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Clinical Trial Results

Phase II Trial of Trifluridine/Tipiracil Plus Irinotecan in Patients with Advanced, Refractory Biliary Tract Carcinoma

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Abstract

Background: We sought to determine the safety and efficacy of trifluridine/tipiracil in combination with irinotecan in a phase II trial setting for refractory, advanced unresectable biliary tract carcinoma (BTC).

Methods: A total of 28 patients (27 were evaluable) with advanced BTCs who progressed on at least one prior systemic therapy were enrolled and were treated with trifluridine/tipiracil 25 mg/m^2 (days 1-5 of 14-day cycle) and irinotecan 180 mg/m^2 (day 1 of the 14-day cycle). The primary endpoint for the study was 16-week progression-free survival (PFS16) rate. Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety were pre-specified secondary endpoints.

Results: Of 27 patients, PFS16 rate was 37% (10/27; 95% CI: 19%-58%), thereby meeting the criteria for success for the primary endpoint. The median PFS and OS of the entire cohort were 3.9 months (95% CI: 2.5-7.4) and 9.1 months (95% CI: 8.0-14.3), respectively. In the patients evaluable for tumor response (n = 20), the ORR and DCR were 10% and 50%, respectively. Twenty patients (74.1%) had at least one grade 3 or worse adverse event (AE), and 4 patients (14.8%) had grade 4 AEs. A total of 37% (n = 10/27) and 51.9% (n = 14/27) experienced dose reductions in trifluridine/tipiracil and irinotecan, respectively. Delay in therapy was noted in 56% of the patients while 1 patient discontinued the therapy, primarily due to hematologic AEs.

Conclusion: The combination of trifluridine/tipiracil plus irinotecan is a potential treatment option for patients with advanced, refractory BTCs with good functional status and no targetable mutations. A larger randomized trial is needed to confirm these results. (ClinicalTrials.gov Identifier: NCT04072445)

Key words: trifluridine/tipiracil; irinotecan; biliary tract cancer; fluoropyrimidine.

Lessons Learned

- Trifluridine/tipiracil in combination with irinotecan demonstrated a promising antitumor activity in advanced, refractory biliary tract carcinoma especially in patients who had no prior exposure to fluoropyrimidine-based therapies.
- The combination of trifluridine/tipiracil and irinotecan has an acceptable safety profile, and the combination should be further evaluated in patients with advanced biliary tract carcinoma that progressed on standard first-line therapy.

Discussion

The combination of gemcitabine and cisplatin (GC) has been established as a first-line standard of care systemic therapy for advanced, unresectable biliary tract cancers (BTCs) based on the Advanced Biliary Tract Cancer-02 (ABC-02) phase III trial.[1] Recently, addition of durvalumab to chemotherapy with GC (TOPAZ-I trial) demonstrated superior efficacy in terms of overall survival (OS), progression-free survival (PFS), and objective response rate (ORR), making it an attractive first-line therapy.[2] Despite the encouraging results seen with ABC-02 and TOPAZ-I trials in advanced BTCs, the median PFS was less than a year, necessitating the need to develop novel therapies in these patients.

Trifluridine/tipiracil (TAS-102) is a novel oral nucleoside consisting of α, α, α-trifluorothymidine (trifluridine) and 5-chloro-6-(2-iminopyrrolidin-1-yl) methyl-2,4 (1H,3H)-pyrimidinedione hydrochloride (tipiracil). Trifluridine primarily incorporates into DNA leading to antitumor effects. Tipiracil is a potent inhibitor of thymidine phosphorylase, which is the enzyme that degrades trifluridine and helps maintain adequate

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plasma concentration needed for its activity. In a phase II trial, we demonstrated a promising anti-tumor activity of trifluridine/tipiracil monotherapy in advanced, refractory BTCs.[3] In addition, trifluridine/tipiracil when combined with other chemotherapy agents such as irinotecan, showed superior efficacy in colorectal and gastric cancer xenograft models.[4] Here, we determine the safety and efficacy of trifluridine/tipiracil in combination with irinotecan in a phase II trial setting for refractory, advanced unresectable BTCs who had progressed or intolerant to at least one prior line of systemic chemotherapy. The primary endpoint of the trial was a 16-week progression-free survival (PFS16) rate of >30%, which means that at least 6 study participants (of the first 25 evaluable) remain progression-free at the end of 16 weeks.

In the overall evaluable population (n = 27), we noticed a PFS rate of 37% (10 of 27, 95% CI, 19-58) at 16 weeks meeting the predefined primary endpoint for efficacy. The median PFS was 3.9 months (95% CI, 2.5-7.4) (Fig. 1) and the median OS was 9.1 months (95% CI, 8.0-14.3; Fig. 2). Twenty patients (74.1%) had at least one grade 3 or worse adverse event (AE), and 4 patients (14.8%) had grade 4 AEs. No grade 5 adverse events were noted. Noteworthy grade 3 events that occurred in at least 7% of patients included neutrophil count decrease (25.9%), lymphocyte count decrease (14.8%), hypertension (14.8%), biliary tract infection (11.1%), platelet count decrease (11.1%), ascites (7.4%), blood bilirubin increase (7.4%), alkaline phosphatase increase (7.4%), diarrhea (7.4%), fatigue (7.4%), and anemia (7.4%). A total of 37% (n = 10/27) and 51.9% (n = 14/27) experienced dose reductions in trifluridine/tipiracil and irinotecan, respectively. Delay in therapy was noted in 56% of the patients while 1 patient discontinued the therapy, primarily due to hematologic AEs.

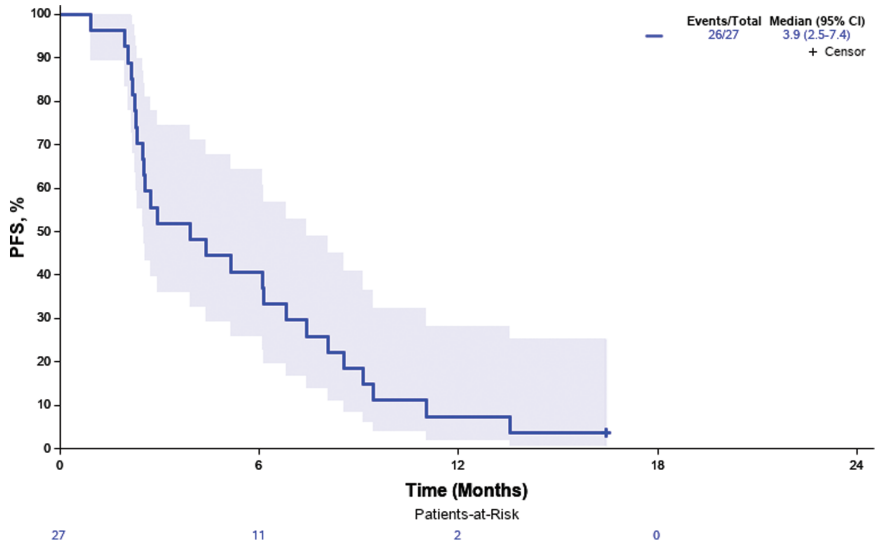

Figure 1. Kaplan–Meier plots depicting the progression-free survival of patients with advanced biliary tract cancer treated with the combination of trifluridine/tipiracil and irinotecan in the advanced biliary tract cancers that progressed after first-line systemic therapy (n = 27). After a median follow up of 15.1 months, the median PFS was 3.9 months (95% CI, 2.5-7.4). Abbreviation: PFS, progression-free survival.

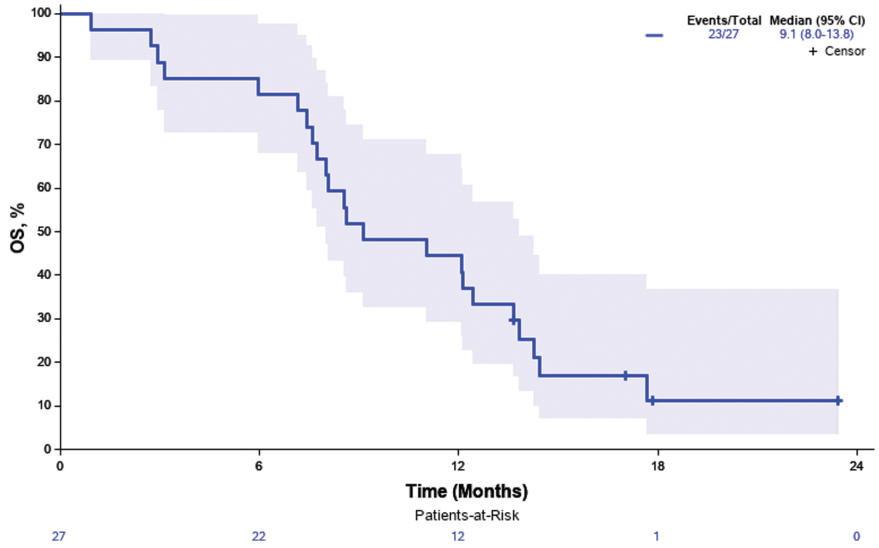

Figure 2. Kaplan-Meier plots depicting the overall survival of patients with advanced biliary tract cancer treated with the combination of trifluridine/tipiracil and irinotecan in the advanced biliary tract cancers that progressed after first-line systemic therapy (n = 27). After a median follow up of 15.1 months, the median OS was 9.1 months (95% CI, 8.0-14.3). Abbreviation: PFS, progression-free survival.

Trial Information***	
Disease	Biliary tract carcinoma: intra-heaptic, extra-hepatic cholangiocarcinoma, and gallbladder cancer
Stage of disease/ treatment	Metastatic and refractory to first-line systemic therapy
Prior therapy	Yes, at least one prior systemic therapy
Type of study	Phase II, single arm, multi-center trial
Primary endpoint	Progression-free survival rate at 16 weeks
Secondary endpoints	Progression-free survival, overall survival, overall response rate, and safety
Investigator's analysis	Active and should be pursued further

Additional Details of Endpoints or Study Design

This is a phase II, single arm study that was conducted at 2 sites of Mayo Clinic at Rochester, MN, and Phoenix, AZ. The study cohort was enrolled between October 28, 2019, and April 23, 2021, according to the good clinical practice guidelines. The study was approved by the institutional review board of Mayo Clinic. The study is registered at http://clinicaltrials.gov (identifier: NCT04072445). A written informed consent was provided by the participating patients.

Patient Eligibility

The patients who met the following inclusion criteria were included in the study: age ≥18 years with a histological confirmation of advanced biliary tract carcinoma including intra-hepatic, extra-hepatic cholangiocarcinoma, and cancers originating in the gallbladder; progression or intolerance to at least one line of systemic anticancer therapy; measurable disease at baseline as defined based on the RECIST criteria, version 1.1); and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Additional inclusion criteria included were absolute neutrophil count ≥1500/μL, platelets ≥100 000/μL, total bilirubin <1.5 × upper limit of normal (ULN), serum aspartate aminotransferase or alanine aminotransferase ≤3 × upper limit normal (ULN), and serum creatinine ≤1.5 × ULN.

Exclusion criteria included patients receiving chemotherapy or radiotherapy or any investigational tumor-directed therapy within 3 weeks of enrollment, patients with HIV on active antiretroviral therapy, pregnant or breastfeeding women, uncontrolled intercurrent illness, including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

Treatment Plan

The study treatment consisted of trifluridine/tipiracil at the dose of 25 mg/m^2 administered orally twice per day after meals, during a 14-day schedule with treatment on days 1-5 and irinotecan 180 mg/m^2 was administer on day 1 of the 14-day cycle. We adopted a reduced dose of trifluridine/tipiracil (25 mg/m^2 instead of the usual dose of 35 mg/m^2) to limit the cumulative side effects of the combination therapy with irinotecan. Therapy was continued until tumor progression, unacceptable side effects, or withdrawal of consent.

Assessment

Radiological assessments were done at baseline and every 4 cycles (8 weeks) thereafter to assess treatment response. Therapy response was assessed using RECIST version 1.1 guidelines. When therapy regimen was discontinued for any reason, follow-up imaging was performed at the discretion of the treating physician. The study participants were monitored for adverse events from the initiation of the study drug to 28 days after the last dose. Safety analysis was performed on the patients who received at least 1 dose of the study treatment. Adverse events were assessed according to the Common Terminology Criteria for Adverse Events version 4.03.

Endpoints and Statistical Analysis

The primary objective of this phase II study was to report the proportion of patients who were alive and progression-free (complete response, partial response, or stable disease) at 16 weeks (PFS16). All patients who met the eligibility criteria signed a consent form and began treatment were included in the primary analysis. A 2-stage phase II Simon optimal design[5] was used to test whether there was sufficient evidence to determine if the PFS16 rate was at least 30%, a rate the study team viewed as clinically promising, versus at most 10%, a rate the study team viewed as not clinically promising. An interim analysis was performed after the first 15 evaluable patients were enrolled. If 2 or more PFS16 successes were observed in this initial cohort, the study would continue to full accrual of 25 evaluable patients. Otherwise, further accrual to the trial would be terminated. Six or more PFS16 successes in the first 25 evaluable patients (defined as patients who are eligible for the trial and who have received at least one dose of therapy) would be considered promising and worthy of further study. This study has 80% power to detect a true PFS16 rate of 30%, with a 5% significance level when the true PFS16 rate is 10%.

Secondary endpoints include descriptive summaries of adverse events, progression-free survival (PFS), overall survival (OS), disease control rate, duration of response, and safety analyses. PFS was defined as the time from study registration to the first of either disease progression or death. OS was defined as the time from study registration to death from any cause. Duration of response was defined as the time from first response to disease progression in those patients that responded and duration of disease control was the time from first response of stable disease or better to disease progression. Time-to-event distributions were estimated with the Kaplan-Meier method.[6] The confirmed response rate was defined as the proportion of patients who experienced either a partial response or complete response as their best response, per the RECIST 1.1 criteria. The disease control rate was defined as the proportion of patients who experienced a partial response, complete response, or have stable

disease as their best response. These endpoints were described descriptively, reporting the rates and 95% CIs. For associations of categorical variables, we used the chi-square test. For the associations of PFS and OS by patient subgroups of interest, we used the log-rank test. Final data for manuscript were frozen on June 3, 2022. SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis, where *P*-values < 0.05 were considered statistically significant.

Drug Information (Drug 1)	
Generic/Working name	Trifluridine/tipiracil
Company Name	Taiho Oncology
Drug Type	Chemotherapy
Drug Class	Antimetabolite
Dose	25 mg/m^2
Route	Oral
Schedule of Administration	Days 1-5 of a 14-day cycle

Drug Information (Drug 2)	
Generic/Working name	Irinotecan
Company Name	Pfizer
Drug Type	Chemotherapy
Drug Class	Topoisomerase I inhibitor
Dose	180 mg/m^2
Route	Intravenous
Schedule of Administration	Day 1 of a 14-day cycle

Patient Characteristics	
Characteristics (*n* = 27)	
Age	
Mean (SD)	65.4 (8.99)
Median	68.0
Range	48.0, 80.0
Gender, *n* (%)	
Female	14 (51.9%)
Male	13 (48.1%)
Race, *n* (%)	
Black or African American	2 (7.4%)
White	25 (92.6%)
Ethnicity, *n* (%)	
Hispanic or Latino	1 (3.7%)
Not Hispanic or Latino	26 (96.3%)
Prior treatment, *n* (%)	
1	10 (37.0%)
2	10 (37.0%)
3+	7 (25.9%)
Primary site of tumor, *n* (%)	
Extrahepatic biliary tract cancer	9 (33.3%)
Gallbladder	2 (7.4%)
Intrahepatic	16 (59.3%)
Degree of differentiation, *n* (%)	
Moderately	17 (63.0%)
Poorly differentiated	10 (37.0%)
PS, n (%)	
0	4 (14.8%)
1	23 (85.2%)
Prior treatment with fluoropyrimidine-based regimen, *n* (%)	
Yes	3 (11.1%)
No	24 (88.9%)

Characteristics (*n* = 27)	
Metastatic sites, n	
Bone	1
Liver	24
Peritoneum	3
Lung	4
Nodal	
Nodal	2
Abdominal wall	1
Interaortocaval LN	2
Pancreas	1
Perisplenic and perihepatic	1
Soft tissue, adrenal gland	1
Abdominal wall, mesenteric node	1
Hepatic duct	1
MedDRA disease code, *n* (%)	
Cholangiocarcinoma, intrahepatic and extrahepatic bile ducts (adenocarcinoma)	24 (88.9%)
Gall bladder carcinoma	3 (11.1%)

Primary assessment method: PFS rate at 16 weeks	
Number of patients screened	28
Number of patients enrolled	28
Number of patients evaluable for toxicity	27
Number of patients evaluated for efficacy	20 (8 patients did not undergo first restaging scans, including withdrawal of consent)
Outcome notes	We observed a 16-week progression-free survival rate of 37% (95% CI:19-58%) in the primary analysis population (*n* = 10 of 27).

Secondary assessment method: overall response rate	
Number of patients screened	28
Number of patients enrolled	28
Number of patients evaluable for toxicity	27
Number of patients evaluated for efficacy	20
Evaluation method	RECIST 1.1
Response assessment, CR	2 (10%)
Response assessment, PR	2 (10%)
Response assessment, SD	6 (30%)
Response assessment, PD	10 (50%)
Median duration assessment, PFS	3.9 months (95% CI: 2.5-7.4)
Median duration assessment, TTP	3.2 months (95% CI: 2.3-6.8)
Median duration assessment, OS	9.1 months (95% CI: 8-14.31)
Response duration	17 months (range: 10.3-not reached)
Duration of treatment	4 cycles (range: 1-20)

Adverse Events

Adverse event	Grade							
	1		2		3		**4**	
	N	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Anemia	6	22.2	17	63	2	7.4		
Neutrophil count decreased	3	11.1	7	25.9	7	25.9	1	3.7

Adverse event	Grade							
	1		2		3		4	
	N	%	*N*	%	*N*	%	*N*	%
Platelet count decreased	10	37.0	4	14.8	3	11.1		
Lymphocyte count decreased			10	37.0	4	14.8		
White blood cells decreased			12	44.4	1	3.7		
Fatigue	2	7.4	5	18.5	2	7.4		
Diarrhea	1	3.7	4	14.8	2	7.4		
Alkaline phosphatase increased			2	7.4	2	7.4		
Hypertension					4	14.8		
Nausea	1	3.7	3	11.1				
Biliary tract infection					3	11.1		
Dysgeusia	2	7.4	1	3.7				
Alopecia	1	3.7	1	3.7				
Ascites					2	7.4		
Blood bilirubin increased					2	7.4		
Dyspnea			2	7.4				
Edema limbs	1	3.7			1	3.7		
Abdominal pain					1	3.7		
Alanine aminotransferase increase					1	3.7		
Anorexia			1	3.7				
Arthralgia					1	3.7		
Arthritis					1	3.7		
Aspartate aminotransferase increase					1	3.7		
Febrile neutropenia							1	3.7
Gastroesophageal reflux disease			1	3.7				
Infections and infestations					1	3.7		
Infusion-related reaction			1	3.7				
Intraoperative hemorrhage							1	3.7
Mucositis oral			1	3.7				
Non-cardiac chest pain			1	3.7				
Paresthesia			1	3.7				
Respiratory failure							1	3.7
Sepsis							1	3.7
Spinal fracture					1	3.7		
Overall adverse events			27	100	20	74	4	15

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's assessment	Active and should be pursued further

Biliary tract cancers (BTCs) are a group of heterogenous neoplasms with dismal prognosis. The combination of gemcitabine and cisplatin (GC) has been the standard of care first-line chemotherapy for advanced, unresectable BTCs for more than a decade.[1] Recently, phase III randomized TOPAZ-1 trial evaluated the addition of durvalumab to GC.[2] The chemo-immunotherapy cohort had a superior PFS (7.2 vs. 5.7 months, P = .001) and OS (12.8 vs. 11.5 months, P = .02) as compared to chemotherapy-only cohort. Apart from the gemcitabine-based therapies, fluoropyrimidine and irinotecan-based regimens were evaluated in advanced BTCs demonstrating modest response rates in both first- and second-line setting.[7-11] A phase II trial evaluated single agent fluoropyrimidine demonstrated a response rate of 31% with median OS of approximately 6 months as a first-line treatment.[12] Another fluoropyrimidine, S-1, which is a combination of tegafur (prodrug that is metabolized to 5-fluorouracil in the liver), 5-chloro-2,4-dihydroxypyridine (inhibits dihydropyrimidine dehydrogenase), and potassium oxonate has also shown modest activity in advanced BTCs as a single agent.[13] Similarly, irinotecan monotherapy demonstrated an overall response rate of 8% in a phase II trial in the first-line setting.[14] However, given the better tolerability and efficacy of gemcitabine, fluoropyrimidine, and irinotecan-based regimens were primarily evaluated in second-line setting with encouraging results.

Common second-line chemotherapies in advanced BTCs include the combination of 5-fluorouracil and oxaliplatin (FOLFOX)[9,15]; capecitabine plus irinotecan (XELIRI),[16] irinotecan monotherapy,[16] and fluoropyrimidine monotherapy.[17]

These studies suggest that there may be a role for fluoropyrimidines in combination with irinotecan in advanced BTCs. Our group recently reported the results of a phase II trial that evaluated the single-agent activity of trifluridine/tipiracil in advanced, refractory BTCs (NCT03278106).[3] Among 27 evaluable patients, the best response was stable disease in 13 (48%) patients. PFS rate at 16 weeks was 29.6% and the median PFS and OS were 3.8 (95% CI: 2.0-5.8) and 6.1 (95% CI: 4.4-11.4) months, respectively.

The mechanism of action of trifluridine/tipiracil is distinct from 5-fluorouracil, providing several advantages over the later. Trifluridine primarily incorporates into DNA leading to antitumor effects as opposed to thymidine synthase inhibition seen with continuous infusion of 5-fluorouracil.[18] Tipiracil is a potent inhibitor of thymidine phosphorylase, which is the enzyme that degrades trifluridine and helps maintain adequate plasma concentration needed for its activity. As such, the antitumor activity of trifluridine is more sustained compared to 5-fluorouracil, whose inhibition of thymidylate synthase rapidly disappears after rapid drug elimination.[19] Notably, Trifluridine/tipiracil has shown activity in both fluoropyrimidine sensitive and resistant tumors.[20] The primary mechanism of resistance to 5-fluorouracil seems to be the decrease in activity of orotate phosphoribosyl transferase resulting in decrease in cellular uptake of 5-fluorouracil in the RNA fraction.[21] Trifluridine has demonstrated activity in 5-fluorouracil resistant colorectal and gastric cancer cell lines as activity of trifluridine/tipiracil is not dependent on orotate phosphoribosyltransferase.[19]

The present study evaluated the safety and efficacy of trifluridine/tipiracil in combination with irinotecan in a phase II trial setting for refractory, advanced unresectable BTCs who had progressed or intolerant to at least one prior line of systemic chemotherapy. A total of 28 patients were enrolled in the trial between October, 2019 and April, 2021. One patient never received therapy, leaving 27 eligible patients. We noticed a PFS rate of 37% (10 of 27; 95% CI, 19-58) at 16 weeks meeting the predefined primary endpoint for efficacy. After a median follow-up of 15.1 months (range, 11.9-10 months), the median PFS was 3.9 months (95% CI, 2.5-7.4; Fig. 1) and the median OS was 9.1 months (95% CI, 8.0-14.3; Fig. 2). The 6-months PFS and 12-month OS rate were 40.7% (95%CI: 25.9%-64.2%) and 44.4% (95% CI: 29.2%-67.8%), respectively. Of the 20 evaluable patients for response, the overall response rate (ORR) was 20% with 2 patients having a complete response, and 2 having a partial response whereas 6 patients had stable disease leading to a disease control rate of 50% (Fig.3). The median duration of disease control was 17.0 months (95% CI: 10.3 to not reached).

The median number of cycles administered was 4 (range, 1-20). Of the 27 evaluable patients, 20 (74.1%) had at least one grade 3 or worse AEs (AE table). Noteworthy grade 3 events that occurred in at least 7% of patients included decrease in neutrophil count (25.9%), decrease in lymphocyte count (14.8%), hypertension (14.8%), biliary tract infection (11.1%), decrease in platelet count (11.1%), ascites (7.4%), increase in blood bilirubin levels (7.4%), elevation of alkaline phosphatase (7.4%), diarrhea (7.4%), fatigue (7.4%), and anemia (7.4%). Four patients (14.8%) had grade 4 AEs that included decrease in neutrophil count (related to therapy) (n = 2), respiratory failure (n = 1), and intraoperative hemorrhage (n=1), the latter 2 side effects were not related to the study drugs. No grade 5 AEs were noted. Secondary to AEs, a total of 37% (n = 10/27) and 51.9% (n =1 4/27) experienced dose reductions in trifluridine/tipiracil and irinotecan, respectively. Delay in therapy was noted in 56% of the patients—primarily due to hematologic AEs, and 1 patient discontinued therapy.

Study limitations are primarily attributed to single-arm study design, a modest sample size, and study conduct at tertiary care center. Given the aggressive nature of the biliary tract cancers, we chose PFS rate at 16 weeks as our primary endpoint. In the current trial, we noticed a disease control rate of 50% including complete responses in 10% (ORR of 20%), which is noteworthy in advanced BTCs that progressed on at least one systemic chemotherapy. Notably, 63% of the patients had received 2 or more lines of prior therapies. The present trial demonstrated favorable results compared to previous trials that evaluated the benefit of second-line chemotherapy in advanced BTC. For instance, ABC-06 trial evaluating FOLFOX as second-line therapy demonstrated ORR of 5% and a disease control rate of 33%.[9] Recently, NALIRICC trial evaluated the combination of 5-fluorouracil plus nanoliposomal irinotecan in second-line setting and demonstrated ORR of 14.3%.[22] The clinical benefit demonstrated in the current trial may be attributed to the mechanism of action of trifluridine/tipiracil as opposed to 5-fluorouracil. Moreover, we noticed higher median OS with the combination of irinotecan and trifluridine/tipiracil as opposed to trifluridine/tipiracil monotherapy.[3,4] Such benefits in OS and ORR in the present trial should be interpreted in caution due to possible differences in baseline characteristics between the trials.

In summary, the combination of trifluridine/tipiracil plus irinotecan is a potential treatment for refractory metastatic and unresectable BTCs, especially in patients with no targetable mutations and good performance status. The PFS, OS outcomes, and response rates are promising compared to previous trials that evaluated systemic chemotherapy in advanced BTCs. Indeed, larger randomized trials are needed to confirm these results.

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Conflict of Interest

Mitesh J. Borad: ADC Therapeutics, Exelixis Pharmaceuticals, Inspyr Therapeutics, G1 Therapeutics, Immunovative Therapies, OncBioMune Pharmaceuticals, Western Oncolytics, Lynx Group, Genentech, Merck, Huya (consulting/advisory), Senhwa Pharmaceutical, Adaptimmune, Agios Pharmaceuticals, Halozyme Pharmaceuticals, Celgene Pharmaceuticals, EMD Merck Serono, Toray, Dicerna, Taiho Pharmaceuticals, Sun Biopharma, Isis Pharmaceuticals, Redhill Pharmaceuticals, Boston Biomed, Basilea, Incyte Pharmaceuticals, Mirna Pharmaceuticals, Medimmune, Bioline,

Sillajen, ARIAD Pharmaceuticals, PUMA Pharmaceuticals, Novartis Pharmaceuticals, QED Pharmaceuticals, Pieris Pharmaceuticals (research funding [institutional]). Robert R. McWilliams: Merck, Bristol-Myers Squibb, Tesaro (research funding). Steven R. Alberts: Merck DMC (Data Monitoring Committee). Sakti Chakrabarti: Natera, Haliodx, and QED Therapeutics (honoraria). Amit Mahipal: AstraZeneca, QED Therapeutics, Taiho Oncology (consulting/advisory). The other authors indicated no financial relationships.

Data Availability

The data underlying this article cannot be shared publicly due to privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

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Figure

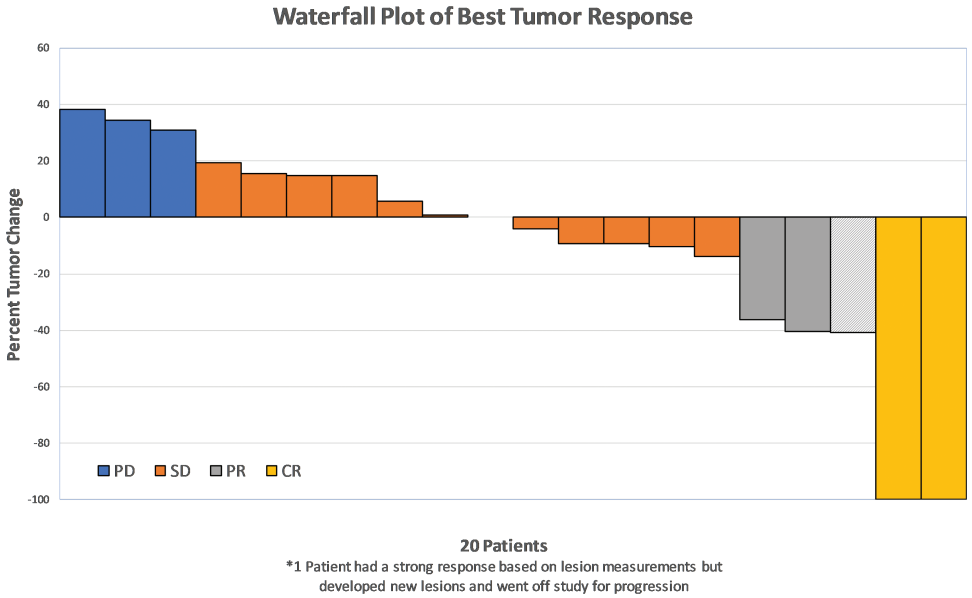

Figure 3. Waterfall plot depicting the best percentage change from baseline in 20 evaluable patients with advanced biliary tract cancer treated with the combination of trifluridine/tipiracil and irinotecan in the advanced biliary tract cancers that progressed after first-line systemic therapy.