P-77 A phase II study of multiple kinase inhibitor, TT-00420, in advanced, refractory cholangiocarcinoma

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Background: Fibroblast growth factor (FGFR) alterations occur in 10-15% adult patients with advanced cholangiocarcinoma (CCA). Pemigatinib and Infigratinib, the first generation FGFR1-3 kinase inhibitors approved for the treatment of the advanced CCA with FGFR2 gene fusions or other rearrangements, are associated with a median progression-free survival of about 6 months after progression on first-line chemotherapy and acquired resistance is common. A novel spectrum-selective multi-kinase inhibitor, TT-00420, has shown clinical responses in multiple CCA patients bearing the gate-keeper mutations acquired from previous FGFR inhibitor treatment(s) in prior phase I study (NCT03654547). TT-00420, inhibits receptor tyrosine kinases (FGFRs and VEGFRs), aurora kinases A/B and janus kinases (JAK), targets cell proliferation, angiogenesis, and immune-oncology pathways, and effectively inhibits the tumor growth in the CCA PDX models bearing the FGFR2 gate-keeper mutations.

Trial design: TT420C1206 is an open-label, multicenter, phase II study of TT-00420 monotherapy, orally administered once daily in the 28-day cycle, in the adult patients with advanced/metastatic and surgically unresectable CCA exhausting standard treatment options. Per baseline FGFR alteration status, patients will be enrolled into four cohorts, which consist of patients bearing FGFR2 fusion(s) who progressed on previous FGFR2 inhibitor(s) (A1 cohort) or patients who responded to previous FGFR2 inhibitor(s) (A2 cohort), patients bearing other FGFR alteration(s) (B cohort), or patients without detectable FGFR alteration (C cohort). Eligible patients, $\geq$18 years old, must have measurable target lesion(s) at baseline and ECOG status of 0 or 1. Primary endpoint-overall response rate (ORR), along with other efficacy endpoints, will be evaluated. Safety, PK parameters, and biomarker profile, will be evaluated and reviewed jointly with the efficacy outcomes. In each cohort, Fleming's two-stage design is adopted to guide the enrollment from Stage I to Stage II. Adverse events (AEs) will be grade per CTCAE version 5.0 and response will be assessed per RECIST version 1.1 criteria. Approximately a total of 80 patients will be enrolled and treated in the study. Study enrollment in all four cohorts is currently ongoing.

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P-78 A phase II study of resection followed by capecitabine plus oxaliplatin for liver metastasis of colorectal cancer (REX study): Final analysis

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Background: Surgical resection has been accepted as the standard therapy for colorectal cancer liver metastases (CRLM), however, high recurrence incidence even after curative resection remains an unsolved problem. Although both mFOLFOX6 (modified infusional fluorouracil, leucovorin, and oxaliplatin) and CapeOx (Capecitabine plus oxaliplatin) are standard therapies for stage III colorectal cancer as adjuvant setting, there was no established adjuvant chemotherapy for CRLM. mFOLFOX6 conferred disease free survival (DFS) but not overall survival (OS) benefit in JCOG 0603 (Kanemitsu Y, et al. J Clin Oncol. 2021 Dec 1;39(34):3789-3799). There were few prospective studies existed that the efficacy and toxicity of CapeOx as adjuvant setting in patients undergoing radical resection for their CRLMs. So we conducted this phase II trial to evaluate the safety and efficacy of adjuvant CapeOx for CRLM in 2013. We previously reported safety analysis in ESMO-GI 2019 (Watanabe T, et al.); here we present the survival analysis.

Methods: Patients with undergoing curative resection of CRLM were eligible for this study. Capecitabine 1,000mg/m2 was given orally twice daily for 14 days followed by a 7-days rest; oxaliplatin 130mg/m2 on day1 was given by intravenous infusion. CapeOx were performed up to 8 cycles. The primary endpoint was 3-year relapse-free survival (RFS), while secondary endpoints were overall survival (OS), relative dose intensity and safety. We calculated a sample size at 50 patients based on the threshold and expected 3-year RFS were 30% and 45%, respectively, with a one-sided alpha error of 0.05 and power of 0.80.

Results: This study was closed prematurely due to poor accrual. In total, 27 patients were enrolled from 9 institutions between September 2014 and January 2019. As two patients who did not start protocol treatment because of condition worsening were excluded from this analysis, 25 patients were evaluated. Median age was 64, male/female; 15/10, ECOG PS 0/1; 24/1, sidedness right/left; 8/17, tub1/tub2; 12/13, number of metastases 1～3/ 4～; 17/8, Hr0/ HrS/ Hr1/ Hr2/ Hr3; 8/5/7/4/1. The completion rate of protocol treatment was 64%. Relative dose intensity of capecitabine and oxaliplatin were 86.0% and 82.2%, respectively. The reasons for discontinuation were adverse events (28%) and recurrence of cancer (8%). The most frequently reported grade 3-4 adverse events were neutropenia (20%), sensory neuropathy (12%) and leucopenia (8%). One treatment related death was observed because of disseminated intravascular coagulation. With a median follow-up of 50.5 months as of the data cutoff date of January 31, 2022, 3-year RFS was 52% (95% CI 31.2 - 69.2), median RFS was 36.6 months (95% CI 16.1-NA). Only six patients were dead during this study, so overall survival was not reached.

Conclusions: Our data suggested that adjuvant chemotherapy with CapeOx was feasible and tolerable in patients with undergoing curative resection of CRLMs.

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