P-69 Intensive follow-up program and oncological outcomes of 278 biliary tract cancer patients after curative intent surgery: A single-center retrospective experience

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Background: Biliary tract cancer (BTC) encompasses a group of rare and heterogeneous malignancies with poor prognosis, including gallbladder cancer, ampulla of Vater cancer, intrahepatic cholangiocarcinoma (iCCA), and extrahepatic cholangiocarcinoma (eCCA), with the latter further subdivided into perihilar (pCCA) and distal (dCCA). Unfortunately, potentially curative surgical resection is possible in approximately the 25% of BTC patients at diagnosis, and even following radical surgery, relapse rates remain high. The aim of this research was to evaluate the impact of an intensive follow-up program in BTC patients who had received surgical resection with curative intent at a tertiary referral hospital.

Methods: Medical records of all consecutive BTC patients treated with curative intent surgery at S. Orsola Malpighi Hospital, Bologna, Italy, from January 2000 to November 2020, were retrospectively reviewed. The BTC-specific overall survival (OS) and disease-free survival (DFS) status were determined by the Kaplan-Meier method; univariate and multivariate analysis were performed to assess the impact of covariates on survival.

Results: A total of 398 BTC patients receiving surgery with curative intent were included in the analysis. Macroscopic residual tumor was observed in 29 patients, while 329 BTCs underwent R0 (n=222; 67%) or R1 (n=107; 33%) surgery. Among these, 278 patients started a follow-up program at our institution based on physical examination, serum CEA and CA19-9 and abdominal/chest CT scan every 3-4 months in the first two years and every 6 months from the third to the fifth year; 80% of this group (222/278) started follow-up after adjuvant chemotherapy (in case of R0 surgery) or chemoradiotherapy (in R1 resection). The median age of the follow-up group was 63 years (range 31-85 years) and 164 (49.5%) were females. Overall, 116 (32.5%) and 126 (38.6%) patients had iCCA and eCCA (78 pCCAs and 48 dCCAs), respectively. At a median follow-up of 37.4 months, median OS was 50.8 and 35 months in R0 and R1 patients, respectively (p=0.04); similarly, median DFS was 16.4 and 12.3 months in the same groups (p=0.02). No relapse was observed in 129 out of 329 BTCs (39%), while the 61% of R0/R1 patients (200/329) experienced disease relapse, including 39% of iCCA and 38% of eCCA; liver was the most frequent site of relapse (78%) followed by peritoneum and locoregional lymph nodes. In terms of treatment at the relapse, 15% (30/200) of patients underwent second surgery (R0=14, R1=6, R2=3, exploratory laparotomy=7) while 20% (40/200) received a locoregional approach, the most frequent of which was radiofrequency ablation (n=22). None of the 14 BTC patients receiving second surgery with R0 experienced disease relapse. Overall, 127 BTCs received first-line chemotherapy following relapse, with gemcitabine-cisplatin as the most commonly used regimen (52%).

Conclusions: Based on the results of our 20-year, single-center experience of 278 BTC patients, an intensive follow-up after surgical resection with curative intent could help in the identification of disease relapse, leading to early treatment and prolonged survival in selected cases, as reported in BTCs treated with second surgical resection with negative margins.

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P-70 First-in-human study of highly selective FGFR2 inhibitor, RLY-4008, in patients with intrahepatic cholangiocarcinoma and other advanced solid tumors

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Background: Oncogenic activation of FGFR2 via genomic rearrangement, gene amplification, or point mutation in advanced solid tumors provides the opportunity for rapid clinical development of highly selective FGFR2 inhibitors using a precision oncology approach to deliver clinical benefit to genomically-defined patient (pt) populations. Unfortunately, this opportunity remains largely unrealized as current, non-selective, small molecule inhibitors (pan-FGFRi) suffer from off-isoform toxicity (FGFR1-hyperphosphatemia; FGFR4-diarrhea) and on-target acquired resistance leading to only modest efficacy primarily limited to FGFR2-fusion+ intrahepatic cholangiocarcinoma (ICC). RLY-4008 is a novel, oral FGFR2 inhibitor designed to overcome the limitations of pan-FGFRi by potently and selectively targeting primary oncogenic FGFR2 alterations and acquired resistance mutations. We initiated a first-in-human (FIH) precision oncology study of RLY-4008 in advanced solid tumor pts with FGFR2 alterations with primary objectives to define the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D) and adverse event (AE) profile of RLY-4008; key secondary objectives are to assess FGFR2 genotype in blood and tumor tissue, pharmacokinetics (PK), and anti-tumor activity. Given the approval of pan-FGFRi and the emerging importance of acquired resistance to pan-FGFRi, key exploratory objectives are measures of RLY-4008 anti-tumor activity with prior treatment (pan-FGFRi versus pan-FGFRi naïve) and baseline mutational status.

Trial design: This is a global, multi-center, FIH dose-escalation/expansion study of RLY-4008 (NCT04526106) in adult pts who have unresectable or metastatic solid tumors with FGFR2 alteration per local assessment, ECOG performance status 0-2, measurable or evaluable disease per RECIST 1.1, and who are refractory, intolerant, or declined standard therapy including pan-FGFRi. FGFR2 alteration will be confirmed retrospectively by central laboratory assessment. For the dose escalation (N ~ 50), RLY-4008 is administered QD/BID on a continuous schedule with 4-week cycles according to a Bayesian Optimal Interval design that allows accelerated dose titration, additional accrual to dose levels declared tolerable, and exploration of alternative schedules if warranted. The MTD is determined via logistic regression of the dose limiting toxicity rate across all dose levels and an RP2D less than the MTD may be considered based on observed AEs, PK, and anti-tumor activity. Following dose escalation, the dose expansion (N ~ 75) will treat pts with RLY-4008 at the MTD/RP2D and includes 5 groups with any prior therapy (except group 2): 1. FGFR2 fusion+ ICC pts; 2. FGFR2 fusion+ ICC pts with no prior FGFRi; 3. FGFR2 fusion+ pts with other solid tumors; 4. FGFR2-mutation+ solid tumor pts and 5. FGFR2-amplified solid tumor pts. The primary endpoints are MTD/RP2D and AE profile; key secondary endpoints are FGFR2 genotype in blood and tumor tissue, PK parameters, overall response rate (ORR), and duration of response (DOR) per RECIST 1.1; and correlations between ORR and DOR per RECIST 1.1 with prior pan-FGFRi treatment and baseline mutational status. US enrollment began SEP2020 and Europe/Asia enrollment is planned for 2H 2021.

Clinical trial identification: RLY-4008-101; NCT04526106.

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