)	15 (52)
Primary tumor site, *n* (%)							
Intrahepatic	42 (84)	33 (87)	33 (92)	75 (85)	33 (92)	47 (86)	26 (90)
Extrahepatic	3 (6)	5 (13)	3 (8)	8 (9)	3 (8)	3 (6)	3 (10)
ECOG PS, *n* (%)							
0	17 (34)	14 (37)	21 (58)	31 (35)	21 (58)	22 (40)	16 (55)
1	33 (66)	24 (63)	15 (42)	57 (65)	15 (42)	33 (60)	13 (45)
Cancer stage, *n* (%)							
Locally advanced	11 (22)	5 (13.2)	5 (14)	16 (18)	5 (14)	8 (15)	4 (14)
Metastatic	39 (78)	33 (87)	31 (86)	72 (82)	31 (86)	47 (86)	25 (86)
Prior treatment, *n* (%)							
Surgery	40 (80)	33 (87)	30 (83)	73 (83)	30 (83)	46 (84)	24 (83)
Radiotherapy	5 (10)	2 (5)	3 (8)	7 (8)	3 (8)	5 (9)	2 (7)
Chemotherapy	4 (8)	2 (5)	1 (3)	6 (7)	1 (3)	3 (6)	0

Abbreviations: C, cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; G, gemcitabine; ITT, intent-to-treat; mITT, modified intent-to-treat.

NE (95% CI, 9.9 months, NE) with G+C (p = 0.1384; HR, 1.562).

In a univariate analysis, the only factor that was statistically significant for PFS (p = 0.0140) and OS (p = 0.0409) was race (Asian vs. non-Asian) (Table S2). Race was also a statistically significant factor for PFS (p = 0.0415) in a multivariate analysis, but not for OS (p = 0.1864) (Table S3).

In the ITT population, the ORR and DCR was 31.9% (n = 23) and 83.3% (n = 60), respectively, with silmitasertib plus G+C and 30.8% (n = 8) and 88.5% (n = 23), respectively, with G+C. In the silmitasertib plus G+C group, one patient had a complete response (CR), 22 patients had a partial response (PR), and 33 patients had stable disease (Figure 3A). In the G+C group, one patient had a CR, seven patients had a PR, and 15 patients had stable disease (Figure 3B).

In the mITT population, 52 patients (silmitasertib plus G+C, n = 41; G+C, n = 11) had elevated CA 19-9 levels at baseline. Twenty-seven patients (65.9%) in the silmitasertib plus G+C group versus six patients (54.6%) in the G+C group showed a reduction in CA 19-9 levels at Cycle 2 (p = 0.503) (Table 2). In the ITT population, 64 patients (silmitasertib plus G+C, n = 53; G+C, n = 11) had elevated CA 19-9 levels at baseline. Thirty-five patients (66.0%) in the silmitasertib plus G+C group versus six patients (54.6%) in the G+C group showed a reduction in CA 19-9 levels at Cycle 2 (p = 0.505) (Table 2).

Safety

In the safety population (n = 117), the majority of patients in the silmitasertib plus G+C (99%) and G+C

TABLE 2 Summary of efficacy results (ITT and mITT populations)

	mITT (*n* = 84)		ITT (*n* = 124)	
	Silmitasertib/G+C (*n* = 55)	**G+C (*n* = 29)**	**Silmitasertib/G+C (*n* = 88)**	**G+C (*n* = 36)**
Median PFS, months (95% CI)	11.2 (7.6, 14.7)	5.8 (3.1, NE)	8.8 (4.3, 11.1)	5.8 (3.1, NE)
p Value	0.0496		0.3190	
HR	0.546		0.857	
10-month PFS, % (95% CI)	56.1 (38.8, 70.2)	22.2 (1.8, 56.7)	40.3 (26.9, 53.2)	22.2 (1.8, 56.7)
HR	0.55			
Median OS, months (95% CI)	17.4 (13.4, 25.7)	14.9 (9.9, NE)	13.6 (10.6, 18.9)	NE (9.9, NE)
p Value	0.3867		0.1384	
HR	0.878		1.562	
	mITT (*n* = 76)[a]		**ITT (*n* = 98)[a]**	
	Silmitasertib/G+C (*n* = 50)	**G+C (*n* = 26)**	**Silmitasertib/G+C (*n* = 72)**	**G+C (*n* = 26)**
ORR, %	34.0	30.8	31.9	30.8
p Value	0.776		0.912	
DCR, %	86.0	88.5	83.3	88.5
p Value	0.763		0.534	
	mITT (*n* = 52)		**ITT (*n* = 64)**	
	Silmitasertib/G+C (*n* = 41)	**G+C (*n* = 11)**	**Silmitasertib/G+C (*n* = 53)**	**G+C (*n* = 11)**
Reduction in tumor marker CA 19-9, *n* (%)	27 (65.9)	6 (54.6)	35 (66.0)	6 (54.6)
p Value	0.503		0.505	

Abbreviations: C, cisplatin; CA 19-9, carbohydrate antigen 19-9; CI, confidence interval; DCR, disease control rate; G, gemcitabine; HR, hazard ratio; ITT, intent-to-treat; mITT, modified intent-to-treat; NE, not evaluable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

[a]Patients with only a baseline scan and nonmeasurable lesions were excluded from the analysis of ORR and DCR.

(93%) groups experienced at least one treatment emergent adverse event (TEAE) (Table 3). The majority of patients had TEAEs that were Grade 3 or 4 in both the silmitasertib plus G+C (80%) and G+C (67%) groups. The most common TEAEs (all grades) in the silmitasertib plus G+C group were diarrhea (*n* = 61, 70%), nausea (*n* = 51, 59%), fatigue (*n* = 41, 47%), vomiting (*n* = 34, 39%), and anemia (*n* = 34, 39%) (Table 4). The most common TEAEs (all grades) in the G+C group were fatigue (*n* = 14, 47%), nausea (*n* = 9, 30%), constipation (*n* = 9, 30%), anemia (*n* = 9, 30%), and decreased appetite (*n* = 9, 30%) (Table 4). Seventy-nine patients (91%) experienced TEAEs that were considered to be related to silmitasertib treatment. The most common silmitasertib treatment-related TEAEs were diarrhea (66%), nausea (51%), vomiting (33%), and fatigue (31%). Twenty-seven serious TEAEs related to silmitasertib treatment occurred in 15 patients (17%). These included anemia, thrombocytopenia, and vomiting (each *n* = 3), and neutropenia, febrile neutropenia, diarrhea, and nausea (each *n* = 1). Life-threatening grade 4 TEAEs occurred in 22 (25%) silmitasertib plus G+C patients and nine (30%) G+C patients (Table 3). Severe Grade 3 TEAEs occurred in 48 (55%) silmitasertib plus G+C patients and 11 (32%) G+C patients (Table 3). Three patients (3%) in the silmitasertib plus G+C group experienced fatal TEAEs (hepatic failure, septic shock, and cerebral infarction), of which the two deaths due to hepatic failure and septic shock were considered to be related to silmitasertib treatment.

PKs

In the dose-escalation cohort, the 2-h postdose plasma concentrations of silmitasertib on Day 0 increased with an escalating silmitasertib dose from 200 to 1000 mg. On Days 1 and 8, predose and 2-h postdose plasma concentrations of silmitasertib increased with an escalating silmitasertib dose. For all days and timepoints, the plasma concentrations of silmitasertib exhibited large variability (Figure 4A,B). The peak plasma concentrations of gemcitabine on Days 1 and 8 appeared to decrease with increasing silmitasertib doses but exhibited large interpatient variability. The peak plasma concentrations of cisplatin on Days 1 and 8 did not change with increasing silmitasertib

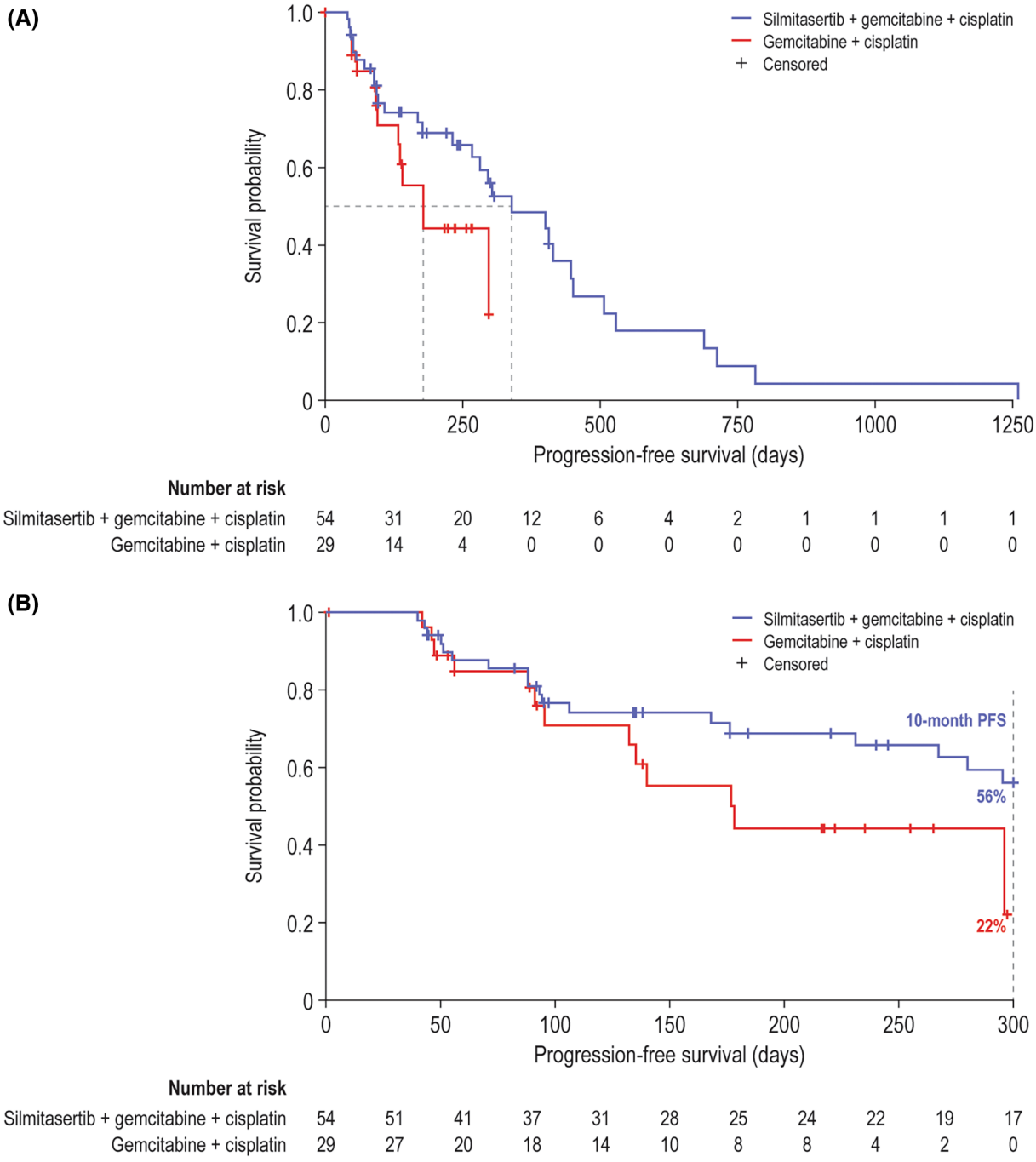

FIGURE 2 Kaplan–Meier plot of PFS (A) and 10-month PFS (B) in the modified intent-to-treat population. PFS, progression-free survival

dose. In the dose-expansion phase, mean (± SD) T_{max} was 1.32 ± 0.541 h, C_{max} was 10,300 ± 8510 ng/ml, and $AUC_{(0–6)}$ and $AUC_{(0–T)}$ were 18,700 ± 14,400 ng·h/ml for silmitasertib 1000 mg twice daily. The C_{max} and AUC of silmitasertib exhibited large variability.

In the 10-day continuous dosing exploratory cohort, silmitasertib 1000-mg, twice-daily mean PK values (± SD) on Days 1 and 8 of Cycle 1 were T_{max} 2.58 ± 2.40 and 2.40 ± 0.894 h, C_{max} 1650 ± 1030 and 6310 ± 4540 ng/ml, and $AUC_{(0–6)}$ 4270 ± 2960 and 17,500 ± 9620 ng·h/ml, respectively. On Day 8, $AUC_{(0–72)}$ was 33,300 ± 12,400 ng h/ml, and $T_{1/2}$ was 13.8 ± 7.45 h. The PK exposure (C_{max} and AUC) of silmitasertib on Day 8 was approximately 4 times higher than that on Day 0. The plasma concentration-time profile of silmitasertib is shown in Figure 4C,D. In the 21-day continuous dosing exploratory cohort, Cycle 1 Days 1 and 8 and Cycle 2 Day 0 silmitasertib mean (± SD) predose concentrations were 1050 ± 1490, 757 ± 1060, and 97.1 ± 128 ng/ml, respectively.

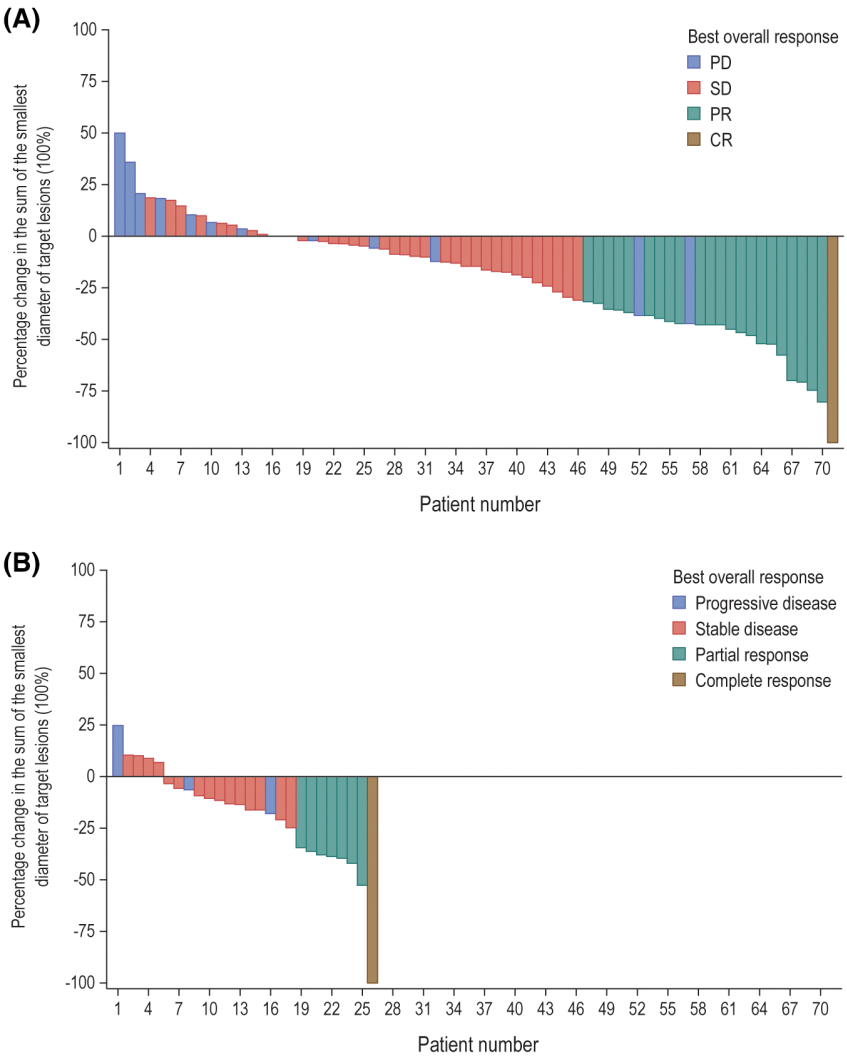

FIGURE 3 Waterfall plot of best response (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) in the silmitasertib plus G+C (A) and G+C (B) groups. C, cisplatin; CR, complete response; G, gemcitabine; PD, progressive disease; PR, partial response

Expression of CSNK2A1, CSNK2A2, and CSNK2B

CSNK2A1, CSNK2A2, and CSNK2B were found to be overexpressed in cholangiocarcinoma tumors compared with normal liver tissue in samples available in TCGA (Figure S1). CSNK2A1 was overexpressed in a higher proportion of advanced T stage tumors compared with earlier T stages (Figure S2A, and higher CSNK2A2 was noted in patients diagnosed at a younger age (Figure S2B). High CSNK2KA1 expression versus not high CSNK2KA1 expression was statistically significant for tumor stage ($p = 0.0196$), and high CSNK2KA2 expression versus not high CSNK2KA2 expression was statistically significant for diagnosis age ($p = 0.0352$).

Using a Kruskal–Wallis test, the diagnosis age of the patient was shown to be statistically significant, differentiating the CSNK2KA2 high group from the not high group. From a Chi-squared test, the tumor stage was shown to be statistically significant, differentiating the CSNK2KA1 high group from the not high group. Custom group comparisons were also performed in cBioPortal to investigate various omic subgroups (Table S4). From a hypergeometric test, isocitrate dehydrogenase 1 (IDH1)/IDH2 mutated samples were shown to be statistically enriched in the CSNK2KA2 high group.

DISCUSSION

The results of this study indicate that silmitasertib at a dosage of 1000 mg twice daily in combination with G+C shows promising efficacy as first-line treatment for patients with locally advanced or metastatic cholangiocarcinoma. The primary endpoint, median PFS in the mITT population, was longer with silmitasertib plus G+C versus G+C (11.2 vs. 5.8 months), a difference that was statistically significant ($p = 0.0496$). Ten-month PFS (56.1% vs. 22.2%) and median OS (17.4 vs. 14.9 months) were also greater with silmitasertib plus

TABLE 3 Treatment-emergent adverse events (safety population)

Number of patients (%)	Silmitasertib/ G+C (*n* = 87)	G+C (*n* = 30)	Total (*n* = 117)
Any TEAE	86 (99)	28 (93)	114 (97)
Severity			
Fatal	3 (3)	0	3 (3)
Life-threatening	22 (25)	9 (30)	31 (27)
Severe	48 (55)	11 (37)	59 (50)
Moderate	11 (13)	6 (20)	17 (15)
Mild	2 (2)	2 (7)	4 (3)
Relationship to silmitasertib			
Related[a]	79 (91)	–	79 (91)
Not related	7 (8)	–	7 (8)
Relationship to gemcitabine			
Related[a]	73 (84)	25 (83)	98 (84)
Not related	13 (15)	3 (10)	16 (14)
Relationship to cisplatin			
Related[a]	73 (84)	24 (80)	97 (83)
Not related	13 (15)	4 (13)	17 (15)
Serious TEAEs related to silmitasertib	15 (17)	–	15 (17)
Severity			
Fatal	2 (2)[b]	–	2 (2)
Life-threatening	3 (3)[c]	–	3 (3)
Severe	8 (9)	–	8 (9)
Moderate	0	–	0
Mild	2 (2)	–	2 (2)

Abbreviations: C, cisplatin; G, gemcitabine; TEAE, treatment emergent adverse event.

[a]Possibly, probably, or definitely related.

[b]Hepatic failure and septic shock.

[c]Neutropenia, thrombocytopenia, and hypokalemia.

G+C versus G+C in the mITT population, although the difference in OS was not statistically significant. Similar results were seen in the ITT population, although median PFS was numerically but not significantly longer with silmitasertib plus G+C versus G+C (8.8 vs. 5.8 months, $p = 0.3190$). Response rates were similar in both treatment groups in the mITT population; the ORR and DCR were 34.0% and 86.0%, respectively, with silmitasertib plus G+C, and 30.8% and 88.5%, respectively, with G+C. Results were similar in the ITT population. In patients who had elevated CA 19-9 levels at baseline, there was a reduction in levels at Cycle 2 in both the silmitasertib plus G+C and G+C groups, although there was no significant difference between the treatment groups in either the mITT or ITT populations.

The efficacy results for silmitasertib plus G+C compared favorably with those for G+C in the ABC-01,[11] ABC-02,[12] and BT22[13] studies. Median PFS and OS with silmitasertib plus G+C in the mITT population (11.2 and 17.4 months, respectively) were longer than with G+C in the ABC-02[12] (8.0 and 11.7 months, respectively) and BT22[13] (5.8 and 11.2 months, respectively) studies. The ORR with silmitasertib plus G+C in the mITT population (34.0%) was similar to that for G+C in the ABC-01[11] (27.8%) and ABC-02[12] (26.1%) studies and higher than for G+C in the BT22 study[13] (19.5%), whereas the DCR (86.0%) with silmitasertib plus G+C in the mITT population was similar to that with G+C in the ABC-02[12] (81.4%) and ABC-01[11] (75.0%) studies and higher than for G+C in the BT22[13] study (68.3%). The TEAE profile of silmitasertib plus G+C compares favorably with that of G+C in the BT22 study,[13] with a lower incidence of hematological adverse event (21%–39% vs. 58.5%–87.8%). The most common silmitasertib-related TEAEs were diarrhea (66%), nausea (51%), vomiting (33%), and fatigue (31%).

Although G+C combination chemotherapy has been the standard of care for the first-line treatment of advanced cholangiocarcinoma for the past decade, there is substantial resistance to treatment, and survival rates remain low. This has led to a number of agents being investigated in clinical trials in combination with this chemotherapy regimen in order to improve survival and response rates, although results have been mixed. Cediranib, an oral inhibitor of vascular endothelial growth factor receptors 1, 2, and 3, did not improve median OS, median PFS, or the DCR versus placebo in the Phase 2 ABC-03 study.[38] In a Phase 2 study, the EGFR monoclonal antibody panitumumab did not improve median OS, median PFS, or the ORR in patients with KRAS wild-type, advanced biliary cancer.[39] In a Phase 2 study of gemcitabine, cisplatin, and nab-paclitaxel, median OS was 19.2 months (95% CI, 13.2 to NE), median PFS was 11.8 months (95% CI, 6.0–15.6), and the DCR was 84%.[40] A Phase 3 study (S1815) evaluating this combination versus G+C is underway. In another Phase 2 study, gemcitabine plus nab-paclitaxel exhibited a response rate of 30%, a DCR of 66%, 6-month PFS of 61%, median PFS of 7.7 months, and median OS of 12.4 months.[41] In a Phase 3 study, S-1 (tegafur, gimeracil, and oteracil) plus G+C significantly improved median OS (13.5 vs. 12.6 months, $p = 0.046$) and median PFS (7.4 vs. 5.5 months, $p = 0.0015$) and improved the response rate (41.5% vs. 15.0%) versus G+C.[42] Additionally, these data compare favorably with the efficacy data from the TOPAZ-1 study, which evaluated G+C ± durvalumab and showed modest improvements in PFS (7.2 vs. 5.7 months) and OS (12.8 vs. 11.5 months) with durvalumab versus the standard-of-care G+C arm.[43] Overall, the efficacy results for silmitasertib in this study appear to be promising and compare favorably with other, to the best of our knowledge, new agents. Although the outcome data are promising, these

TABLE 4 Most common TEAEs occurring in ≥10% of patients (all grades) (safety population)

	All grades			Grade ≥3		
	Silmitasertib/ G+C (*n* = 87)	G+C (*n* = 30)	Total (*n* = 117)	Silmitasertib/ G+C (*n* = 87)	G+C (*n* = 30)	Total (*n* = 117)
Gastrointestinal disorders						
Diarrhea	61 (70)	4 (13)	65 (56)	13 (15)	0	13 (11)
Nausea	51 (59)	9 (30)	60 (51)	10 (12)	0	10 (9)
Vomiting	34 (39)	2 (7)	36 (31)	6 (7)	0	6 (5)
Abdominal pain	25 (29)	4 (13)	29 (25)	5 (6)	1 (3)	6 (5)
Constipation	17 (20)	9 (30)	26 (22)	0	0	0
Stomatitis	13 (15)	2 (7)	15 (13)	1 (1)	0	1 (1)
General disorders and administration site conditions						
Fatigue	41 (47)	14 (47)	55 (47)	9 (10)	0	9 (8)
Pyrexia	28 (32)	5 (17)	33 (28)	5 (6)	0	5 (4)
Asthenia	17 (20)	1 (3)	18 (15)	2 (2)	0	2 (2)
Chills	11 (13)	1 (3)	12 (10)	0	0	0
Investigations						
Platelet count decreased	28 (32)	6 (20)	34 (29)	14 (16)	1 (3)	15 (13)
Neutrophil count decreased	25 (29)	5 (17)	30 (26)	18 (21)	5 (17)	23 (20)
White blood cell count decreased	18 (21)	6 (20)	24 (21)	4 (5)	2 (7)	18 (15)
Gamma-glutamyltransferase increased	12 (14)	3 (10)	15 (13)	7 (8)	1 (3)	8 (7)
Weight decreased	9 (10)	4 (13)	13 (11)	0	0	0
Blood and lymphatic system disorders						
Anemia	34 (39)	9 (30)	43 (37)	17 (20)	5 (17)	22 (19)
Neutropenia	27 (31)	7 (23)	34 (29)	20 (23)	6 (20)	26 (22)
Thrombocytopenia	24 (28)	2 (7)	26 (22)	11 (12)	1 (3)	12 (10)
Metabolism and nutrition disorders						
Decreased appetite	27 (31)	9 (30)	36 (31)	1 (1)	0	1 (1)
Hypokalemia	17 (20)	3 (10)	10 (17)	12 (14)	0	12 (10)
Hypomagnesaemia	12 (14)	1 (3)	13 (11)	1 (1)	0	1 (1)
Respiratory, thoracic, and mediastinal disorders						
Cough	17 (20)	2 (7)	19 (16)	0	0	0
Dyspnea	16 (18)	2 (7)	18 (15)	2 (2)	1 (3)	3 (3)
Nervous system disorders						
Headache	17 (20)	0	17 (15)	0	0	0
Dizziness	13 (15)	2 (7)	15 (13)	1 (1)	0	1 (1)
Dysgeusia	10 (12)	3 (10)	13 (11)	0	0	0
Neuropathy peripheral	10 (12)	2 (7)	12 (10)	1 (1)	1 (3)	2 (2)
Skin and subcutaneous tissue disorders						
Rash	15 (17)	1 (3)	16 (14)	1 (1)	0	1 (1)
Alopecia	11 (13)	4 (13)	15 (13)	0	0	0
Psychiatric disorders						
Insomnia	11 (13)	5 (17)	16 (14)	0	0	0

Abbreviations: C, cisplatin; G, gemcitabine; TEAE, treatment emergent adverse event.

must be taken in the context of cross-trial comparisons that are not in the setting of controlled trials and must be interpreted with caution. Additionally, the response rate for G+C and silmitasertib is not higher than G+C in the ITT population. However, the impetus for conducting a subsequent Phase 3 study is the efficacy data for PFS

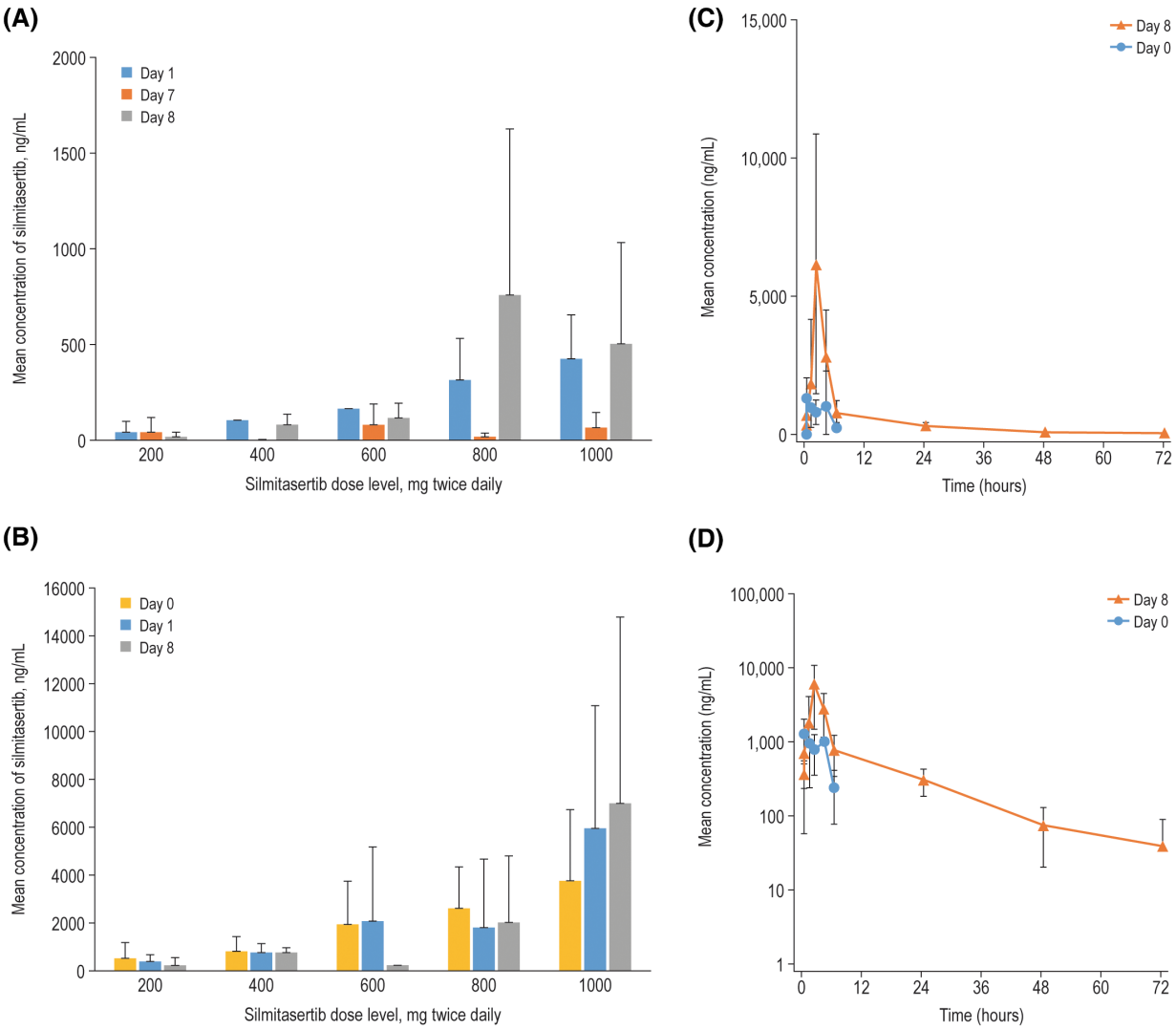

FIGURE 4 Mean plasma concentrations of silmitasertib at predose (A) and 2-h postdose (B) on Days 0, 1, 7, and 8 of Cycle 1 in the dose-escalation cohort and mean plasma concentration-time profile of silmitasertib on Days 0 and 8 of Cycle 1 in the 10-day continuous dosing exploratory cohort. (C) Linear scale. (D) Semilogarithmic scale

in the mITT population, which accounts for early discontinuations during dose escalation with the experimental combination while determining the optimal dosing and schedule for the combination.

CK2 was not examined as a biomarker in this study because of the somewhat ubiquitous nature of its overexpression in tumors compared with normal liver tissue, as shown by the analysis of the TCGA cholangiocarcinoma study, and potential issues with interpretation of assays that would need to be used, such as immunohistochemistry, in which protein staining cutoffs and reproducibility are not established, are qualitative in nature and subject to intraobserver and interobserver variability. Based on findings from the TCGA analysis, planned subgroup assessments in younger patients and those with advanced T stage should be considered in the design of the planned phase 3 study. Genomic subgroups were evaluated (FGFR2, IDH1/IDH2, KRAS/NRAS, TP53 and BAP1) in the TCGA analysis. Of these, only patients with IDH1/IDH2 mutations were enriched for high levels of CSNK2A2 (p = 0.04). However, these data should be interpreted with some caution given the small number of patients with IDH1/IDH2 mutations (n = 7) and relatively modest statistical significance (p = 0.04) in these exploratory analyses. Genomic profiling was not undertaken in the current study because of the absence of extremely strong correlations from the preliminary analyses described above, other than a potential enrichment of CSNK2A2 in IDH1/IDH2 mutant tumors. As such, the absence of genomic profiling in the current study should be considered to be a minor study limitation.

In conclusion, this study shows that silmitasertib in combination with G+C has promising efficacy for the first-line treatment of patients with locally advanced or metastatic cholangiocarcinoma. Based on these results, a randomized Phase 3 trial is planned, which is currently under development and would build upon a G+C/durvalumab backbone.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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