Introduction: Gemcitabine (Gem) and oxaliplatin (Ox) based chemotherapy represent a relevant therapeutic option in BTC given the promising activity and favorable tolerability of m– GEMOX. Combining the potential benefits of targeting VEGF and the Ras/Raf pathway with chemotherapy could be a good therapeutic strategy in BTC patients. We propose a two-step program to evaluate the feasibility (Phase Ib) and the efficacy (Phase II) of the combination of regorafenib (Reg) with m-GEMOX in advanced BTC. BREGO is a multicenter phase Ib, followed by a phase II, randomized trial. Primary objective of the phase Ib is to determine the dose of Reg in combination with a fixed-dose of mGEMOX. The phase II part of the study will assess the efficacy of m-GEMOX with or without Reg. Ancillary studies are also planned focusing on early tumor evaluation by FDG-PET-scan and on K-Ras mutational status using circulating-DNA analysis.

Methods: Three daily dose-levels of oral Reg are planned (80mg, 120mg and 160mg) from day 1 to day 14, with fixed doses of Gem and Ox (900 mg/m² of Gem over 30 minutes IV followed by 80 mg/m² of Ox over 120 minutes IV) on day 1 and 8 followed by 2 weeks rest (Figure 1). Three to six patients by dose-level are planned and the recommended dose will be confirmed in an extension cohort of six patients. The phase II randomized trial will assess the safety and efficacy of m-GEMOX plus Reg versus m-GEMOX alone. The stratification (1:2) of the 63 planned-patients will be made according to center and tumor localization (intra- versus extra-hepatic) (Figure 2). Since September 2014, three patients have been included and treated at the first level (80 mg of Reg). The phase Ib will be followed by an intermediate analysis before starting the phase II. The BREGO trial was developed to propose an alternative and probably a highly active regimen in front-line metastatic or locally advanced biliary tract cancer patients. This project is supported by Bayer HealthCare. Authors thank the numerous participating teams.