Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date	v 1.0, 09 MAR 2018
Study type / Study phase	☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4934
Active substance	Protein Kinase Inhibitors (L01XE21), regorafenib
Medicinal product	Stivarga®
Product reference	EMEA/H/C/002573
Procedure number	n/a
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany
Research question and objectives	The aim of this study was to investigate the effectiveness and safety of Stivarga® in patients with mCRC under routine conditions in Germany. Primary objective: to investigate overall survival among patients with mCRC treated with Stivarga®. Secondary objectives: to determine progression free survival (either clinical progression and/or radiological progression), time to progression (either clinical progression and/or radiological progression), disease control rate, duration of Stivarga® treatment, tumor status at different visits, and incidence of treatment emergent adverse events.
Country(-ies) of study	Germany
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer Pharma AG, D-13342 Berlin, Germany
MAH contact person	[redacted]

Confidentiality statement:

Table of contents

1. Abstract

Acronym/Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date **Author**	v 1.0, 09 MAR 2018 [redacted]
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 11APR2017.
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 Authorization 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 (see Annex 1: List of stand-alone documents) which is available upon request.

2. List of abbreviations

AE	Adverse Event
AG	Aktiengesellschaft
AJCC	American Joint Committee on Cancer
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ATC	Anatomical Therapeutic Chemical (Classification System)
DCR	Disease Control Rate
CI	Confidence Interval
CFR	Code of Federal Regulations
CR	Complete Response
CRC	Colorectal Cancer
CRF	Case Report Form
CRO	Contract Research Organization
DMP	Data Management Plan
EC	European Commission
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicine Agency
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GPP	Good Publication Practice
HFSR	Hand-Foot-Skin Reaction
ICH	International Conference of Harmonization
ID	Identifier
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IT	Information Technology
ITT	Intent-To-Treat Set
MAH	Marketing Authorization Holder
mCRC	Metastatic Colorectal Cancer
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
N/D	Not Determinable
NOS	Not Otherwise Specified
OS	Observational Study
OSP	Observational Study Protocol

OSR	Observational Study Report
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PD	Progressive Disease
PR	Partial Response
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPC	Summary of Product Characteristics
SD	Stable Disease
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TEAE	Treatment-Emergent Adverse Events
ULN	Upper Limit of Normal

3. Investigators

Contact details of the principal investigators for each site participating in the study are listed in a stand-alone document (see Annex 1: List of stand-alone documents which is available upon request.

4. Other responsible parties

The marketing authorization holder is Bayer Pharma AG, D-13342 Berlin, Germany [redacted]

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	Q4 2013	17OCT2013	
End of data collection (clean database)	Q2 2017	07JUL2017	Database lock was extended by 1 week due to additional AE documentation (2 AEs by 2 sites)
Registration in the EU PAS register		09OCT2013	
IEC approval - Study protocol version 1.1		17OCT2013	
IEC approval - Study protocol version 2		22OCT2014	
IEC approval - Study protocol version 3		18MAY2016	
Interim analysis 1 (of baseline and safety data)	Q2/2015 or if half the patients are enrolled (whatever is earlier)	30SEPT2015 (Version 1.1)	Version 1.0: 30JUL 2015
Interim analysis 2 (of efficacy and safety data)	JUL 2016	25JUL2016	
Final report of study results	Q1 2018	09MAR2018	

6. Rationale and background

Colorectal cancer (CRC) is a disease in which malignant cancer cells form in the tissues of the colon or rectum. Most colon and rectum cancers are adenocarcinomas, which account for more than 90% of all large

bowel tumors. CRC is the third most common cancer worldwide, with over one million new cases occurring each year. Mortality is about half of its incidence. Incidence rates vary according to geographical region, being higher in more developed countries. Incidence rates are also higher in men than in women and strongly increase with age. About half of CRC patients develop metastatic disease (1, 2). Five-year survival is on average 65%, but is highly variable depending on the stage of disease being only 13.9% for patients with distant stage CRC (3).

Several drugs are currently approved for use in metastatic colorectal cancer (mCRC): 5-fluorouracil (5-FU), capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, and panitumumab. Several 5-FU/ leucovorin (FL) regimens with varying schedules and dosages resulted in similar efficacy and safety outcomes with median survival times of about 12 months, as demonstrated by multiple studies. In 3 randomized trials, the effect of combining FL with either irinotecan or oxaliplatin was investigated. Here, the addition of irinotecan or oxaliplatin to FL resulted in longer progression-free survival (PFS), overall survival (OS) and better response rates (4, 5). Results of the intergroup study N9741 indicated that oxaliplatin in combination with FL (FOLFOX regime) as first-line therapy for metastatic colorectal cancer results in longer PFS and OS as compared to irinotecan in combination with FL (FOLFIRI regime) (6). In two other trials, similar PFS and OS outcomes were observed with both treatment regimens (7, 8). Hence, both regimens are acceptable first-line therapies for metastatic colorectal cancer.

Significant improvements in survival (OS and PFS) were demonstrated when bevacizumab, an antibody directed against the vascular endothelial growth factor (VEGF), was added to fluorouracil-based combination chemotherapies. Adding bevacizumab to the FOLFIRI regimen resulted in significant improvements among patients with previously untreated mCRC (9). The addition to the FOLFOX regimen resulted in significant improvements among patients, who have failed prior 5-FU/irinotecan therapy, as results from the Eastern Cooperative Oncology Group (ECOG) study E3200 demonstrate (10).

Second-line irinotecan in patients previously treated with 5-FU/leucovorin showed improvements in OS as compared to infusional 5-FU or best supportive care (11, 12). In patients, who progressed after FOLFIRI, second-line FOLFOX resulted in a longer time to progression (TTP) as compared to infusional 5-FU/leucovorin, as demonstrated in a phase III study (13). In a phase II trial, the addition of cetuximab, an antibody against the epidermal growth factor receptor (EGFR), to irinotecan in patients with irinotecan-refractory mCRC, also resulted in a longer TTP (14). As a consequence, cetuximab was approved for mCRC after progression with 5-FU and irinotecan. These results were substantiated by further findings showing significant improvements in OS and PFS with the addition of cetuximab to best supportive care (BSC) in patients with EGFR-positive CRC, who were previously treated with a fluoropyrimidine, irinotecan and oxaliplatin (15). A phase III trial showed that the addition of another EGFR antibody, panitumumab, to BSC also resulted in prolonged PFS in patients, who progressed after standard chemotherapy. There was, however, no improvement in OS, likely confounded by the fact that 76% of BSC patients entered the cross-over study (i.e. received panitumumab after progression) (16). Based on data from this trial, the Food and Drug Administration (FDA) and European Medicines Agency (EMA) granted approval for panitumumab for chemotherapy-refractory CRC.

Regorafenib is an oral multikinase inhibitor that inhibits tumor growth by inhibiting both the proliferation of tumor cells and the formation of new tumor vasculature. Regorafenib was selected based on its kinase inhibition profile, which includes angiogenic (VEGFR 2/3, Tie2), stromal (PDGFR-ß, FGFR) and oncogenic (c-KIT, RET and B-RAF) (receptor tyrosine) kinases. Those kinases are inhibited in biochemical and cell-based assays with inhibitory concentrations (IC50) between 3 and about 300 nM. Regorafenib was also shown to potently inhibit the Raf/MEK/ERK pathway in vitro with an IC50 between 20 and 400 nM. This pathway has a pivotal role in transmitting growth and angiogenic signals, and is often aberrantly activated in human tumors due to the presence of mutated RAS, B-RAF or growth factor receptors (17). About 12% of CRC carry a mutation in B-RAF and approximately 35% carry a mutation in RAS (18). Thus, inhibition of this pathway may be of clinical benefit for patients with CRC. Regorafenib inhibits the proliferation of a wide

range of human tumor cell lines with an IC50 between 40 and 5000 nM including the colon cancer cell lines SW620 and Colo-205, which are inhibited with about 1000 and 3300 nM, respectively. In a hepatocellular cancer cell line, anti-proliferative activity was demonstrated to be accompanied by induction of apoptosis. The compound also potently inhibits growth factor dependent proliferation of vascular cells with an IC50 of 3 to 150 nM, thereby mediating its anti-angiogenic effects.

In vivo, regorafenib inhibits tumor growth in a dose-dependent manner in multiple human xenografts growing subcutaneously in mice. These include the CRC models Colo-205 and HT-29, which carry mutant B-RAFV600E, and the HCT-116 and HCT-15 models, which carry mutant K-RASG13D with the latter being multidrug resistant and insensitive to taxol treatment. Furthermore, regorafenib was efficacious in oxaliplatin insensitive patient-derived human colon xenografts, where added benefit was observed with the combinatorial treatment of regorafenib and irinotecan in one case. Additionally, the compound revealed antimetastatic activity observed in a syngeneic orthotopic breast cancer model. In functional assays, regorafenib exhibits anti-proliferative and anti-angiogenic effects in colon and breast xenografts as demonstrated by a reduced microvessel area, and Ki67 and pERK1/2 staining in tissue sections. The compound exerts further anti-angiogenic effects by prolonging inhibition of extravasation in the tumor vasculature of a rat GS9L glioblastoma model, as shown by dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) (19).

M-2 (BAY 75-7495) and M-5 (BAY 81-8752), two major metabolites of regorafenib in human plasma, were analyzed and were shown to have similar activities in biochemical and cell-based assays in vitro compared to regorafenib. In vivo, both metabolites inhibited the growth of colorectal HT-29 tumor xenografts and the VEGF-induced vascular effects (e.g., extravasation and hypotension) with similar efficacy as regorafenib (20). In summary, the findings in the preclinical regorafenib studies support advancement to clinical trials in patients with CRC.

The evidence of efficacy and safety in mCRC patients was based on the multi-national, multi-center phase III CORRECT study, titled “A randomized, double-blind, placebo-controlled phase III study of regorafenib plus BSC versus placebo plus BSC in patients with metastatic colorectal cancer who have progressed after standard therapy”. The study met its primary endpoint to significantly improve OS by 29% (HR=0.77, p=0.0052). The median OS was 6.4 months in the regorafenib group compared to 5.0 months in the placebo group. The trial also met two secondary efficacy endpoints, including a significant improvement in PFS (HR=0.49, p=0.000001), and a significant improvement in the disease control rate (DCR) (p<0.000001). The overall safety and tolerability profile for regorafenib was consistent with results from previous studies. The most common drug-related, treatment-emergent adverse events (occurring in at least 25% of patients in the regorafenib group) included fatigue (47% vs. 28%), hand-foot-skin reaction (47% vs. 8%), diarrhea (34% vs. 8%), anorexia (30% vs. 15%), voice changes (29% vs. 6%), hypertension (28% vs. 6%), oral mucositis (27% vs. 4%), and rash/desquamation (26% vs. 4%). These data demonstrate that regorafenib can stabilize disease, even at an advanced stage, and prolong life in patients with mCRC, who have no other treatment options available. To date regorafenib is the only oral multi-kinase inhibitor that has demonstrated improvements in clinical outcomes as a single agent in a large Phase III trial in patients with advanced treatment-refractory CRC (21).

Stivarga® is indicated for the treatment of patients with mCRC, who have previously been treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy. Abnormalities of liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have frequently been observed in patients treated with Stivarga®. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a small proportion of patients. Therefore, for patients with observed worsening of liver function tests considered related to treatment with regorafenib (i.e. where no alternative cause is evident, such as post-hepatic cholestasis or disease progression), the dose modification and monitoring advice in the Summary of Product Characteristics (SPC) should be followed. According to the SPC, it is recommended to perform liver function tests (ALT, AST and bilirubin) before

initiation of treatment with Stivarga® and monitor closely (at least every 2 weeks) during the first 2 months of treatment. Thereafter, periodic monitoring should be continued at least monthly and as clinically indicated.

7. Research question and objectives

The pivotal phase III CORRECT trial was conducted in a closely defined patient population according to strict inclusion and exclusion criteria. After approval of regorafenib, patients with mCRC receiving this drug are usually more heterogeneous with various comorbid conditions. Therefore, the aim of this non-interventional study was to investigate the effectiveness and safety of Stivarga® in routine use in Germany.

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 (either clinical progression and/or radiological progression),
- time to progression (either clinical progression and/or radiological progression),
- disease control rate,
- duration of Stivarga® treatment,
- tumor status at different visits,
- incidence of treatment emergent adverse events.

Additionally possible prognostic factors e.g. presence of severe comorbidities, metastatic sites, early relapse after adjuvant treatment, and KRAS mutations were evaluated.

8. Amendments and updates

There were two amendments to the study protocol.

Table 2: Amendments

No.	Date	Section of study protocol	Amendment / Update	Reason
1	22SEPT 2014	9.2.2. Inclusion criteria 9.5 Study size 6. Milestones	Amendment 1	Male or female patients ≥ 18 years of age with metastatic CRC for whom the decision has been taken by the investigator to treat with Stivarga® *as 3rd or 4th line treatment*. Also, reduction of planned patient number (from 1000 to 500) and extension of recruitment period of 3 months due to low recruitment.
2	06APR 2016	6. Milestones 9.3.13 Adverse Events 11. Management and reporting of adverse events	Amendment 2	Further extension of recruitment period of 4 months due to low recruitment, and addition of second interim analysis. Also minor clarifications regarding (S)AE documentation.

9. Research methods

9.1 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®. The study was conducted in Germany. The study started after Stivarga® was authorized and made commercially available in Germany. All patients, who fulfilled the selection criteria were eligible for enrollment into the study. The patient's clinical information was documented at the initial visit and at follow-up visits every 4 to 6 weeks.

The actual treatment duration was determined solely by the physician. Patient data were collected according to local clinical practice during personal or phone visits. The study ended 12 months after enrollment of the last patient. Serious adverse events were followed up until resolution.

A prospective, non-interventional design was chosen since at the time of study initiation no data were available on real-life treatment with Stivarga®.

9.2 Setting

The aim of this study was to investigate the effectiveness and safety of Stivarga® in a real life setting, which can only be accomplished by an observational study design. Here, a diverse patient population in a broad range of settings (natural environment) reflecting reality is observed. All decisions in terms of diagnostic procedures, treatments, management of the disease and resource utilization are fully dependent on mutual agreement between the patient and the attending physician, without interference by a sponsor or study protocol.

Metastatic CRC patients (male or female) treated with Stivarga® by office-based or clinic oncologists and gastroenterologists in Germany were enrolled in this study. Duration of treatment was determined by the treating physician. Information on each patient was recorded at the initial and at follow-up visits every 4 to 6 weeks. End of observation was planned to be 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 11APR2017.

BAYER stopped active marketing and sales of Stivarga® in Germany at 15th of April 2016 – since this timepoint, Stivarga® is only available by international pharmacies according § 73 sec. 1 German Drug Law.

9.3 Subjects

The study population consisted of male and female patients with metastatic colorectal cancer (mCRC), for whom the decision has been taken by the investigator to treat with Stivarga® according to the local summary of product characteristics (SPC).

Inclusion criteria were:

- Diagnosis of mCRC (IC 01)
- Decision for Stivarga® treatment as third- or forth-line treatment (for patients enrolled after amendment 1) by investigator

  Decision for Stivarga® treatment (for patients enrolled prior to amendment 1) by investigator (IC 02)
- Male or female patient ≥ 18 years of age (IC 03)

No exclusion criteria were defined.

9.4 Variables

All patient-related data required for this study were collected during the initial and routine follow-up visits. The investigator collected historical data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient and documented the study-relevant data for each patient in the eCRF. Likewise, the investigator collected treatment-related data during the initial and routine follow-up visits.

The primary outcome variable was **overall survival (OS)**. OS was defined as the time interval from start of Stivarga® therapy to the date of death due to any cause. Patients alive or lost to follow-up at the time of analysis were censored at the last date known to be alive.

Secondary outcome variables were:

- **Progression free survival (PFS)**, defined as the time interval from the start of Stivarga® therapy to diagnosed (radiological or clinical) progression or death, whichever comes first. Progression-free survival for patients without disease progression or death at the time of analysis were censored at the last date of tumor evaluation.
- **Time to progression (TTP)**, defined as the time interval from start of Stivarga® therapy to diagnosed (radiological or clinical) progression. Patients without tumor progression at the time of analysis were censored at their last date of tumor evaluation.
- **Disease control rate (DCR)**, defined as the percentage of patients, whose best response was not progressive disease (i.e. complete response, partial response or stable disease).
- **Duration of Stivarga® treatment**, defined as the time interval from start of Stivarga® therapy to permanent discontinuation of Stivarga® therapy (regardless of the reason for discontinuation). Treatment duration was calculated as last dosing date - first dosing date + 1. Patients with only one dose of Stivarga® were considered as having a treatment duration of 1 day.
- **Tumor status at different visits**, evaluated according to the categories “complete response”, “partial response”, “stable disease”, “progressive disease by clinical judgment”, “progressive disease measurement proven”, “unknown” and “not applicable”. The best overall response was analyzed providing absolute and relative frequencies of the tumor status categories.
- **Incidence of treatment-emergent adverse events (TEAE)**, including a description of the event, its duration, seriousness, relationship to Stivarga®, action taken, and clinical outcome. AEs were reported according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

For demographic assessment, the following data were recorded at the initial visit:

- Date of birth
- Sex
- Race

The following vital signs were recorded:

- Height
- Weight
- Blood pressure (weekly, up to 6 weeks from start of therapy)

Medical history (baseline data):

- Tumor characteristics at initial diagnosis
- Prior CRC diagnostics and therapies
- Prior systemic cancer therapies

- Prior radiotherapies
- Concomitant diseases of special interest

Medical history (initial and follow-up visits):

- Laboratory data (AST, ALT, bilirubin)
- ECOG performance status
- Tumor characteristics (initial visit) and tumor status
- New concomitant mCRC diagnostics and therapies (follow-up visits)
- Concomitant radiotherapies since last visit (follow-up visits)
- Stivarga® treatment (date of first administration, initial dose, regular time of intake; initial visit) and changes in Stivarga® treatment (dose modifications and interruptions, regular time of intake; follow-up visits)
- HFSR prevention/therapy
- Concomitant medication
- Adverse events since last visit (follow-up visits)

9.5 Data sources and measurement

Each patient was identified by a unique central patient identification code, which was only used for study purposes. The patient code consisted of a combination of a country code, site number and patient number. For the duration of the study and afterwards, only the patient's investigator was able to identify the patient based on this code.

The investigator collected historical data (demographic and clinical characteristics) from medical records if available, and treatment related data during visits that took place in routine practice. All study-relevant data were documented in a pseudonymized manner in an eCRF, which was developed by Alcedis GmbH. The eCRF is available upon request (see List of stand-alone documents, Annex 1).

9.6 Bias

The study was representative for an unselected study population of patients with mCRC in Germany, treated by office-based or clinic oncologists and gastroenterologists. 464 patients of 90 sites were included in the analysis. Investigators and patients documented in the study were selected based on eligibility according to inclusion and exclusion criteria. No further selection was applied. A representative sample of sites was included in the study, and investigators were asked to sample consecutive patients whenever possible to avoid any selection bias, thereby increasing representativeness.

9.7 Study size

Assuming an exponentially distributed OS with a median of 6.4 months, approximately 73% of patients were expected to die within a 12 months observation period. It was aimed to enroll 500 patients in this study. With 500 patients and a loss-to-follow-up of 20%, approximately 292 deaths were expected within 12 months. Thus, the 95% confidence interval for a 1-year survival rate of 27% would be 23% to 32%, i.e. 9 percentage points in length. This time frame and number of events seemed to be reasonable to adequately describe the Kaplan-Meier-curve for OS in routine daily practice conditions, in particular considering the fact that the pivotal phase III study CORRECT had similar patient numbers randomized to the regorafenib treatment arm (n=505 regorafenib patients valid for ITT analysis).

9.8 Data transformation

All issues concerning patient validity, data consistency checks, permissible data modifications and coding of medical terms and concomitant medication are described in detail in the Data Management Plan. All

statistical issues including derived variables for analysis, handling of missing data and proposed format and content of tables are detailed in the Statistical Analysis Plan (SAP). The SAP was finalized before study database lock.

Patients, who received at least one dose of Stivarga®, were included in the analysis. Primary and secondary outcome data were stratified by the following subgroups: age at registration (< 65 vs. ≥ 65 years), gender (female vs. male), baseline ECOG (0/1 vs. 2 vs. 3 vs. missing), KRAS mutation at initial diagnosis (no vs. yes vs. unknown), prior Bevacizumab treatment (no vs. yes), time from initial CRC diagnosis to start of therapy (< 18 months vs. ≥ 18 months vs. missing), number of prior systemic cancer therapies (≤3 vs. >3 prior treatment lines), primary tumor site (colon vs. rectum), tumor sidedness (left = splenic flexure, descending colon, sigmoid colon, recto-sigmoid colon and rectum, vs. right = appendix, caecum, ascending colon, hepatic flexure and transverse colon) and metastasis location (1. Liver only vs. other, 2. Liver/no lung vs. lung/no liver vs. liver/lung vs. no liver/no lung, and 3. Liver/no skeleton vs. lung/no skeleton vs. liver/lung/no skeleton vs. skeleton (includes skeleton, skeleton/liver, skeleton/lung, and skeleton/liver/lung) vs. no liver/no lung/no skeleton).

9.9 Statistical methods

All statistical analyses were performed by Alcedis GmbH, Germany (by means of SAS 9.4 software).

9.9.1 Main summary measures

The statistical part was exploratory and contained analytical and descriptive segments.

Continuous variables were described by sample statistics (i.e. mean, standard deviation, minimum, median, quantiles and maximum).The description of categorical variables was done with frequency tables displaying the actual number of patients in a category as well as percentages. The number of patients with missing data was presented as a separate category. Percentages were calculated based on non-missing values, except for baseline tables.

9.9.2 Main statistical methods

Descriptive summaries of Kaplan-Meier (KM) estimates (including number of failed, number of censored, 25th and 75th percentiles with respective 95% CI and median with 95% CI) and KM curves were presented for the primary outcome variable OS as well as for the secondary outcome variables PFS and TTP. DCR was calculated with the corresponding 95% confidence interval. Summary statistics were calculated for the duration of Stivarga® treatment. Category counts and frequencies (percentages) were calculated for the tumor status at different visits and as best overall tumor response. Summary tables presented the number of subjects observed with TEAEs and corresponding percentages.

9.9.3 Missing values

Missing data were not replaced. Missing data were given as “missing” in the tables.

9.9.4 Sensitivity analyses

None

9.9.5 Amendments to the statistical analysis plan

Changes made to Version 1.0 (from 08.04.2015):

- Minor corrections of incomplete information
- “Time to first dose modification [days]” added to 4.6 (definition of derived variables)
- Addition of tables: “Patient validity status”, “Inclusion and exclusion criteria”, “Demographics”, “Baseline cancer characteristics”

- Single tables for “Prior diagnostics or therapeutic procedures associated with mCRC” were combined into one table
- Single tables for “Prior radiotherapy” were combined into one table
- Presentation of “Laboratory test-AST, ALT” and “Performance status (ECOG)” values according to time periods of 8 weeks (instead of visits)
- Tables related to Stivarga® treatment restructured in order to keep these together, and Table for “Time to first dose modification” added
- Table “Overview of TEAEs” added
- Rows for “any SOC” and “any PT” added to tables where adverse events are shown according to MedDRA-SOC and PT

Changes made to Version 2.0 (from 24.04.2017):

- Minor corrections of typing errors and incomplete information
- Total bilirubin (Table 15): Addition of one row in order to show Min and Max values instead of only one value

Changes to Version 3.0 (23.11.2017):

- Clarifications regarding primary tumor site, sidedness of primary tumor and metastasis localization for stratified analysis (4.1)
- Minor correction regarding the definition of OS, PFS and TTP (4.6): event date – treatment start date +1
- Clarification regarding the definition of the duration of Stivarga treatment (4.6): “For patients who died without end of therapy being documented the date of end of therapy will be set to date of death. For patients without end of therapy and without documented date of death the date of end of therapy will be set to the last documented visit date” was added.
- Clarification regarding population characteristic (6.1): “For patients with implausible intent of prior systemic anti-cancer therapy, the intent will be considered as ‘missing’ in the statistical evaluation” was added.
- Rewording in Table 27: “Number of patients without permanently discontinued Stivarga® treatment” (previous versions: Number of patients with regular end of Stivarga® treatment)

9.10 Quality control

Before study start at the sites, all investigators were trained on the principles of the study and the handling of the EDC system by means of a web-based seminar. The CRF data were collected with an EDC system developed by the CRO. All outcome variables and covariates were recorded in a standardized eCRF. After data entry, missing or implausible data were queried and the data were validated. A check for multiple documented patients was done. Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan specifies measures for handling of missing data and permissible clarifications. The DMP is available upon request (see list of stand-alone documents, Annex 1). National and international data protection laws as well as regulations on observational non-interventional studies were followed. Electronic records used for patient documentation were validated according to 21 Code of Federal Regulations (CFR) Part 11 (FDA) (22).

Quality reviews were performed in two waves; telephone interviews in an early phase (after half the sites started enrolment) and on-site visits in a late phase (the latest until 6 months after end of enrolment). 5 sites

were randomly selected for a structured interview to ensure that the study was conducted according to protocol (including all applicable amendments) and to identify additional need for training. Moreover, focused source data verification allowed to confirm the patients' existence, to estimate an error rate and to detect systematic errors (the 5 sites had 10 patients enrolled). All but one interview were conducted in May 2014. Due to long-term sickness of the study nurse the last interview was conducted in August 2014. Overall, the training of the sites was sufficient and the sites were conducting the study according to protocol. Only one site had to be retrained on the inclusion criteria. No deviations between source data and entries in the EDC system were found during the interviews. Thus, data quality regarding the reviewed parameters was good.

25 sites were randomly selected for on-site visits, which were conducted between November 2016 and March 2017. In total 2925 data items of 124 patients (26% of enrolled patients) were reviewed. The overall error rate was 2.7%. Errors were found regarding informed consents (date, signature, filing), inclusion criteria (prior therapy lines), date of initial CRC diagnosis (missing for 4 patients at one site), Stivarga® treatment (documented dates), tumor status (missing evaluation for 16 patients, documentation in source data but not in eCRF for 2 patients), date of death, and (S)AEs (40 AEs and 8 SAEs were not reported). Allover, source data were found to be sufficient in most cases but eCRF documentation was found to be incomplete in some cases, especially with regard to treatment schedule and (S)AE documentation. In these cases, sites were retrained and requested to complete documentation. Moreover, sites had difficulties with protocol amendment 1, after which only patients with regorafenib as 3rd or 4th line therapy were eligible. Cases with a higher number of previous therapy lines were discussed and approved by the medical expert of Bayer. In general, data quality was good and no further actions were required.

10. Results

10.1 Participants

Between 17OCT2013 and 13JUN2016, 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®. One 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 fourth-line treatment). It was decided to include these 9 patients in all analyses.

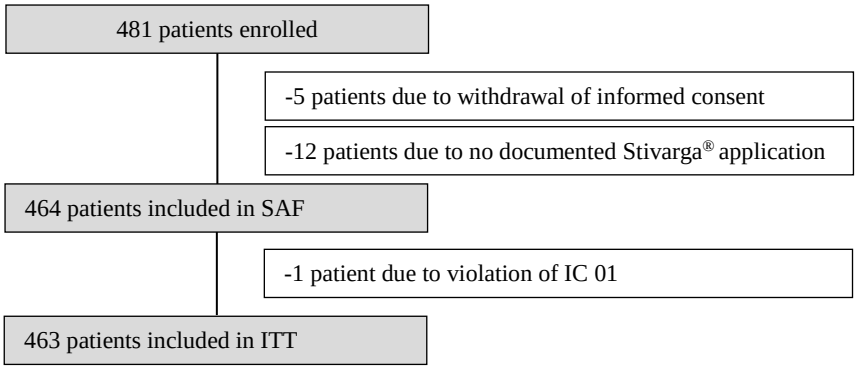


Figure 1: Patient flow chart

10.2 Descriptive data

Descriptive data are shown for the safety analysis set (SAF; n=464).

10.2.1 Demographics and vital signs

The majority of patients was male (60.34%) and white (97.41%; Table 3 a). The median age was 67 years (range: 30 – 89 years; Table 3 b). The median weight was 73 kg (range: 38 – 145 kg), the median height was 1.70 m (range: 1.45 – 1.97 m) and the median body mass index (BMI) was 24.92 kg/m^2 (range: 14.36 – 44.08 kg/m^2; Table 4 a). Blood pressure was measured at least once for almost 3/4 of patients. Within the first week of the initial visit the median blood pressure was 134/80 mmHg (n=329), within the 2nd week it was 130/80 mmHg (n=150), within the 3rd week it was 129/80 mmHg (n=48) and within the 4th week it was 127.5/81 mmHg (n=23). After week 4, blood pressure measurements were infrequent (Table 4 b; Figure 2).

Table 3: Patient demographics (SAF) (Data source: Table 3 of statistical report V1.0)

a.

Gender and race	*N (%)*
Number of patients	464 (100.0)
Gender	
Female	184 (39.66)
Male	280 (60.34)
Race	
White	452 (97.41)
Black	0 (0.00)

Asian	9 (1.94)
Not reported	3 (0.65)

b.

Age (years)	*N (Nmiss)*	*Mean (SD)*	*Median (Min, Max)*
Age at informed consent	464 (0)	66.66 (9.87)	67 (30, 89)

Table 4: Vital signs (SAF) (Data source: Table 3 and 11 - 13 and of statistical report V1.0)

a.

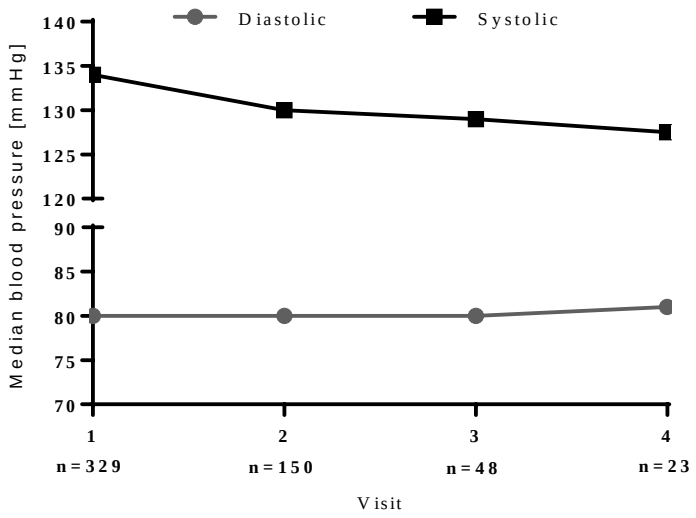
Weight and height	*N (Nmiss)*	*Mean (SD)*	*Median (Min, Max)*
Weight (kg)	409 (55)	74.23 (16.31)	73 (38, 145)
Height (cm)	423 (41)	170.81 (9.09)	170 (145, 197)
BMI (kg/m^2)	402 (62)	25.34 (4.92)	24.92 (14.36, 44.08)

b.

Blood pressure measurement	*N (%)*
Number of patients	464 (100)
≥ 1 measurement	343 (73.92)
no measurement	121 (26.08)

Blood pressure [mmHg]		*N*	*Mean (SD)*	*Median (Min, Max)*
Week 1 after initial visit	diastolic	329	81.55 (9.45)	80 (58, 112.5)
	systolic	329	135.68 (17.19)	134 (90, 185)
Week 2 after initial visit	diastolic	150	80.72 (11.09)	80 (58.5, 115)
	systolic	150	132.04 (18.16)	130 (85, 200)
Week 3 after initial visit	diastolic	48	79.15 (8.32)	80 (61, 100)
	systolic	48	131.35 (15.94)	129.17 (90, 175)
Week 4 after initial visit	diastolic	23	81.84 (9.07)	81 (58, 100)
	systolic	23	131.69 (14.43)	127.5 (107, 165)
Week 5 after initial visit	diastolic	7	75.33 (8.73)	75 (60, 90)
	systolic	7	126 (14.82)	128 (100, 150)
Week 6 after initial visit	diastolic	7	87.71 (11.76)	90 (70, 105)
	systolic	7	147.57 (14.25)	145 (130, 175)

Figure 2: Median blood pressure between initial visit and 4 weeks after initial visit



10.2.2 Medical history

10.2.2.1 Tumor characteristics

At the initial diagnosis, more than 90% of colorectal carcinomas (CRC) were adenocarcinomas. In most tumors cancer cells were moderately differentiated (73.06%), in 17.24% of cases they were poorly differentiated. Stage IVA and IVB cancers occurred most frequently (39.87% and 21.34%, respectively). Most tumors were located in the rectum (36.85%) and the sigmoid colon (23.06%). 46.34% of tumors harbored a KRAS mutation at the initial diagnosis (Table 5 a).

At the start of study treatment, most CRCs were resected (83.62%) with the absence or presence of residual/recurrent cancer being about equally distributed. The great majority of cancers were stage IVA and IVB (52.16% and 42.46%, respectively). Metastases in liver and/or lung occurred most frequently (liver: 75.22%, lung: 59.48%; Table 5 b).

The median duration from the initial diagnosis to the most recent progression/relapse was 30.12 days (range: 0.82 – 312.07 days; n=362). Most progressions/relapses were assessed radiologically (86.85%; Table 5 c).

Table 5: Tumor characteristics (SAF) (Data source: Table 4 of statistical report V1.0)

a.

Tumor characteristics at initial diagnosis	*N (%)*
Number of patients	464 (100)
Histology*	
Adenocarcinoma in situ	3 (0.65)
Adenocarcinoma	422 (90.95)
Medullary carcinoma	0 (0.00)
Mucinonuous carcinoma (colloid type)	14 (3.02)
Signet ring cell carcinoma	2 (0.43)
Squamous cell (epidermoid) carcinoma	1 (0.22)
Adenosquamous carcinoma	1 (0.22)
Small cell carcinoma	0 (0.00)

Undifferentiated carcinoma	1 (0.22)
Carcinoma, NOS	23 (4.96)
Missing	0 (0.00)
Grading (AJCC)	
G1, well differentiated	7 (1.51)
G2, moderately differentiated	339 (73.06)
G3, poorly differentiated	80 (17.24)
G4, undifferentiated	1 (0.22)
GX, grade cannot be assessed	37 (7.97)
Stage (TNM classification)	
Stage 0	6 (1.29)
Stage I	19 (4.09)
Stage IIA	27 (5.82)
Stage IIB	12 (2.59)
Stage IIC	5 (1.08)
Stage IIIA	37 (7.97)
Stage IIIB	46 (9.91)
Stage IIIC	28 (6.03)
Stage IVA	185 (39.87)
Stage IVB	99 (21.34)
Anatomical tumor location*	
Cecum	34 (7.33)
Ascending colon	49 (10.56)
Transverse colon	23 (4.96)
Splenic flexure	8 (1.72)
Appendix	7 (1.51)
Sigmoid colon	107 (23.06)
Recto-sigmoid colon	43 (9.27)
Rectum	171 (36.85)
Descending colon	15 (3.23)
Hepatic flexure	6 (1.29)
Missing	1 (0.22)
KRAS mutation	
No	160 (34.48)
Yes	215 (46.34)
Unknown	89 (19.18)

* multiple answers possible

b.

Tumor characteristics at start of therapy	*N (%)*
Number of patients	464 (100)
Status of primary tumor	
Unresected	76 (16.38)

Resected, no residual or recurrent tumor	153 (32.97)
Resected, presence of residual or recurrent tumor	156 (33.62)
Resected, status of residual tumor unknown	79 (17.03)
Stage (TNM classification)	
Stage I	4 (0.86)
Stage IIA	2 (0.43)
Stage IIC	1 (0.22)
Stage IIIA	3 (0.65)
Stage IIIB	8 (1.72)
Stage IIIC	2 (0.43)
Stage IVA	242 (52.16)
Stage IVB	197 (42.46)
Missing	5 (1.08)
Locations of metastases*	
Lymph nodes	129 (27.80)
Liver	349 (75.22)
Lung	276 (59.48)
Both Liver and Lung	197 (42.46)
Peritoneum	74 (15.95)
Bones	38 (8.19)
Brain	4 (0.86)
Other	50 (10.78)
Missing	0 (0.00)

* multiple answers possible

c.

Most recent progression/relapse	*N (%)*
Number of patients	464 (100)
Type of assessment	
Radiological	403 (86.85)
Clinical	61 (13.15)
Duration from initial diagnosis to most recent progression/relapse [days]	
N (Nmiss)	326 (138)
Mean (SD)	38.95 (34.01)
Median (Min, Max)	30.12 (0.82, 312.07)
P25, P75	18.16, 49.67

10.2.2.2 Comorbidities

The majority of patients (88.79%) suffered from comorbidities of special interest. Hypertension was most frequently observed (in 246 patients; 53.02%; Table 6 a) with grade I and II occurring more often than grade III (Table 6 b).

Table 6: Comorbidities of special interest (SAF) (Data source: Table 5 of statistical report V1.0)

a.

Comorbidities of special interest*	*N (%)*
Number of patients	464 (100)
Hemorrhagic stroke	1 (0.22)
Ischemic stroke	7 (1.51)
Transient ischemic attack	3 (0.65)
Myocardial infarction	14 (3.02)
Angina pectoris	4 (0.86)
Congestive heart failure	19 (4.09)
Hypertension	246 (53.02)
Diabetes mellitus	96 (20.69)
Leucocytopenia	9 (1.94)
Thrombocytopenia	11 (2.37)
Hand-foot skin reaction in the past	31 (6.68)
Pulmonary embolism in the past 12 months	10 (2.16)
Deep vein thrombosis in the last 12 months	25 (5.39)
Adipositas	26 (5.6)
Metabolic syndrome	4 (0.86)
Renal insufficiency	18 (3.88)
Liver insufficiency	3 (0.65)
Malignant tumors	36 (7.76)
Other diseases	261 (56.25)
None	52 (11.21)
Unknown	6 (1.29)

* multiple answers possible

b.

Hypertension- CTC grade	*N (%)*
Patients with hypertension	246 (100)
I	32 (13.01)
II	38 (15.45)
III	16 (6.5)
Unknown	160 (65.04)

10.2.3 CRC diagnostics and treatments

10.2.3.1 Prior CRC diagnostics and therapies

Prior to inclusion into the study, the great majority of patients (91.38%) underwent diagnostic and therapeutic approaches for their colorectal cancer. Most of these patients had a colectomy (41.59% had a partial and 3.23% had a total colectomy). Affected areas were mainly colon (44.4%), rectum (40.73%) and liver (20.69%). In most cases the procedure was therapeutic (47.84%) or both diagnostic and therapeutic (45.26%).

The therapeutic intent was palliative in 42.67% of cases and curative in 34.91% of cases. A tumor-free margin was obtained in 45.91% of cases (Table 7 a).

Almost all patients (99.35%) had prior systemic treatments for their CRC, with a median number of 3 regimens (range: 1 - 11 regimens). In most cases (94.83%) the prior systemic treatment was palliative. It was adjuvant in 31.47%, neo-adjuvant in 10.99% and curative in 2.16% of cases. Chemotherapy and chemotherapy in combination with signal transduction inhibitors were most often applied (89.66% and 23.92%). The median duration per treatment was 5.19 months (range: 1.12 – 19.73 months) with partial response (45.69%), stable disease (25%) or complete response (12.5%) being the most often observed best response over all regimens (Table 7 b).

26.08% of patients had prior radiotherapy. Mostly, colorectal regions were irradiated (18.54%). In most cases (12.72%) the radiotherapy was palliative or neo-adjuvant (9.91%). It was adjuvant in 3.88% and curative in 1.08% of cases. The median total cumulative dose was 50.4 Gy (range: 0 – 102 Gy). The best response over all irradiation regimens was partial response (6.25%), stable disease (3.45%) or complete response (2.16%; Table 7 c).

Table 7: Prior diagnostic and therapeutic approaches for CRC (SAF) (Data source: Table 8 – 10 and Appendix 9 of statistical report V1.0)

a.

Prior CRC diagnostics/therapies	*N (%)*
Number of patients	464 (100.0)
Prior CRC diagnostics or therapies	424 (91.38)
Procedure*	
Colectomy, partial	193 (41.59)
Colectomy, total	15 (3.23)
Colostomy	6 (1.29)
Ileostomy	8 (1.72)
Lymphadenectomy	12 (2.59)
Other	296 (63.79)
Location*	
Colon	206 (44.40)
Rectum	189 (40.73)
Liver	96 (20.69)
Other	93 (20.04)
Purpose*	
Diagnostic	92 (19.83)
Therapeutic	222 (47.84)
Diagnostic and therapeutic	210 (45.26)
Therapeutic intent*	
Palliative	198 (42.67)
Curative	162 (34.91)
Unknown	71 (15.30)
Missing	1 (0.22)
Surgical margins*	
Tumor negative	213 (45.91)

Tumor positive	33 (7.11)
Unknown	190 (40.95)
Missing	1 (0.22)

* multiple answers possible

b.

Prior systemic cancer therapy	*N (%)*
Number of patients	464 (100.0)
Prior systemic cancer therapy	461 (99.35)
Number of regimens	
N (Nmiss)	461 (0)
Mean (SD)	3.74 (1.76)
Median (Min, Max)	3 (1, 11)
P25, P75	2, 5
Intent (per patient)*	
Neo-adjuvant	51 (10.99)
Adjuvant	146 (31.47)
Palliative	440 (94.83)
Curative	10 (2.16)
Missing	5 (1.08)
Type (per patient)*	
Chemotherapy	416 (89.66)
Signal transduction inhibitors	31 (6.68)
Chemotherapy/signal transduction inhibitors	111 (23.92)
Other	53 (11.42)
Missing	1 (0.22)
Duration [months]	
N (Nmiss)	412 (49)
Mean (SD)	5.78 (3.09)
Median (Min, Max)	5.19 (1.12, 19.73)
P25, P75	3.56, 6.93
Best response over all regimens	
Complete response	58 (12.50)
Partial response	212 (45.69)
Stable disease	116 (25.00)
Progressive disease (clinical)	21 (4.53)
Progressive disease (radiological)	41 (8.84)
Unknown	11 (2.37)
Not applicable	1 (0.22)
Missing	1 (0.22)

* multiple answers possible

c.

Prior radiotherapy	*N (%)*
Number of patients	464 (100.0)
Prior radiotherapy	121 (26.08)
Irradiated location*	
Primary tumor	13 (2.8)
Colon	5 (1.08)
Rectal	26 (5.60)
Pelvis	39 (8.41)
Abdomen; Peritoneum	3 (0.65)
Liver	12 (2.59)
Lymph node	4 (0.86)
Lung	4 (0.86)
Brain	7 (1.51)
Other	19 (4.09)
Intent*	
Neo-adjuvant	46 (9.91)
Adjuvant	18 (3.88)
Palliative	59 (12.72)
Curative	5 (1.08)
Total cumulative dose [Gy]	
N (Nmiss)	116 (5)
Mean (SD)	45.18 (13.41)
Median (Min, Max)	50.4 (0, 102)
P25, P75	40, 50.4
Best response over all regimens	
Complete response	10 (2.16)
Partial response	29 (6.25)
Stable disease	16 (3.45)
Progressive disease (clinical)	1 (0.22)
Progressive disease (radiological)	8 (1.72)
Unknown	44 (9.48)
Not applicable	13 (2.80)

* multiple answers possible; **see Annex 2 (additional information) for a complete list of all free texts and allocated categories**

10.2.3.2 Concomitant mCRC diagnostics and therapies

There were in total 67 diagnostic and therapeutic approaches for metastatic colorectal cancer during the study. See Table 8 for details regarding procedure, location and purpose. 21 radiotherapies were performed during the study. For further details regarding irradiated location, intent, type and total cumulative dose see Table 21 - 24 and Appendix 9 of the statistical report.

Table 8: Concomitant diagnostic and therapeutic approaches for mCRC (SAF) (Data source: Table 18 – 20 of statistical report V1.0)

Concomitant mCRC diagnostics/therapies	Week 0-8	Week 9-16	Week 17-24	Week 25-32	Week 33-40	Week 41-48	End of therapy	End of observation
N	19	7	3	5	4	1	23	5
Procedure*								
Biopsy							1 (4.35)	
Segmentectomy								1 (20)
Other	19 (100)	7 (100)	3 (100)	5 (100)	4 (100)	1 (100)	22 (95.65)	4 (80)
Location*								
Colon	1 (5.26)	2 (28.57)						1 (20)
Rectum	2 (10.53)						1 (4.35)	1 (20)
Liver	2 (10.53)						9 (39.13)	1 (20)
Other	14 (73.68)	5 (71.43)	3 (100)	5 (100)	4 (100)	1 (100)	13 (56.52)	2 (40)
Purpose*								
Diagnostic	12 (63.16)	5 (71.43)	2 (66.67)	5 (100)	1 (25)	1 (100)	10 (43.48)	1 (20)
Therapeutic	7 (36.84)	1 (14.29)	1 (33.33)				8 (34.78)	4 (80)
Diagnostic and therapeutic		1 (14.29)			3 (75)		5 (21.74)	

* multiple answers possible

10.2.4 Laboratory data

Liver function test results were categorized into time intervals of 8 weeks. For the great majority of patients levels of aspartate transaminase (AST) and alanine transaminase (ALT) were normal or slightly elevated (≤ 3 times ULN; Table 9 a). The median bilirubin level at the initial visit was 0.55 mg/dl (range: 0.15 – 8.99 mg/dl). Within the first 56 weeks of the study, median levels ranged between 0.48 mg/dl (week 41 – 48) and 0.9 mg/dl (week 1 – 8). The highest median level was observed at the end of observation with 1.1 mg/dl. Table 9 b shows the median of the lowest and highest values within the respective 8-week time intervals. There was a median change from baseline of 0.43 mg/dl (range: -1.05 – 10.31 mg/dl) at the end of therapy and of 0.82 mg/dl (range: -0.2 – 14.2 mg/dl) at the end of observation (Table 9 b).

Table 9: Liver function tests (SAF) (Data source: Table 14 - 16 of statistical report V1.0)

a. AST and ALT

AST and ALT		***AST*** *N (%)*	***ALT*** *N (%)*
Initial visit	Below normal limit	2 (1.33)	3 (1.8)
	Within normal limit	81 (54)	131 (78.44)
	Within 1-3x ULN	58 (38.67)	30 (17.96)
	Within >3-5x ULN	8 (5.33)	2 (1.2)
	Within >5-20x ULN	1 (0.67)	1 (0.6)
	Total (non-missing)	150 (100)	167 (100)
Week 1-8	Below normal limit	4 (1.41)	4 (1.36)
	Within normal limit	123 (43.46)	191 (64.75)
	Within 1-3x ULN	128 (45.23)	86 (29.15)

	Within >3-5x ULN	19 (6.71)	9 (3.05)
	Within >5-20x ULN	9 (3.18)	5 (1.69)
	Total (non-missing)	283 (100)	295 (100)
Week 9-16	Below normal limit	0 (0)	3 (1.88)
	Within normal limit	74 (50.68)	108 (67.5)
	Within 1-3x ULN	58 (39.73)	41 (25.63)
	Within >3-5x ULN	13 (8.9)	7 (4.38)
	Within >5-20x ULN	1 (0.68)	1 (0.63)
	Total (non-missing)	146 (100)	160 (100)
Week 17-24	Below normal limit	0 (0)	1 (1.41)
	Within normal limit	38 (55.88)	53 (74.65)
	Within 1-3x ULN	28 (41.18)	15 (21.13)
	Within >3-5x ULN	1 (1.47)	0 (0)
	Within >5-20x ULN	1 (1.47)	2 (2.82)
	Total (non-missing)	68 (100)	71 (100)
Week 25-32	Below normal limit	1 (3.23)	2 (6.06)
	Within normal limit	20 (64.52)	22 (66.67)
	Within 1-3x ULN	10 (32.26)	6 (18.18)
	Within >3-5x ULN	0 (0)	3 (9.09)
	Total (non-missing)	31 (100)	33 (100)
Week 33-40	Below normal limit	1 (8.33)	1 (6.67)
	Within normal limit	7 (58.33)	11 (73.33)
	Within 1-3x ULN	4 (33.33)	3 (20)
	Total (non-missing)	12 (100)	15 (100)
Week 41-48	Within normal limit	9 (75)	7 (58.33)
	Within 1-3x ULN	3 (25)	5 (41.67)
	Total (non-missing)	12 (100)	12 (100)
Week 49-56	Within normal limit	6 (85.71)	8 (100)
	Within 1-3x ULN	1 (14.29)	0 (0)
	Total (non-missing)	7 (100)	8 (100)
End of therapy	Below normal limit	1 (0.6)	2 (1.1)
	Within normal limit	60 (36.14)	116 (63.74)
	Within 1-3x ULN	85 (51.2)	56 (30.77)
	Within >3-5x ULN	17 (10.24)	7 (3.85)
	Within >5-20x ULN	3 (1.81)	1 (0.55)
	Total (non-missing)	166 (100)	182 (100)
End of observation	Below normal limit	1 (1.67)	1 (1.54)
	Within normal limit	16 (26.67)	37 (56.92)
	Within 1-3x ULN	29 (48.33)	23 (35.38)
	Within >3-5x ULN	10 (16.67)	2 (3.08)
	Within >5-20x ULN	4 (6.67)	2 (3.08)
	Total (non-missing)	60 (100)	65 (100)

in case of > 1 measurement in the respective time window, the worst value is shown

b. Bilirubin

		Lowest value		*Highest value*	
Total bilirubin [mg/dl]	*N (Nmiss)*	*Mean (SD)*	*Median (Min, Max)*	*Mean (SD)*	*Median (Min, Max)*
Initial visit	154 (20)	0.74 (0.82)	0.55 (0.15, 8.99)	0.74 (0.82)	0.55 (0.15, 8.99)
Week 1-8	284 (17)	1.01 (2.00)	0.62 (0.15, 27.10)	2.15 (10.82)	0.90 (0.15, 178)
Week 9-16	148 (13)	1.23 (2.48)	0.60 (0.15, 20.18)	1.35 (2.50)	0.71 (0.18, 20.18)
Week 17-24	69 (5)	1.25 (2.64)	0.60 (0.17, 20.77)	1.39 (2.70)	0.70 (0.21, 20.77)
Week 25-32	32 (2)	0.70 (0.41)	0.63 (0.20, 2.22)	0.76 (0.41)	0.68 (0.20, 2.22)
Week 33-40	15 (0)	1.19 (2.15)	0.60 (0.23, 8.83)	1.27 (2.12)	0.75 (0.23, 8.83)
Week 41-48	12 (0)	0.54 (0.28)	0.48 (0.23, 1.28)	0.65 (0.26)	0.64 (0.23, 1.28)
Week 49-56	7 (1)	0.59 (0.23)	0.50 (0.35, 0.90)	0.64 (0.21)	0.60 (0.35, 0.90)
End of therapy	158 (27)	1.52 (3.01)	0.70 (0.15, 28.8)	1.78 (3.77)	0.80 (0.15, 38.60)
End of observation	63 (5)	2.39 (4.98)	1.06 (0.10, 34.33)	2.81 (5.21)	1.10 (0.27, 34.33)
Maximum change from baseline					
End of therapy	62 (112)	1.02 (1.77)	0.43 (-1.05, 10.31)		
End of observation	14 (160)	2.17 (3.93)	0.82 (-0.20, 14.20)		

10.2.5 Performance status

At the initial visit, more than 60% of patients had an ECOG performance status of 1 (i.e. restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work). The proportion of grade 1 patients stayed relatively stable during the study, but was, however, lower at the end of therapy (37.59%) and at the end of observation (12.2%). However, for 15.52% and 6.71% of patients no more data were available at the end of therapy and observation, respectively. The proportion of patients with a grade 3 performance status (i.e. capable of only limited self-care, confined to bed or chair, more than 50% waking hours) was below 5% during the study except at the end of therapy (12.07%). 56.1% of patients had a grade 4 performance status (i.e. completely disabled; cannot carry on any self-care; totally confined to bed or chair) at the end of observation as compared to hardly any patients during the course of the study (Table 10).

Table 10: ECOG performance status (SAF) (Data source: Table 17 of statistical report V1.0)

Performance status (ECOG)	***0***	***1***	***2***	***3***	***4***	***Total (non-missing)***
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*
Initial visit	93 (20.35)	279 (61.05)	80 (17.51)	5 (1.09)	0 (0)	457 (100)
Week 1-8	47 (14.78)	180 (56.60)	81 (25.47)	9 (2.83)	1 (0.31)	318 (100)
Week 9-16	29 (15.68)	106 (57.30)	45 (24.32)	5 (2.70)	0 (0)	185 (100)
Week 17-24	5 (5.49)	47 (51.65)	35 (38.46)	4 (4.40)	0 (0)	91 (100)
Week 25-32	5 (11.90)	26 (61.90)	11 (26.19)	0 (0)	0 (0)	42 (100)
Week 33-40	2 (11.11)	10 (55.56)	6 (33.33)	0 (0)	0 (0)	18 (100)
Week 41-48	3 (21.43)	8 (57.14)	3 (21.43)	0 (0)	0 (0)	14 (100)
Week 49-56	2 (20.00)	7 (70.00)	1 (10.00)	0 (0)	0 (0)	10 (100)
End of therapy[1]	17 (5.86)	109 (37.59)	81 (27.93)	35 (12.07)	3 (1.03)	294 (100)
End of observation[2]	27 (16.46)	20 (12.2)	12 (7.32)	2 (1.22)	92 (56.1)	165 (100)

if more than one visit is documented in the time window the worst ECOG is presented

[1] no new data available of 45 patients (15.52%)
[2] no new data available of 11 patients (6.71%)

10.2.6 Stivarga® therapy

For more than half of patients the initial treatment dose was 160 mg and for about one quarter it was 80 mg. (Table 11 a). The median treatment duration was 71 days (range: 1 – 1085 days). There were in total 383 dose modifications and 260 treatment interruptions. 137 of the dose modifications (35.77%) and 201 of the interruptions (77.31%) were due to adverse events. The median duration until the first dose modification was 28 days (range: 2 – 427 days) and the median duration of the dose modification was 20 days (range: 0 – 611 days). With respect to treatment interruptions, the median duration was 8 days (range: 0 – 52 days; Table 11 b). 93 patients (20.04%) had dose modifications only, 62 patients (13.36%) had treatment interruptions only, 107 patients (23.06%) had both, whereas 202 patients (43.53%) had neither (Table 11 c). The new dose after the dose modification was in most cases 120 mg (44.13%), 80 mg (32.9%) or 160 mg (17.23%; Table 11 a). Most patients took the tablet in the morning (60.78%; Table 11 d).

Table 11: Stivarga® treatment (SAF) (Data source: Table 25, 26, 28, 29, 31, 32, 33 of statistical report V1.0)

a. Daily treatment dose

Daily treatment dose [mg]	***Initial*** *N (%)*	***New*** *N (%)*
40	16 (3.45)	14 (3.66)
60	0 (0)	1 (0.26)
80	117 (25.22)	126 (32.90)
120	81 (17.46)	169 (44.13)
140	1 (0.22)	0 (0)
160	249 (53.66)	66 (17.23)
Other	0 (0)	7 (1.83)
Total	464 (100)	383 00)

b. Duration of treatment, dose modifications and interruptions

	N (Nmiss)	*Mean (SD)*	*Median (Min, Max)*	*P25, P75*
Duration of treatment [days]	464 (0)	93.15 (98.63)	71 (1, 1085)	31.5, 115.5
Time to first dose modification [days]	200 (0)	33.34 (40.01)	28 (2, 427)	12, 37
Duration of dose modification [days]	379 (4)	39.88 (55.76)	20 (0, 611)	7, 52
Duration of interruption [days]	232 (28)	11.51 (9.78)	8 (0, 52)	6, 15.5

c. Dose modifications and interruptions

Number of patients with…	*N (%)*
Dose modifications only	93 (20.04)
Interruptions only	62 (13.36)
Dose modifications and interruptions	107 (23.06)
No dose modifications or interruptions	202 (43.53)
Number of patients	464 (100)

d. Usual time of intake

Usual time of intake*	*N (%)*
In the morning	282 (60.78)
In the evening	54 (11.64)
Other time	24 (5.17)
Unknown	215 (46.34)
Missing	2 (0.43)
Number of patients	464 (100)

* multiple answers possible

10.2.7 End of therapy/observation

294 patients (63.36%) permanently discontinued treatment (with completed 'end of therapy' form). Premature treatment discontinuation was mainly due to disease progression or adverse events/toxicities (Table 12). All of these patients participated in the study after end of therapy.

165 patients (35.56%) had a documented end of observation (with completed 'end of observation' form). Death was the reason for most patients (n=92; 19.83%), followed by patient's decision (n=31; 6.68%) and lost to follow-up (n=23; 4.96%; Table 13).

Table 12: End of therapy (SAF) (Data source: Table 35 and 36 of statistical report V1.0)

	N (%)
Number of patients	464 (100)
Premature termination of study treatment	294 (63.36)
Reasons for treatment discontinuation	
Patient's decision	25 (5.39)
Disease progression	160 (34.48)
Deterioration of general condition	37 (7.97)
Adverse event/toxicity	62 (13.36)
Other	10 (2.16)
Missing	170 (36.64)

Table 13: End of observation (SAF) (Data source: Table 52 of statistical report V1.0)

	N (%)
Number of patients	464 (100)
End of observation	165 (35.56)
Reasons for end of observation	
Death	92 (19.83)
Lost to follow-up	23 (4.96)
End of study	3 (0.65)
Patient's decision	31 (6.68)
Other	16 (3.45)
Missing	299 (64.44)

10.2.8 Concomitant medication

389 patients (83.84%) received concomitant medication at the end of treatment. Indications were mainly adverse events (except hand-foot-skin reaction) and concomitant diseases/conditions (Table 14 a). Most often used concomitant medications were pyrazolones (143 patients, 30.82%), proton pump inhibitors (129 patients, 27.8%), natural opium alkaloids (84 patients, 18.1%), propulsives (84 patients, 18.1%), antipropulsives (79 patients, 17.03%), selective beta blocking agents (80 patients, 17.24%) and ACE inhibitors (78 patients, 16.81%; Table 14 b).

Table 14: Concomitant medication at end of treatment (SAF) (Data source: Table 37 - 39 of statistical report V1.0)

a. Indication

Concomitant medication	*N (%)*
Number of patients	464 (100)
Concomitant medication	389 (83.84)
Indication	
AE, except HFSR	266 (57.33)
Concomitant disease/condition	244 (52.59)
Other	191 (41.16)
Missing	3 (0.65)

b. List of concomitant medications with a frequency of ≥ 5%

Concomitant medication according to WHO (patient based)		*N (%)*
Number of patients		464 (100)
Alimentary tract and metabolism	Antiinfectives and antiseptics for local oral treatment	31 (6.68)
	Antipropulsives	79 (17.03)
	Osmotically acting laxatives	40 (8.62)
	Other agents for local oral treatment	50 (10.78)
	Propulsives	84 (18.10)
	Proton pump inhibitors	129 (27.80)
Antiinfectives for systemic use	Fluoroquinolones	32 (6.90)
Blood and blood forming organs	Platelet aggregation inhibitors excl. heparin	36 (7.76)
Cardiovascular system	Ace inhibitors, plain	78 (16.81)
	Angiotensin ii antagonists, plain	32 (6.90)
	Beta blocking agents, selective	80 (17.24)
	Dihydropyridine derivatives	56 (12.07)
	Other cardiac preparations	25 (5.39)
	Sulfonamides, plain	44 (9.48)
Dermatologicals	Corticosteroids, moderately potent (group ii)	37 (7.97)
Genitourinary system and sex hormones	Antiinflammatory products for vaginal administration	29 (6.25)
Musculoskeletal	Antiinflammatory preparations, non-steroids for topical use	38 (8.19)

system	Propionic acid derivatives	28 (6.03)
Nervous system	Benzodiazepine derivatives	30 (6.47)
	Natural opium alkaloids	84 (18.10)
	Opioid anesthetics	31 (6.68)
	Other antiepileptics	31 (6.68)
	Other opioids	44 (9.48)
	Phenylpiperidine derivatives	37 (7.97)
	Pyrazolones	143 (30.82)
	Salicylic acid and derivatives	33 (7.11)
Sensory organs	Corticosteroids, plain	52 (11.21)
	Fluoroquinolones	31 (6.68)
Systemic hormonal preparations*	Glucocorticoids	64 (13.79)
	Thyroid hormones	48 (10.34)

*excl. sex hormones and insulins

10.2.9 Hand-Foot-Skin Reaction (HFSR)

168 patients (36.21%) received preventive or therapeutic treatment for HFSR. Treatment was mainly preventive and urea-based creams were most frequently used (Table 15 a and b; for a list of the applied oral analgesics see Table 44 of the statistical report). 107 patients had at least one ongoing preventive treatment and 22 patients had at least one ongoing therapeutic treatment. For patients with completed treatment, the median total treatment duration was 70 days (range: 0 – 314 days) for preventive and 31.5 days (range: 6 – 198 days) for therapeutic treatment (Table 15 c).

Table 15: Treatment for HFSR (SAF) (Data source: Table 41 – 43 and 46 of statistical report V1.0)

a.

Treatment for HFSR	*N (%)*
Number of patients	464 (100)
HFSR treatment	168 (36.21)
Preventive treatment only	122 (26.29)
Therapeutic treatment only	35 (7.54)
Preventive and therapeutic treatment	11 (2.37)

b.

Which treatment	***Preventive*** *N (%)*	***Therapeutic*** *N (%)*	***Total*** *N (%)*
Urea-based cream	101 (75.94)	17 (36.96)	114 (67.86)
Non-urea based cream	23 (17.29)	4 (8.70)	27 (16.07)
Keratolytic cream	0 (0)	1 (2.17)	1 (0.60)
Topical corticosteroids	6 (4.51)	9 (19.57)	15 (8.93)
Topical analgesics	0 (0)	2 (4.35)	2 (1.19)
Oral analgesics	2 (1.50)	5 (10.87)	7 (4.17)
Other	18 (13.53)	16 (34.78)	34 (20.24)

Patients with corresponding therapy	133 (100)	46 (100)	168 (100)

c.

Duration per patient [days]*	*N (Nmiss)*	*Mean (SD)*	*Median (Min, Max)*	*P25, P75*
Preventive treatment	26 (0)	82.08 (77.19)	70 (0, 314)	14, 101
Therapeutic treatment	24 (0)	57.04 (57.80)	31.5 (6, 198)	14, 107

*from first treatment to last (interruptions are not subtracted); ongoing treatments are not included

10.3 Outcome data

The survival status was assessed for the vast majority of patients during all follow-up visits (Table 16 a). Lack of assessment was mainly because the patient was lost to follow-up (Table 16 b).

Table 16: Assessment of survival status (SAF) (Data source: Table 47 and 48 of statistical report V1.0)

a.

Survival status assessed	*N*
Follow-up visit 1 (n=293)	288
Follow-up visit 2 (n=209)	200
Follow-up visit 3 (n=139)	136
Follow-up visit 4 (n=109)	108
Follow-up visit 5 (n=97)	91
Follow-up visit 6 (n=72)	70
Follow-up visit 7 (n=59)	59
Follow-up visit 8 (n=43)	39
Follow-up visit 9 (n=33)	32
Follow-up visit 10 (n=29)	29
Follow-up visit 11 (n=21)	20
Follow-up visit 12 (n=19)	17
Follow-up visit 13-26 (n=1-10)	1-10

b.

Reason for no assessment	***Lost to follow-up***	***Patient's decision***	***Other***
	N	*N*	*N*
Follow-up visit 1 (n=5)	2	1	2
Follow-up visit 2 (n=9)	5	1	3
Follow-up visit 3 (n=3)	2	0	1
Follow-up visit 4 (n=1)	1	0	0
Follow-up visit 5 (n=6)	5	0	1
Follow-up visit 6 (n=2)	1	0	1
Follow-up visit 8 (n=4)	4	0	0
Follow-up visit 9 (n=1)	1	0	0
Follow-up visit 11 (n=1)	1	0	0
Follow-up visit 12 (n=2)	1	0	1

10.4 Main results

10.4.1 Primary objective

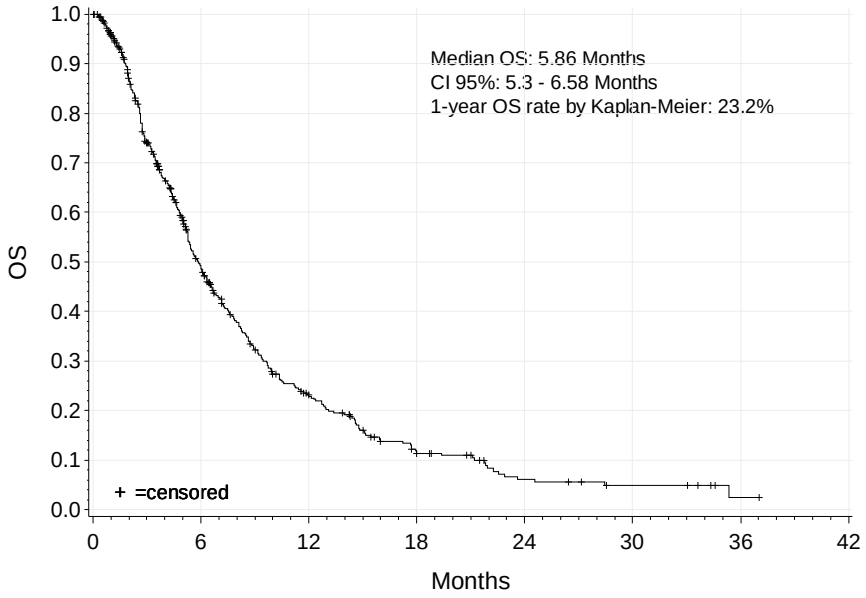
10.4.1.1 Overall survival (OS)

Median overall survival of the intent-to-treat set (ITT; n=463) was 5.86 months (CI 95%: 5.3 – 6.58 months; Table 17). 1-year survival was 23.2% (Figure 3).

Table 17: Overall survival [months] (ITT) (Data source: Table 53 of statistical report V1.0)

N	*Death*	*Censored*	*Mean (SE)*	*Median (CI 95%)*	*P25 (CI 95%)*	*P75 (CI 95%)*
463	341	122	8.77 (0.46)	5.86 (5.30- 6.58)	2.89 (2.63- 3.45)	11.22 (9.67- 12.93)

Figure 3: Overall survival [months] (ITT) (Data source: Fig. 1 of statistical report V1.0)



10.4.2 Secondary objectives

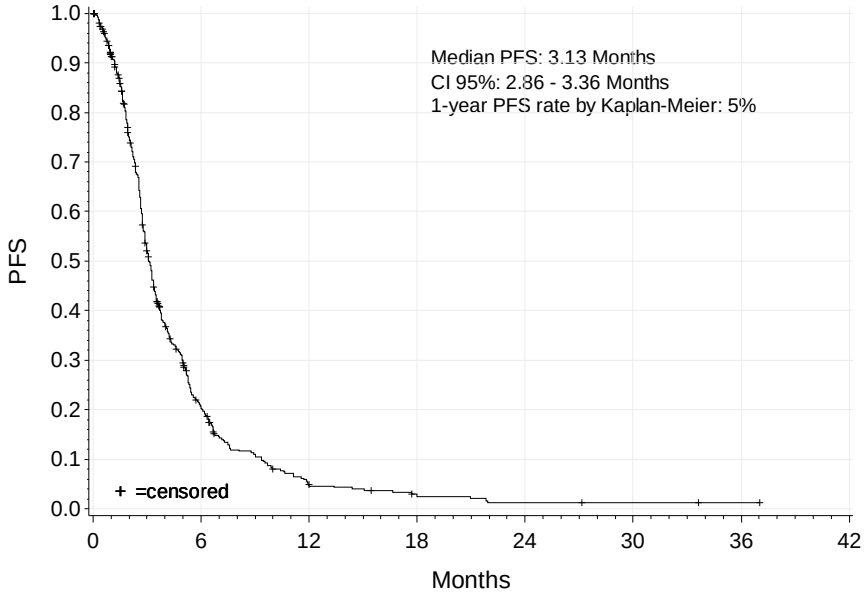
10.4.2.1 Progression-free survival (PFS)

Median progression-free survival of the ITT was 3.13 months (CI 95%: 2.86 – 3.36 months; Table 18). 1-year PFS was 5% (Figure 4).

Table 18: Progression-free survival [months] (ITT) (Data source: Table 54 of statistical report V1.0)

N	*Progress/Death*	*Censored*	*Mean (SE)*	*Median (CI 95%)*	*P25 (CI 95%)*	*P75 (CI 95%)*
463	390	73	4.46 (0.21)	3.13 (2.86- 3.36)	2.01 (1.81- 2.27)	5.36 (5.03- 5.95)

Figure 4: Progression-free survival [months] (ITT) (Data source: Fig. 2 of statistical report V1.0)



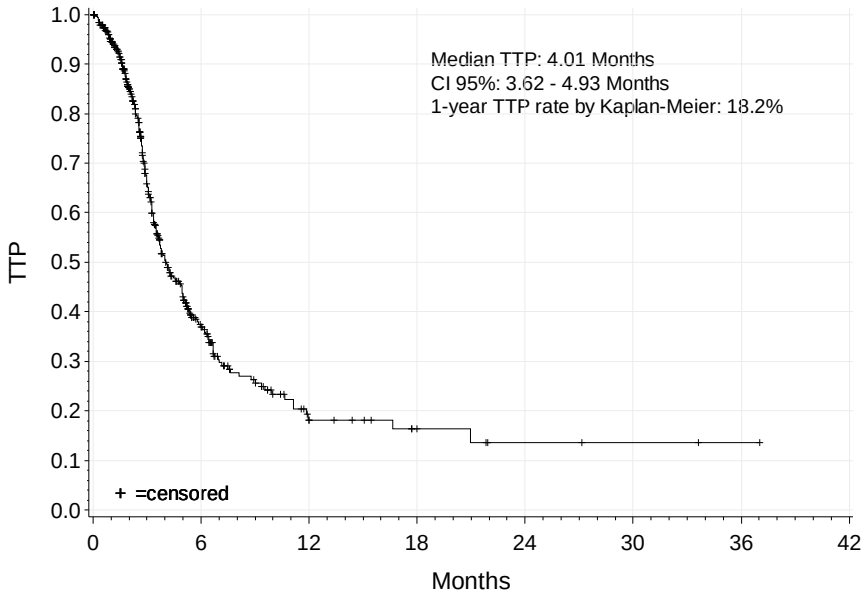
10.4.2.2 Time to progression (TTP)

Median time to tumor progression of the ITT was 4.01 months (CI 95%: 3.62 – 4.93 months; Table 19). 1-year TTP was 18.2% (Figure 5).

Table 19: Time to progression [months] (ITT) (Data source: Table 55 of statistical report V1.0)

N	*Progress*	*Censored*	*Mean (SE)*	*Median (CI 95%)*	*P25 (CI 95%)*	*P75 (CI 95%)*
463	240	223	7.23 (0.46)	4.01 (3.62- 4.93)	2.7 (2.47- 2.80)	9.34 (6.97- 11.94)

Figure 5: Time to progression [months] (ITT) (Data source: Fig. 3 of statistical report V1.0)



10.4.2.3 Disease control rate (DCR)

277 patients (59.83%) had an evaluation of the tumor status post-baseline. 26.71% of these patients (CI 95%: 21.6 – 32.34%) had partial response (PR) or stable disease (SD) as best response. No patient achieved complete response (CR). However, a post-baseline evaluation of the tumor status was only performed for about 60% of patients (Table 20).

Table 20: Disease control rate (ITT) (Data source: Table 56 of statistical report V1.0)

N	*CR+PR+SD*	*=DCR (CI 95%)*
277	74	26.71 (21.60- 32.34)

10.4.2.4 Duration of Stivarga® treatment

The median treatment duration within the ITT was 71 days (range: 1 – 1085 days; Table 21).

Table 21: Duration of treatment [days] (ITT) (Data source: Table 57 of statistical report V1.0)

Duration of treatment [days]	*N (Nmiss)*	*Mean (SD)*	*Median (Min, Max)*	*P25, P75*
	463 (0)	93.25 (98.72)	71 (1, 1085)	31, 116

10.4.2.5 Tumor status

Table 22 gives an overview of the tumor status during the observational period. At the majority of visits, stable disease (SD) and progressive disease (PD; clinical or radiological) occurred most often. At the end of therapy, 1 patient (0.54%) had partial response (PR), 3 patients (1.63%) had SD and 178 patients (96.74%) had PD (49 patients (26.63%) clinical and 129 patients (70.11%) radiological). At the end of observation, 4 patients (11.76%) had SD and 30 patients (88.23%) had PD (9 patients (26.47%) clinical and 21 patients (61.76%) radiological; Table 22 a).

For most patients with an evaluation of the tumor status post-baseline (202 of 277 patients; 72.92%) PD was the best response (for 61 patients (22.02% clinical and for 141 patients (50.9%) radiological). 64 patients (23.1%) had SD and 10 patients (3.61%) had PR as best response (Table 22 b).

Table 22: Tumor status (ITT) (Data source: Table 58 of statistical report V1.0)

a.

Tumor status	*N (Nmiss)*	***PR*** *N (%)*	***SD*** *N (%)*	***PD (clinical)*** *N (%)*	***PD (radiolog.)*** *N (%)*	***n/a*** *N (%)*
Week 0-8	45 (382)	3 (6.67)	19 (42.22)	12 (26.67)	11 (24.44)	
Week 9-16	76 (175)	5 (6.58)	43 (56.58)	4 (5.26)	22 (28.95)	2 (2.63)
Week 17-24	32 (97)	2 (6.25)	18 (56.25)	3 (9.38)	9 (28.13)	
Week 25-32	18 (44)	1 (5.56)	7 (38.89)	2 (11.11)	8 (44.44)	
Week 33-40	9 (21)	1 (11.11)	7 (77.78)		1 (11.11)	
Week 41-48	6 (11)		3 (50.00)		3 (50.00)	
Week 49-56	5 (8)	3 (60.00)		1 (20.00)	1 (20.00)	
Week 57-64	4 (5)	1 (25.00)	3 (75.00)			
Week 65-72	2 (4)		2 (100)			
Week 73-80	1 (4)		1 (100)			
Week 81-88	1 (3)	1 (100)				
Week 89-96	0 (3)					
Week 97-104	0 (1)					
Week 105-112	1 (0)		1 (100)			
Week 113-120	0 (2)					
Week 121-128	0 (1)					
Week 129-136	0 (1)					
Week 137-144	1 (1)		1 (100)			
Week 145-152	0 (1)					
Week 153-160	0 (1)					
End of therapy	184 (110)	1 (0.54)	3 (1.63)	49 (26.63)	129 (70.11)	2 (1.09)
End of observation	34 (130)	0 (0)	4 (11.76)	9 (26.47)	21 (61.76)	0 (0)

b.

Best response	*N (%)*
Number of patients with tumor status	277 (100)
Partial response	10 (3.61)

Stable disease	64 (23.10)
Progressive disease (clinical)	61 (22.02)
Progressive disease (radiological)	141 (50.90)
Not applicable	1 (0.36)

10.5 Other analyses

Stratified analyses were performed for the following subgroups: age, gender, baseline ECOG, KRAS mutation at initial diagnosis, prior Bevacizumab treatment, time from initial CRC diagnosis to start of therapy, number of prior systemic cancer therapies, primary tumor site, tumor sidedness and metastasis location. These analyses were of explorative nature and are hypothesis generating only. Due to the non-interventional study design, it cannot be excluded that identified subgroup differences might be due to differences in prognostic factors rather than effects of study treatment.

Trends for subgroup differences for OS were observed for baseline ECOG, prior Bevacizumab treatment, time from diagnosis, tumor sidedness and metastasis location. OS was longer for patients with a better performance status, without prior Bevacizumab treatment, with a duration from initial CRC diagnosis to start of therapy of ≥ 18 months, with a left-sided tumor, with metastases in lung and not liver as well as with metastases in lung and not skeleton (Table 23).

Subgroup differences for PFS followed a similar trend as for OS. In addition, PFS was longer for older patients and for patients with metastases only in liver (Table 24). Subgroup differences for TTP followed an allover similar trend as for PFS (Table 25). DCR was higher for older and male patients, for patients with an asymptomatic performance status, with a KRAS mutation, with more than 3 prior treatment lines, and with a left-sided tumor. DCR was lower in patients with a shorter time (< 18 months) from diagnosis. Regarding metastases locations, DCR was highest in patients with metastases only in liver, in lung and not liver, and in lung and not skeleton (Table 26). However these data refer to post-baseline evaluations of the tumor status, which were only performed for about 60% of patients. The duration of Stivarga® treatment was longer in older patients, in patients with a better performance status, a KRAS mutation, no prior Bevacizumab treatment, a longer time from diagnosis, with more than 3 prior treatment lines, and a left-sided tumor location. Regarding metastases locations, treatment was longest in patients with metastases only in liver, in lung and not liver, and in lung and not skeleton (Table 27).

Table 23: Overall survival according to subgroups [months] (ITT) (Data source: Table 94, 104, 114, 130, 143, 154, 166, 176, 186, 196, 197, 198 of statistical report V1.0)

OS- Stratification		*N*	*Death*	*Censored*	*Mean (SE)*	*Median (CI 95%)*	*P25 (CI 95%)*	*P75 (CI 95%)*
Total		463	341	122	8.77 (0.46)	5.86 (5.30- 6.58)	2.89 (2.63- 3.45)	11.22 (9.67- 12.93)
Age	< 65 years	179	133	46	7.83 (0.56)	5.99 (4.70- 6.94)	2.83 (2.34- 3.72)	9.93 (8.62- 12.70)
	≥ 65 years	284	208	76	9.29 (0.64)	5.82 (5.26- 6.71)	2.99 (2.63- 3.62)	11.55 (9.67- 14.57)
Gender	Female	183	134	49	8.90 (0.81)	5.82 (4.70- 6.64)	2.76 (2.50- 3.52)	9.64 (8.62- 13.09)
	Male	280	207	73	8.61 (0.50)	6.02 (5.30- 7.07)	3.19 (2.60- 3.72)	11.91 (9.74- 14.64)
ECOG*	0/1	371	274	97	9.19 (0.51)	6.12 (5.39- 6.94)	3.42 (2.80- 3.78)	12.27 (10.00- 14.57)
	2	80	59	21	5.44 (0.51)	4.44 (2.50- 6.58)	1.64 (1.15- 2.37)	8.91 (6.71- 11.55)
KRAS mutation	No	160	117	43	7.81 (0.55)	5.56 (4.61- 7.30)	3.16 (2.53- 3.72)	11.22 (9.01- 14.28)
	Yes	214	157	57	9.13 (0.77)	5.95 (5.07- 7.17)	2.80 (2.34- 3.49)	10.36 (8.85- 13.39)
	Unknown	89	67	22	9.25 (0.95)	5.99 (5.16- 7.57)	2.89 (2.60- 4.67)	14.41 (9.14- 21.84)
Prior Be-vacizumab	No	302	217	85	9.22 (0.57)	6.38 (5.30- 7.57)	2.96 (2.66- 3.68)	12.14 (9.93- 14.54)
	Yes	161	124	37	7.17 (0.50)	5.36 (4.51- 6.12)	2.63 (2.11- 3.55)	9.21 (7.37- 12.27)
Time from diagnosis to therapy	< 18 months	72	54	18	6.13 (0.70)	4.14 (2.66- 5.95)	1.97 (1.61- 2.34)	8.62 (5.95- 12.14)
	≥ 18 months	263	198	65	8.55 (0.52)	5.76 (5.26- 6.71)	3.42 (2.76- 3.78)	10.63 (9.01- 13.39)
	Missing	128	89	39	9.68 (0.93)	6.94 (5.33- 8.62)	2.83 (2.37- 4.44)	12.96 (10.00- 15.95)
Prior treat-ment lines	≤ 3	442	326	116	8.76 (0.47)	5.86 (5.26- 6.58)	2.89 (2.63- 3.45)	11.22 (9.44- 12.93)
	> 3	21	15	6	7.71 (1.14)	8.29 (2.73- 10.53)	2.73 (1.78- 5.56)	12.96 (8.29- N/D)
Primary tumor site	Colon	292	217	75	8.02 (0.49)	5.43 (4.84- 6.32)	2.73 (2.53- 3.29)	10.36 (8.62- 12.83)
	Rectum	171	124	47	9.55 (0.78)	6.58 (5.43- 7.83)	3.45 (2.73- 4.41)	12.14 (9.67- 15.13)
Tumor sidedness	Left	344	254	90	9.19 (0.55)	5.95 (5.26- 6.94)	3.22 (2.66- 3.72)	12.14 (9.93- 14.64)
	Right	119	87	32	7.22 (0.70)	5.56 (4.18- 6.84)	2.60 (1.97- 3.45)	8.91 (7.73- 11.28)
Metastasis location	Liver only	101	64	37	8.30 (0.65)	6.51 (5.59- 8.52)	3.42 (2.53- 5.20)	12.7 (9.34- 17.99)
	Other	362	277	85	8.48 (0.49)	5.43 (5.00- 6.35)	2.83 (2.60- 3.42)	10.63 (9.18- 12.96)

Liver/No lung	152	100	52	8.18 (0.58)	6.28 (5.49- 7.60)	3.09 (2.47- 4.77)	10.36 (8.91- 15.16)
Lung/No liver	78	54	24	11.09 (1.11)	8.13 (5.99- 10.36)	4.47 (2.80- 5.72)	15.13 (10.63- 24.57)
Liver/Lung	197	162	35	7.30 (0.55)	5.00 (4.34- 6.02)	2.66 (2.34- 3.22)	9.41 (7.83- 11.41)
No liver/No lung	36	25	11	8.16 (1.31)	5.23 (3.16- 11.22)	2.60 (1.55- 4.18)	13.09 (5.43- N/D)
Liver/No Skeleton	144	95	49	8.05 (0.55)	6.32 (5.56- 8.22)	3.42 (2.53- 5.07)	10.36 (8.91- 15.16)
Lung/No Skeleton	71	49	22	11.45 (1.18)	8.26 (5.99- 10.63)	4.84 (2.80- 5.86)	17.20 (12.01- 24.57)
Liver/Lung/No Skeleton	175	143	32	7.62 (0.60)	5.13 (4.54- 6.58)	2.73 (2.50- 3.36)	9.90 (8.09- 12.14)
Skeleton	38	29	9	6.06 (1.00)	4.24 (2.60- 5.26)	2.30 (1.58- 3.45)	6.35 (4.44- 12.40)
No Liver/No Lung/No Skeleton	35	25	10	7.66 (1.26)	4.34 (3.16- 9.18)	2.37 (1.55- 4.18)	12.96 (5.30- 21.09)

* due to low patient numbers ECOG of 3 and missing ECOG are not shown here

Table 24: Progression-free survival according to subgroups [months] (ITT) (Data source: Table 95, 105, 117, 132, 144, 155, 167, 177, 187, 199, 200, 201 of statistical report V1.0)

PFS- Stratification		*N*	*Progress/ Death*	*Censored*	*Mean (SE)*	*Median (CI 95%)*	*P25 (CI 95%)*	*P75 (CI 95%)*
Total		463	390	73	4.46 (0.21)	3.13 (2.86- 3.36)	2.01 (1.81- 2.27)	5.36 (5.03- 5.95)
Age	< 65 years	179	152	27	3.76 (0.23)	2.96 (2.63- 3.36)	1.94 (1.64- 2.20)	4.97 (3.78- 5.86)
	≥ 65 years	284	238	46	4.87 (0.31)	3.22 (2.89- 3.55)	2.11 (1.81- 2.50)	5.43 (5.13- 6.68)
Gender	Female	183	153	30	4.01 (0.26)	2.86 (2.63- 3.22)	1.97 (1.74- 2.27)	5.20 (4.18- 5.95)
	Male	280	237	43	4.66 (0.29)	3.36 (2.96- 3.62)	2.11 (1.78- 2.37)	5.56 (5.00- 6.38)
ECOG*	0/1	371	313	58	4.64 (0.24)	3.29 (2.96- 3.55)	2.14 (1.91- 2.37)	5.43 (5.13- 6.18)
	2	80	68	12	3.64 (0.38)	2.57 (2.20- 3.06)	1.64 (0.89- 1.94)	4.18 (3.22- 8.91)
KRAS mutation	No	160	132	28	4.14 (0.30)	3.03 (2.70- 3.68)	1.94 (1.64- 2.24)	5.20 (4.61- 6.22)
	Yes	214	183	31	4.16 (0.28)	3.06 (2.73- 3.36)	1.97 (1.64- 2.34)	5.30 (4.21- 5.99)
	Unknown	89	75	14	5.55 (0.62)	3.36 (2.86- 4.31)	2.37 (1.81- 2.76)	6.25 (4.97- 9.44)
Prior Be-	No	302	248	54	4.86 (0.29)	3.26 (2.93- 3.62)	2.17 (1.84- 2.37)	5.99 (5.26- 6.68)

vacizumab	Yes	161	142	19	3.73 (0.26)	2.86 (2.63- 3.36)	1.91 (1.64- 2.17)	4.31 (3.78- 5.30)
Time from diagnosis to therapy	< 18 months	72	62	10	3.19 (0.42)	2.63 (1.97- 2.96)	1.64 (1.22- 1.97)	3.65 (3.13- 4.14)
	≥ 18 months	263	223	40	4.54 (0.27)	3.26 (2.89- 3.68)	2.20 (1.91- 2.53)	5.36 (5.13- 6.25)
	Missing	128	105	23	4.98 (0.46)	3.29 (2.73- 3.98)	1.94 (1.64- 2.53)	6.41 (5.00- 7.17)
Prior treat-ment lines	≤ 3	442	372	70	4.47 (0.22)	3.16 (2.86- 3.42)	2.01 (1.81- 2.27)	5.33 (5.00- 5.95)
	> 3	21	18	3	4.21 (0.71)	2.96 (1.91- 5.56)	1.91 (0.69- 2.73)	7.50 (2.96- 9.54)
Primary tumor site	Colon	292	248	44	4.32 (0.26)	2.96 (2.73- 3.26)	1.97 (1.74- 2.27)	5.30 (4.61- 5.95)
	Rectum	171	142	29	4.47 (0.28)	3.42 (2.86- 3.85)	2.01 (1.81- 2.53)	5.79 (5.03- 6.68)
Tumor sidedness	Left	344	293	51	4.67 (0.26)	3.22 (2.96- 3.49)	2.01 (1.81- 2.34)	5.43 (5.07- 6.22)
	Right	119	97	22	3.81 (0.32)	2.86 (2.57- 3.36)	1.97 (1.61- 2.37)	5.00 (3.98- 5.99)
Metastasis location	Liver only	101	78	23	4.94 (0.45)	3.45 (2.96- 5.00)	2.53 (1.94- 2.73)	6.38 (5.20- 7.60)
	Other	362	312	50	4.31 (0.23)	2.96 (2.76- 3.29)	1.91 (1.74- 2.17)	5.23 (4.64- 5.66)
	Liver/No lung	152	119	33	4.52 (0.33)	3.42 (2.89- 4.21)	2.17 (1.84- 2.53)	5.99 (5.20- 6.68)
	Lung/No liver	78	65	13	5.58 (0.51)	4.38 (3.22- 5.26)	2.60 (2.11- 3.16)	7.01 (5.33- 9.54)
	Liver/Lung	197	175	22	3.84 (0.30)	2.80 (2.63- 3.06)	1.81 (1.64- 2.07)	4.21 (3.65- 5.20)
	No liver/No lung	36	31	5	4.86 (0.95)	2.93 (2.20- 4.90)	1.84 (1.38- 2.60)	5.36 (3.16- 11.15)
	Liver/No Skeleton	144	114	30	4.63 (0.34)	3.45 (2.96- 4.34)	2.27 (1.91- 2.57)	6.09 (5.30- 7.30)
	Lung/No Skeleton	71	59	12	5.67 (0.55)	4.84 (3.22- 5.26)	2.60 (1.81- 3.16)	7.01 (5.33- 10.63)
	Liver/Lung/No Skeleton	175	156	19	3.91 (0.33)	2.80 (2.63- 3.09)	1.81 (1.61- 2.14)	4.24 (3.65- 5.30)
	Skeleton	38	30	8	3.53 (0.52)	2.37 (1.91- 3.29)	1.81 (1.22- 2.24)	4.14 (3.22- 6.41)
	No Liver/No Lung/No Skeleton	35	31	4	4.27 (0.79)	2.86 (2.20- 4.18)	1.84 (1.38- 2.60)	5.23 (3.16- 7.17)

* due to low patient numbers ECOG of 3 and missing ECOG are not shown here

Table 25: Time to progression according to subgroups [months] (ITT) (Data source: Table 96, 106, 120, 134, 145, 157, 168, 178, 188, 202, 203, 204 of statistical report V1.0)

TTP- Stratification		*N*	*Progress*	*Censored*	*Mean (SE)*	*Median (CI 95%)*	*P25 (CI 95%)*	*P75 (CI 95%)*
Total		463	240	223	7.23 (0.46)	4.01 (3.62- 4.93)	2.70 (2.47- 2.80)	9.34 (6.97- 11.94)
Age	< 65 years	179	100	79	4.80 (0.31)	3.59 (3.22- 4.57)	2.37 (1.91- 2.73)	6.68 (5.79- 10.66)
	≥ 65 years	284	140	144	7.95 (0.60)	4.47 (3.88- 5.36)	2.80 (2.57- 2.96)	11.15 (7.63- N/D)
Gender	Female	183	96	87	5.40 (0.36)	3.72 (3.09- 5.03)	2.57 (2.20- 2.73)	9.34 (6.09- N/D)
	Male	280	144	136	7.50 (0.59)	4.21 (3.72- 5.03)	2.76 (2.47- 3.03)	9.54 (6.68- 20.99)
ECOG*	0/1	371	200	171	7.26 (0.50)	4.21 (3.72- 5.03)	2.70 (2.37- 2.83)	8.78 (6.68- 16.64)
	2	80	34	46	5.68 (0.59)	3.52 (2.96- 9.01)	2.57 (2.34- 3.06)	9.93 (5.36- N/D)
KRAS mutation	No	160	80	80	5.63 (0.41)	4.24 (3.49- 5.13)	2.63 (1.94- 2.83)	9.54 (5.86- N/D)
	Yes	214	115	99	6.70 (0.65)	3.72 (3.26- 4.97)	2.60 (2.37- 2.89)	7.01 (6.38- 11.84)
	Unknown	89	45	44	7.54 (0.79)	4.97 (3.52- 7.50)	2.96 (2.20- 3.36)	11.12 (7.50- N/D)
Prior Be-vacizumab	No	302	156	146	5.85 (0.28)	4.57 (3.62- 5.33)	2.70 (2.37- 2.89)	9.93 (7.01- N/D)
	Yes	161	84	77	6.52 (0.78)	3.72 (3.26- 4.24)	2.63 (2.17- 2.86)	7.17 (5.36- 20.99)
Time from diagnosis to therapy	< 18 months	72	32	40	3.55 (0.22)	3.36 (2.86- 3.98)	2.57 (1.88- 2.96)	5.49 (3.75- N/D)
	≥ 18 months	263	138	125	7.59 (0.63)	4.31 (3.72- 5.20)	2.63 (2.34- 2.86)	10.66 (6.68- N/D)
	Missing	128	70	58	6.45 (0.60)	4.14 (3.36- 6.41)	2.73 (2.20- 3.06)	8.09 (6.71- 16.64)
Prior treat-ment lines	≤ 3	442	228	214	7.33 (0.48)	4.08 (3.65- 4.93)	2.70 (2.47- 2.80)	9.34 (6.71- 16.64)
	> 3	21	12	9	5.45 (0.93)	3.26 (2.60- 9.54)	2.60 (0.69- 3.09)	9.54 (3.26- 9.93)
Primary tumor site	Colon	292	148	144	7.06 (0.58)	3.98 (3.39- 5.00)	2.57 (2.34- 2.86)	9.34 (6.97- 16.64)
	Rectum	171	92	79	5.76 (0.37)	4.24 (3.59- 5.20)	2.73 (2.37- 2.96)	11.12 (6.38- N/D)
Tumor sidedness	Left	344	184	160	6.68 (0.40)	4.14 (3.62- 4.97)	2.63 (2.34- 2.83)	9.54 (6.97- N/D)
	Right	119	56	63	6.02 (0.85)	3.98 (2.96- 5.39)	2.70 (2.37- 2.89)	9.34 (5.49- 11.15)
Metastasis location	Liver only	101	42	59	6.05 (0.42)	5.49 (3.49- 9.34)	2.96 (2.53- 3.29)	N/D (7.63- N/D)
	Other	362	198	164	6.75 (0.48)	3.98 (3.39- 4.57)	2.60 (2.30- 2.76)	7.50 (6.41- 11.15)

Liver/No lung	152	64	88	5.82 (0.34)	5.00 (3.59- 6.68)	2.86 (2.5- 3.26)	N/D (7.63- N/D)
Lung/No liver	78	44	34	7.29 (0.73)	5.33 (4.14- 8.09)	3.09 (2.37- 4.01)	10.66 (7.01- N/D)
Liver/Lung	197	114	83	4.75 (0.33)	3.36 (2.96- 3.78)	2.34 (1.91- 2.7)	5.86 (4.47- 11.94)
No liver/No lung	36	18	18	7.57 (1.70)	4.93 (2.86- 7.17)	2.70 (1.61- 4.9)	11.15 (5.36- N/D)
Liver/No Skeleton	144	60	84	5.95 (0.35)	5.03 (3.75- 7.63)	2.96 (2.57- 3.29)	N/D (9.34- N/D)
Lung/No Skeleton	71	41	30	7.25 (0.75)	5.33 (4.01- 8.09)	3.09 (2.34- 4.01)	10.66 (7.01- N/D)
Liver/Lung/No Skeleton	175	104	71	4.73 (0.34)	3.36 (2.96- 3.78)	2.37 (1.94- 2.73)	5.86 (4.31- 11.94)
Skeleton	38	17	21	4.04 (0.41)	3.72 (2.37- 6.41)	2.07 (1.55- 3.26)	N/D (4.14- N/D)
No Liver/No Lung/No Skeleton	35	18	17	6.52 (1.52)	4.93 (2.86- 7.17)	2.70 (1.61- 4.9)	7.17 (5.36- 20.99)

* due to low patient numbers ECOG of 3 and missing ECOG are not shown here

Table 26: Disease control rate according to subgroups (ITT) (Data source: Table 97, 107, 123, 136, 146, 159, 169, 179, 189, 205, 206, 207 of statistical report V1.0)

DCR- Stratification		*N*	*CR+PR+SD*	*=DCR (CI 95%)*
Total		277	74	26.71 (21.60- 32.34)
Age	< 65 years	112	25	22.32 (15.00- 31.16)
	≥ 65 years	165	49	29.70 (22.85- 37.29)
Gender	Female	110	25	22.73 (15.28- 31.70)
	Male	167	49	29.34 (22.56- 36.87)
ECOG*	0	58	19	32.76 (21.01- 46.34)
	1	172	44	25.58 (19.24- 32.78)
	2	40	10	25.00 (12.69- 41.20)
KRAS mutation	No	95	24	25.26 (16.91- 35.22)
	Yes	129	37	28.68 (21.07- 37.30)
	Unknown	53	13	24.53 (13.76- 38.28)
Prior Be-vacizumab	No	179	48	26.82 (20.48- 33.94)
	Yes	98	26	26.53 (18.12- 36.41)
Time from diagnosis to therapy	< 18 months	36	7	19.44 (8.19- 36.02)
	≥ 18 months	162	43	26.54 (19.92- 34.04)
	Missing	79	24	30.38 (20.53- 41.75)
Prior treat-ment lines	≤ 3	264	70	26.52 (21.29- 32.27)
	> 3	13	4	30.77 (9.09- 61.43)
Primary tumor site	Colon	177	49	27.68 (21.24- 34.9)
	Rectum	100	25	25.00 (16.88- 34.66)
Tumor sidedness	Left	212	60	28.30 (22.34- 34.88)
	Right	65	14	21.54 (12.31- 33.49)
Metastasis location	Liver only	52	18	34.62 (21.97- 49.09)
	Other	225	56	24.89 (19.38- 31.07)
	Liver/No lung	78	25	32.05 (21.93- 43.58)
	Lung/No liver	50	18	36.00 (22.92- 50.81)
	Liver/Lung	129	25	19.38 (12.95- 27.26)
	No liver/No lung	20	6	30.00 (11.89- 54.28)
	Liver/No Skeleton	74	25	33.78 (23.19- 45.72)
	Lung/No Skeleton	47	18	38.30 (24.51- 53.62)
	Liver/Lung/No Skeleton	117	23	19.66 (12.89- 28.02)
	Skeleton	19	2	10.53 (1.30- 33.14)
	No Liver/No Lung/No Skeleton	20	6	30.00 (11.89- 54.28)

* due to low patient numbers ECOG of 3 and missing ECOG are not shown here

Table 27: Duration of Stivarga® treatment [days] (ITT) (Data source: Table 98, 108, 124, 137, 147, 160, 170, 180, 190, 208, 209, 210 of statistical report V1.0)

Treatment duration- Stratification		*N*	*Mean (SE)*	*Median (Min, Max)*
Total		463	93.25 (98.72)	71 (1, 1085)
Age	< 65 years	179	84.36 (68.16)	69 (1, 378)
	≥ 65 years	284	98.85 (113.60)	76.5 (1, 1085)
Gender	Female	183	92.85 (111.49)	71 (1, 1085)
	Male	280	93.51 (89.61)	73 (1, 638)
ECOG*	0	93	85.99 (63.33)	77 (1, 337)
	1	278	99.73 (108.09)	76.5 (1, 1085)
	2	80	84.90 (102.52)	50.5 (1, 649)
KRAS mutation	No	160	82.22 (73.52)	63 (1, 447)
	Yes	214	98.02 (96.01)	77 (1, 649)
	Unknown	89	101.58 (136.88)	69 (1, 1085)
Prior Be-vacizumab	No	302	98.42 (104.05)	73.5 (1, 1085)
	Yes	161	83.55 (87.34)	63 (1, 638)
Time from diagnosis to therapy	< 18 months	72	74.99 (82.66)	60 (1, 649)
	≥ 18 months	263	100.64 (109.32)	77 (1, 1085)
	Missing	128	88.33 (81.55)	73 (1, 492)
Prior treat-ment lines	≤ 3	442	92.41 (98.25)	71.5 (1, 1085)
	> 3	21	110.81 (109.23)	70 (1, 440)
Primary tumor site	Colon	292	94.26 (109.10)	71 (1, 1085)
	Rectum	171	91.51 (78.13)	74 (1, 447)
Tumor sidedness	Left	344	97.01 (103.39)	73 (1, 1085)
	Right	119	82.35 (83.22)	67 (1, 638)
Metastasis location	Liver only	101	100.02 (132.96)	73 (1, 1085)
	Other	362	91.36 (86.94)	70.5 (1, 638)
	Liver/No lung	152	94.15 (114.16)	71 (1, 1085)
	Lung/No liver	78	117.24 (114.68)	82 (1, 492)
	Liver/Lung	197	81.49 (71.19)	63 (1, 512)
	No liver/No lung	36	101.75 (113.88)	71.5 (1, 638)
	Liver/No Skeleton	144	95.01 (116.47)	72 (1, 1085)
	Lung/No Skeleton	71	120.76 (118.12)	82 (1, 492)
	Liver/Lung/No Skeleton	175	84.15 (72.43)	75 (1, 512)
	Skeleton	38	67.00 (58.71)	53.5 (1, 253)
	No Liver/No Lung/No Skeleton	35	104.14 (114.62)	72 (1, 638)

* due to low patient numbers ECOG of 3 and missing ECOG are not shown here

10.6 Adverse events/adverse reactions

Adverse events (AEs) were summarized using the MedDRA coding system (version 20.0). Event rates for single AEs were calculated based on the total number of patients valid for safety analysis. Patients, who took at least one dose of Stivarga®, were eligible for safety analysis (safety analysis set, n=464). AEs were categorized according to CTCAE grade (version 4.03), relationship to study drug, seriousness, usual time of study drug intake, action taken and outcome. Special attention was paid to serious AEs and unexpected or unlisted ADRs. Category counts and frequencies (percentages) were calculated for overall tolerability. The analysis described in this section was performed on incident treatment-emergent adverse events (TEAEs). AEs were considered as treatment-emergent, if they started after the first Stivarga® treatment and no later than 30 days after the last Stivarga ® treatment (even if this period exceeded the end of observation). If no unambiguous allocation was possible, the AE was treated as treatment-emergent. Events, which were not treatment-emergent, were tabulated without further stratification.

In total, 18 non-TEAEs occurred in 14 patients. 5 of these events were classified as serious (death, general physical health deterioration and neoplasm progressions; Table 28).

Table 28: Non-TEAEs according to MedDRA (event-based) (Data source: Table 61 and 63 of statistical report V1.0)

Non-TEAEs (event-based)		*N*
Blood and lymphatic system disorders	Anaemia	1
Gastrointestinal disorders	Faecal vomiting	1
	Nausea	1
General disorders and administration site conditions	Death (serious)	1
	Disease progression	1
	Fatigue	1
	General physical health deterioration (serious)	1
Hepatobiliary disorders	Hepatic failure	1
Investigations	Alanine aminotransferase increased	1
	Aspartate aminotransferase increased	3
	Blood bilirubin increased	1
Musculoskeletal and connective tissue disorders	Back pain	1
Neoplasms benign, malignant and unspecified	Neoplasm progression (serious)	3
Respiratory, thoracic and mediastinal disorders	Apnoea	1
Total		**18**

10.6.1 Treatment-emergent adverse events (TEAEs)

A total of 1970 TEAEs were observed in 426 patients (91.81%). Most of the events belonged to the system organ class (SOC) “general disorders and administration site conditions” (19.19% of events in 52.16% of patients), “gastrointestinal disorders” (23.05% of events in 51.94% of patients), “skin and subcutaneous tissue disorders” (8.83% of events in 26.51% of patients) and “investigations” (10.41% of events in 25.86% of patients). 7.97% of patients had grade 1, 26.29% had grade 2, 25.65% had grade 3, and 2.8% had grade 4 TEAEs. 29.09% of patients had TEAEs resulting in death (grade 5). Most fatal events belonged to the SOC “general disorders and administration site conditions” and “neoplasms benign, malignant and unspecified” (Table 29).

The most commonly observed events were diarrhea (7.1% of events in 21.98% of patients) and fatigue (5.99% of events in 24.14% of patients). Most of the fatal outcomes were observed in patients with general physical health deterioration and neoplasm progression (Table 30).

According to the usual time of Stivarga® intake (at the initial visit), TEAEs were observed in 223 of 248 patients (89.92%), who took Stivarga® in the morning, in 38 of 40 patients (95%), who took Stivarga® in the evening, in 14 of 16 patients (87.5%) of patients, who took Stivarga® at another time, in 149 of 158 patients (94.3%), who took Stivarga® at an unknown time, and in 2 of 2 patients (100%) with a missing time (Table 31; see table 68 of the statistical report for incidence rates of the respective events according to time of intake).

For more than half of the events the Stivarga® dose was not changed (1063 events, 53.96%). The dose was reduced for 168 events (8.53%) and increased for 1 event (0.05%). Stivarga® treatment was interrupted for 288 events (14.62%) and withdrawn for 213 events (10.81%). Most events were recovered/resolved (1237 events, 62.79%). 16 events (0.81%) were recovering/resolving and 12 events (0.61%) were recovered/resolved with sequelae. 365 events (18.53%) were not recovered/resolved and 138 events (7.01%) were fatal (Table 32 a). The worst outcome per patient was recovered/resolved for 186 patients (43.66%), recovering/resolving for 5 patients (1.17%) and recovered/resolved with sequelae for 2 patients (0.47%). For 83 patients (19.48%) the worst outcome was not recovered/resolved and for 137 patients (32.16%) it was fatal (Table 32 b). One patient had two fatal events documented (respiratory tract infection and sepsis). Among 137 patients with fatal TEAEs, two TEAEs were not documented as grade 5 (general physical health deterioration, grade 3 and grade 4).

For 858 events (43.55%) another specific treatment was chosen; for 625 events (31.73%) this was a remedial drug therapy (Table 72 of the statistical report).

Table 29: TEAEs according to MedDRA System Organ Class (event-based and patient-based) (Data source: Table 66 and 67 of statistical report V1.0)

TEAE according to MedDRA (SOC), n (%)	*Event-based*	*Patient-based*			
		Any grade	*Grade 3*	*Grade 4*	*Grade 5*
Any (events/patients)	**1970 (100)**	**426 (91.81)**	**119 (25.65)**	**13 (2.80)**	**135 (29.09)**
Blood and lymphatic system disorders	45 (2.28)	40 (8.62)	11 (2.37)		
Cardiac disorders	25 (1.27)	17 (3.66)	5 (1.08)		3 (0.65)
Congenital, familial and genetic disorders	1 (0.05)	1 (0.22)			
Ear and labyrinth disorders	18 (0.91)	15 (3.23)			
Endocrine disorders	6 (0.30)	6 (1.29)			
Eye disorders	5 (0.25)	5 (1.08)	1 (0.22)		
Gastrointestinal disorders	454 (23.05)	241 (51.94)	43 (9.27)	6 (1.29)	4 (0.86)
General disorders and administration site conditions	378 (19.19)	242 (52.16)	37 (7.97)	1 (0.22)	54 (11.64)
Hepatobiliary disorders	47 (2.39)	41 (8.84)	17 (3.66)	3 (0.65)	8 (1.72)
Immune system disorders	2 (0.10)	1 (0.22)			
Infections and infestations	71 (3.60)	57 (12.28)	19 (4.09)	1 (0.22)	4 (0.86)
Injury, poisoning and procedural complicat.	11 (0.56)	11 (2.37)	3 (0.65)		
Investigations	205 (10.41)	120 (25.86)	21 (4.53)	4 (0.86)	
Metabolism and nutrition disorders	87 (4.42)	72 (15.52)	13 (2.80)	4 (0.86)	1 (0.22)
Musculoskeletal and connective tissue disorders	77 (3.91)	62 (13.36)	8 (1.72)		
Neoplasms benign, malignant and unspecified*	81 (4.11)	75 (16.16)	12 (2.59)	2 (0.43)	54 (11.64)
Nervous system disorders	71 (3.60)	53 (11.42)	11 (2.37)		
Product issues	1 (0.05)	1 (0.22)	1 (0.22)		
Psychiatric disorders	20 (1.02)	16 (3.45)			
Renal and urinary disorders	24 (1.22)	20 (4.31)	5 (1.08)	1 (0.22)	1 (0.22)
Reproductive system and breast disorders	7 (0.36)	5 (1.08)	1 (0.22)		
Respiratory, thoracic and mediastinal disorders	109 (5.53)	82 (17.67)	15 (3.23)	3 (0.65)	6 (1.29)
Skin and subcutaneous tissue disorders	174 (8.83)	123 (26.51)	17 (3.66)		
Vascular disorders	51 (2.59)	42 (9.05)	21 (4.53)	3 (0.65)	

*(incl. cysts and polyps)

Table 30: Common TEAEs (observed in ≥ 1% of patients) (Data source: Table 66 and 67 of statistical report V1.0)

TEAE according to MedDRA (SOC and PT), n (%)		***Event-based***	***Patient-based***			
			Any grade	***Grade 3***	***Grade 4***	***Grade 5***
Any (events/patients)		**1970 (100)**	**426 (91.81)**	**119 (25.65)**	**13 (2.80)**	**135 (29.09)**
Blood and lymphatic system disorders	Anaemia	18 (0.91)	18 (3.88)	5 (1.08)		
	Thrombocytopenia	15 (0.76)	15 (3.23)	3 (0.65)		
Ear and labyrinth disorders	Vertigo	13 (0.66)	12 (2.59)			
Endocrine disorders	Hypothyroidism	6 (0.30)	6 (1.29)			
Gastrointestinal disorders	Abdominal pain	65 (3.31)	59 (12.72)	15 (3.24)		
	Ascites	17 (0.86)	17 (3.66)	6 (1.29)		1 (0.22)
	Constipation	31 (1.57)	30 (6.47)	1 (0.22)		
	Diarrhoea	140 (7.11)	102 (21.98)	8 (1.72)		
	Dry mouth	9 (0.46)	9 (1.94)			
	Dysphagia	13 (0.66)	12 (2.59)	1 (0.22)		
	Ileus	5 (0.25)	5 (1.08)		2 (0.43)	2 (0.43)
	Nausea	55 (2.79)	52 (11.21)	5 (1.08)		
	Stomatitis	22 (1.12)	20 (4.31)	4 (0.86)		
	Subileus	7 (0.36)	5 (1.08)	1 (0.22)		
	Vomiting	35 (1.78)	31 (6.68)	2 (0.43)	2 (0.43)	
General disorders and administration site conditions	Asthenia	14 (0.71)	14 (3.02)	2 (0.43)		
	Chest pain	8 (0.41)	8 (1.72)	1 (0.22)		
	Chills	8 (0.41)	8 (1.72)			
	Death	8 (0.41)	8 (1.72)			8 (1.72)
	Fatigue	118 (5.99)	112 (24.14)	19 (4.09)		
	General physical health deterioration	75 (3.81)	73 (15.73)	10 (2.16)	1 (0.22)	34 (7.33)

	Mucosal inflammation	47 (2.39)	42 (9.05)	5 (1.08)		
	Multiple organ dysfunction syndrome	12 (0.61)	12 (2.59)			12 (2.59)
	Oedema	22 (1.11)	21 (4.53)	1 (0.22)		
	Pain	33 (1.68)	32 (6.90)	4 (0.86)		
	Pyrexia	27 (1.37)	25 (5.39)	1 (0.22)		
Hepatobiliary disorders	Cholecystitis	7 (0.35)	6 (1.30)	3 (0.65)	1 (0.22)	
	Hepatic failure	10 (0.51)	10 (2.16)	1 (0.22)	1 (0.22)	8 (1.72)
	Hepatic pain	5 (0.25)	5 (1.08)	1 (0.22)		
	Hyperbilirubinaemia	6 (0.30)	5 (1.08)	1 (0.22)	1 (0.22)	
	Jaundice	7 (0.36)	7 (1.51)	4 (0.86)		
Infections and infestations	Pneumonia	5 (0.25)	5 (1.08)	3 (0.65)		1 (0.22)
	Urinary tract infection	17 (0.86)	16 (3.45)	5 (1.08)		
Investigations	Alanine aminotransferase increased	42 (2.13)	40 (8.62)	3 (0.65)		
	Aspartate aminotransferase increased	67 (3.40)	62 (13.36)	5 (1.08)		
	Blood alkaline phosphatase increased	5 (0.25)	5 (1.08)			
	Blood bilirubin increased	31 (1.57)	30 (6.47)	7 (1.51)	2 (0.43)	
	C-reactive protein increased	8 (0.41)	8 (1.72)	4 (0.86)	1 (0.22)	
	Gamma-glutamyltransferase increased	7 (0.36)	7 (1.51)	1 (0.22)		
	Liver function test increased	6 (0.30)	5 (1.08)	1 (0.22)	1 (0.22)	
	Weight decreased	23 (1.17)	23 (4.96)	1 (0.22)		
Metabolism and nutrition disorders	Decreased appetite	50 (2.54)	49 (10.56)	7 (1.51)	1 (0.22)	
	Dehydration	12 (0.61)	10 (2.16)	3 (0.65)	1 (0.22)	
	Hypokalaemia	9 (0.46)	8 (1.72)	1 (0.22)		
	Hyponatraemia	7 (0.36)	6 (1.29)	2 (0.43)	2 (0.43)	
Musculoskeletal and	Pain (various)	59 (2.97)	58 (12.51)	6 (1.30)		

connective tissue disorders	Muscle spasms	10 (0.51)	10 (2.16)	1 (0.22)		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Colon/Colorectal cancer	7 (0.35)	7 (1.51)			7 (1.51)
	Metastases to liver	6 (0.30)	6 (1.29)		1 (0.22)	4 (0.86)
	Neoplasm progression	40 (2.03)	40 (8.62)	3 (0.65)		35 (7.54)
	Tumour/Cancer pain	9 (0.46)	9 (1.94)	6 (1.30)		
Nervous system disorders	Dizziness	5 (0.25)	5 (1.08)			
	Headache	17 (0.86)	17 (3.66)	2 (0.43)		
	Paraesthesia	8 (0.41)	8 (1.72)			
	Polyneuropathy	11 (0.56)	10 (2.16)	2 (0.43)		
Psychiatric disorders	Sleep disorder	5 (0.25)	5 (1.08)			
Respiratory, thoracic and mediastinal disorders	Cough	6 (0.30)	5 (1.08)			
	Dysphonia	28 (1.42)	27 (5.82)			
	Dyspnoea	43 (2.18)	39 (8.41)	10 (2.16)		4 (0.86)
	Epistaxis	6 (0.30)	6 (1.29)			
	Oropharyngeal pain	5 (0.25)	5 (1.08)			
	Pleural effusion	7 (0.36)	7 (1.51)	3 (0.65)		1 (0.22)
Skin and subcutaneous tissue disorders	Alopecia	9 (0.46)	9 (1.94)			
	Erythema	5 (0.25)	5 (1.08)			
	Palmar-plantar erythrodysaesthesia syndrome	91 (4.62)	71 (15.3)	14 (3.02)		
	Pruritus	5 (0.25)	5 (1.08)			
	Rash	30 (1.52)	29 (6.26)	3 (0.65)		
Vascular disorders	Hypertension	36 (1.83)	32 (6.90)	17 (3.66)	2 (0.43)	

Table 31: TEAEs according to usual time of Stivarga® intake (at initial visit) (Data source: Table 65 of statistical report V1.0)

TEAEs acc. to time of Stivarga intake (patient-based)	*N (%)*
In the morning (n=248)	223 (89.92)
In the evening (n=40)	38 (95.00)
Other time (n=16)	14 (87.50)
Unknown time (n=158)	149 (94.30)
Missing (n=2)	2 (100)

Table 32: TEAEs – Action taken and outcome (Data source: Table 69 - 71 of statistical report V1.0)

a.

Action taken per TEAE	*N (%)*
Stivarga withdrawn	213 (10.81)
Stivarga interrupted	288 (14.62)
Stivarga dose reduced	168 (8.53)
Stivarga dose not changed	1063 (53.96)
Stivarga dose increased	1 (0.05)
Not applicable	181 (9.19)
Unknown	56 (2.84)
Outcome per TEAE	*N (%)*
Recovered/ Resolved	1237 (62.79)
Recovering/ Resolving	16 (0.81)
Not recovered/ Not resolved	365 (18.53)
Recovered/ Resolved with sequelae	12 (0.61)
Fatal	138 (7.01)*
Unknown	202 (10.25)
Total number of TEAEs	**1970 (100)**

*1 patient had 2 fatal TEAEs documented

b.

Worst outcome per patient	*N (%)*
Recovered/ Resolved	186 (43.66)
Recovering/ Resolving	5 (1.17)
Not recovered/ Not resolved	83 (19.48)
Recovered/ Resolved with sequelae	2 (0.47)
Fatal	137 (32.16)*
Unknown	13 (3.05)
Patients with TEAE	**426 (100)**

*2 events that were not grade 5 resulted in death

10.6.2 Drug-related TEAEs

A relation to Stivarga® treatment was documented for 834 of the 1970 TEAEs, which were reported in 303 patients (65.3% of the safety set). Most of the drug-related events belonged to the SOC “gastrointestinal disorders” (27.58% of events in 32.33% of patients), “general disorders and administration site conditions” (17.99% of events in 24.78% of patients), “skin and subcutaneous tissue disorders” (18.47% of events in 24.35% of patients) and “investigations” (8.75% of events in 10.56% of patients). 14.44% of patients had grade 1, 31.9% had grade 2, 17.89% had grade 3, and 0.65% had grade 4 drug-related TEAEs. 2 patients (0.43%) had TEAEs resulting in death (grade 5; Table 33).

The most commonly observed drug-related events were diarrhea (12.71% of events in 17.46% of patients), fatigue (8.51% of events in 14.22% of patients) and palmar-plantar erythrodysesthesia syndrome (10.79% of events in 15.09% of patients), which is the MedDRA term for hand-foot skin reaction. 4 life-threatening events were observed in 3 patients (0.65%), which were vomiting, hypertension, cholecystitis and hyponatremia. The 2 fatal events (0.43% of patients) were myocardial infarction and infectious pleural effusion (Table 34; Table 78 of statistical report).

According to the usual time of Stivarga® intake (at the initial visit), TEAEs were observed in 148 of 248 patients (59.68%), who took Stivarga® in the morning, in 30 of 40 patients (75%), who took Stivarga® in the evening, in 9 of 16 patients (56.25%) of patients, who took Stivarga® at another time, in 114 of 158 patients (72.15%), who took Stivarga® at an unknown time, and in 2 of 2 patients (100%) with a missing time (Table 35; see table 79 of the statistical report for incidence rates of the respective events according to time of intake).

For almost half of the drug-related events the Stivarga® dose was not changed (404 events, 48.44%) and for 138 events (16.55%) it was reduced. Stivarga® treatment was interrupted for 168 events (20.14%) and withdrawn for 85 events (10.19%). Three-quarter of events were recovered/resolved (629 events, 75.42%). 11 events (1.32%) were recovering/resolving and 2 events (0.24%) were recovered/resolved with sequelae. 119 events (14.27%) were not recovered/resolved and 2 events (0.24%) were fatal (Table 36 a). The worst outcome per patient was recovered/resolved for 2/3 (202 patients), recovering/resolving for 1.98% (6 patients) and recovered/resolved with sequelae for 0.66% (2 patients). For almost 1/4 (71 patients, 23.43%) the worst outcome was not recovered/resolved and for 0.66% (2 patients) it was fatal (Table 36 b).

Table 33: Drug-related TEAEs according to MedDRA System Organ Class (event-based and patient-based) (Data source: Table 77 and 78 of statistical report V1.0)

Drug-related TEAE according to MedDRA (SOC), n (%)	***Event-based***	***Patient-based***			
		Any grade	***Grade 3***	***Grade 4***	***Grade 5***
Any (events/patients)	**834 (100)**	**303 (65.30)**	**83 (17.89)**	**3 (0.65)**	**2 (0.43)**
Blood and lymphatic system disorders	23 (2.76)	20 (4.31)	5 (1.08)		
Cardiac disorders	2 (0.24)	2 (0.43)	1 (0.22)		1 (0.22)
Ear and labyrinth disorders	6 (0.72)	5 (1.08)			
Endocrine disorders	3 (0.36)	3 (0.65)			
Eye disorders	3 (0.36)	3 (0.65)			
Gastrointestinal disorders	230 (27.58)	150 (32.33)	18 (3.88)	1 (0.22)	
General disorders and administration site conditions	150 (17.99)	115 (24.78)	17 (3.66)		
Hepatobiliary disorders	9 (1.08)	8 (1.72)	5 (1.08)	1 (0.22)	
Immune system disorders	2 (0.24)	1 (0.22)			
Infections and infestations	14 (1.68)	12 (2.59)	2 (0.43)		1 (0.22)
Injury, poisoning and procedural complications	2 (0.24)	2 (0.43)			
Investigations	73 (8.75)	49 (10.56)	7 (1.51)		
Metabolism and nutrition disorders	39 (4.68)	38 (8.19)	6 (1.29)	1 (0.22)	
Musculoskeletal and connective tissue disorders	21 (2.52)	16 (3.45)	2 (0.43)		
Nervous system disorders	31 (3.72)	26 (5.60)	4 (0.86)		
Psychiatric disorders	1 (0.12)	1 (0.22)			
Renal and urinary disorders	2 (0.24)	2 (0.43)	1 (0.22)		
Reproductive system and breast disorders	2 (0.24)	1 (0.22)			
Respiratory, thoracic and mediastinal disorders	35 (4.20)	30 (6.47)	2 (0.43)		
Skin and subcutaneous tissue disorders	154 (18.47)	113 (24.35)	16 (3.45)		
Vascular disorders	32 (3.84)	28 (6.03)	15 (3.23)	1 (0.22)	

Table 34: Common drug-related TEAEs (observed in ≥ 1% of patients) (Data source: Table 77 and 78 of statistical report V1.0)

Drug-related TEAE according to MedDRA (SOC and PT), n (%)		***Event-based***	***Patient-based***		
			Any grade	***Grade 3***	***Grade 4***
Any (events/patients)		**834 (100)**	**303 (65.30)**	**83 (17.89)**	**3 (0.65)**
Blood and lymphatic system disorders	Anaemia	6 (0.72)	6 (1.29)	2 (0.43)	
	Thrombocytopenia	13 (1.56)	13 (2.80)	3 (0.65)	
Ear and labyrinth disorders	Vertigo	6 (0.72)	5 (1.08)		
Gastrointestinal disorders	Abdominal pain	13 (1.56)	13 (2.80)	3 (0.65)	
	Constipation	8 (0.96)	8 (1.72)		
	Diarrhoea	106 (12.71)	81 (17.46)	7 (1.51)	
	Dry mouth	8 (0.96)	8 (1.72)		
	Nausea	38 (4.56)	36 (7.76)	2 (0.43)	
	Stomatitis	19 (2.28)	18 (3.88)	4 (0.86)	
	Vomiting	16 (1.92)	15 (3.23)	2 (0.43)	1 (0.22)
General disorders and administration site conditions	Asthenia	8 (0.96)	8 (1.72)		
	Fatigue	71 (8.51)	66 (14.22)	11 (2.37)	
	General physical health deterioration	11 (1.32)	11 (2.37)	1 (0.22)	
	Mucosal inflammation	42 (5.04)	38 (8.19)	5 (1.08)	
	Pain	5 (0.60)	5 (1.08)		
	Pyrexia	5 (0.60)	5 (1.08)		
Investigations	Alanine aminotransferase increased	16 (1.92)	16 (3.45)	1 (0.22)	
	Aspartate aminotransferase increased	23 (2.76)	20 (4.31)	1 (0.22)	
	Blood bilirubin increased	12 (1.44)	12 (2.59)	2 (0.43)	
	Weight decreased	11 (1.32)	11 (2.37)	1 (0.22)	
Metabolism and nutrition disorders	Decreased appetite	31 (3.72)	31 (6.68)	3 (0.65)	
Musculoskeletal and connective	Pain (various)	19 (2.28)	18 (3.89)	2 (0.43)	

tissue disorders

Nervous system disorders	Headache	11 (1.32)	11 (2.37)	2 (0.43)	
Respiratory, thoracic and mediastinal disorders	Dysphonia	18 (2.16)	18 (3.88)		
	Dyspnoea	10 (1.20)	9 (1.94)	2 (0.43)	
Skin and subcutaneous tissue disorders	Alopecia	8 (0.96)	8 (1.72)		
	Palmar-plantar erythrodysaesthesia syndrome	90 (10.79)	70 (15.09)	13 (2.80)	
	Rash	22 (2.64)	22 (4.76)	3 (0.65)	
Vascular disorders	Hypertension	31 (3.72)	27 (5.82)	14 (3.02)	1 (0.22)

Table 35: Drug-related TEAEs according to usual time of Stivarga® intake (at initial visit) (Data source: Table 65 and 79 of statistical report V1.0)

Drug-related TEAEs acc. to time of Stivarga intake (patient-based)	*N (%)*
In the morning (n=248)	148 (59.68)
In the evening (n=40)	30 (75.00)
Other time (n=16)	9 (56.25)
Unknown time (n=158)	114 (72.15)
Missing (n=2)	2 (100)

Table 36: Drug-related TEAEs – Action taken and outcome (Data source: Table 80 - 82 of statistical report V1.0)

a.

Action taken per TEAE	*N (%)*
Stivarga withdrawn	85 (10.19)
Stivarga interrupted	168 (20.14)
Stivarga dose reduced	138 (16.55)
Stivarga dose not changed	404 (48.44)
Not applicable	30 (3.60)
Unknown	9 (1.08)
Outcome per TEAE	*N (%)*
Recovered/ Resolved	629 (75.42)
Recovering/ Resolving	11 (1.32)
Not recovered/ Not resolved	119 (14.27)
Recovered/ Resolved with sequelae	2 (0.24)
Fatal	2 (0.24)
Unknown	71 (8.51)
Total number of drug-related TEAEs	**834 (100)**

b.

Worst outcome per patient	*N (%)*
Recovered/ Resolved	202 (66.67)
Recovering/ Resolving	6 (1.98)
Not recovered/ Not resolved	71 (23.43)
Recovered/ Resolved with sequelae	2 (0.66)
Fatal	2 (0.66)
Unknown	20 (6.60)
Patients with drug-related TEAE	**303 (100)**

10.6.3 Serious TEAEs

A total of 403 TEAEs were documented to be serious. These were reported in 235 patients (50.65% of the safety set). Most frequently reported serious events belonged to the SOC “general disorders and administration site conditions” (22.83% of events in 17.89% of patients), “neoplasms benign, malignant and unspecified” (17.12% of events in 14.44% of patients) and “gastrointestinal disorders” (17.12% of events in 11.42% of patients). The serious TEAE was fatal (grade 5) for almost 30% of the safety set (135 patients, 29.09%). Most of the fatal events belonged to the SOC “general disorders and administration site conditions” and “neoplasms benign, malignant and unspecified”. 1.08% of patients had grade 1, 5.17% had grade 2, 12.72% had grade 3, and 2.59% had grade 4 serious TEAEs (Table 37).

Most commonly observed serious events were general physical health deterioration (11.41% of events in 9.48% of patients) and neoplasm progression (9.18% of events in 7.97% of patients), which also had most of the fatal outcomes (Table 38).

According to the usual time of Stivarga® intake (at the initial visit), serious TEAEs were observed in 119 of 248 patients (47.98%), who took Stivarga® in the morning, in 16 of 40 patients (40%), who took Stivarga® in the evening, in 6 of 16 patients (37.5%) of patients, who took Stivarga® at another time, and in 94 of 158 patients (59.49%), who took Stivarga® at an unknown time (Table 39; see table 86 of the statistical report for incidence rates of the respective events according to time of intake).

A hospitalization or a prolongation of a hospitalization was required for almost 3/4 of serious events (297 events, 73.7%). 138 events (34.24%) were fatal and 3 were life-threatening (0.74%). 19 events (4.71%) were medically important and 1 event (0.25%) resulted in persistent or significant disability or incapacity. For more than a quarter of serious events the Stivarga® dose was not changed (107 events, 26.55%) and for 3 events (0.74%) it was reduced. Stivarga® treatment was interrupted for 79 events (19.6%) and withdrawn for 102 events (25.31%). Almost half of the events were recovered/resolved (197 events, 48.88%) and 3 events (0.61%) were recovered/resolved with sequelae. 50 events (12.41%) were not recovered/resolved and 138 events (34.24%) were fatal (Table 40 a).

For about 1/3 of patients with serious events the worst outcome was recovered/resolved (79 patients, 33.62%) and for 1 patient (0.43%) it was recovered/resolved with sequelae. The worst outcome was not recovered/resolved for 15 patients (6.38%) and fatal for 137 patients (58.3%; Table 40 b).

Table 37: Serious TEAEs according to MedDRA System Organ Class (event-based and patient-based)
(Data source: Table 84 and 85 of statistical report V1.0)

Serious TEAE according to MedDRA (SOC), n (%)	***Event-based***	***Patient-based***			
		Any grade	***Grade 3***	***Grade 4***	***Grade 5***
Any (events/patients)	**403 (100)**	**235 (50.65)**	**59 (12.72)**	**12 (2.59)**	**135 (29.09)**
Blood and lymphatic system disorders	3 (0.74)	3 (0.65)	3 (0.65)		
Cardiac disorders	14 (3.47)	12 (2.59)	4 (0.86)		3 (0.65)
Gastrointestinal disorders	69 (17.12)	53 (11.42)	25 (5.39)	6 (1.29)	4 (0.86)
General disorders and administration site conditions	92 (22.83)	83 (17.89)	21 (4.53)	1 (0.22)	54 (11.64)
Hepatobiliary disorders	31 (7.69)	26 (5.60)	13 (2.80)	2 (0.43)	8 (1.72)
Infections and infestations	32 (7.94)	26 (5.60)	15 (3.23)	1 (0.22)	4 (0.86)
Injury, poisoning and procedural complications	3 (0.74)	3 (0.65)	2 (0.43)		
Investigations	10 (2.48)	8 (1.72)	5 (1.08)	1 (0.22)	
Metabolism and nutrition disorders	12 (2.98)	11 (2.37)	6 (1.29)	3 (0.65)	1 (0.22)
Musculoskeletal and connective tissue disorders	7 (1.74)	7 (1.51)	4 (0.86)		
Neoplasms benign, malignant and unspecified*	69 (17.12)	67 (14.44)	9 (1.94)	2 (0.43)	54 (11.64)
Nervous system disorders	5 (1.24)	4 (0.86)	3 (0.65)		
Product issues	1 (0.25)	1 (0.22)	1 (0.22)		
Renal and urinary disorders	11 (2.73)	10 (2.16)	4 (0.86)	1 (0.22)	1 (0.22)
Reproductive system and breast disorders	1 (0.25)	1 (0.22)	1 (0.22)		
Respiratory, thoracic and mediastinal disorders	26 (6.45)	25 (5.39)	10 (2.16)	2 (0.43)	6 (1.29)
Skin and subcutaneous tissue disorders	8 (1.99)	7 (1.51)	5 (1.08)		
Vascular disorders	9 (2.23)	9 (1.94)	5 (1.08)	3 (0.65)	

*(incl. cysts and polyps)

Table 38: Common serious TEAEs (observed in ≥ 1% of patients) (Data source: Table 84 and 85 of statistical report V1.0)

Serious TEAE according to MedDRA (SOC and PT), n (%)		***Event-based***	***Patient-based***			
			Any grade	***Grade 3***	***Grade 4***	***Grade 5***
Any (events/patients)		**403 (100)**	**235 (50.65)**	**59 (12.72)**	**12 (2.59)**	**135 (29.09)**
Gastrointestinal disorders	Abdominal pain	14 (3.74)	14 (3.02)	11 (2.37)		
	Diarrhoea	10 (2.48)	10 (2.16)	6 (1.29)		
	Ileus	5 (1.24)	5 (1.08)		2 (0.43)	2 (0.43)
	Vomiting	5 (1.24)	5 (1.08)	1 (0.22)	2 (0.43)	
General disorders and administration site conditions	Death	8 (1.99)	8 (1.72)			8 (1.72)
	Fatigue	11 (2.73)	11 (2.37)	10 (2.16)		
	General physical health deterioration	46 (11.41)	44 (9.48)	7 (1.51)	1 (0.22)	34 (7.33)
	Multiple organ dysfunction syndrome	12 (2.98)	12 (2.59)			12 (2.59)
	Pain	6 (1.49)	6 (1.29)	4 (0.86)		
	Pyrexia	6 (1.49)	6 (1.29)	1 (0.22)		
Hepatobiliary disorders	Hepatic failure	9 (2.23)	9 (1.94)		1 (0.22)	8 (1.72)
	Jaundice	5 (1.24)	5 (1.08)	4 (0.86)		
Infections and infestations	Pneumonia	5 (1.24)	5 (1.08)	3 (0.65)		1 (0.22)
	Urinary tract infection	7 (1.74)	7 (1.51)	3 (0.65)		
Investigations	Blood bilirubin increased	5 (1.24)	5 (1.08)	3 (0.65)	1 (0.22)	
Musculoskeletal and connective tissue disorders	Pain (various)	5 (1.25)	5 (1.09)	2 (0.43)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon/Colorectal cancer	7 (1.74)	7 (1.51)			7 (1.51)
	Metastases to liver	6 (1.49)	6 (1.29)		1 (0.22)	4 (0.86)
	Neoplasm progression	37 (9.18)	37 (7.97)	2 (0.43)		35 (7.54)
Respiratory, thoracic and mediastinal disorders	Dyspnoea	16 (3.97)	15 (3.23)	7 (1.51)		4 (0.86)

Table 39: Serious TEAEs according to usual time of Stivarga® intake (at initial visit) (Data source: Table 83 of statistical report V1.0)

Serious TEAEs acc. to time of Stivarga intake (patient-based)	*N (%)*
In the morning (n=248)	119 (47.98)
In the evening (n=40)	16 (40.00)
Other time (n=16)	6 (37.50)
Unknown time (n=158)	94 (59.49)
Missing (n=2)	0 (0)

Table 40: Serious TEAEs – Reason for seriousness, action taken and outcome (Data source: Table 90 - 93 of statistical report V1.0)

a.

Reason for seriousness per TEAE*	*N (%)*
Hospitalization necessary or prolonged	297 (73.70)
Persistent or significant disability/incapacity	1 (0.25)
Important medical event	19 (4.71)
Life threatening	3 (0.74)
Fatal	138 (34.24)**
Action taken per TEAE	*N (%)*
Stivarga withdrawn	102 (25.31)
Stivarga interrupted	79 (19.60)
Stivarga dose reduced	3 (0.74)
Stivarga dose not changed	107 (26.55)
Not applicable	81 (20.10)
Unknown	31 (7.69)
Outcome per TEAE	*N (%)*
Recovered/ Resolved	197 (48.88)
Not recovered/ Not resolved	50 (12.41)
Recovered/ Resolved with sequelae	3 (0.74)
Fatal	138 (34.24)**
Unknown	15 (3.72)
Total number of serious TEAEs	**403 (100)**

*multiple answers possible
** 1 patient had 2 fatal TEAEs documented

b.

Worst outcome per patient	*N (%)*
Recovered/ Resolved	79 (33.62)
Not recovered/ Not resolved	15 (6.38)
Recovered/ Resolved with sequelae	1 (0.43)
Fatal	137 (58.30)*
Unknown	3 (1.28)

Patients with serious TEAE	**235 (100)**

*2 events that were not grade 5 resulted in death

10.6.4 Serious drug-related TEAEs

For 42 patients (9.05%) TEAEs were documented to be serious and causally related to the study drug. 10 patients (2.16%) had grade 1 and 2, 27 patients (5.82%) had grade 3, and 3 patients (0.65%) had grade 4 serious drug-related TEAEs. 2 patients (0.43%) had TEAEs resulting in death (grade 5; myocardial infarction and infectious pleural effusion). Diarrhea and fatigue occurred with the highest frequency (in 1.51% and 1.08% of patients, respectively; Table 41).

According to the usual time of Stivarga® intake (at the initial visit), serious drug-related TEAEs were observed in 22 of 248 patients (8.87%), who took Stivarga® in the morning, in 1 of 40 patients (2.5%), who took Stivarga® in the evening, and in 19 of 158 patients (12.03%), who took Stivarga® at an unknown time (Table 42; see table 89 of the statistical report for incidence rates of the respective events according to time of intake).

Table 41: Serious drug-related TEAEs according to MedDRA SOC and PT (patient-based) (Data source: Table 88 of statistical report V1.0)

Serious drug-related TEAE acc. to MedDRA (SOC and PT) (patient-based), n (%)		***All Grades***	***Grade 1***	***Grade 2***	***Grade 3***	***Grade 4***	***Grade 5***
Any		**42 (9.05)**	**5 (1.08)**	**5 (1.08)**	**27 (5.82)**	**3 (0.65)**	**2 (0.43)**
Blood and lymphatic system disorders	*Any PT*	1 (0.22)			1 (0.22)		
	Anaemia	1 (0.22)			1 (0.22)		
Cardiac disorders	*Any PT*	2 (0.43)			1 (0.22)		1 (0.22)
	Atrial flutter	1 (0.22)			1 (0.22)		
	Myocardial infarction	1 (0.22)					1 (0.22)
Gastrointestinal disorders	*Any PT*	13 (2.8)	1 (0.22)	3 (0.65)	8 (1.72)	1 (0.22)	
	Abdominal pain	2 (0.43)			2 (0.43)		
	Diarrhoea	7 (1.51)	1 (0.22)	1 (0.22)	5 (1.08)		
	Duodenal ulcer haemorrhage	1 (0.22)		1 (0.22)			
	Haematemesis	1 (0.22)			1 (0.22)		
	Nausea	2 (0.43)		2 (0.43)			
	Vomiting	3 (0.65)	1 (0.22)		1 (0.22)	1 (0.22)	
General disorders and administration site conditions	*Any PT*	7 (1.51)	1 (0.22)		6 (1.29)		
	Fatigue	5 (1.08)			5 (1.08)		
	General physical health deterioration[1]	1 (0.22)			1 (0.22)		
	Pyrexia	1 (0.22)	1 (0.22)				
Hepatobiliary disorders	*Any PT*	7 (1.51)	1 (0.22)		5 (1.08)	1 (0.22)	
	Cholecystitis	2 (0.43)			1 (0.22)	1 (0.22)	
	Hepatotoxicity	1 (0.22)			1 (0.22)		
	Hyperbilirubinaemia	1 (0.22)	1 (0.22)				
	Jaundice	2 (0.43)			2 (0.43)		
	Liver disorder	1 (0.22)			1 (0.22)		
Infections and	*Any PT*	4 (0.86)	1 (0.22)		2 (0.43)		1 (0.22)

infestations	Enteritis infectious	1 (0.22)			1 (0.22)		
	Febrile infection	1 (0.22)			1 (0.22)		
	Gastroenteritis	1 (0.22)	1 (0.22)				
	Infectious pleural effusion	1 (0.22)					1 (0.22)
Investigations	*Any PT*	1 (0.22)		1 (0.22)			
	Blood bilirubin increased	1 (0.22)		1 (0.22)			
Metabolism and nutrition disorders	*Any PT*	5 (1.08)	1 (0.22)		3 (0.65)	1 (0.22)	
	Decreased appetite	1 (0.22)			1 (0.22)		
	Dehydration	2 (0.43)			2 (0.43)		
	Hyponatraemia	2 (0.43)	1 (0.22)			1 (0.22)	
Nervous system disorders	*Any PT*	1 (0.22)		1 (0.22)			
	Haemorrhage intracranial	1 (0.22)		1 (0.22)			
Renal and urinary disorders	*Any PT*	1 (0.22)			1 (0.22)		
	Hydronephrosis	1 (0.22)			1 (0.22)		
Respiratory, thoracic and mediastinal disorders	*Any PT*	2 (0.43)			2 (0.43)		
	Dyspnoea	2 (0.43)			2 (0.43)		
Skin and subcutaneous tissue disorders	*Any PT*	6 (1.29)		1 (0.22)	5 (1.08)		
	Blister	1 (0.22)			1 (0.22)		
	Drug eruption	1 (0.22)		1 (0.22)			
	Palmar-plantar erythrodysaesthesia syndrome	3 (0.65)			3 (0.65)		
	Rash	2 (0.43)			2 (0.43)		
Vascular disorders	*Any PT*	3 (0.65)			2 (0.43)	1 (0.22)	
	Deep vein thrombosis	1 (0.22)			1 (0.22)		
	Hypertension	2 (0.43)			1 (0.22)	1 (0.22)	

Table 42: Serious drug-related TEAEs according to usual time of Stivarga® intake (at initial visit) (Data source: Table 87 of statistical report V1.0)

Serious drug-related TEAEs acc. to time of Stivarga intake (patient-based)	*N (%)*
In the morning (n=248)	22 (8.87)
In the evening (n=40)	1 (2.50)
Other time (n=16)	0 (0)
Unknown time (n=158)	19 (12.03)
Missing (n=2)	0 (0)

10.6.5 Hand-foot skin reaction (HFSR)

73 patients (15.73%) had hand-foot skin reaction (HFSR), which is among the most frequently observed dermatological adverse reaction with Stivarga®. Most cases were mild to moderate in severity (59 patients, 12.71%); 14 cases were severe (3.02%). 31 patients with HFSR (42.47%) received preventive treatment for HFSR (Table 43). About 3/4 of patients with HFSR were recovered/resolved (55 patients, 75.34%), 4 patients (5.48%) were recovering/resolving and 1 patient (1.37%) was recovered/resolved with sequelae. For 9 patients (12.33%) the reaction was not recovered/resolved (Table 44).

The median duration of resolved reactions was 33 days (range: 0 – 233 days). For 44 of these events no therapeutic measure was initiated. The median duration of these events was 25.5 days (range: 0 – 219 days). Urea-based creams were initiated for 13 events. For these cases the median duration of the reactions was 31 days (range: 6 – 233). In 8 cases topical corticosteroids were used. Here, the median duration of the reactions was 33 days (range: 13 – 120; Table 45).

Table 43: HFSR among patients with and without preventive treatment (Data source: Table 73 of statistical report V1.0)

HFSR according to HFSR prevention, n (%)	***with prevention***	***without prevention***	***Total***
No HFSR	102 (76.69)	289 (87.31)	391 (84.27)
HFSR worst grade 1	10 (7.52)	12 (3.63)	22 (4.74)
HFSR worst grade 2	16 (12.03)	21 (6.34)	37 (7.97)
HFSR worst grade 3	5 (3.76)	9 (2.72)	14 (3.02)
Number of patients	**133 (100)**	**331 (100)**	**464 (100)**

Table 44: Outcome of HFSR (Data source: Table 74 of statistical report V1.0)

Outcome of HFSR	*N (%)*
Recovered/ Resolved	55 (75.34)
Recovering/ Resolving	4 (5.48)
Not recovered/ Not resolved	9 (12.33)
Recovered/ Resolved with sequelae	1 (1.37)
Unknown	4 (5.48)
Number of patients with HFSR	**73 (100)**

Table 45: Duration of HFSR according to therapeutic measure (Data source: Table 75 of statistical report V1.0)

Duration of HFSR (event-based) [days]*	*N (Nmiss)*	*Mean (SD)*	*Median (Min, Max)*	*P25, P75*
No therapeutic treatment	44 (14)	42.61 (49.34)	25.5 (0, 219)	7, 54
Urea-based cream	13 (1)	63.85 (73.59)	31 (6, 233)	26, 47
Non-urea based cream	3 (1)	35.00 (30.20)	31 (7, 67)	7, 67
Keratolytic cream	1 (0)	20.00 (n/a)	20 (20, 20)	20, 20
Topical corticosteroids	8 (0)	38.50 (34.68)	33 (13, 120)	16, 38.5
Topical analgesics	1 (1)	120.00 (n/a)	120 (120, 120)	120, 120
Oral analgesics	2 (1)	39.00 (2.83)	39 (37, 41)	37, 41
Other	11 (3)	72.82 (63.52)	43 (7, 189)	37, 113
Total	**83 (21)**	**49.84 (53.95)**	**33 (0, 233)**	**14, 54**

11. Discussion

There is a high unmet clinical need for mCRC treatment options. Regorafenib is the first oral multikinase inhibitor with proven efficacy and safety in patients with mCRC that have progressed after previous standard therapies (CORRECT phase III trial). In this observational study, effectiveness and safety of regorafenib are investigated in a more heterogeneous patient population in routine use in Germany.

11.1 Key results

In this study, median overall survival was 5.9 months (CI 95%: 5.3 – 6.6 months), with a 1-year survival of 23.3%, comparable to results obtained from the phase III CORRECT trial (21). Median progression-free survival was with 3.1 months (CI 95%: 2.86 – 3.36 months) longer than in the CORRECT trial (1.9 months vs. 1.7 months for placebo), indicating a benefit of regorafenib on progression. The 1-year PFS was 5%. Median time to tumor progression was 4 months (CI 95%: 3.6 – 4.9 months) with a 1-year TTP of 18.2%. The disease control rate was 26.7%, which was lower than in the regorafenib arm (41%) but higher than in the placebo arm (14.9%) of the CORRECT trial. Not all patients had an evaluation of the tumor status post-baseline, therefore the DCR was only determined for 277 patients (59.8%) as compared to 505 patients in the CORRECT trial (regorafenib arm).

Patients in the subgroups with a better performance status, a longer time since initial diagnosis, no prior Bevacizumab treatment, and lung-limited disease seemed to benefit more from regorafenib, which is in line with previous findings (23). There also seemed to be a difference in the treatment response according to the primary tumor location, with a left-sided location having a better prognosis. This was previously shown for other targeted therapies (24).

Median duration of study treatment was 71 days (range: 1 – 1085 days). 262 patients (56.5% of the safety set) had dose modifications and/or interruptions. At the start of therapy, the recommended dose of 160 mg was taken by more than half of all patients (53.7%). After the dose modification, 80 mg and 120 mg were the most frequently used doses (32.9% and 44.1%, respectively), 160 mg was used in only 17.2% of cases. Adverse events were the reason for 137 of the 383 dose modifications (35.8%) and for 201 of the 260 interruptions (77.3%). Most patients took Stivarga® in the morning (60.8%).

294 patients (63.4%) prematurely discontinued study treatment. Main reasons were disease progression (34.5%), adverse event/toxicity (13.4%), deterioration of general condition (8%) and patient's decision (5.4%). 389 patients (83.84%) received concomitant medication at the end of treatment, mainly for the treatment of adverse events (57.3%; except hand-foot-skin reaction) and concomitant diseases/conditions

(52.6%). 168 patients (36.2%) received medication for hand-foot skin reaction (HFSR), which was mainly used as preventive and not therapeutic medication. HFSR belongs to the most frequently observed dermatological adverse reactions with Stivarga® (SPC Stivarga, Sept 2017). In this study, HFSR occurred in 73 patients (15.7%), with most cases being mild to moderate in severity (grade 1 and 2: 12.7%). The incidence of HFSR in this study was lower than in the phase III CORRECT trial (46.6%). Most patients had recovered from the reaction (75.3% recovered,1.4% with sequelae and 5.5% were recovering).

Allover, treatment-emergent adverse events (TEAEs) were observed in more than 90% of patients with a total of 1970 events. Among the most common TEAEs were fatigue (24.1%) and diarrhea (22%). TEAEs, which were judged as causally related to Stivarga® treatment by the investigator, were observed in about 2/3 of patients with a total of 834 events. Almost half of the patients (46.3%) had grade 1 and 2 TEAEs, 17.9% had grade 3 TEAEs. Fatigue and diarrhea were also among the most common drug-related TEAEs (14.2% and 17.5%, respectively), but still having a lower incidence than in the phase III CORRECT trial (47.4% and 33.8%, respectively). Serious drug-related TEAEs were observed in less than 10% of patients, with diarrhea and fatigue occurring with the highest frequency (1.5% and 1.1%, respectively). Four life-threatening events (grade 4) were observed in 3 patients (0.7%), which were vomiting, hypertension, cholecystitis and hyponatremia. Myocardial infarction and infectious pleural effusion were fatal (grade 5; 0.4%). For almost half of the drug-related events the Stivarga® dose was not changed (404 events, 48.4%) and for 138 events (16.6%) it was reduced. Stivarga® treatment was interrupted for 168 events (20.1%) and withdrawn for 85 events (10.2%). Most events were resolved (629 events, 75.4%), 119 events (14.3%) were not resolved. The worst outcome per patient was recovered/resolved for 2/3 (202 patients) and not recovered/resolved for almost 1/4 (71 patients, 23.4%).

11.2 Limitations

Because of the non-interventional study design and limitations inherent to observational studies, estimates for incidence rates of adverse events and effectiveness variables might be biased. Results for secondary effectiveness variables (PFS, TTP, DCR) should be interpreted carefully because of the uncontrolled setting, in which time periods between follow-up visits were much more variable than in controlled clinical studies with fixed visit schedules. Moreover, a post-baseline evaluation of the tumor status was only performed for about 60% of patients. Thus, the DCR could only be evaluated for these patients. Due to the temporal variability of follow-up visits, tumor status evaluations were grouped into time intervals of 8 weeks.

In this single arm study, comparison of outcomes after treatment with Stivarga® versus treatment with a comparator could not be performed. Thus, a differentiation between predictive and prognostic factors was not possible. Comparisons can only be performed with historical data from clinical studies, which is prone to bias and confounding.

11.3 Interpretation

In this observational study, effectiveness and safety of regorafenib were determined in patients with mCRC, who have failed prior standard therapy. Survival in a real-life setting as determined in this study was comparable to survival in a strictly controlled setting (phase III CORRECT trial).

Fatigue, diarrhea and HFSR are very common adverse drug reactions in patients treated with Stivarga® in clinical trials (SPC Stivarga, Sept 2017). The frequencies observed in this study are still below the reported frequencies of the placebo-controlled phase III trial with mCRC patients (CORRECT) (21).

11.4 Generalizability

The data of this study have been collected from office-based and clinic oncologists and gastroenterologists in Germany. At inclusion, the great majority of patients had 3 or less prior treatment lines (95.5%) and only about 1/3 had previously received bevacizumab (34.8%).

12. Other information

Not applicable

13. Conclusion

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. Adverse events were generally manageable, although posology adjustments were required. The TEAEs revealed do not indicate a change of the established safety profile of Stivarga®.

14. References

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Appendices

Annex 1: List of stand-alone documents

Table 46: List of stand-alone documents

Document Name	Final version and date
16665_ SV1313_RECORA_Investigator list_20170707	07 JUL 2017
16665_SV1313_CRF_V3.0_20160407	07 APR 2016
SV1313_Recora_Statistical Report_Final_1.0_Tables_only_2017-11-27	27 NOV 2017
SV1313_SAP_final_3.0_2017-11-23	23 NOV 2017
DMP_2.0_RECORA_2013-11-26_final	26 NOV 2013

Annex 2 Additional information

Prior radiotherapy – Irradiated location: Free texts and **ALLOCATED CATEGORIES** (Annex to Table 7 c)

Prior radiotherapy - irradiated location	*N (%)*
PRIMARY TUMOR	**13 (2.80)**
Bereich Raumforderung und pelvine Lymphabflusswege	1 (0.81)
CRC	1 (0.81)
Ehem.Tumorregion und Lymphabflusswege	1 (0.81)
ehemalige Tumorregion mit Lymphabfluss	1 (0.81)
Primärtumor	2 (1.61)
Primärtumor + Lymphabflussgebiet	1 (0.81)
Primärtumor sowie regionäre Lymphabflußgebiete	1 (0.81)
Primärtumor, Lymphabflußgebiet	1 (0.81)
Primärtumorbereich	1 (0.81)
Tumorregion	1 (0.81)
Tumorregion mit lokoregionärem Lymphabfluss	1 (0.81)
ursprüngliche Tumorregion unter Einschluß der pelvinen Lymphabflußwege	1 (0.81)
COLON	**5 (1.08)**
Darm	2 (1.61)
Kolon	1 (0.81)
Rezidiv sigmakarzinom und Lymphknotenmetastasen	1 (0.81)
Sigma	1 (0.81)
RECTAL	**26 (5.60)**
Radiotherapie Tu-Region Rektum 50,4 GyZVD+parallele Systemtherapie 5FU+parallel regionale Tiefenhyperthermie 2xwö. HT01Studie UKT	1 (0.81)
Rektum	12 (9.68)
Rektum (Tumor) , Lymphabflusswege	2 (1.61)
Rektum / Becken	1 (0.81)
Rektum + LAG	2 (1.61)
Rektum und locoregionärer Lymphabfluss	1 (0.81)
Rektum und pelvine Lyamphabflusswege	1 (0.81)
Rektum, Lymphabflußgebiet im Bereich des Beckens	1 (0.81)
Rektum, Vagina, Lymphabfluss, Analregion	1 (0.81)
Rektumloge	1 (0.81)
Rektumregion, pelvine Lymphabflusswege	1 (0.81)
Rektumstumpf, kleines Becken, pelvine Lymphabflusswege	1 (0.81)
Rektumtumor	1 (0.81)
PELVIS	**39 (8.41)**
Becken	13 (10.48)
Becken und Lymphabfluss	1 (0.81)
Beckenrezidiv	6 (4.84)
kleines Becken	1 (0.81)
Neurocranium 30 Gy, Os sacrum 30 Gy, Boost Metastase Neurocranium 42GY	1 (0.81)

Os ileum li	1 (0.81)
Os ilium re. mit Weichteilanteil	1 (0.81)
Os sacrum	2 (1.61)
pelviner Tumor	1 (0.81)
perirektales Fettgewebe,Blase, Uterus,Vagina, Präsakralregion	1 (0.81)
prä Sacralraum, LK gebiet	1 (0.81)
Radiochemotherpie kleines Becken	1 (0.81)
Rektum / Becken	1 (0.81)
Rektumstumpf, kleines Becken, pelvine Lymphabflusswege	1 (0.81)
Rezidivregion präsacral und retroanal	1 (0.81)
Sakralhöhle	1 (0.81)
Sakralhöhle und Lymphablussgebiet	1 (0.81)
Sakralwirbelkörper 2-3 Infiltration rechts	1 (0.81)
Sakrum	1 (0.81)
Schmerzbestrahlung becken	1 (0.81)
Teilbecken links	1 (0.81)
ABDOMEN; PERITONEUM	**3 (0.65)**
Abdomen	1 (0.81)
Peritonealmetastase	1 (0.81)
Peritoneum	1 (0.81)
LIVER	**12 (2.59)**
(ESRT) der Leberfilia im Leberlappen	1 (0.81)
Brachytherapie Leber Afterloading	1 (0.81)
Leber	5 (4.03)
Leber- u. Lungen-Metastase	1 (0.81)
Lebermetastasen	1 (0.81)
rechte Leber	1 (0.81)
rechter Leberlappen, SIRT	1 (0.81)
SIRT - Leber	1 (0.81)
LYMPH NODE	**4 (0.86)**
Lymphknoten paraaortal	1 (0.81)
prä Sacralraum, LK gebiet	1 (0.81)
Primärtumor, Lymphknoten	1 (0.81)
Rezidiv sigmakarzinom und Lymphknotenmetastasen	1 (0.81)
LUNG	**4 (0.86)**
Leber- u. Lungen-Metastase	1 (0.81)
Lunge	2 (1.60)
Lungenmetastase	1 (0.81)
BRAIN	**7 (1.51)**
frontobasale Metastase	1 (0.81)
frontoparietal	1 (0.81)
Ganzhirn	1 (0.81)
Ganzhirn + supratentorielle Metastasen	1 (0.81)

Hirnschädel	1 (0.81)
Neurocranium	1 (0.81)
Neurocranium 30 Gy, Os sacrum 30 Gy, Boost Metastase Neurocranium 42GY	1 (0.81)
OTHER	**19 (4.09)**
10. Rippe rechts, Oberschenkelschaft links, Kniegelenk links	1 (0.81)
BWK 10	1 (0.81)
BWK 1-3	1 (0.81)
HWK 1-3	1 (0.81)
Knochen	1 (0.81)
Kopf	1 (0.81)
Leiste, links	1 (0.81)
LWK 5	1 (0.81)
LWK3	1 (0.81)
mediastinum	1 (0.81)
perirektales Fettgewebe,Blase, Uterus,Vagina, Präsakralregion	1 (0.81)
Prostataregion bei Rektum-CA	1 (0.81)
Radiochemo	1 (0.81)
Rektum, Vagina, Lymphabfluss, Analregion	1 (0.81)
Rezidivregion, Harnblasenregion	1 (0.81)
Rippen- und Weichteilmetastase	1 (0.81)
TH 7 - LWK 4 (Schmerz- und Stabilisierung)33	1 (0.81)
unbekannt	1 (0.81)
unbekannt,und Xeloda, keine weiteren Inormationen verfügbar. GY ebenfalls unbekannt,	1 (0.81)
Total	**124 (100)**

A single free text was allocated to more than one category, if applicable.

Annex 3 Signature Pages

Signature Page - Study Medical Expert

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date	Version 1.0, 09 MAR 2018
IMPACT study number	16665
Study type	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4934
Medicinal product (Active substance)	Stivarga® (Protein Kinase Inhibitors (L01XE21), regorafenib)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: [redacted]

Signature Page - Study Conduct Responsible

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date	Version 1.0, 09 MAR 2018
IMPACT study number	16665
Study type	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4934
Medicinal product (Active substance)	Stivarga® (Protein Kinase Inhibitors (L01XE21), regorafenib)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: [redacted]

Signature Page - Study Statistician

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date	Version 1.0, 09 MAR 2018
IMPACT study number	16665
Study type	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4934
Medicinal product (Active substance)	Stivarga® (Protein Kinase Inhibitors (L01XE21), regorafenib)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: [redacted]

Signature Page - Study Data Manager

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date	Version 1.0, 09 MAR 2018
IMPACT study number	16665
Study type	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4934
Medicinal product (Active substance)	Stivarga® (Protein Kinase Inhibitors (L01XE21), regorafenib)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: [redacted]

Signature Page - Study Safety Lead

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date	Version 1.0, 09 MAR 2018
IMPACT study number	16665
Study type	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4934
Medicinal product (Active substance)	Stivarga® (Protein Kinase Inhibitors (L01XE21), regorafenib)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: [redacted]

Signature Page - Qualified Person Responsible for Pharmacovigilance

Title	**RECORA- Re**gorafenib in patients with metastatic **co**lo**r**ectal cancer (mCRC) **a**fter failure of standard therapy
Report version and date	Version 1.0, 09 MAR 2018
IMPACT study number	16665
Study type	PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS4934
Medicinal product (Active substance)	Stivarga® (Protein Kinase Inhibitors (L01XE21), regorafenib)
Study Initiator and Funder	Bayer Pharma AG, D-13342 Berlin, Germany

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: [redacted]

Date, Signature: [redacted]