Comprehensive clinico-molecular profile and efficacy of anti-HER2 therapy for *HER2*-amplified biliary tract cancer.

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Background: Biliary tract cancer (BTC) is an aggressive malignancy with poor prognosis and limited treatment options. The prevalence of *HER2* amplification in BTC has been reported to be 5-20%, and clinical trials suggested the clinical benefit of HER2-targeted treatment in this disease subpopulation. In a global collaboration, we investigated the comprehensive clinico-molecular characterization as well as the efficacy of anti-HER2 therapy in *HER2*-amplified BTC. **Methods:** Patients with advanced BTC who received systemic therapy were included from the GOZILA and MONSTAR studies in Japan and from the COLOMATE trial in the US. Genomic alterations were detected by tissue next-generation sequencing (NGS), including FoundationOne CDx and TempuslxT, and plasma circulating tumor DNA NGS including Guardant360 and FoundationOne Liquid CDx. The clinico-molecular characteristics were evaluated in an exploratory cohort comprised of patients from Japan, whereas the efficacy of anti-HER2 therapy was assessed in a biomarker selected cohort with patients from both Japan and the US. **Results:** Of 439 patients included in the exploratory cohort, 43 (10%) had *HER2* amplification. BTC with primary tumor location in the gallbladder accounted for 58% of primary sites of patients with *HER2* amplification. *TP53* mutation (84% vs 61%, p=0.003) and *BRAF* amplification (9% vs 2%, p=0.030) were significantly more frequent in patients with *HER2* amplification compared to those without, and no *KRAS* mutation co-occurred with *HER2* amplification. There was no significant difference in overall survival (OS) between patients with and without *HER2* amplification (17.7 months [M] vs 16.9 M, hazard ratio [HR] 0.95, 95% confidence interval [CI] 0.65-1.40, p=0.799). Of 58 patients with *HER2*-amplified BTC included in the biomarker selected cohort (43 Japan, 15 US), 27 (47%) received anti-HER2 therapy. The median OS of patients treated with anti-HER2 therapy was significantly longer than that of patients who did not receive anti-HER2 therapy (24.3 M vs. 12.1 M, HR 0.43, 95% CI 0.23-0.82, p=0.011). Multivariate analysis also identified anti-HER2 therapy as an independent prognostic factor for OS (HR 0.42, 95% CI 0.20-0.85, p=0.015). **Conclusions:** *HER2* amplifications were found in 10% of advanced BTC and did not represent an independent predictive factor for OS. Of clinical significance, patients with *HER2*-amplified BTC derive a significant benefit from anti-HER2 therapy. Research Sponsor: SCRUM-Japan Funds.