PD-8 Outcomes by disease status in patients with advanced biliary tract cancer treated with durvalumab or placebo plus gemcitabine and cisplatin in the phase 3 TOPAZ-1 study

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Background: TOPAZ-1 (NCT03875235) was a randomised, double-blind, global, phase 3 study evaluating the efficacy and safety of durvalumab plus gemcitabine and cisplatin (durvalumab) as first-line treatment for patients with advanced biliary tract cancer (BTC; Oh D-Y, et al. J Clin Oncol 2022;40[suppl 4]. Abs 378). Durvalumab significantly improved overall survival (OS) versus placebo plus gemcitabine and cisplatin (placebo) and represents a potential new treatment option for patients with advanced BTC. In BTC, disease status at baseline (initially unresectable vs recurrent [>6 months after surgery with curative intent or >6 months after adjuvant therapy]) may impact response to treatment.

Methods: The aim of this exploratory subgroup analysis of TOPAZ-1 was to assess efficacy outcomes by disease status at baseline in patients receiving durvalumab versus placebo. Patients with BTC were randomised 1:1 to receive durvalumab (1500 mg) or placebo on Day 1 Q3W, plus gemcitabine (1000 mg/m^2) and cisplatin (25 mg/m^2) on Day 1 and 8 Q3W, for up to 8 cycles, followed by durvalumab or placebo monotherapy until disease progression, unacceptable toxicity or other discontinuation criteria were met. Randomisation was stratified by disease status and primary tumour location (intrahepatic cholangiocarcinoma vs extrahepatic cholangiocarcinoma vs gallbladder cancer). Subgroup analysis of OS, progression-free survival (PFS), objective response rate (ORR) and duration of response (DoR) per RECIST v1.1 by disease status at baseline (initially unresectable or recurrent) was performed. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated for OS and PFS using a Cox proportional hazards model, and odds ratios (ORs) and 95% CIs for ORR were calculated using the Cochran-Mantel Haenszel test.

Results: The study included more patients with initially unresectable than recurrent disease (durvalumab, n=274 [80.4%] vs n=67 [19.6%]; placebo, n=279 [81.1%] vs n=64 [18.6%]). HRs for OS favoured durvalumab for both initially unresectable (0.84; 95% CI, 0.69−1.03) and recurrent (0.56; 95% CI, 0.32−0.96) disease; HRs for PFS also favoured durvalumab in both subgroups (0.79; 95% CI 0.66−0.95 and 0.63; 95% CI 0.42−0.94, respectively). ORs for ORR favoured durvalumab for both initially unresectable (1.61; 95% CI, 1.06−2.45) and recurrent (1.52; 95% CI 0.73−3.18) disease. Median DoR for durvalumab versus placebo was 6.0 versus 5.1 months for initially unresectable, and 9.7 versus 7.9 months for recurrent disease. Percentage of responders with a DoR of at least 9 and 12 months was numerically higher with durvalumab versus placebo for both initially unresectable (9-month, 21.5% vs 20.3%; 12-month, 16.7% vs 10.7%) and recurrent (9 months, 58.8% vs 38.1%; 12 months, 48.1% vs 25.4%) disease.

Conclusions: In TOPAZ-1, addition of durvalumab to GemCis improved efficacy outcomes both in patients with initially unresectable and patients with recurrent disease at baseline, though the relative benefit versus placebo appears greater for recurrent compared with initially unresectable disease. These findings support the use of durvalumab plus GemCis as a potential new treatment option for patients with advanced BTC, irrespective of disease status.

Clinical trial identification: NCT03875235.

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PD-9 Three-arm phase II/III randomized controlled trial in patients with unresectable/metastatic gall bladder cancer with poor performance status: Erlotinib or capecitabine v/s best supportive care

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Background: Currently there is no standard of care for Eastern Cooperative Oncology Group (ECOG) poor performance status (PS) patients (PS-III) with unresectable/metastatic Gall Bladder Cancer (GBC). Being unfit for chemotherapy, these patients receive only best supportive care (BSC) resulting in a very dismal outcome. A report published from M.D. Anderson Cancer Centre stated median overall survival (OS) of only one month in patients with poor PS with GBC.

Methods: This single centre, prospective randomized controlled phase II/III, open label trial was done at a tertiary health care centre in India. Patients (above 18 years) with histologically confirmed unresectable/ metastatic GBC with adequate organ function and ECOG PS-III were included. Patients with prior adjuvant chemotherapy/ erlotinib/capecitabine in last 6 months, active malignancy other than GBC, lactating and pregnant women, and HIV-positive status were excluded. Random allocation (1:1:1) was done to one of the three arms - Erlotinib (150 mg OD) + BSC, Capecitabine + BSC or BSC alone using computer-generated sequence. The primary end point was median OS, defined as time from randomisation to death, in the intention-to-treat population. A sample size of 105 was estimated, assuming median OS in BSC, Erlotinib+BSC and Capecitabine+BSC as 2, 4 and 5 months respectively (taking two-sided alpha error as 0.05 and power as 80%).

Results: Between Dec 27, 2017 and January 18, 2021, 201 patients were screened, of which 105 were randomized to Erlotinib +BSC (n = 36), Capecitabine +BSC (n = 36) or BSC alone arm (n = 33). After a median follow up of 10 months (IQR 3.9- 11.5), there were 82 deaths in the whole cohort. The median OS in Erlotinib arm was significantly higher at 3.84 months (2.33- 4.67) compared to 1.77 months (1.18- 2.73) in BSC only arm, with hazard ratio (HR) of 0.50 (95% CI - 0.26 -0.95), p = 0.02. However, there was no statistically significant difference observed in survival between Capecitabine +BSC over BSC alone - median OS 2.46 months (1.67-3.58), HR - 0.70 (95% CI - 0.38-1.2), p = 0.30. Compared to only 15.1% (5/33) in BSC arm, the disease control rate (complete response + partial response + stable disease) at 6-8 weeks was 58.3% (21/36) in Erlotinib arm (p = 0.004) and 47.2% (17/36) in Capecitabine arm (p = 0.04). Grade III/IV toxicities were reported in 12 patients (33.3%) in Erlotinib arm (skin rash and diarrhea being most common at 8% each) and in 5 patients (13.8%) in Capecitabine arm (anemia and fatigue most common at 6 % each). No treatment related deaths were reported in either group.

Conclusions: Addition of Erlotinib to BSC significantly improves OS in patients with unresectable/metastatic GBC, otherwise unfit to receive chemotherapy, with acceptable toxicity profile.

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PD-10 Comprehensive circulating tumor (ct) DNA NGS for molecular profiling in advanced cholangiocarcinoma

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Background: Cholangiocarcinoma (CCA) is a rare and heterogeneous cancer with dismal prognosis. At the molecular level, CCA is highly heterogeneous, with multiple druggable alterations some of them with already targeted therapies approved. Accordingly, ESMO has recently recommended NGS tissue testing in routine clinical practice for patients with advanced CCA. However, access to tumor biopsy for CCA is technically difficult in a subset of patients. Sequencing of circulating tumor (ct) DNA (liquid biopsy) is a potential alternative to tissue molecular testing, that overcomes