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CLINICAL TRIAL PROTOCOL

COMPANION-002 A clinical trial of investigational drug CTX-009 plus paclitaxel vs paclitaxel in second line advanced BTC

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ABSTRACT

Treatment options for patients with biliary tract cancer are limited, and the prognosis is poor. CTX-009, a novel bispecific antibody targeting both DLL4 and VEGF-A, has demonstrated antitumor activity in patients with advanced cancers as both a monotherapy and in combination with chemotherapy. In a phase II study of patients with advanced biliary tract cancer who had received one or two prior therapies, CTX-009 with paclitaxel demonstrated a 37.5% overall response rate (ORR). Described here is the design of and rationale for COMPANION-002, a randomized phase II/III study, which will evaluate the safety and efficacy of CTX-009 in combination with paclitaxel versus paclitaxel alone as second-line treatment for patients with advanced biliary tract cancer. The primary end point is ORR, and crossover is allowed.

Clinical Trial Registration: NCT05506943 (ClinicalTrials.gov)

TWEETABLE ABSTRACT

Looking for new options for patients with advanced biliary tract cancer? Explore COMPANION-002, Compass Therapeutics' phase II/III study of CTX-009 + paclitaxel as a second line treatment. #CMPX #biotech #healthcare #rarecancer

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anti-angiogenesis; biliary tract cancer; cholangiocarcinoma; clinical trial; CTX-009; DLL4; Paclitaxel; VEGF

1. Introduction

Biliary tract cancer (BTC) is a group of gastrointestinal tumors that are classified into four anatomic subtypes: intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and ampullary cancer. The American Cancer Society estimates approximately 18,600 people in the USA will be diagnosed with BTC in 2024 [1]. Advanced BTCs are generally aggressive tumors with median survival time from diagnosis of approximately 12 months, and the 5-year relative survival rates remain low, generally less than 10% [2].

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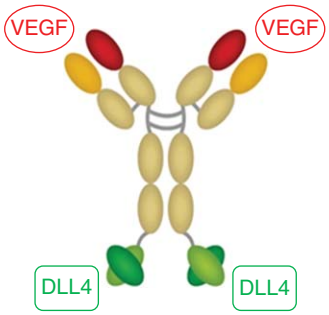

Figure 1. Molecular Structure of CTX-009. Reused with permission from [16]. Source: https://investors.compasstherapeutics.com/static-files/5016a517-1ab1-4f48-b6e1-ee78951fefe3.

For locally advanced, unresectable or metastatic BTC, first-line treatment options include the combination of gemcitabine and cisplatin with either an anti-PD-1 or anti-PD-L1 agent [3,4]. In a randomized study in the second-line setting, the three drug combination regimen FOLFOX improved median overall survival by 0.9 months compared with best supportive care [5]. While several targeted therapies have gained approval for addressing gene alterations that are relevant in BTC, only a minority of BTCs harbor these alterations. Agents are approved for tumors with *FGFR2* fusions and/or *IDH1* mutations, both of which are seen in approximately 10–15% of intrahepatic cholangiocarcinomas, but rarely in the other biliary tract cancer subtypes [6–9]. At least two HER2-targeting agents have shown promise in BTC as part of pan-cancer clinical trials [10,11]. Disease-agnostic approved agents are available for tumors with *BRAF V600E* mutations (4–5% frequency in BTC), *NTRK* fusions (<1%), *RET* fusions (<1%), and/or microsatellite instability (1–2%) [6–9,12–15]. A treatment option is urgently needed for patients with tumors without an obvious actionable alteration.

CTX-009 is a recombinant bispecific antibody that contains two single chain variable fragments (scFv) binding to human DLL4 linked to the C-terminus of heavy chains that bind to human VEGF-A (Figure 1) [16].

VEGF-A overexpression has been reported in BTC, correlating with stage, the presence of metastases and prognosis of the disease [17–19]. In addition, VEGF upregulation has been reported to be one of the mechanisms of chemoresistance of BTC, suggesting the potential therapeutic importance of inhibition of angiogenesis in BTC [18,19].

DLL4/Notch signal transduction occurs via a direct interaction of the extracellular domain of receptor and ligand expressed on the intra-tumoral endothelial cell surface. In mammals, there are four types of Notch receptors (Notch 1, Notch 2, Notch 3 and Notch 4) and the ligands binding to these receptors are Jagged1, Jagged2, DLL1, DLL3 and DLL4. Among these, the DLL4 protein acts as a major ligand for the Notch 1 receptor and has an important role in angiogenesis.

The Notch signaling pathway has been reported to be involved with cholangiocarcinogenesis [20–22]. DLL4 is highly expressed in BTC and up-regulation of DLL4 expression is associated with poor survival in patients with BTC [23]. Importantly, DLL4-Notch 1 signaling can be a part of the development of resistance to anti-VEGF therapeutics [24,25].

Hence, given that the VEGF/VEGFR signal transduction pathway and the DLL4/Notch signal transduction pathway affect angiogenesis via different mechanisms of action, CTX-009 was designed to block both pathways in a novel therapeutic format [25,26].

2. Background & rationale

2.1. Monotherapy study: phase I study (NCT03292783)

A phase I monotherapy dose-escalation study evaluated the safety and tolerability of CTX-009. In total, 45 patients with a variety of solid tumors received CTX-009. Nine dose levels were tested in the phase I monotherapy study, at doses ranging from 0.3 to 17.5 mg/kg biweekly. There were four partial responses (PRs) observed among 40 patients evaluable for response; three of the four responses were confirmed by RECIST. There were two confirmed PRs in patients with colorectal cancer and one confirmed PR and one unconfirmed PR in patients with gastric cancer.

These patients had received a median of four prior lines of therapy. The most frequent treatment emergent adverse events (TEAEs) (>10% of patients) were hypertension (37.8%), headache (22.2%), asthenia (13.3%) anemia (13.3%) and fatigue (11.1%). There were no dose-limiting toxicities observed. All responses were seen at dose levels above 10 mg/kg, and all confirmed responses were seen at the 10 mg/kg or 12.5 mg/kg dose levels [27].

2.2. Combination study: phase Ib/II (NCT04492033)

A phase Ib study conducted in South Korea, evaluated CTX-009 in combination with either irinotecan or paclitaxel in patients with metastatic or advanced solid tumors. Two out of three patients with cholangiocarcinoma who received CTX-009 in combination with paclitaxel achieved confirmed PRs. This observation in the phase Ib study led to the addition of a phase II cohort that enrolled patients with BTC who were treated in the second- or third-line setting.

In the phase II cohort, patients with advanced BTC who had received one or two prior systemic therapies were enrolled. In this study, patients received 10 mg/kg of CTX-009 on days 1 and 15 plus paclitaxel 80 mg/m^2 on

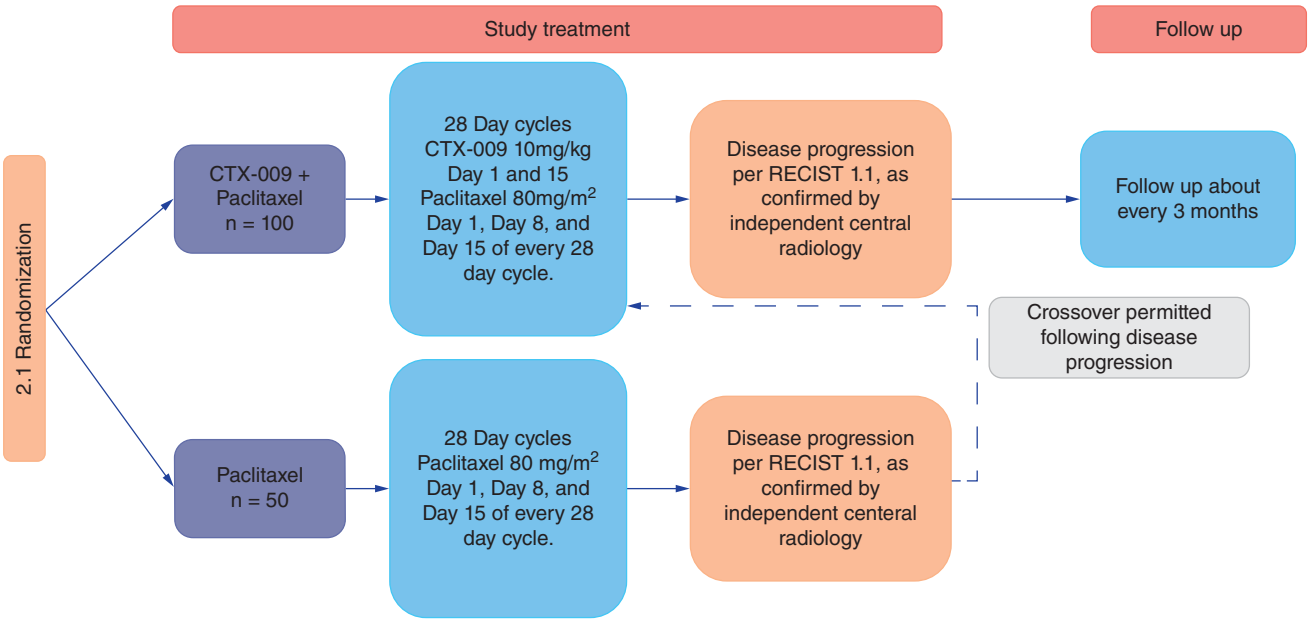

Figure 2. COMPANION-002 study design. Reused with permission from [16]. Source: https://investors.compasstherapeutics.com/static-files/5016a517-1ab1-4f48-b6e1-ee78951fefe3.

days 1, 8 and 15 of a 28-day cycle. Paclitaxel was chosen based on the safety and efficacy data from this phase Ib study. A total of 24 patients were enrolled: nine (37%) with intrahepatic cholangiocarcinoma, three (13%) with extrahepatic cholangiocarcinoma, seven (29%) with gallbladder cancer and five (21%) with ampullary carcinoma.

The primary end point of the phase II study was overall response rate (ORR) and the ORR was 37.5% (n = 9/24 patients). Among 11 patients treated in the second-line, the ORR was 63.6% (n = 7/11) versus 15% (n = 2/13) among patients treated in the third-line setting. The median duration of response was 6.9 months, and responses were seen in patients with all anatomic subtypes of BTC, including ampullary cancer. The median progression-free survival was 9.4 months and the survival rate at 1 year was 53%. All patients experienced one or more adverse events. The most frequent TEAEs of grade 3 or higher were neutropenia (50.0%), hypertension (16.7%), anemia (12.5%) and thrombocytopenia (8.3%) [28].

2.3. Objectives

The COMPANION-002 study (NCT05506943) evaluates the efficacy and safety of CTX-009 in combination with paclitaxel versus paclitaxel alone in patients with BTC treated in the second-line setting.

2.4. Trial design

COMPANION-002 is a multicenter, randomized, phase II/III study (Figure 2) [16]. Patients are randomized to a 2:1 ratio, and crossover is allowed to the experimental arm at the time of progression in the control arm for patients that continue to meet eligibility criteria. Stratification factors include stage (locally advanced vs metastatic), anatomic subtype of the primary tumor (intrahepatic cholangiocarcinoma vs other) and ECOG performance status (0 or 1).

3. Methods

3.1. Eligibility criteria

See Table 1 below [29]. Safety will be monitored throughout the study and for 30 days after the end of treatment. Adverse events will be assessed as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

3.2. Interventions

CTX-009 will be administered at 10 mg/kg on Day 1 and Day 15 of every 28-day cycle. Paclitaxel will be administered 80 mg/m2 on Day 1, Day 8 and Day 15 of every 28-day cycle.

3.3. Outcomes

The primary end point is ORR per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) by independent central review (ICR). The secondary end points are progression free survival, duration of response, overall survival, disease control rate, safety and quality of life measured with EORTC QLQ-C30.

Table 1. Eligibility criteria for COMPANION-002 enrollment.

Inclusion criteria	Exclusion criteria
1. 18 years of age or older 2. Histologically or cytologically confirmed unresectable advanced, metastatic, or recurrent biliary tract cancers (including intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and ampullary carcinoma) 3. Patients must have radiologically documented progression after a prior gemcitabine and platinum containing chemotherapy regimen as first-line therapy for locally advanced unresectable or metastatic disease a. Patients who received perioperative treatment (adjuvant and neoadjuvant) may be eligible, as determined by the Sponsor Medical Monitor b. Patients whose first-line regimen was modified due to toxicity before disease progression may be eligible, as determined by the Sponsor Medical Monitor 4. At least one lesion measurable as defined by RECIST v1.1 5. ECOG Performance Status 0–1 6. Predicted life expectancy of at least 12 weeks 7. No evidence of ongoing infection and adequate biliary excretion or patients whose adequate biliary excretion can be confirmed with the following procedures: a. Patients who underwent ERBD at least 1 week before the investigational drug treatment b. Patients with endobiliary stents are eligible, provided there is no evidence of obstruction c. Patients free of any signs of active or suspected uncontrolled infection after a drainage procedure d. Patients free of any risk of hemorrhage and with incision completely healed 8. Adequate bone marrow, hepatic and renal function within 14 days of randomization as described below. Patient must be free of G-CSF treatment and blood transfusion within 14 days prior to the lab test: a. ANC $\geq$1500/mm^3 b. Hemoglobin $\geq$9.0 g/dl c. Platelet count $\geq$100,000/mm^3 d. Total bilirubin $\leq$1.5 $\times$ ULN e. AST/ALT $\leq$3.0 $\times$ ULN ($\leq$5 $\times$ ULN in case of hepatic metastasis) f. Estimated creatinine clearance $\geq$30 ml/min based on Cockroft-Gault g. Urine protein $\leq$1+ by Dipstick (only when urinalysis shows a protein dipstick result of $>$1 positive [+], the total protein volume [$<$1.0 g/24 h] can be confirmed with a 24 h urine test) h. Serum amylase and lipase level $\leq$3 $\times$ ULN i. Serum Albumin $\geq$3.0 g/dl 9. Female patients who are WCBP must have a negative pregnancy test (serum-hCG or urine-hCG performed at the Investigator's discretion) within 14 days of randomization 10. Female patients must be surgically sterile (or have a monogamous partner who is surgically sterile), or be at least 2 years postmenopausal, or commit to use two acceptable forms of birth control (defined as the use of an IUD, a barrier method with spermicide, condoms, or any form of hormonal contraceptives) or abstinence for the duration of the study and for 6 months following the last dose of study treatment. Male patients must be sterile (biologically or surgically) or commit to the use of a reliable method of birth control (condoms with spermicide) for the duration of the study and for 6 months following the last dose of study treatment 11. Signed and dated IRB/IEC approved ICF before any protocol-directed screening procedures are performed	1. Patients who are eligible to be treated with a molecularly targeted therapy on a labelled regimen after receiving first-line chemotherapy. Patients who received a molecularly targeted therapy as part of their first line treatment may be eligible, as determined by the Sponsor Medical Monitor 2. From the time point of screening, a. Less than 4 weeks have elapsed since patients had a surgery or major procedure b. Less than 2 weeks have elapsed from the last treatment date since patients had any radiation therapy 3. Patients with PTBD 4. Prior to the initial treatment of study drug, a. Less than 2 weeks have elapsed since patients had chemotherapy or hormone therapy b. Less than 2 weeks have elapsed since patients had anticancer immunotherapy or investigational drug treatment c. Less than 4 weeks since cryotherapy, radiofrequency ablation, anhydrous alcohol therapy, or photodynamic therapy, including TACE and TARE 5. A history of the following cardiovascular diseases (please, consult the Sponsor Medical Monitor for a case-by-case evaluation): a. CHF that corresponds to Class II or a higher class under NYHA classification, or less than 50% of left LVEF b. Uncontrolled hypertension (SBP/DBP $>$140/90 mmHg) (e.g., patient with SBP/DBP $>$140/90 mmHg despite the best care including optimizing the anti-hypertensive medication regimen) c. Patients with any history of hypertensive crisis or pre-existing hypertensive encephalopathy d. Pulmonary hypertension e. Myocardial infarction f. Uncontrolled arrhythmia g. Unstable angina h. Patients with any significant vascular diseases (e.g., aortic aneurysm requiring surgery or recent peripheral artery thrombosis) within 6 months prior to the initial treatment of the investigational product 6. History of hypersensitivity reactions to any components of the investigational product or other drugs of the same class (humanized/human monoclonal antibody drugs) or paclitaxel 7. Patients with contraindications to paclitaxel therapy 8. Patients with persistent, clinically significant toxicities (excluding hair loss) from previous anticancer treatment that corresponds to Grade 2 or a higher grade under NCI-CTCAE v5.0 9. Symptomatic or uncontrolled CNS metastasis However, patients with asymptomatic CNS metastasis that have been treated with either surgery or radiation can participate provided that systemic corticosteroid treatment was discontinued at least 4 weeks prior to screening and that the patient is radiologically and neurologically stable or improving 10. A history of the following hemorrhage-related or gastroenterological disease: a. Active hemorrhage, hemorrhagic diathesis, coagulopathy or tumor in great arteries b. History of clinically significant gastroenterological disease, such as peptic ulcer, GI bleeding, GI or non-GI fistula, perforation, abdominal abscess, clinical symptoms and signs of GI obstruction, need for parenteral hydration or nutrition, or IBD 11. Current or recent (within 10 days prior to study treatment) use of full-dose oral or parenteral anticoagulants or thrombolytic agents for therapeutic (as opposed to prophylactic) purpose will be excluded a. Prophylactic (i.e., for the patency of venous access devices) use of low molecular-weight heparin (i.e., enoxaparin 40 mg/day) is allowed if patient has INR $<$2 or aPTT $<$/=2x ULN within 14 days of study treatment 12. Patients with current or recent (within 10 days of study treatment) use of aspirin ($>$81 mg/day), or other NSAIDs, or other antiplatelets (i.e., dipyridamole, ticlopidine, clopidogrel and cilostazol) will be excluded 13. Severe infection requiring ongoing systemic antibiotics, antivirus drugs, etc., or other uncontrolled acute active infectious diseases

Created using data from [29]. Source: https://clinicaltrials.gov/study/NCT05506943.

ANC: Absolute neutrophil count; aPTT: Activated partial thromboplastin time; BT: Biliary tract cancer; BTC: Biliary tract cancer; CHF: Congestive heart failure; CNS: Central nervous system; DBP: Diastolic blood pressure; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ERBD: Endoscopic retrograde biliary drainage; G-CSF: Granulocyte colony-stimulating factor; GI: Gastrointestinal; HBV: Hepatitis B virus; hCG: Human chorionic gonadotropin; HCV: Hepatitis C virus; IBD: Inflammatory bowel disease; ICF: Informed consent form; IEC: Independent Ethics Committee; INR: International normalized ratio; IRB: Institutional Review Board; IUD: Intrauterine device; LVEF: Left ventricular ejection fraction; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; NSAIDS: Nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; PTBD: Percutaneous transhepatic biliary drain; QT: absolute QT interval; QTcF: absolute QT interval corrected for heart rate by Fridericia's formula; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SBP: Systolic blood pressure; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; ULN: Upper limit of normal; WCBP: Women of childbearing potential.

Table 1. Eligibility criteria for COMPANION-002 enrollment (cont.).

Inclusion criteria	Exclusion criteria
	14. Patients with evidence of active HBV or HCV infection. Patients with positive HBsAg and/or detectable HBV DNA are eligible only if adequately controlled on antiviral therapy according to institutional standards and liver function eligibility criteria are also met. HCV patients showing sustained viral response or patients with immunity to HBV infection may enroll 15. Patients with other severe diseases or uncontrolled illnesses that warrant the exclusion from the study (permitted only if medically controlled) including but not limited to: a. Pre-existing hemoptysis (≥1/2 teaspoon of bright red blood per episode) within 28 days prior to screening b. Major, unhealed injury, active ulcer, or untreated fracture c. Pre-existing conditions of cerebrovascular incident (ischemic or hemorrhagic stroke), transient ischemic attack or subarachnoid hemorrhage within 6 months prior to screening d. Moderate to severe ascites and/or pleural effusion. However, enrollment is permitted for patients with ascitic fluid as long as paracentesis is not required to improve the condition e. Interstitial lung disease or pulmonary fibrosis 16. Patients expected to require anticancer treatment other than the investigational product during the clinical study 17. Pregnant or lactating patients, or patients planning to become pregnant during the clinical study 18. A history of primary malignant tumor other than BTC will be excluded, except for malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate >90%). Prior malignancy history will be evaluated on a case-by-case basis by the Sponsor Medical Monitor 19. Clinically significant abnormal ECG findings or history determined as clinically significant by the Investigator 20. QTcF interval >450 msec at the time of screening

Created using data from [29]. Source: https://clinicaltrials.gov/study/NCT05506943.

ANC: Absolute neutrophil count; aPTT: Activated partial thromboplastin time; BT: Biliary tract cancer; BTC: Biliary tract cancer; CHF: Congestive heart failure; CNS: Central nervous system; DBP: Diastolic blood pressure; ECG: Electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ERBD: Endoscopic retrograde biliary drainage; G-CSF: Granulocyte colony-stimulating factor; GI: Gastrointestinal; HBV: Hepatitis B virus; hCG: Human chorionic gonadotropin; HCV: Hepatitis C virus; IBD: Inflammatory bowel disease; ICF: Informed consent form; IEC: Independent Ethics Committee; INR: International normalized ratio; IRB: Institutional Review Board; IUD: Intrauterine device; LVEF: Left ventricular ejection fraction; NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Events; NSAIDS: Nonsteroidal anti-inflammatory drug; NYHA: New York Heart Association; PTBD: Percutaneous transhepatic biliary drain; QT: absolute QT interval; QTcF: absolute QT interval corrected for heart rate by Fridericia's formula; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SBP: Systolic blood pressure; TACE: Transarterial chemoembolization; TARE: Transarterial radioembolization; ULN: Upper limit of normal; WCBP: Women of childbearing potential.

3.4. Sample size

The planned sample size is approximately 150 patients. This is a multicenter study with 32 study sites.

3.5. Statistical methods

This study was designed to detect a 23% absolute difference in response rate between the two arms, with 90% power and a two-sided alpha of 0.05.

4. Conclusion

Based on the clinical results from a previous phase Ib/II investigation, the utilization of CTX-009 with paclitaxel could potentially offer a favorable risk-benefit profile in patients with advanced BTC. This manuscript delineates the methodology employed in the COMPANION-002 study, an ongoing phase II/III trial designed to assess the effectiveness and safety of CTX-009 combined with paclitaxel compared with paclitaxel as a monotherapy in the second-line setting for patients with advanced BTC.

Article highlights

- Most patients with biliary tract cancer (BTC) receive diagnoses at an advanced stage of the disease when prognoses are poor.
- Given the limited survival benefit observed with current therapies, there remains a need for novel therapeutic regimens to treat patients with advanced BTC in the second-line setting after failure of front-line regimens.

Background & rationale

- CTX-009 combined with paclitaxel has shown clinical benefit with manageable toxicity in patients with advanced BTC.
- The combination of CTX-009 and paclitaxel could be beneficial for patients with BTC as a second-line therapy for advanced disease.

COMPANION-002 study design & eligibility criteria

- COMPANION-002 is a multicenter, randomized, phase II/III study evaluating the efficacy and safety of CTX-009 in combination with paclitaxel as second-line treatment for patients with advanced or metastatic BTC.
- Eligible patients with a histologically or cytologically confirmed diagnosis of previously treated, locally advanced unresectable or metastatic BTC will be randomly assigned to receive CTX-009 in combination with paclitaxel or paclitaxel alone in a 2:1 ratio.

Outcome measures/end points

- The primary end point is overall response rate.
- Secondary end points are progression free survival and overall survival.

Conclusion

- The CTX-009 study will further define the role of CTX-009 in patients with advanced BTC.

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Author contributions

All authors have fulfilled authorship criteria, including critically reviewing the manuscript for important intellectual content. All authors reviewed the final version and agreed with the content and approved of the decision to submit.

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Competing interests disclosure

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Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors attest that the study protocol was approved by the appropriate ethics committee or institutional review board at each participating center (please, see the full list below). The procedures defined in the protocol were established to ensure that performance and evaluation of the study and recording of the outcomes by the sponsor and the investigator comply with the ethical regulations based on the Declaration of Helsinki, US FDA, and relevant bylaws. All participants will provide written informed consent before enrollment.

List of institutional review boards (IRBs) that approved the study protocol

- Central IRB: WCG
- Local IRBs:
  - McKesson IRB

- Mayo Clinic IRB
- Northwestern IRB
- University of Chicago IRB
- Stanford IRB
- Massachusetts General Hospital IRB
- Johns Hopkins Medicine IRB
- University of California San Francisco IRB
- Cleveland Clinic IRB
- Roswell Park Comprehensive Cancer Center IRB
- BRANY-Montefiore IRB
- Columbia University IRB

Previous presentation

For any studies that have been presented at a conference prior to submission need to be acknowledged and the abstract cited in the reference list [30–33].

References

Papers of special note have been highlighted as: •• of considerable interest

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin. 2024;74:12–49. doi:10.3322/caac.21820
2. SEER*Explorer Application [Internet]. [cited 2024 Mar 5]. Available from: https://seer.cancer.gov/statistics-network/explorer/application.html?site=1&data_type=1&graph_type=2&compareBy=sex&chk_sex_3=3&chk_sex_2=2&rate_type=2&race=1&age_range=1&hdn_stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_show_apc=on&advopt_display=2#resultsRegion0.
3. Oh D-Y, Ruth He A, Qin S, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer. NEJM Evidence [Internet]. 2022 [cited 2023 Dec 20];1. Available from: https://evidence.nejm.org/doi/10.1056/EVIDoa2200015. doi:10.1056/EVIDoa2200015
4. Kelley RK, Ueno M, Yoo C, et al. Pembrolizumab in combination with gemcitabine and cisplatin compared with gemcitabine and cisplatin alone for patients with advanced biliary tract cancer (KEYNOTE-966): a randomised, double-blind, placebo-controlled, Phase III trial. The Lancet. 2023;401:1853–1865. doi:10.1016/S0140-6736(23)00727-4
5. Lamarca A, Palmer DH, Wasan HS, et al. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a Phase III, open-label, randomised, controlled trial. Lancet Oncol. 2021;22:690–701. doi:10.1016/S1470-2045(21)00027-9
6. Goyal L, Meric-Bernstam F, Hollebecque A, et al. Futibatinib for FGFR2-rearranged intrahepatic cholangiocarcinoma. N. Engl. J. Med. 2023;388:228–239. doi:10.1056/NEJMoa2206834
7. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, Phase II study. Lancet Oncol. 2020;21:671–684. doi:10.1016/S1470-2045(20)30109-1
8. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, Phase III study. Lancet Oncol. 2020;21:796–807. doi:10.1016/S1470-2045(20)30157-1
9. Benson AB, D'Angelica MI, Abrams T, et al. NCCN Guidelines® Insights: Biliary Tract Cancers, Version 2.2023. J Natl Compr Canc Netw. 2023;21:694–704. doi:10.1200/JCO.23.02005
10. Meric-Bernstam F, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 Phase II trial. JCO. 2024;42:47–58. doi:10.1200/JCO.23.02005
11. Harding JJ, Fan J, Oh D-Y, et al. Zanidatamab for HER2-amplified, unresectable, locally advanced or metastatic biliary tract cancer (HERIZON-BTC-01): a multicentre, single-arm, Phase IIb study. Lancet Oncol. 2023;24:772–782. doi:10.1016/S1470-2045(23)00242-5
12. Graham RP, Barr Fritcher EG, Pestova E, et al. Fibroblast growth factor receptor 2 translocations in intrahepatic cholangiocarcinoma. Hum Pathol. 2014;45:1630–1638. doi:10.1016/j.humpath.2014.03.014
13. Ross JS, Wang K, Gay L, et al. New routes to targeted therapy of intrahepatic cholangiocarcinomas revealed by next-generation sequencing. Oncologist. 2014;19:235–242. doi:10.1634/theoncologist.2013-0352
14. Arai Y, Totoki Y, Hosoda F, et al. Fibroblast growth factor receptor 2 tyrosine kinase fusions define a unique molecular subtype of cholangiocarcinoma. Hepatology. 2014;59:1427–1434. doi:10.1002/hep.26890
15. Boscoe AN, Rolland C, Kelley RK. Frequency and prognostic significance of isocitrate dehydrogenase 1 mutations in cholangiocarcinoma: a systematic literature review. J Gastrointest Oncol. 2019;10:751–765. doi:10.21037/jgo.2019.03.10
16. Compass Therapeutics: Corporate Presentation [Internet]. 2024 [cited 2024 Apr 25]. Available from: https://investors.compasstherapeutics.com/static-files/5016a517-1ab1-4f48-b6e1-ee78951fefe3
17. Cai C, Wang X, Fu Q, et al. The VEGF expression associated with prognosis in patients with intrahepatic cholangiocarcinoma: a systematic review and meta-analysis. World J Surg Oncol. 2022;20:40. doi:10.1186/s12957-022-02511-7
    •• Supports the potential benefit of targeting VEGF in patients with biliary tract cancer.
18. Mancinelli R, Mammola CL, Sferra R, et al. Role of the angiogenic factors in cholangiocarcinoma. Appl Sci. 2019;9:1393. doi:10.3390/app9071393
19. Simone V, Brunetti O, Lupo L, et al. Targeting angiogenesis in biliary tract cancers: an open option. Int J Mol Sci. 2017;18:418. doi:10.3390/ijms18020418
20. Ishimura N, Bronk SF, Gores GJ. Inducible nitric oxide synthase up-regulates Notch-1 in mouse cholangiocytes: implications for carcinogenesis. Gastroenterology. 2005;128:1354–1368. doi:10.1053/j.gastro.2005.01.055
21. Mazur PK, Riener M-O, Jochum W, et al. Expression and clinicopathological significance of notch signaling and cell-fate genes in biliary tract cancer. Am J Gastroenterol. 2012;107:126–135. doi:10.1038/ajg.2011.305
22. Rauff B, Malik A, Bhatti YA, et al. Notch signalling pathway in development of cholangiocarcinoma. World

J Gastrointest Oncol. 2020;12:957–974. doi:10.4251/wjgo.v12.i9.957

•• Supports the potential benefit of targeting the Notch signaling cascade in patients with biliary tract cancer.

23. Yoon HA, Noh MH, Kim BG, et al. Clinicopathological significance of altered Notch signaling in extrahepatic cholangiocarcinoma and gallbladder carcinoma. World J Gastroenterol. 2011;17:4023–4030. doi:10.3748/wjg.v17.i35.4023
24. Lobov IB, Renard RA, Papadopoulos N, et al. Delta-like ligand 4 (Dll4) is induced by VEGF as a negative regulator of angiogenic sprouting. Proc Natl Acad Sci USA. 2007;104:3219–3224. doi:10.1073/pnas.0611206104
25. Li J-L, Sainson RCA, Oon CE, et al. DLL4-Notch signaling mediates tumor resistance to anti-VEGF therapy *in vivo*. Cancer Res. 2011;71:6073–6083. doi:10.1158/0008-5472.CAN-11-1704

•• Supports the rationale for simultaneously targeting VEGF and DLL4.

26. Kuhnert F, Chen G, Coetzee S, et al. Dll4 blockade in stromal cells mediates antitumor effects in preclinical models of ovarian cancer. Cancer Res. 2015;75:4086–4096. doi:10.1158/0008-5472.CAN-14-3773
27. Lee J, Kim S, Hong J, et al. Abstract P02–03: phase Ia/Ib dose-escalation study of ABL001 (CTX-009, bispecific antibody targeting DLL4 and VEGF-A) as a single agent in patients with advanced solid tumors. Mol Cancer Therapeut. 2021;20:P02–03. doi:10.1158/1535-7163.TARG-21-P02-03

•• Presented the phase I data for CTX-009.

28. Oh D-Y, Park JO, Kim JW, et al. CTX-009 (ABL001), a bispecific antibody targeting DLL4 and VEGF A, in combination with paclitaxel in patients with advanced biliary tract cancer (BTC): a Phase II study. JCO. 2023;41:540–540. doi:10.1200/JCO.2023.41.4_suppl.540

•• Phase II study supporting the design of the COMPANION-002 randomized study.

29. National Library of Medicine [Internet]. Bethesda, MD; [cited 2024 Apr 25]. Available from: https://clinicaltrials.gov/study/NCT05506943
30. ASCO GI. January 20, 2023, San Francisco [#TPS640].
31. Cholangiocarcinoma Foundation Annual Conference. April 13, 2023, Salt Lake City [#20984].
32. Cholangiocarcinoma Summit. October 20, 2023, Scottsdale [none].
33. ASCO GI. January 17, 2024, San Francisco [#TPS587].