# A Study of CTX-009 With Paclitaxel in Adult Patients With Unresectable Advanced, Metastatic or Recurrent Biliary Tract Cancer

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## Background

### Background of Disease

- Biliary tract cancer (BTC) is a group of gastrointestinal tumors that are anatomically classified into four subtypes: intrahepatic cholangiocarcinomas, extrahepatic cholangiocarcinomas, gallbladder cancers, and ampullary carcinomas.
- For locally advanced and metastatic BTC, first-line chemotherapy includes the use of gemcitabine and cisplatin. Recently, the addition of durvalumab to gemcitabine and cisplatin was approved.[1]
- Presently, there is no consensus second-line therapy for patients with BTC in whom first-line therapy has failed.[2]

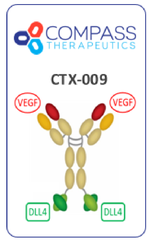
### CTX-009: A Novel DLL4 x VEGF-A Bispecific Antibody

### Bispecific rationale

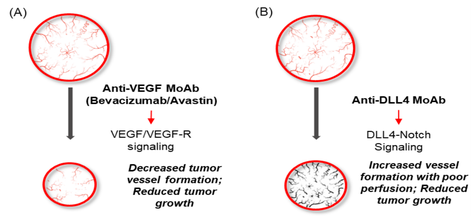
- Dual blockade of DLL4-Notch1 signaling is synergistic in preclinical models
- DLL4 upregulation in the tumor microenvironment mediates resistance to VEGF-targeted agents
- DLL4 expression is a negative prognostic factor in various malignancies including gastric, renal cell, ovarian, and colorectal cancers

### Differentiation of CTX-009

- Unique proprietary DLL4 binding epitope
- 2:2 valency effectively blocks both signaling pathways




### Dual blockade of DLL4 and VEGF overcomes VEGF resistance:




### VEGF/VEGFR inhibition

- Reduced blood vessel growth and expansion in tumors
- Regression of existing tumor vessels
- Loss of VEGF-mediated endothelial cell (EC) survival, and sensitizes ECs to effects of chemotherapy and radiation

### DLL4/Notch inhibition

- Increased EC proliferation and sprouting, non-productive angiogenesis
- Reduces cancer stem cell frequency and delays tumor recurrence[3]

## Clinical Summary

### Phase 1 Program Summary[5]

**Phase 1a: Dose Escalation Monotherapy Study**

**N=45: Gastric, CRC, Other**
Nine dose-escalation cohorts (0.3-17.5 mg/kg)
Four dose-expansion cohorts (7.5-15 mg/kg)

**Phase 1b: Combination Study with Chemotherapy**

**N=17: 4 arms, multiple indications**
1. CTX-009 10.0 mg/kg + paclitaxel
2. CTX-009 10.0 mg/kg + irinotecan
3. CTX-009 12.5 mg/kg + paclitaxel
4. CTX-009 12.5 mg/kg + irinotecan

**Results:**

- **Safety:** well-tolerated; MTD has not been determined
- **Activity:** 8 PRs, 6 confirmed by RECIST in 33 advanced solid tumor patients treated
- **Responses as a monotherapy:** colorectal and gastric
- **Responses in combination with chemotherapy:** cholangiocarcinoma, pancreatic
  - Cholangiocarcinoma ORR= 50%; Clinical benefit rate = 75% with a median duration of response of 9.7 months

### Phase 2 Program Summary: (as of 09NOV2022)

- Expansion of Phase 1b combination study of CTX-009 in combination with paclitaxel in patients with previously treated biliary tract cancer
- 10 partial responses (PRs) for a 37.5% ORR (defined in study objectives) in patients treated in the second- and third-line settings (64% ORR of patients treated in the second-line setting)
- Adverse event profile similar to Phase 1 studies

### Combination Safety Summary

| | n (%) |
|---|---|
| Any Treatment Emergent AE (TEAE) | 24 (100) |
| CTX-009 Related AE | 24 (100) |
| Serious AE | 11 (45.8) |
| AE Leading to Discontinuation | 6 (25.0) |

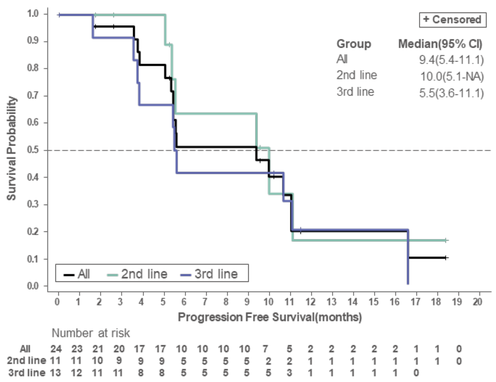
**TEAEs in Greater Than 10% of Patients**

| TEAEs | n (%)* | |
|---|---|---|
| | Any Grade | Grade≥3 |
| Neutrophil count decreased | 22 (91.7) | 20 (83.3) |
| Hypertension | 12 (50.0) | 4 (16.7) |
| Platelet count decreased | 9 (37.5) | 3 (12.5) |
| Anaemia | 5 (20.8) | 5 (20.8) |
| Ascites | 4 (16.7) | 2 (8.3) |
| Decreased appetite | 4 (16.7) | 2 (8.3) |

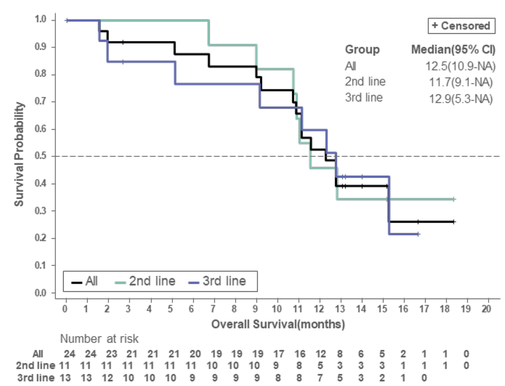
**AEs of Special Interest in Any Patients**

| AESI | n (%)* | |
|---|---|---|
| | Any Grade | Grade≥3 |
| Haemoptysis or haemorrhage | 10 (41.7) | 3 (12.5) |
| Pulmonary hypertension | 4 (16.7) | 0 (0) |
| Gastrointestinal or tumor perforation | 2 (8.3) | 2 (8.3) |

**Phase 2: Median PFS 9.4 months (5.4-11.1)**




**Phase 2: Median OS 12.5 months (12.5-NA)**




## Methods

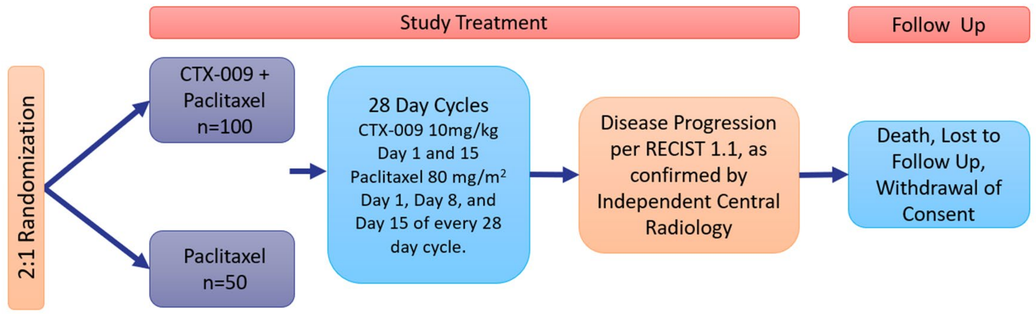
### Study Rationale

- Presently, there is no consensus second-line therapy for patients with BTC in whom first-line therapy has failed.
- Combination chemotherapy regimens have demonstrated limited efficacy in patients with BTC in the second-line setting,[5] The recommended regimen by NCCN guideline, FOLFOX, demonstrated 5% ORR in the second and third line settings. There is anecdotal data suggesting that taxanes have activity in patients with BTC. Recently, in the SWOG 1815 study, nab-paclitaxel was beneficial when it was added to front line gemicitabine and cisplatin regimen.[6]
- Phase 1b and Phase 2 data of CTX-009 in combination with paclitaxel showed compelling activity in patients with advanced BTC treated in the second and third line setting.
- In this study we will assess the relative contribution of CTX-009 with paclitaxel versus paclitaxel alone

### Phase 2/3 Study Design

- CTX-009 is being evaluated in an **open-label, randomized, controlled study** in patients with previously treated, advanced or metastatic BTC
- 150 patients will be randomized in a 2:1 ratio to receive either CTX-009 plus paclitaxel or paclitaxel alone
- The study will open at approximately 30 sites across the United States, additional countries may be added
- Patients will be stratified by:
  - **Stage:** Locally advanced vs. Metastatic
  - **Anatomic subsite of primary tumor:** intrahepatic cholangiocarcinoma vs. other (extrahepatic cholangiocarcinoma, gallbladder, or ampullary)
  - **Eastern Cooperative Oncology Group (ECOG):** Performance status (0 vs. 1)

### Study Schema




### Key Eligibility Criteria

**Inclusion Criteria**

- ✓ Unresectable advanced, metastatic, or recurrent BTC (all four subtypes allowed)
- ✓ Radiologically documented progression after prior gemcitabine and platinum containing chemotherapy regimen
- ✓ ECOG performance status 0-1
- ✓ Predicted lift expectancy of at least 12 weeks
- ✓ No evidence of ongoing infection and adequate biliary excretion
- ✓ Adequate bone marrow, hepatic, and renal function

**Exclusion Criteria**

- × Eligible to be treated with a molecularly targeted therapy after 1st line
- × Adequate wash-out period from prior regimen
- × Specific cardiovascular history including uncontrolled hypertension
- × Infection requiring systemic antibiotics or antiviral drugs, etc. or other severe or uncontrolled illnesses

Additional I/E criteria as defined in the latest version of the study protocol

### Study Drug Dosing

| Drug | Cycle Administration | Starting Dose |
|---|---|---|
| CTX-009 | D1 and D15 of each 28-day cycle | 10.0 mg/kg |
| Paclitaxel | D1, D8 and D15 of each 28-day cycle | 80 mg/m$^2$ |

- Dose adjustments are permitted and required for specific adverse events, as detailed in the protocol.
- Treatment will continue until confirmed PD, unacceptable toxicity, withdrawal of consent, or other protocol-defined end of treatment criteria.

### Study Objectives

| Primary Objective | Primary Endpoint |
|---|---|
| To assess the efficacy of CTX-009 in combination with paclitaxel vs. paclitaxel alone in patients with biliary tract cancers (BTC) who have received one systemic therapy for advanced disease, as measured by Overall Response Rate (ORR) assessed by an Independent Central Radiology (ICR) review | Percentage of patients whose Best Overall Response (BOR) is assessed as Complete Response (CR), or Partial Response (PR) as assessed by RECIST 1.1 |

Secondary Objectives and Endpoints include **Disease Control Rate**, **Duration of Response**, **Progression Free Survival**, **Overall Survival**, **Safety**, **Quality of Life**, and **Exposure Response** through PK Analysis

## Study Information

**Protocol Number:** CTX-009-002

**Status:** Active, recruiting

**ClinicalTrials.gov Identifier:** NCTC05506943

**Contact:** CTX-009-002@compasstherapeutics.com

## References

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5.Lamarca A, Palmer DH, Wasan HS, Ross PJ, Ma YT, et al; Advanced Biliary Cancer Working Group. Second-line FOLFOX chemotherapy versus active symptom control for advanced biliary tract cancer (ABC-06): a phase 3, open-label, randomised, controlled trial. Lancet Oncol. 2021 May;22(5):690-701. doi: 10.1016/S1470-2045(21)00027-9. Epub 2021 Mar 30. PMID: 33798493; PMCID: PMC8082275.
6.Unseld M, Scheithauer W, Weigl R, Kornek G, Stranzl N, et al. Nab-paclitaxel as alternative treatment regimen in advanced cholangiocellular carcinoma. J Gastrointest Oncol. 2016;7(4):588-594. doi:10.21037/jgo.2016.05.01.