Clinical Study Synopsis

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1 Abstract

Acronym/Title	REFINE: Regorafenib observational study in hepatocellular carcinoma
Report version and date **Author**	V1.0, 12 OCT 2022 PPD Peter Merian Strasse 84 CH-4052, Basel Switzerland
Keywords	unresectable hepatocellular carcinoma, regorafenib, real-world evidence, safety, effectiveness
Rationale and background	This observational study aimed to evaluate safety and effectiveness of regorafenib in patients with unresectable hepatocellular carcinoma (uHCC) under real-world practice conditions. The study also evaluated regorafenib treatment in a variety of hepatocellular carcinoma (HCC) patient subsets and provided information on treatment patterns and outcomes for patients with uHCC in the real-world setting.
Research question and objectives	The primary objective was to evaluate the safety of regorafenib in patients with uHCC, including incidence of all treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs in real-world practice conditions. The secondary objectives included the description of effectiveness and treatment patterns of regorafenib, as well as patient characteristics and practice patterns in uHCC treatment. The tertiary objective was to describe sorafenib treatment and other therapies for HCC prior to regorafenib treatment.
Study design	International, prospective, open-label, multicenter, observational study.
Setting	The study was conducted in Austria, Belgium, Canada, China, Denmark, Egypt, France, Greece, Italy, Japan, Korea, Netherlands, Russia, Saudi Arabia, Spain, Sweden, Taiwan, Thailand, Turkey, and the United States of America (USA). Patients with uHCC and for whom a decision to treat with regorafenib had been made (by the treating physician) were eligible for enrollment into the study.
Subjects and study size, including dropouts	This final analysis had a data cut-off date of 21 JUN 2022. Overall, 1028 patients were enrolled and 1005 of these patients (97.8%) were included in the safety analysis set (SAF) (patients with a diagnosis of uHCC who had received at least one

	regorafenib dose and signed an informed consent form).
Variables and data sources	The investigator collected historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collected treatment-related data during the initial visit and follow-up visits that took place in routine practice.
Results	The highest proportions of patients were from Korea (16.9%), Japan (14.5%), and France (13.7%). Most were male (83.1%) and the mean ± standard deviation (SD) age was 65.2 ± 10.5 years. The median observational period was 41 weeks. The etiology of HCC was most commonly reported as hepatitis B (38.0%), alcohol use (24.9%), and hepatitis C (24.1%). The vast majority of patients (96.0%) had been previously treated with sorafenib. A total of 921 patients (91.6%) experienced any TEAE with most graded as worst grade Grade 3 (348 patients, 34.6%) or Grade 2 (268 patients, 26.7%). A total of 746 patients (74.2%) experienced any drug-related TEAEs. A total of 374 patients (37.2%) experienced any treatment-emergent serious adverse events (TESAEs) and 90 patients (9.0%) experienced drug-related TESAEs. A total of 264 patients (26.3%) experienced any TEAEs leading to dose reduction, 271 patients (27.0%) experienced TEAEs leading to dose interruption, and 311 patients (30.9%) experienced TEAEs leading to permanent discontinuation of regorafenib. A total of 163 patients (16.2%) experienced any TEAEs with a fatal outcome, most commonly hepatocellular carcinoma (32 patients, 3.2%). Most commonly, patients had an initial regorafenib daily dose of 160 mg (469 patients, 46.7%) or 80 mg (398 patients, 39.6%). Regarding death and progression, 151 patients (15.0%) died during or within 30 days of last dose of regorafenib, and 482 patients (48.0%) died after 30 days succeeding the last dose of regorafenib. The median overall survival for the observational period was 13.2 months. The median progression-free survival for the observational period was 3.9 months, and the median time to progression for the observational period was 4.1 months. For patients with prior sorafenib therapy, the median time from initial diagnosis to start of sorafenib treatment was 11.73 months. The median duration of prior sorafenib treatment was 4.93 months. A total of 200 patients had treatment with prior systemic anti-cancer therapy other than sorafenib, most commonly nivolumab, lenvatinib, and pembrolizumab. Prior immune checkpoint inhibitors were reported for 97 patients (9.7%).

Discussion	This final analysis of the observational REFINE study assessed a more varied patient population than the previously conducted phase 3 RESORCE trial, including a higher proportion of patients with eastern cooperative oncology group (ECOG) performance status ≥1 and with Child-Pugh B liver function. Further, patients with prior treatments other than sorafenib, patients who were intolerant to sorafenib, and patients who received regorafenib in third-line or later were also included in the REFINE study. The incidence of TESAEs was slightly lower than that reported in the RESORCE trial. The median overall survival, as well as the median progression-free survival, was longer than that reported in the RESORCE trial. In summary, safety and effectiveness were comparable to previous studies.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany
Names and affiliations of principal investigators	A list of names and affiliations of the principal investigators is available upon request (Annex 1).