Chemo-Immunotherapy combination of mFOLFOX6, bevacizumab and atezolizumab after first line therapy for advanced biliary tract cancer – the COMBATBIL (ESS-2) imCORE trial

Translational

Lungs

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ABSTRACT

Background

The standard first-line treatment for advanced biliary tract cancer (BTC) involves GemCis and PD1/PDL1 inhibitors, supported by TOPAZ-1 and KEYNOTE-966 trials. Second-line therapy typically involves mFOLFOX6, backed by the ABC-06 trial's 6.2 month survival advantage over the control arm's 5.3 months. Our phase 1b/2 study, COMBATBIL (EudraCT 2018-000257-45), explores the efficacy of mFOLFOX6, bevacizumab and atezolizumab in patients PD1/PDL1 naive who have progressed after first-line therapy.

Methods

Eligible patients with unresectable/metastatic disease and ≥ 1 prior therapy, measurable disease per RECIST v1.1, and ECOG ≤ 1 received mFOLFOX (standard doses), atezolizumab 840 mg and bevacizumab 10 mg/kg IV biweekly until disease progression, unacceptable toxicity, or voluntary withdrawal. Primary endpoint: overall response rate (ORR) by RECIST v1.1. Secondary endpoints included disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), ORR by independent radiological review, overall survival (OS), and safety assessed by NCI CTCAE v5.0. Exploratory analyses include tumor biopsies (genomic alterations, biomarker expression), blood samples (immuno-phenotyping), and fecal samples (microbiome analysis).

Results

Recruitment completed between 22 October 2021 and 04 September 2023 with 36 patients (efficacy-evaluable population) and we present here the final data analysis done on June 16, 2025. 17 patients (47.2%) were female and 36 (100%) Caucasian. BTC subtypes were 20 (55.6%) ICC, 4 (11.1%) PCC, 5 (13.8%) DCC and 7 (19.4%) GBC. Median follow-up was 26.4 (95% CI: 20.7 – not reached) months. All 36 pts (100%) had ≥ 1 prior line of therapy, 5 patients had > 1 prior line of therapy and 3 patients (8.3%) had previous targeted therapy (1 ivosidenib and 2 pemigatinib respectively). Median age was 61 (range 30-78), with 18 male and 17 female participants. The ORR was 30.6% (95% CI:16.4 −48.1) (1 CR, 10 PR, 23 SD out of 35 pts). DCR was 75.0% (95% CI: 57.8 – 87.9) at week 12 and 66.7% (95% CI: 49.0 – 81.4) at week 18. Median DOR was 6.9 mo (95%CI 2.8-9.4). Median PFS was 9.2 months (95% CI: 7.8– 12.4) and median OS was 14.7 months (95% CI: 12.4 − 29.3) . No new safety signals were observed. Adverse events of special interest (AESI) observed in 8% of patients (3/35), one grade ≥3. 24.3% experienced AE leading to study drug discontinuation . Translational studies are ongoing and will be presented at the meeting.

Conclusions

mFOLFOX6, bevacizumab and atezolizumab showed a clinically meaningful ORR of 30% and a relevant improvement in OS in advanced BTC patients who progressed after 1st line therapy compared to the ABC-06 trial. Further randomized data is needed to confirm these promising findings and corroborate the use of this combination in clinical practice.

SCIENTIFIC IMPACT

For advanced biliary tract cancer (BTC), TOPAZ-1 and KEYNOTE-966 established PD-1/PD-L1 inhibitor plus GemCis as first-line standard, while ABC-06 supports mFOLFOX6 as second-line with modest OS gain (6.2 vs. 5.3 mo). The COMBATBIL trial demonstrates that adding bevacizumab and atezolizumab to mFOLFOX6 yields a notable ORR of 30.6%, median PFS of 9.2 mo, and OS of 14.7 mo in PD-1/PD-L1-naïve patients post-GemCis — outcomes exceeding historical ABC-06 benchmarks. This suggests synergistic benefit from combined cytotoxic, anti-angiogenic, and immunotherapeutic strategies in BTC, addressing the urgent need for more effective second-line options. Randomized confirmation could shift the post-GemCis treatment paradigm and inform biomarker-driven patient selection.