PROJECT TITLE LONG	Evaluation of the impact of target-therapy on the quality of life in patients with advanced cholangiocarcinoma (PLATON-san) - A PLATON Network Analysis Project (ikf-t003)
PROJECT ACRONYM	PLATON-san
SUB-ANALYSIS NO	PL003
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RATIONALE	Cholangiocarcinoma (CCA) is the second most common primary liver tumor after hepatocellular carcinoma. With a 5-year survival rate below 10%, it is one of the most aggressive cancers. Surgery is considered to be the only potential curative management. However, at time of diagnosis only less than one third of patients showed a resectable stage. Furthermore, majority of patients develop recurrent disease even after complete resection. Although the combination of gemcitabine and cisplatin has evolved as standard first-line therapy for patients with advanced CCA, no standardized second-line therapy has established so far due to the lack of prospective, randomized controlled phase III trials. In the last years, the advent of next generation sequencing technologies lead to the unravelling of the molecular events occurring in biliary cancers. These analyses revealed among others genetic alterations such as fusions or rearrangements of the tyrosine kinase fibroblast growth factor receptor 2 (FGFR2) in 10-15% of patients with intrahepatic CCA, but in almost no with extrahepatic CCA (Goyal et al., 2021). Fusion of the FGFR2 result in a ligand-independent receptor signalling, thus leading to a constitutive activation of the downstream pathway. The sustained signalling then activates oncogenesis through progressive growth and invasiveness, neoangiogenesis as well as promote chemoresistance (Goyal et al. 2021). To curb the uncontrolled FGFR2 activity in these tumors, several therapies targeting this pathway are under development including FGFR tyrosine kinase inhibitors (TKIs) or neutralizing antibodies. Although the treatment with non-selective TKIs showed clinical benefit, usage of these compounds has pitfalls as issues with off-target side-effects. The use of more specific TKIs has therefore been the rational approach to address these issues. A second generation of selective FGFR TKIs is currently under investigation (such as derazatinib and futibatinib) or is already approved, like infigratinib and pemigatinib (Ghedini et al., 2018). Due to the common tumor symptoms impacting the physical function as well as the emotional well-being, advanced CCAs are associated with a poor health-related quality of life (QoL) (Hunter & Soares, 2021). Although cancer therapy could relieve tumor-related symptoms and improve QoL and survival in selected patients, in others, especially with already poor performance status, treatments may further deteriorate the QoL due to the occurrence of side effects. An increased symptoms load is associated with higher levels of emotional suffering and poor physical as well as social functioning.

OBJECTIVES	The primary objective of the PLATON-san project is to evaluate quality of life in patients with advanced CCC under systemic therapy. The secondary objective is to analyze the impact of targeted therapies and chemotherapy on QoL in patients with FGFR2 fusions.
SUB-STUDY POPULATION	In this analysis project data from the PLATON network of at least 90 patients diagnosed with advanced cholangiocellular carcinoma (CCA) will be used.
OBSERVATIONAL TIMEPOINTS	Baseline; Follow-Up under therapy every 4-6 weeks; Follow-up (irrespective of therapy): after 6, 12 and 24 months.
VARIABLES REQUIRED	Demography Anamnesis Cancer and Therapy History Diagnosis ECOG Performance Status Survival Status Anti-tumor therapies Tumor response Tumor genome profile (NGS) QoL data (EORTC-QLQ-C30, EORTC-QLQ-BIL21, EQ-5D-5L)
STATISTICAL METHODS	Due to the explorative nature of this analysis only descriptive statistics will be performed, providing means, medians, interquartile and total ranges, standard deviations and/or confidence intervals, counts and proportions as appropriate for the respective data types. A detailed methodology for the statistical analysis will be described in the statistical analysis plan (SAP). If additional p values for correlative research are calculated for selected items, they will be presented explicitly without referring to pre-specified hypotheses or a significance level. Usually, no error adjustment for multiple testing will be performed. Thus, the p values will reflect the comparison-wise error and not the experiment-wise error. All explorative p values will be two-sided, if not defined otherwise. Accompanying correlative research will be conducted using descriptive statistics, correlation, bivariate or multivariable analysis as appropriate. Bivariate analysis may be performed using linear or logistic regression models to observe the association between each single predictor and outcomes. Multivariable analysis might be additionally performed to assess potential predictors while controlling for other covariates using backward elimination with significant threshold of 0.2. Non-significant variables will be excluded from the model in each step. Assumption of regressions may be illustrated using residual plots, if applicable. The strength of association between predictors and outcomes may be characterized using regression coefficients with standard error, least square means with 95%CI, Pearson and Spearman correlation coefficients, coefficient of determination, related plots, or ORs with corresponding 95% CI and p-values as appropriate. It should be noted that regression models in correlative research can only be interpreted in an exploratory manner. This implies that excluding a covariate from the model during variable section process may not indicate that the covariate is not casually related to a dependent variable.
FUNDING	Taiho Oncology, Inc.
REFERENCES	Ghedini GC, Ronca R, Presta M, Giacomini A. Future Applications of FGF/FGFR Inhibitors in Cancer. Expert Rev Anticancer Ther. 2018; 18:861-872.

	Goyal L, Kongpetch S, Crolley VE, Bridgewater J. Targeting FGFR Inhibition in Cholangiocarcinoma. Cancer Treat Rev. 2021; 95:102170. Hunter LA & Soares HP. Quality of Life and Symptom Management in Advanced Biliary Tract Cancers. Cancers 2021; 13:5074.