Science For A Better Life

Clinical Study Synopsis

This Clinical Study Synopsis is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research. This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labelling information approved for the patient's country or region. Data in this document or on the related website should not be considered as prescribing advice.
The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Keywords	Metastatic colorectal cancer (mCRC), regorafenib, multi-kinase inhibitor, survival
Rationale and background	There is a high incidence of CRC especially in developed countries such as Germany. About half of all CRC patients develop metastatic disease. Metastatic CRC has a critical prognosis with a 5-year survival rate of less than 10%. Regorafenib is an oral multi-kinase inhibitor that inhibits tumor growth by inhibiting both the proliferation of tumor cells and the formation of new tumor vasculature. Evidence of efficacy and safety in mCRC patients were based on the multi-national, multi-center phase III CORRECT study. This study was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. Upon approval of regorafenib, the patient population that receives this drug is usually more heterogeneous with various comorbidities. This non-interventional study was performed to investigate the effectiveness and safety of regorafenib in routine use in Germany.
Research question and objectives	The primary objective of this study was to investigate overall survival among patients with mCRC treated with Stivarga®. Secondary objectives were to determine progression free survival (PFS; either clinical progression and/or radiological progression), time to progression (TTP; either clinical progression and/or radiological progression), disease control rate (DCR), duration of Stivarga® treatment, tumor status at different visits, and incidence of treatment emergent adverse events (TEAEs). Additionally, possible prognostic factors e.g. presence of severe comorbidities, metastatic sites, early relapse after adjuvant treatment, and KRAS mutations were evaluated.

Study Design	This was a prospective, open-label, multi-center, single arm, cohort, non-interventional post-authorization safety study of patients with mCRC treated with Stivarga®.
Setting	The study was conducted in a real-life setting in 91 sites across Germany. Information on each patient was recorded at the initial and at follow-up visits every 4 to 6 weeks. End of observation was approx. 12 months after the last patient entered the study. First patient first visit (FPFV) was on 17OCT2013, last patient first visit (LPFV) on 13JUN2016 and last patient last visit (LPLV) on 11APR 2017.
Subjects and Study Size, including dropouts	In total, 481 patients of 91 sites gave their written informed consent and were enrolled in the study. 5 patients withdrew their written informed consent and 12 patients were not treated with the study drug. Thus, 464 patients of 90 sites were included in the safety analysis set (SAF). Patients in the SAF received at least one dose of Stivarga®. 1 patient had no diagnosis of mCRC (violation of IC 01) and was therefore excluded from the intent-to-treat set (ITT). Thus, 463 patients were included in the ITT. Moreover, 9 patients that were enrolled after amendment 1violated IC 02 (decision for Stivarga® treatment as third- or forth-line treatment). These 9 patients were included in all analyses.
Variables and Data sources	All patient-related data for this study were collected during the initial and routine follow-up visits. The investigator documented the study-relevant data for each patient in a pseudonymized manner in the eCRF. The primary outcome variable was overall survival, defined as the time interval from start of Stivarga® therapy to the date of death due to any cause. Secondary outcome variables were progression free survival, time to progression, disease control rate, duration of Stivarga® treatment, tumor status at different visits, and incidence of treatment emergent adverse events.
Results	Within the ITT (n=463), median overall survival was 5.86 months (CI 95%: 5.3 – 6.58 months). 1-year survival was 23.3%. Median progression-free survival was 3.13 months (CI 95%: 2.86 – 3.36 months). 1-year PFS was 5%. Median time to tumor progression was 4.01 months (CI 95%: 3.62 – 4.93 months). In 18.2% of patients median tumor progression occurred after one year (1-year TTP). 277 patients (59.83%) had an evaluation of the tumor status post-baseline. The disease control rate was 26.71% (CI 95%: 21.6 – 32.34%) within this population. Median duration of Stivarga® treatment was 71 days (range: 1 – 1085 days) within the ITT.

	During the course of the study, stable disease (SD) and progressive disease (PD) was the most frequent tumor status. PD occurred most often at the end of therapy (96.74%) as well as at the end of observation (88.23%). At the end of observation few patients had SD (11.76%). PD was the best response for most patients with an evaluation of the tumor status post-baseline (72.92%). SD occurred in almost 1/4 (23.1%) and partial response (PR) in 3.61% of patients. Within the SAF (n=464), 91.81% of patients had treatment-emergent adverse events. A total of 1970 TEAEs were observed, most of which were fatigue (in 24.14% of patients) and diarrhea (in 21.98% of patients). Almost 2/3 of patients had TEAEs that were judged as causally related to Stivarga® treatment. A total of 834 drug-related TEAEs were observed, most of which were diarrhea (in 17.46% of patients), palmar-plantar erythrodysesthesia syndrome (in 15.09% of patients) and fatigue (in 14.22% of patients). Almost half of these cases were mild to moderate in severity (grade 1 in 14.44% of patients and grade 2 in 31.9% of patients). Events were severe for 17.89% of patients. Rarely observed were life-threatening and fatal TEAEs (in 0.65% and 0.43% of patients, respectively). The two events that resulted in death were myocardial infarction and infectious pleural effusion. Almost 1/10 of patients had TEAEs that were documented to be serious and causally related to the study drug, with diarrhea and fatigue occurring with the highest frequencies (in 1.51% and 1.08% of patients, respectively).
Discussion	There is a high unmet clinical need for mCRC treatment options. RECORA showed an overall survival time similar to the phase III study CORRECT despite patients were older, more restricted in their performance status, had more concomitant diseases, and were treated with lower starting doses of regorafenib than in the phase III CORRECT study. This demonstrates regorafenib's ability to improve survival also in an unselected patient population.
Marketing Authorisation Holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
Names and affiliations of principal investigators	Contact details of the principal investigators for each site participating in the study are listed in a stand-alone document which is available upon request.