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

intratumoral heterogeneity with a minimal invasive approach and easy access. We aimed at assessing the feasibility and clinical utility of ctDNA genotyping for patients with advanced CCA in a group of referral Oncology centers across Spain.

Methods: We genotyped ctDNA from blood samples from patients with advanced CCA, treated between 2019 and 2021 at 9 Spanish University Hospitals. ctDNA sequencing was performed by an NGS-based comprehensive approach using Guardant360™ (G360).

Results: ctDNA sequencing data were available for 112 patients. The main clinical characteristics were as follow: median age was 62.5 years (range: 28-86), 62 patients (55.3%) were men, 65 patients (58%) had intrahepatic cholangiocarcinoma, 70 patients (62.5%) had stage IV disease at diagnosis and 98 patients (87.5%) had received cisplatin plus gemcitabine as first-line treatment for advanced disease. Determination of ctDNA was performed at baseline in 36.6% of patients and at the time of progression to first-line treatment in 48 patients (42.8%). 96% of patients had $\geq$ 1genomic alteration detected. Median number of alterations per patient was 2 and median VAF was 0.5%. 245 genomic alterations (GAs) have been identified among 35 different genes. 89% of GAs identified were SNVs, being the most frequent TP53 (33.9%), KRAS (9.8%), IDH1 (6.5%), ATM (6.5%), PIK3CA (4.9%) and ARID1A (4.5%). CNVs accounted for 7.7% of GA and consisted in amplifications of: EGFR (1.6%), MYC (1.6%), BRAF (1.2%) and ERBB2 (0.8%). FGFR2 and FGFR3 fusions were identified in 1.2% and 0.4% patients, respectively. High-microsatellite instability was identified in 1.2% of patients. These findings are similar to previously reported data on tissue molecular profiling in CCA. Importantly, sixty-seven patients (53%) had GA considered as actionable, including three patients with FGFR2 fusions, for which Pemigatinib is approved.

Conclusions: ctDNA genotyping for molecular profiling of advanced cholangiocarcinoma patients is feasible and a non-invasive procedure, especially relevant for CCA patients in which increase in actionable biomarkers and insufficient tissue availability is becoming a challenge.

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PD-11 In depth analysis of label-free infrared (IR) imaging-based microsatellite instability (MSI) classification in early colon cancer (CC) on samples from the AIO ColoPredictPlus 2.0 (CPP) registry trial

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Background: MSI occurs in 15-20% of all early CC due to a deficient mismatch repair system and testing is now considered standard for all colon cancers as MSI is of prognostic and predictive value. Presently, protein analysis using immunohistochemistry targeting the mismatch repair proteins is most frequently used in routine clinical pathology with high sensitivity. Alternatively, fragment length analysis of microsatellite loci or next-generation sequencing can be used. All the techniques referred to are time and tissue consuming. We utilize label-free quantum cascade laser (QCL) based IR imaging combined with artificial intelligence (AI) approaches to test unstained tissue samples for MSI. IR imaging is an emerging microscopic technique based on the interaction of electromagnetic waves with the molecules within the tissue creating molecular fingerprints. To establish the methodological robustness of our approach, we analyzed samples from the multicentric prospective AIO ColoPredict Plus (CPP) 2.0 registry trial.

Methods: IR imaging can analyze unstained paraffin-embedded tissue slides within an average of 30 min/slide. All tissue samples were obtained from the CPP registry trial. For development of the MSI/MSS classification model the cohort was split into a training, test, and validation set. The training set was utilized for the optimization of a modified VGG-16 convolutional neural network (CNN) with area under receiver operating characteristic (AUROC) and area under precision recall curve (AUPRC) evaluated on the test set as endpoints. The final classification model is validated on the validation set and in depth analyzed for sub-cohorts (BRAF, KRAS, UICC stage, grading).

Results: A cohort of 547 patients (training n=331 (43% MSI), test n=69 (43% MSI), validation n=147 (18% MSI)) was selected from CPP. Baseline characteristics including BRAF mutations, were balanced between training and test set, thus providing a balanced ground-truth for the training of the classifier. By contrast, the validation set (18% MSI) corresponds to the natural occurrence of MSI, showing a typically pattern for MSI and MSS with a higher proportion of female patients, more right-sided cases and more BRAF mutations for MSI-samples. The selected MSI/MSS classifier reached a validation AUROC of 0.90 (sensitivity 85%, specificity 84%) and AUPRC of 0.74. The AUROC of the sub-cohorts range between 0.78 and 0.99 (BRAF: 0.93 (wt), 0.78 (mt); KRAS: 0.84 (wt), 0.99 (mt); Grading: 0.93 (G2), 0.84 (G3); UICC Staging: 0.93 (II), 0.86 (III)).

Conclusions: AI integrated IR imaging demonstrates a reliable classification performance for MSI/MSS with an AUROC of 0.90 (sensitivity 85%, specificity 84%) and robustness over sub-cohorts e.g., BRAF, KRAS, or staging. It further approaches the performance of the present gold standard immunohistochemistry. The combination of spatial and biochemical information encoded in the IR images allows CNNs to track changes on the molecular level. Additionally, this method requires fewer samples than other AI approaches and maintains intact tissue for further molecular analysis. Overall, this method has the potential to become an applicable diagnostic tool beyond the scope of known biomarkers for tumor-agnostic assessments.

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PD-12 Characterization of best responder patients to oxaliplatin rechallenge in patients with refractory metastatic colorectal cancer (mCRC)

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Background: Oxaliplatin in combination with fluoropyrimidines constitute one of the most effective treatments in front-line mCRC patients. Rechallenge with oxaliplatin-based regimens in the refractory setting is practiced although based on scarce and heterogeneous evidence. Further clinical and molecular data to determine which patients do benefit from this treatment strategy are needed.

Methods: We analyzed all patients treated with oxaliplatin in a third- or fourth-line setting in our institution between 2015 and 2021. Outcomes were analyzed with overall response rate (ORR), disease control rate (DCR) and median progression free survival (mPFS). The best-responders group was defined-as those patients who achieved mPFS $>$ 6 months. As part of the descriptive analysis, we divided patients into three clinical groups according to the prognostic characteristics previously reported: Good Prognostic Characteristics (GPC) defined as having passed $\geq$18 months since metastatic disease debut, $<$ 3 metastatic sites and presence of liver metastasis, Best Prognostic Characteristics (BPC) defined as $\geq$18 months since metastatic disease debut, $<$ 3 metastatic sites and absence of liver metastases and Poor Prognostic Characteristics (PPC) defined as $<$ 18 months since metastatic disease debut and/or with $\geq$3 metastatic sites. An Amplicon-seq panel was used to analyze regions of interest in 61 genes using an Illumina sequencing platform.