Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	REFINE: Regorafenib observational study in hepatocellular carcinoma
Report version and date	V1.0, 12 OCT 2022
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS20981
Active substance	ATC L01EX05, Protein kinase inhibitors, Regorafenib
Medicinal product	STIVARGA®, regorafenib
Product reference	EU marketing authorization number: EU/1/13/858/001 (28 tablets) EU/1/13/858/002 (3x28 tablets)
Procedure number	EU procedure number: EMEA/H/C/002573
Study initiator and funder	Bayer AG, 51368 Leverkusen, Germany
Research question and objectives	The purpose of this observational study was to evaluate, under real-world practice conditions, the safety and effectiveness of regorafenib in patients with unresectable hepatocellular carcinoma (uHCC) for whom a decision to treat with regorafenib had been made before study enrollment. The study also evaluated regorafenib treatment in a broader population of hepatocellular carcinoma (HCC) patients and also provided information on treatment patterns and outcomes for patients with uHCC in the real-world setting. The primary objective of this study was to evaluate the safety of regorafenib in patients with uHCC, including incidence of all treatment-emergent adverse events (TEAEs)

	and dose modifications due to TEAEs in real-world practice conditions. The secondary objectives included the description of effectiveness and treatment patterns of regorafenib, as well as patient characteristics and practice patterns in uHCC treatment. The tertiary objective was to describe sorafenib treatment and other therapies for HCC prior to regorafenib treatment.
Country(-ies) of study	Austria, Belgium, Canada, China, Denmark, Egypt, France, Greece, Italy, Japan, Korea, Netherlands, Russia, Saudi Arabia, Spain, Sweden, Taiwan, Thailand, Turkey, and the United States of America (USA)
Author	PPD Peter Merian Strasse 84 CH-4052, Basel Switzerland

Marketing authorization holder

Marketing authorization holder(s) (MAH)	Bayer AG, 51368 Leverkusen, Germany
MAH contact person	PPD PPD Bayer AG, 13353 Berlin, Germany

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1 Abstract

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

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

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

2 List of abbreviations

AE	Adverse event
AJCC	American Joint Committee on Cancer
ALBI	Albumin-bilirubin
ALT	Alanine aminotransferase
AFP	Alpha-fetoprotein
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
BCLC	Barcelona Clinic Liver Cancer
BMI	Body mass index
CFR	Code of federal regulations
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common terminology criteria adverse event
DD	Drug dictionary
DMP	Data management plan
DOT	Duration of treatment
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EU	European Union
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
GIST	Gastrointestinal stromal tumors
HAI	Hepatic artery infusion
HCC	Hepatocellular carcinoma
HEOR	Health economics and outcomes research
HR	Hazard ratio
IEC	Independent ethics committee
IRB	Institutional review board
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LKAD	Last known to be alive date
MAH	Marketing authorization holder

Max	Maximum
mCRC	Metastatic colorectal cancer
MedDRA	Medical dictionary for regulatory activities
Min	Minimum
MRP	Medical review plan
NCI	National cancer institute
NOS	Not otherwise specified
ORR	Overall tumor response
OS	Overall survival
PASS	Post authorization safety study
PEI	Percutaneous ethanol injection
PFS	Progression-free survival
PMDA	Pharmaceuticals and medical devices agency
PT	Preferred term
QRP	Quality review plan
RWE	Real-world evidence
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SmPC	Summary of product characteristics
SOC	System organ class
SSAF	Sorafenib treated safety analysis set
TACE	Transarterial chemoembolization
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TKI	Tyrosine kinase inhibitor
TLF	Tables, listings, and figures
TNM	Tumor, node, metastasis
TTP	Time to progression
uHCC	Unresectable hepatocellular carcinoma
VEGFR	Vascular endothelial growth factor receptor
USA	United States of America
VDR	Validity review and data decision report
WHO	World Health Organization

3 Investigators

Contact details and the list of all investigators are provided in a stand-alone document in Annex 1 and can be provided upon request.

4 Other responsible parties

4.1 Sponsor contact names

Role: Conduct Responsible
Name: PPD
E-mail: PPD

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
Name: PPD

Role: Safety Lead
Name: PPD

Role: Medical Expert
Name: PPD

Role: Statistician
Name: PPD

Role: Data Manager
Name: PPD

Role: Epidemiologist
Names: PPD

Role: Health Economics and Outcomes Research (HEOR) responsible
Name: PPD

Role: Real World Evidence (RWE) responsible
Name: PPD

Role: Regulatory Affairs responsible
Name: PPD

Role: Ops Ex & PM
Name: PPD

Role: MA Oncology Representative (J-PMS)
Name: PPD

Role: Conduct Responsible (J-PMS)
Name: PPD

Contact details of the responsible parties at Bayer AG are available upon request.

4.2 Contract research organization

Contract research organization (CRO) contact details:

Cerner Enviza (formerly Kantar Health)
Landsberger Straße 284, 80687 Munich, Germany

5 Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	Q3 2017	13 SEP 2017	
Registration in the EU PAS register	23 OCT 2017	19 SEP 2017	
Database cut-off for first interim analysis	Based on sample size	11 NOV 2019	When a minimum of 500 patients have been enrolled in the study (reached on 20 MAY 2019) for at least 4 months
First interim analysis report	Based on first interim analysis	17 APR 2020	
Database cut-off for second interim analysis	Q2 2021	08 MAR 2021	Second interim analysis 1.5 years before final analysis
Second interim analysis report	Based on second interim analysis	20 JUL 2021	
End of data collection	Q2 2022	31 JAN 2022	
Database cut-off for final analysis	Q2 2022	21 JUN 2022	
Final report of study results	Q4 2022	12 OCT 2022	

EU: European Union, PAS: Post authorization study

Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approvals were obtained per country and can be provided upon request.

6 Rationale and background

The phase III RESORCE (REgorafenib after SORafenib in patients with hepatoCEllular carcinoma) study demonstrated that regorafenib prolongs survival in patients with unresectable hepatocellular carcinoma (uHCC) who tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment), progressed on sorafenib, and had Child-Pugh A liver function. However, at the time of study start there were no real-world data available on the use of regorafenib as second-line after first-line treatment with sorafenib. The purpose of this study was to describe the safety and effectiveness of treatment with regorafenib in real-world settings. In addition, this study provided information about baseline characteristics, treatments, and management of uHCC in real-world practice that enabled greater understanding of the disease and practice patterns in a rapidly evolving treatment landscape.

Hepatocellular carcinoma (HCC) is an aggressive cancer that frequently occurs in the setting of chronic liver disease and cirrhosis and accounts for up to 85% of all primary liver cancers worldwide. Cancer of the liver and intrahepatic bile ducts is the sixth most frequently diagnosed malignancy worldwide, with approximately 841,000 cases in 2018. In addition, primary liver cancer is the fourth leading cause of cancer-related mortality worldwide, with over 780,000 deaths in 2018 (1).

Regorafenib is an oral multikinase inhibitor that blocks various kinases within the mechanisms involved in tumor growth and progression. In vitro, regorafenib demonstrated a distinct kinase inhibition profile which includes kinases involved in angiogenesis (vascular endothelial growth factor receptor [VEGFR]1/2/3 and tyrosine kinase with immunoglobulin-like and epidermal growth factor (EGF)-like domains [TIE]2), oncogenesis (stem cell factor receptor [KIT], rearranged during transfection [RET], and a type of serine/threonine kinase [BRAF]), metastasis (VEGFR3, platelet-derived growth factor receptor [PDGFR]-β, fibroblast growth factor receptor [FGFR]), and tumor immunity (colony-stimulating factor 1 receptor [CSF1R]) (2).

The efficacy and safety of regorafenib were evaluated in three different international, multicenter, randomized, double-blinded placebo-controlled phase III trials. One study in metastatic colorectal cancer (mCRC) demonstrated significant improvement in survival with regorafenib compared with placebo (median overall survival [OS]: 6.4 vs 5.0 months, p=0.00529). Another study in gastrointestinal stromal tumors (GIST) demonstrated a significant improvement in progression-free survival (PFS) for regorafenib compared with placebo (median PFS: 4.8 vs 0.9 months, respectively, p<0.0001). These studies resulted in regorafenib approvals for both mCRC and GIST. The phase III RESORCE data indicated that the safety profile of regorafenib in HCC was consistent with that reported in the phase III studies in mCRC and GIST. In all three indications, the most common grade ≥3 adverse events (AEs) included hand-foot skin reaction, hypertension, fatigue, and diarrhea, and AEs leading to discontinuation were relatively low (6–18% among all three studies) (3-6).

Data from the phase III RESORCE study showed clinically and statistically significant OS prolongation with regorafenib in patients with uHCC who have progressed on the first-line therapy of sorafenib. The median OS was 10.6 months for patients receiving regorafenib versus 7.8 months for those receiving placebo (hazard ratio [HR] 0.63; 95% confidence interval [CI]: 0.50, 0.79; P<0.001), which translates to a 37% reduction in the risk of death over the study period (3).

For uHCC, sorafenib demonstrated a statistically significant OS benefit, shown in two phase III randomized, placebo-controlled trials (Sorafenib Hepatocellular carcinoma Assessment Randomized Protocol (SHARP) and Asia Pacific study) (7, 8). Sorafenib (Nexavar) was the first oral multi-tyrosine kinase inhibitor (TKI) to be approved for the treatment of advanced HCC in 2007. Reports

from the phase III REFLECT trial demonstrated non-inferiority of the kinase inhibitor lenvatinib to sorafenib as first-line treatment (9). In the phase III IMbrave-150 study atezolizumab + bevacizumab combination was superior to sorafenib in OS and this led to the modification of first-line standard for all patients with HCC eligible for systemic treatment (10). Optimal sequencing after atezolizumab + bevacizumab is not yet determined. In second-line treatment after sorafenib regorafenib was the first approved TKI after many years. Further, it was shown in a phase III trial that the TKI cabozantinib improves OS compared to placebo, as a second- or third-line treatment in patients pre-treated with sorafenib (11). Ramucirumab, a monoclonal anti-VEGFR2 antibody, showed improved OS compared to placebo in patients with increased alpha-fetoprotein (AFP) levels who progressed on sorafenib (12).

The purpose of this observational study was to describe the safety and effectiveness of regorafenib in patients with uHCC under real-world practice conditions. Patients enrolled were those for whom a decision to treat with regorafenib had already been made, and included a variety of HCC patient subsets, such as patients grouped by Child-Pugh score regionally and globally, that were not addressed in the RESORCE study. The study also aimed to provide information on treatment patterns and outcomes for patients with uHCC in the real-world setting, and to collect baseline information, including retrospective data on sorafenib treatment.

7 Research question and objectives

The primary objective of this international observational study was to evaluate the safety of regorafenib in patients with uHCC, including incidences of all treatment-emergent adverse events (TEAEs) and dose modifications due to TEAEs under real-world practice conditions.

The secondary objectives were:

- To describe the effectiveness of regorafenib, including OS, PFS, time to progression (TTP), and overall tumor response (ORR)
- To describe the patterns of regorafenib treatment, including actual doses, duration of treatment (DOT), and other dosing parameters
- To describe patient characteristics, comorbidities, prior therapies, and assess their potential influence on treatment and outcomes under real-life conditions
- To describe the physicians' practice patterns, including regional differences in the management and treatment of uHCC under real-life conditions

Additional objectives, based on patients' prior treatments, were evaluated. The tertiary objectives included:

- To describe sorafenib treatment prior to regorafenib treatment, including doses, DOT, best response, and reasons for discontinuation (in relevant patients)
- To describe other therapies for HCC prior to regorafenib, including doses, DOT, best response, and reasons for discontinuation (in relevant patients)

8 Amendments and updates

Table 2: Amendments to the protocol

No.	Date	Section of study protocol	Amendment / Update	Reason
AM01	07 MAR 2017	Multiple	The global REFINE protocol has been revised to comply with Japanese regulations. The amendment was generated as proof of written-based study design specific in Japan and will be reviewed by Japanese regulatory authority (Pharmaceuticals and Medical Devices Agency [PMDA]). To avoid redundant description or any conflict, the local Japanese amendment only focuses on critical information for PMDA communication (e.g., number of patients, observation period, timing of interim/final analysis, etc.).	For compliance with Japanese regulations.
AM02	03 MAY 2018	Multiple	The global REFINE protocol was revised to reflect changes to the collected variables (e.g., addition of survival assessment) and to remove inconsistencies and include administrative and timeline updates. The local amendment for Japan was updated accordingly. No other, Japan-specific changes were made.	Administrative and timeline changes. Change in collected variables.
Update 01	20 JUN 2018	Title page and signature page	Brand name removed from first page and signature page.	Regulatory reasons.
Update 02	27 Nov 2018	Multiple	Responsible safety lead, Epidemiologist, and MA Oncology Representative (J-PMS) were changed as well as deletion of 5 lab parameters. The local amendment for Japan was updated. The statement of enrollment period in Japanese population was updated.	Administrative and timeline changes. Change in collected lab parameters.
AM03	06 JUL 2020	Multiple	Second interim analysis and clarification for end of study were	Administrative and timeline changes.

No.	Date	Section of study protocol	Amendment / Update	Reason
			added, study timelines and changes to study responsible party updated. The local amendment for Japan was updated accordingly. No other, Japan-specific changes were made.	As there was a gap of nearly three years between the first interim analysis and the final analysis an additional interim analysis 1.5 years before final analysis was added.

9 Research methods

9.1 Study design

This was an international, prospective, open-label, multicenter, observational study. Patients with uHCC for whom a decision to treat with regorafenib had been made before enrollment were eligible for the study. The decision on the dose and DOT was solely at the discretion of the treating physician, based on the recommendations written in the local product information. Examinations and the laboratory monitoring schedule followed local label recommendations in line with local standard of care. No control arm was planned in this study because regorafenib was the only agent with proven survival benefit in patients with uHCC after prior sorafenib treatment; there was no alternative treatment available at the time of this study.

This study was designed to evaluate AEs in patients treated with regorafenib. It also collected data to describe the effectiveness of regorafenib in uHCC, patterns of treatment, and the influence of baseline characteristics and treatment history.

Data were collected from 1028 patients globally over a total study period of approximately 5 years, including 24 months observation time from study entry. A first interim data analysis for safety monitoring was performed after the first 500 patients enrolled were observed for at least 4 months. A second interim analysis 1.5 years before final analysis was added by protocol amendment 3. The final analysis was conducted 24 months after the last patient was enrolled in the study.

Patients were observed from the time of the start of therapy with regorafenib until the end of observation owing to premature discontinuation, withdrawal of consent, or death, or until the end of the study.

Physicians participating in this study were recommended to include consecutive patients. The data for this study were collected using an electronic case report form (CRF).

9.2 Setting

The international, observational study design enabled data to be collected from patients treated under local standard of care clinical practice; all decisions in terms of diagnostic procedures, treatments, management of the disease, and resource utilization were fully dependent on mutual agreement between the patient and the attending physician, without interference by the study protocol.

This study was conducted in Austria, Belgium, Canada, China, Denmark, Egypt, France, Greece, Italy, Japan, Korea, Netherlands, Russia, Saudi Arabia, Spain, Sweden, Taiwan, Thailand, Turkey, and the United States of America (USA).[a]

The investigator documented the baseline / initial visit, follow-up visits and the end of observation / final visit for each patient in the CRF. Follow-up visits occurred during routine practice; the study protocol did not define exact referral dates for those visits. The end of observation / final visit was to be documented after a patient had been in the study for at least 24 months, was lost to follow-up, had withdrawn consent, or had died, whichever occurred first. If the documentation was stopped

[a] Additionally, one site in Argentina enrolled patients, but those patients were excluded.

prematurely, the reasons for the end of observation had to be given. If a patient joined an interventional clinical study during the course of observation, information on survival was to be collected up to the end of this study. If a patient remained alive at the time of study closure, this was documented in the final visit.

In this observational study, withdrawal from the study was independent of the underlying therapy and did not affect the patient's medical care. Each patient could withdraw from the study at any time and without giving a reason. If a patient wanted to terminate the study participation, no further data were collected. The patient was asked whether he/she agrees that the data collected so far can be used.

The start of the study was the date from which information on the first patient could be first recorded in the study dataset. The end of the study was 24 months after the last patient was enrolled in the study.

A visit was defined as any status assessment or new treatment decision the treating physician took in the presence of the patient. The time interval between two documented status assessments was assumed to be 6–12 weeks, although this was at the discretion of the treating physician.

An overview of the variables collected during the study is presented in Table 3.

Table 3: Tabulated overview on variables collected during the study

Variables	**Baseline / Initial visit[a]**	**Follow-up visit(s)**	**Survival Assessment[b]**	**End of observation / final visit**
Visit date	X	X		X
Eligibility assessment	X			
Patient information and consent	X			
Demography	X			
Comorbidities (medical history, concomitant diseases)	X			
HCC classification	X			
HCC assessment under sorafenib	X			
Prior systemic anti-cancer therapy (including sorafenib)	X			
Tolerability of prior systemic anti-cancer therapy (including sorafenib)	X			
Prior and concomitant non-systemic anti-cancer therapy	X	X		
Prior and concomitant radiotherapy	X	X		
Prior medication	X			
Lifestyle records (smoking & alcohol use)	X			

Variables	Baseline / Initial visit[a]	Follow-up visit(s)	Survival Assessment[b]	End of observation / final visit
Vital signs	X			
BCLC Staging	X			
Tumor status and metastases	X	X		X
Child-Pugh classification	X	X		X
ECOG performance status	X	X		X
Laboratory parameters	X	X		X
Concomitant medication	X	X		X
Exposure/treatment with regorafenib	X	X		X
AEs on regorafenib	X	X		X[c]
Information collection date			X[b]	
Survival status			X[b]	
Tumor evaluation (post regorafenib)			X[b]	
Anti-cancer therapy (post regorafenib)			X[b]	
Reason for end of observation				X
Death and reason for death				X

a: Initial visit was the visit when treatment with regorafenib was started. Baseline and Initial visit could be at the same day
b: Survival assessment from >30 days after discontinuation of regorafenib until end of observation
c: AEs (up to 30 days after the final treatment with regorafenib/ last treatment within the observation period)
AE: adverse event, BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Cooperative Oncology Group, HCC: hepatocellular carcinoma

9.3 Subjects

Patients with uHCC and for whom a decision to treat with regorafenib had been made (by the treating physician) were eligible for enrollment into the study. Patients considered for study enrollment and treatment with regorafenib were to meet the criteria for regorafenib use according to the local health authority-approved product information, including indications and contraindications with respect to the local market authorization / summary of product characteristics (SmPC).

9.3.1 Inclusion criteria

- Patients with confirmed diagnosis of unresectable HCC
- Physician-initiated decision to treat with regorafenib (prior to study enrollment)
- Signed informed consent form

9.3.2 Exclusion criteria

- Participation in an investigational program with interventions outside of routine clinical practice
- Past treatment with regorafenib

9.4 Variables

The investigator collected historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collected treatment-related data during initial visit and follow-up visits. The investigator documented the study-relevant data for each patient in the CRF. The CRF is available upon request.

Information was collected from laboratory tests performed according to the local standard of care. For potential TEAE reporting of any laboratory abnormalities please refer to Section 10.4.1.

9.4.1 Variables to determine the primary endpoints

The variables for the primary objective were:

- AEs and serious adverse event (SAEs)
- TEAEs leading to dose modifications (including reductions, interruptions, and permanent discontinuation)

An AE was defined as any untoward medical occurrence in a patient administered a medicinal product and did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

The term also covered laboratory findings or results of other diagnostic procedures that were considered to be clinically relevant (e.g. that required unscheduled diagnostic procedures or treatments or result in withdrawal from the study). All AEs, including laboratory abnormalities, leading to dose modifications (i.e. interruptions, reductions, permanent discontinuation) needed to be documented as AE.

An AE was serious (SAE) if it resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or was medically important (meaning that it jeopardized the patient).

New lesions per se were not considered AEs. Instead, the associated signs and symptoms were reported as AEs. If progressive disease led to signs and symptoms that met the criteria of AE/SAE, the signs and symptoms had to be reported as an AE/SAE and not the underlying (progressive) disease.

Starting with the first application of regorafenib after enrollment into the study, all non-serious AEs had to be documented on the AE report form or in the CRF / electronic data capture (EDC) system and forwarded to the marketing authorization holder (MAH) within 7 calendar days of awareness. All SAEs had to be documented and forwarded immediately (within one business day of awareness). For each AE, the investigator had to assess and document the seriousness, duration, relationship to product, action taken and outcome of the event. If a pregnancy occurred during the study, although it

was not an SAE itself, it had to be documented and forwarded to the MAH within the same time limits as a SAE.

The documentation of any AE/SAE ended with completion of the observational period of the patient. However, any AE/SAE – regardless of relationship and seriousness – occurring up to 30 days after the last dose of regorafenib within the study period had to be documented and forwarded to the MAH within the given timelines, even if this period was after the end of observation.

9.4.2 Variables to determine the secondary and tertiary endpoints

The outcome variables for secondary objectives were:

- Demographic data and disease history
- Regorafenib use (including start/stop dates and dosage)
  - Initiation and termination dates
  - Dosage and dose modification
- Tumor assessment after initiation of regorafenib
- Date of radiological or clinical progression on regorafenib
- Child-Pugh score
- Eastern cooperative oncology group (ECOG) performance status
- Laboratory examination data
- Date of death

Outcome variables for tertiary endpoints included:

- Sorafenib treatment history (prior to study entry)
  - Initiation and termination dates
  - Tolerability of sorafenib treatment
  - Radiological progression on sorafenib
  - Best tumor response to sorafenib
- Previous systemic therapy other than sorafenib
  - Initiation and termination dates
  - Tolerability of systemic therapy
  - Radiological progression on therapy
  - Best tumor response to therapy

A detailed description of variables collected is presented in the study protocol, Section 9.3.3 (see Annex 1).

9.5 Data sources and measurement

The investigator collected historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collected treatment-related data during visits that took place in routine practice. Each patient was identified by a unique central patient identification code, which was only used for study purposes. For the

duration of the study and afterwards, only the patient's treating physician or authorized site personnel were able to identify the patient based on the patient identification code.

For information on quality control, please refer to Section 9.10.

9.6 Bias

Because of the non-interventional study design and limitations inherent to observational studies, findings generated from this study are subject to biases, such as selection bias, limitations to availability of historical medical data, and differences in treatment or reporting owing to local guidelines.

Results for secondary effectiveness variables PFS or TTP must be interpreted carefully because of the uncontrolled setting: time periods between follow-up visits were more variable than in controlled clinical studies, in which a fixed visit schedule is maintained. The quality of the tumor status evaluation differed from that in controlled clinical studies.

Comparison of outcomes after treatment with regorafenib versus treatment with a comparator could not be performed in this single-arm study. Comparisons could only be performed with historical data from clinical or observational studies, which is prone to bias and confounding. Historical patient data collected with respect to prior sorafenib, or other treatments could be incomplete and/or differ relating to sorafenib use and standard of care in local practice. Historical data provided by patient interview is prone to errant recall.

Although the study aimed to include participants from a variety of geographic regions, there may be local limitations that reduce the representativeness of patients recruited, such as patient access to recruiting physicians (including differences in patient profile in specialized, recruiting sites vs local general practice), regorafenib availability and reimbursement, and decisions relating to local standard of care. In addition, the sample size from Japan may result in comparative over-representation of this country with respect to other individual nations, as 150 patients were planned based on the Japanese protocol (see Annex 1), and 146 patients were eventually included.

Physicians were asked to sample consecutive patients whenever possible to avoid selection bias and thus increase the likelihood of representativeness. At each site, all screened patients were documented consecutively in an anonymous screening log with reasons for non-participation (without recording patient-specific data).

9.7 Study size

Data collected from 1000 patients with uHCC treated with regorafenib globally should allow for sufficient evaluation of safety monitoring of all treated patients, as well as different subsets of patients, including evaluations between subgroups based on region etc. With this number of patients, it was possible to observe at least one patient with a particular AE, if the true incidence proportion of the AE was 0.2% (2:1000), with approximately 86% probability. A particular event with a true incidence proportion of 0.5% could be observed in at least two patients with 96% probability, and in at least three patients with 87% probability. Please refer to study protocol, Section 9.5 (see Annex 1) for tables showing the probabilities of observing one, two, or three patients with the event for different true incidence proportions, with a sample size of 1000 patients.

The sample size was also supported by the feasibility based on a previous global study in 3000 patients with uHCC who received sorafenib. Based on the information from external experts

and market research, 30-35% of patients who were treated with sorafenib would be subsequently treated with regorafenib; therefore, 1000 patients would be feasible for this observational study.

9.8 Data transformation

Not applicable.

9.9 Statistical methods

9.9.1 Main summary measures

The statistical evaluation was performed by using the software package SAS version 9.2 or higher (SAS Institute Inc., Cary, NC, USA), except when noted otherwise.

All analyses were performed for the total study population. Whenever reasonable, data were stratified by subgroups (e.g., by region and by initial dose level).

All variables were analyzed by descriptive statistical methods. Descriptive analysis of the data was performed using summary statistics for categorical and quantitative (continuous) data. Continuous data were described by the number of non-missing values, median, mean, standard deviation (SD), minimum, and maximum as well as lower and upper quartiles. Continuous variables were described by absolute values and as change from baseline per analysis time point, if applicable. Selected continuous variables were categorized in a clinically meaningful way.

Frequency tables were generated for categorical data.

Creation of tables followed the standard as described in the document Bayer global standards tables for global non-intervenational studies and for oncology.

A second interim analysis 1.5 years before final analysis was added by protocol amendment 3 considering all documented patients. The interim analysis focused on population characteristics, safety and selected endpoints.

9.9.2 Main statistical methods

Statistical analyses were of explorative and descriptive nature.

9.9.2.1 Analysis Sets

Patients with a diagnosis of uHCC who took at least one dose of regorafenib and had signed informed consent were included in the safety analysis set (SAF). Since this study was a safety study in the indication HCC, the criteria for the SAF and full analysis set (FAS) were the same. The analysis was therefore only done for the SAF and the sorafenib treated safety analysis set (SSAF).

The SSAF included all patients who were valid for safety analysis (SAF) and received prior sorafenib. The SSAF was a subpopulation from SAF introduced for specific analysis endpoints.

9.9.2.2 Population characteristics

The numbers of patients enrolled and included in the SAF were displayed in the tables, listings, and figures (TLF), as well as the reasons for exclusion of patients from the SAF. Patients valid for safety affected by coronavirus disease 2019 (COVID-19) related study disruption were summarized and separately listed with relevant details on COVID-19 disruption. Screening failures were described in the validity review and data decision report (VDR) (see Annex 1). Reasons for discontinuation of study were tabulated, others were separated in whether or not COVID-19 related. In addition,

number of patients was presented by number of follow-up visits in total and by type of visit (on-site / remote due to COVID-19 / remote other than COVID-19).

COVID-19 related study disruption was defined either as COVID-19 related end of observation, COVID-19 related end of treatment, COVID-19 related remote visits, or COVID-19 infection. The string 'COVID-19' indicated relevant records in free text fields and Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs). In addition, medical review was performed to ensure considering all relevant cases.

Baseline data such as patient demographics, baseline cancer characteristics (Barcelona Clinic Liver Cancer [BCLC], Child-Pugh score and classification, albumin-bilirubin [ALBI] grade, ECOG performance status), vital signs, disease history, medical history and concomitant diseases, prior and concomitant medications, systemic, non-systemic therapies and radiotherapies were described by presenting frequency distributions and/or basic summary statistics for the SAF and SSAF. Baseline ALBI grade and baseline Child-Pugh classification were cross-tabulated.

9.9.2.3 Analysis of primary outcome variables

The primary objective of this study was to evaluate the safety of regorafenib in patients with uHCC, including incidences of all TEAEs and dose modifications due to TEAEs in real-world practice conditions.

AEs during treatment with regorafenib, i.e., 'treatment-emergent' AEs were defined as any event arising or worsening on the day of start or after the start of regorafenib treatment until 30 days after last regorafenib intake. In case of missing dates, the respective AE was considered as 'treatment-emergent' as a worst case assumption in the case that the partial dates were compatible with being under treatment or within the 30-day time window after stop of treatment.

Incidence proportions were calculated and presented for the following AEs:

- TEAEs
- Drug-related TEAEs
- Treatment-emergent serious adverse events (TESAEs)
- Drug-related TESAEs
- TEAEs leading to dose reduction, dose interruption, or permanent discontinuation
- TEAEs with fatal outcome

This analysis of AEs was presented for the overall population and stratified by regorafenib starting dose.

9.9.2.3.1 Adverse events by NCI CTCAE

Incidence proportions were calculated and presented for the AEs classified by National Cancer Institute common terminology criteria adverse event (NCI CTCAE) v4.03 category, term and worst CTCAE grade.

9.9.2.3.2 Adverse events by MedDRA

Incidence proportions were calculated and presented for the AEs classified by MedDRA system organ class (SOC), PT and worst CTCAE grade.

This analysis of AEs was presented for the overall population and stratified by regorafenib starting dose.

Incidences of TEAEs as well as drug-related TEAEs were presented by MedDRA SOC, PT, and worst CTCAE grade for the subgroup of sorafenib intolerant patients.

Interval specific incidences were calculated within theoretical cycle intervals (i.e., 28 days) for common AEs (PTs) with ≥5% incidence.

Listings of AEs indicating COVID-19 infection were provided with all relevant parameters including the corresponding concomitant treatments.

In addition, incidences of AEs by CTCAE grade were provided for the following time periods:

- AEs occurred within the first two theoretical cycles (i.e., 56 days after regorafenib start)
- AEs occurred within the first three theoretical cycles (i.e., 84 days after regorafenib start)

9.9.2.3.3 Laboratory parameters

Summary statistics were calculated by time interval for platelets, hemoglobin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, albumin, leukocytes, erythrocytes, hematocrit, lymphocytes, neutrophils, creatinine, international normalized (INR), sodium, lactate dehydrogenase, alpha-fetoprotein, C-reactive protein and gamma-glutamyl transferase. Absolute values and the changes from baseline to follow-up visits were summarized. The mean values as well as the last value per patient, parameter and time interval were analyzed, where time intervals were 4 weeks until week 12 and 8 weeks thereafter, until end of treatment.

Hematological and biochemical laboratory values were graded based on the NCI CTCAE version 4.03. Only numerical laboratory values (no clinical assessments) were used for the grading of the laboratory data. Laboratory toxicities reported as AEs that include clinical assessments can be found in AE tables. Hematological and biochemical laboratory toxicities assessed by the investigator that include clinical assessments are available in the AE database and were summarized in AE tables. If the reference ranges or other information necessary to derive grades were unavailable, the grade was set to 'not graded'. Further information and the CTCAE grade calculation for this study are presented in statistical analysis plan (SAP), Table 6-1 (see Annex 1).

Worst grades for hematological and biochemical abnormalities were calculated according to NCI CTCAE, version 4.03 and the rules described in the SAP, Table 6-1 (see Annex 1), and were summarized by NCI CTCAE category and worst grade (not graded, grade 2, grade 3, grade 4, grade 3-4[b], all). Incidence tables as well as tables with change in worst grade from baseline were generated. The denominator for each laboratory parameter was the number of subjects with a specific laboratory value available.

9.9.2.3.4 Other safety parameters

For Child-Pugh classification and ECOG performance status, Kaplan-Meier (KM) estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% CI and median with 95% CI) and KM curves were presented for the time to deterioration. A deterioration in

[b] Grade 3-4 was analyzed instead of grade 2-4 as stated in the SAP.

ECOG was defined as worsening from one ECOG status to a higher value (e.g., 0 to 1, 1 to 2, 0 to 2). A deterioration in Child-Pugh was defined as a worsening considering the categories A, B (score 7), B (scores 8 or 9), C, i.e., a change from a score of 7 to 8 is considered a deterioration, but a change from 8 to 9 is not. KM estimates were also presented for the time to deterioration of ALBI grade which was defined as a worsening to a higher value (i.e., 1 to 2, 2 to 3, 1 to 3).

9.9.2.4 Analysis of secondary outcome variables

Analysis of secondary variables was presented for the SAF and SSAF populations.

All summaries with respect to the effectiveness data were descriptive. Effectiveness endpoints included OS, PFS, TTP, and best ORR. Investigator-assessed data according to local standard, were used to evaluate the tumor response and radiological progression. KM estimates (including number of failed, number censored, 25th and 75th percentiles with respective 95% CI and median with 95% CI) and KM curves were presented in days as well as in months (calculated as 30.44 days) for OS, PFS, and TTP (as appropriate).

9.9.2.4.1 Overall Survival (OS)

OS was defined in this study as the time (days) from start of regorafenib treatment to date of death due to any cause. Patients alive or lost to follow-up at time of analysis were censored at their last known to be alive date (LKAD) (see statistical methods used for missing values presented in the SAP available in Annex 1). Patients without documentation of any post baseline data were censored at day 1.

The patient follow-up time was described by summary statistics for the censored patients.

9.9.2.4.2 Progression-free Survival (PFS)

PFS was defined as the time in days from start of regorafenib treatment to the date of first observed disease progression (any radiological or clinical) or death due to any cause, whichever was earlier. Patients without disease progression or death up to end of study were censored at the date of last tumor evaluation. Patients without any tumor evaluation after inclusion and who did not die were censored at day 1. PFS was calculated considering all assessment methods.

The date used for the calculation of PFS was the actual date of tumor evaluation procedure; missing scans were not considered.

9.9.2.4.3 Time to progression (TTP)

TTP was defined as the time in days from start of regorafenib treatment to the date of first documented disease progression (radiological or clinical). Patients without radiological or clinical progression up to end of study were censored at the date of last tumor evaluation. Patients without any tumor evaluation after inclusion were censored at day 1.

9.9.2.4.4 Overall tumor response (ORR)

Radiologically or clinically documented progression of tumor was considered as disease progression. Estimates and exact binomial 95% CIs were calculated for best overall response categories complete response, partial response, stable disease and progressive disease by radiographic imaging only or by clinical judgement.

9.9.2.4.5 Exposure to regorafenib

For regorafenib treatment, descriptive statistics were calculated for treatment duration. The following frequencies were calculated for regorafenib treatment: initial dose, last daily dose, the number of patients with dose modification (e.g., reduction, escalation, interruption, restart), number of dose modification for each patient, frequencies of reasons for dose modifications, and primary reason for discontinuation of regorafenib (others were separated in whether or not COVID-19 related). These exposure analyses were performed overall, by prior sorafenib dosing pattern, by regorafenib starting dose, as well as for the subgroup of sorafenib intolerant patients.

In addition, individual time courses of regorafenib doses over 84 days (i.e., three theoretical cycles) were depicted graphically, by initial regorafenib dose, and with color codes for the different possible regorafenib doses (40 mg, 80 mg, 120 mg, 160 mg).

DOT [months] was defined as (date of last intake of regorafenib minus date of initial regorafenib treatment +1), divided by 30.44. Patients with ongoing treatment of regorafenib at time of analysis were censored at LKAD (see statistical methods used for missing values presented in the SAP available in Annex 1). In addition to the usual summary statistics, the KM median and quartiles were calculated.

9.9.2.5 Analysis of tertiary outcome variables

9.9.2.5.1 Prior sorafenib treatment

This analysis was provided for the subgroup of patients with prior sorafenib treatment.

Summary of prior sorafenib treatment, such as treatment duration, initial daily dose, highest daily dose, lowest daily dose, last daily dose, dose changes, reason for discontinuation, best tumor response and details on progression and cancer assessments were provided descriptively.

Duration of prior sorafenib treatment [days] was defined as sorafenib discontinuation (stop date) minus sorafenib initiation (start date) +1.

Time from initial diagnosis to start of sorafenib [months] was defined as sorafenib initiation (start date) minus initial diagnosis of uHCC, divided by 30.44.

Time from start of sorafenib to progression during or after treatment with sorafenib [months] was defined as date of tumor progression during or after treatment with sorafenib minus date of sorafenib initiation (start date) divided by 30.44.

OS from start of prior sorafenib was defined in this study for patients with second-line regorafenib therapy as the time (days) from start of prior sorafenib treatment to date of death due to any cause. Patients alive or lost to follow-up at time of analysis were censored at their LKAD (see statistical methods used for missing values presented in the SAP available in Annex 1). Patients without documentation of any post baseline data were censored at day 1.

Potential side effects during prior sorafenib treatment such as hand-foot skin reaction, hypertension, diarrhea, fatigue, anorexia and proteinuria were summarized by maximal severity and action taken with respect to sorafenib therapy.

9.9.2.5.2 Prior treatment other than sorafenib

This analysis was provided for the SAF population.

Summaries of other prior systemic treatment, such as treatment duration, type of treatment, dose changes, initial daily dose, last daily dose, reason for discontinuation, best response and details on progression were provided descriptively. For the analyses, the prior treatment other than sorafenib was classified manually by medical review as 'multikinase inhibitor', 'immune checkpoint inhibitor', 'other immunotherapy' and as other systemic anti-cancer therapy.

Duration of other prior systemic treatment [days] was defined as discontinuation (stop date) minus initiation (start date) +1.

OS from start of prior systemic treatment other than sorafenib was defined in this study for patients with second-line regorafenib therapy as the time (days) from start of prior treatment to date of death due to any cause. Patients alive or lost to follow-up at time of analysis were censored at their LKAD (see statistical methods used for missing values presented in the SAP available in Annex 1). Patients without documentation of any post baseline data were censored at day 1.

Potential side effects during other prior systemic therapy such as hand-foot skin reaction, hypertension, diarrhea, fatigue, anorexia, proteinuria, rash, pruritus and liver dysfunction were summarized by maximal severity and action taken.

9.9.2.6 Additional Analyses Planned to be Reported Outside the Study Report

Characteristics of patients who received regorafenib which would be predominantly excluded from second-line phase 3 trials

This analysis presented oversight on specific second-line phase 3 trial criteria based on patients who were valid for safety (SAF). Patients fulfilling any of the following criteria were summarized overall and by criteria as well as listed by respective criterion and value.

1. Patients with baseline ECOG > 1
2. Patients with baseline Child-Pugh > A
3. Patients with moderate or severe ascites at baseline (using Child-Pugh sub-items)
4. Patients with a history of hepatic encephalopathy (using Child-Pugh)
5. Patients with a history of encephalopathy (using medical history data)
6. Patients with prior immunotherapy (Patients with prior immune checkpoint inhibitor or Patients with prior other immunotherapy as in Table 14.1.1/1, could be monotherapy or combination treatment)
7. Patients with oesophageal varices in medical history
8. Patients with medical history of autoimmune disorders (see table of these autoimmune disorders presented in the SAP available in Annex 1)
9. Patients with prior transplantation
10. Patients with current or recent (within 10 days of first dose of study treatment) use of aspirin (> 325 mg/day) or treatment with dipyramidole, ticlopidine, clopidogrel, and cilostazol. These were to be selected using the chemical abstracts service number (and dose for aspirin as well as relative start day). Details are presented in the SAP available in Annex 1.

9.9.3 Missing values

The full information on the statistical methods used for missing values is presented in the SAP available in Annex 1.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

The original SAP v1.0 was issued on 07-OCT-2019.

The following changes were implemented in SAP v2.0 (30-OCT-2020):

- COVID-19 endpoints were added
- OS from start of first-line treatment (sorafenib and other) was restricted to patients with regorafenib in second-line
- Criteria for patients who received regorafenib and would be predominantly excluded from second-line phase 3 trials were added
- Subgroup analysis of sorafenib intolerant patients were added
- Sorafenib treated analysis set was introduced

9.10 Quality control

9.10.1 Data quality

Before study start at the sites, all investigators were sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators had the chance to discuss and develop a common understanding of the OS protocol and the CRF.

The CRO Cerner Enviza (formerly Kantar Health) was assigned to carry out EDC system development, quality control, verification of the data collection, data analysis and data transfer to Bayer.

All outcome variables and covariates were recorded in a standardized CRF. 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 were given in the data management plan (DMP). The same plan specified measures for handling of missing data and self-evident corrections.

Medical Review of the data was performed according to the medical review plan (MRP). The purpose of the Medical Review was to verify the data from a medical perspective for plausibility, consistency, and completeness and to identify potential issues that could affect the robustness of the collected study data or the progress of the study.

National and international data protection laws as well as regulations on observational studies were followed. Electronic records used for capturing patient documentation (electronic CRF) were validated according to 21 code of federal regulations (CFR) Part 11 (Food and Drug Administration, FDA) (13).

9.10.2 Quality review

Quality review was done in three steps:

In the first step, to assess the site's training status, telephone interviews were conducted with 20% of the sites in each country (including at least one site in each country) without further selection criteria. The study-specific interview guide was used for interviews. In cases where training needs were identified, follow-up actions were implemented. The telephone interviews confirmed successful training of site staff.

In the second step, source data verification was conducted. The purpose was to review the documented data for completeness and plausibility, adherence to the OS protocol and verification with source documents. To accomplish this, study monitors accessed medical records on-site for data verification. Data from 127 patients at 35 randomly selected sites were reviewed. If patients were not allocated equally to sites, either more sites were to be added or patients were to be selected at random for the review to meet the target number of patients for review. The following data were subject to on-site data review: patient informed consent, demography, date of initial diagnosis of HCC, comorbidities, regorafenib treatment, (S)AEs, tumor evaluation at follow-up visits, any systemic treatment prior to regorafenib treatment; survival assessment.

In the third step, the same data were reviewed as for step 2, with additional sites considered to be conspicuous and being selected for review due to findings from remote checks or according to other criteria associated with the course of enrollment or documentation. Selection of sites for this step was supported by pre-defined reports with possible criteria such as average time between data collection and data entry, open queries per patient, average time to manual query response, open (S)AE queries per patient, or (S)AE average time to manual query response. In the third step, 205 patients at 34 sites were reviewed.

Detailed measures for quality reviews are described in the Quality Review Plan (QRP). The QRP is available upon request.

After database closure, minor discrepancies between the EDC and source data were discovered for 2 patients in Turkey. Since the impact on data quality was minor, the database was not reopened. Details are described in the VDR (see Annex 1).

9.10.3 Storage of records and archiving

The study initiator and funder ensured that all relevant documents of this post authorization safety study (PASS), including CRFs and other patient records, are stored after the end or discontinuation of the study for at least 25 years. Other instructions for storage of medical records remain unaffected.

The investigators participating in the study are required to archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to store documents for a retention period of at least 25 years.

Statistical programming performed to generate results will be stored in the productive area of the programming system for at least 25 years at the sponsor's site.

Bayer as well as all investigators ensured adherence to applicable data privacy protection regulation. Data were transferred in encoded form only. The entire documentation made available to Bayer does not contain any data which, on its own account or in conjunction with other freely available data, could be used to re-identify natural persons. The investigators were obligated to ensure that no

documents contain such data. All records identifying the subject were kept confidential. The investigator maintained a list to enable patients' records to be identified in case of queries.

10 Results

The results of the final analysis with the cut-off date of 21 JUN 2022 are presented in this report. The results can be found in the TLF, dated 30 SEP 2022 and can be found in Annex 1 as a stand-alone document.

10.1 Participants

A VDR has been prepared, which identified the patient population valid for analyses (see Annex 1). A summary of patient enrollment is presented in Table 4:

Table 4: Patient enrollment (ENR, N=1028)

	n	(%)
Patients screened[a]	1076	
Total patients enrolled	1028	(100%)
Number of patients in SAF	1005	(97.8%)
Reason for exclusion from SAF	23	(2.2%)
Retrospectively excluded	19	(1.8%)
No documented dose of regorafenib	4	(0.4%)
Primary reason for end of observation	1018	(99.0%)
Death	633	(61.6%)
Completed	137	(13.3%)
Other[b]: NOT COVID-19	130	(12.6%)
Lost to follow-up	84	(8.2%)
Withdrawal by subject	34	(3.3%)

a: Further details on screening failures are stated in VDR, other reasons for non-enrollment are listed in Table 14.5 / 1
b: Other main reasons for end of observation are listed in Table 14.5 / 2
ENR: enrolled patients, COVID-19: coronavirus disease 2019, N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set, VDR: validity review and data decision report
Source: Table 14.1 / 1, Table 14.1 / 3

A total of 1076 patients were screened and 1028 were enrolled. A total of 19 patients were retrospectively excluded, and 4 patients had no documented dose of regorafenib. Therefore, the SAF consisted of 1005 patients (97.8%). Details on primary reason for end of observation for patients in the SAF are provided in Table 14.1 / 4. The SSAF contained 965 patients (93.9%); 40 patients were excluded as they had no prior sorafenib treatment, 19 patients were retrospectively excluded, and 4 patients had no documented dose of regorafenib (Table 14.1 / 2).

Of the 1005 patients in the SAF, at least 1 follow-up visit was reported for 895 patients. Of these, 700 patients had 2 follow-up visits (78.2%), 554 patients had at least 3 follow-up visits (61.9%), 440 patients had at least 4 follow-up visits (49.2%), 345 patients had at least 5 follow-up visits (38.5%), 273 patients had at least 6 follow-up visits (30.5%), and 216 patients had at least 7 follow-up visits (24.1%). In total, 110 patients in the SAF did not have any follow-up visits. On-site visits were reported for a total of 886 patients and 81 patients had remote visits. For 53 patients, remote visits were due to the COVID-19 pandemic, and for 32 patients, remote visits were due to other reasons than COVID-19 (Table 14.1 / 7). The number of subjects with n follow-up visits is presented in Table 14.1 / 5.

Overall, 56 patients were affected by COVID-19 related study disruptions. Of these, 53 patients had remote visits, and for almost all of these patients (all except 7 visits) this was due to COVID-19

(Listing 14.1 / 1). COVID-19 infection was reported for 2 patients and COVID-19 pneumonia was reported for 1 additional patient. None of these patients received COVID-19 related concomitant medication (Listing 14.2.6 / 1). One of these patients interrupted regorafenib due to COVID-19 infection (Table 14.2.3 / 18).

For the SAF, the mean ± SD observational period was 52.96 ± 41.10 weeks (median: 41.00 weeks) (Table 14.1 / 6).

10.2 Descriptive data

10.2.1 Demographics and baseline disease characteristics

10.2.1.1 Demographic characteristics

The countries and regions from which the patients in this non-interventional study originated are presented in Table 5.

Table 5: Countries and regions (SAF, N=1005)

	n	(%)
Country		
Austria	49	(4.9%)
Belgium	13	(1.3%)
Canada	2	(0.2%)
China	100	(10.0%)
Denmark	7	(0.7%)
Egypt	2	(0.2%)
France	138	(13.7%)
Greece	40	(4.0%)
Italy	49	(4.9%)
Japan	146	(14.5%)
Korea	170	(16.9%)
Netherlands	31	(3.1%)
Russia	14	(1.4%)
Saudi Arabia	1	(<0.1%)
Spain	27	(2.7%)
Sweden	3	(0.3%)
Taiwan	136	(13.5%)
Thailand	5	(0.5%)
Turkey	7	(0.7%)
USA	65	(6.5%)
Region[a]		
Asia	557	(55.4%)
Non-Asia	448	(44.6%)

a: Region Asia included China, Japan, Korea, Taiwan, and Thailand.
N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set
Source: Table 14.1 / 8

The highest proportions of enrolled patients were from Korea (16.9%) followed by Japan (14.5%), France (13.7%), Taiwan (13.5%), and China (10.0%). Of the remaining countries, each accounted for less than 10% of the SAF. The majority of patients (55.4%) were from Asia (including China,

Japan, Korea, Taiwan, and Thailand). Among the patients that were previously treated with sorafenib (SSAF), the distribution was similar (Table 14.1 / 11).

The demographic characteristics of the patients are presented in Table 6.

Table 6: Demographic characteristics (SAF, N=1005)

Parameter		
Sex	**n**	**(%)**
Male	835	(83.1%)
Female	170	(16.9%)
Age (years)		
Mean ± SD	65.2 ± 10.5	
Median	66.0	
Min	21	
Max	94	
Age (categories)	**n**	**(%)**
<65 years	450	(44.8%)
≥65 – <75 years	360	(35.8%)
≥75 – <85 years	178	(17.7%)
≥85 years	17	(1.7%)
Ethnicity	**n**	**(%)**
Not Hispanic or Latino	789	(78.5%)
Hispanic or Latino	34	(3.4%)
Unknown / Not reported	182	(18.1%)
Race	**n**	**(%)**
White	254	(25.3%)
Black or African American	20	(2.0%)
Asian	567	(56.4%)
Unknown / Not reported	164	(16.3%)

Max: maximum, Min: minimum, N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set, SD: standard deviation
Source: Table 14.1 / 8

The majority of patients (83.1%) were male. The mean ± SD age of patients was 65.2 ± 10.5 years (median: 66.0 years). The majority of patients were of not Hispanic or Latino ethnicity (78.5%). More than half of the patients (56.4%) were Asian and approximately a quarter (25.3%) was White.

Demographic characteristics by region (Asia/non-Asia) are presented in Table 14.1 / 9 and by initial dose level in Table 14.1 / 10. Among the patients that were previously treated with sorafenib (SSAF), the demographic characteristics were similar (Table 14.1 / 10).

The lifestyle characteristics of the patients are presented in Table 7.

Table 7: Lifestyle characteristics (SAF, N=1005)

Parameter		
Alcohol use	**n**	**(%)**
Never	404	(40.2%)
Former	476	(47.4%)
Current	114	(11.3%)
Missing	11	(1.1%)
Alcohol consumption level (current/former alcohol use)	**n**	**(%)**
Light	227	(22.6%)
Moderate	181	(18.0%)
Heavy	161	(16.0%)
Missing	436	(43.4%)
Status of cigarette smoking	**n**	**(%)**
Never	460	(45.8%)
Former	377	(37.5%)
Current	146	(14.5%)
Missing	22	(2.2%)
Number of cigarettes per day (current smokers)		
n	135	
Mean ± SD	14.64 ± 9.89	
Median	12.00	
Min	1.0	
Max	60.0	
Duration of smoking [years] (current smokers)		
n	116	
Mean ± SD	38.06 ± 12.82	
Median	40.25	
Min	0.3	
Max	61.0	
Time from end of smoking [years] (former smokers)		
n	344	
Mean ± SD	13.17 ± 12.79	
Median	8.96	
Min	0.0	
Max	54.3	

Max: maximum, Min: minimum, N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set, SD: standard deviation
Source: Table 14.1 / 12

Almost half of the patients (47.4%) reported former alcohol use, while only 11.3% of patients reported current alcohol use. For the current and former alcohol users, 22.6% reported light use while fairly equal proportions of patients reported moderate (18.0%) and heavy (16.0%) use; this information was missing for 43.4% of patients.

A total of 45.8% of patients reported never smoking cigarettes. A large proportion of patients reported former cigarette use (37.5%), while 14.5% of patients were current cigarette users. Of the current cigarette smokers, the mean ± SD number of cigarettes smoked was reported to be 14.64 ± 9.89 per day (median: 12 cigarettes per day). Current users had smoked a mean ± SD of

38.06 ± 12.82 years (median: 40.25 years). The mean ± SD time from end of smoking for former smokers was 13.17 ± 12.79 years (median: 8.96 years).

Lifestyle characteristics by region (Asia/non-Asia) are presented in Table 14.1 / 13 and by initial dose level in Table 14.1 / 14.

The baseline vital signs of patients are presented in Table 8.

Table 8: Baseline vital signs (SAF, N=1005)

Parameter	
Baseline height [cm]	
n	860
Mean ± SD	167.11 ± 8.97
Median	168.0
Min	117.0
Max	194.0
Missing	145
Baseline weight [kg]	
n	869
Mean ± SD	68.42 ± 14.65
Median	67.0
Min	35.0
Max	133.0
Missing	136
Baseline BMI [kg/m²]	
n	831
Mean ± SD	24.28 ± 4.51
Median	23.88
Min	13.7
Max	57.0
Missing	174
Baseline BMI (categories)	**n (%)**
<20	121 (12.0%)
≥20 – <25	393 (39.1%)
≥25 – <30	246 (24.5%)
≥30	71 (7.1%)
Missing	174 (17.3%)
Baseline systolic blood pressure [mmHg]	
n	753
Mean ± SD	130.55 ± 16.46
Median	130.0
Min	90.0
Max	213.0
Missing	252

Parameter	
Baseline diastolic blood pressure [mmHg]	
n	752
Mean ± SD	77.40 ± 11.49
Median	77.00
Min	43.0
Max	117.0
Missing	253
Baseline heart rate [beats/min]	
n	626
Mean ± SD	78.30 ± 14.19
Median	76.50
Min	20.0
Max	141.0
Missing	379

BMI: body mass index, Max: maximum, Min: minimum, N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set, SD: standard deviation
Source: Table 14.1 / 15

At baseline, the mean ± SD height of patients was 167.11 ± 8.97 cm (median: 168.0 cm), the mean ± SD weight was 68.42 ± 14.65 kg (median: 67.0 kg) and the mean ± SD body mass index (BMI) was 24.28 ± 4.51 kg/m^2. Patients had a mean ± SD systolic blood pressure of 130.55 ± 16.46 mmHg (median: 130.00 mmHg) and a mean ± SD diastolic blood pressure of 77.40 ± 11.49 mmHg (median: 77.00 mmHg). At baseline patients had a mean ± SD heart rate of 78.30 ± 14.19 beats/minute (median: 76.50 beats/minute).

Baseline vital signs by region (Asia/non-Asia) are presented in Table 14.1 / 16 and by initial dose level in Table 14.1 / 17.

10.2.1.2 Baseline characteristics of cancer

Of the 1005 patients in the SAF, 5 patients had newly diagnosed cancer at study entry (Table 14.1 / 18). The baseline characteristics of cancer for all patients in the SAF are presented in Table 9.

Table 9: Baseline cancer characteristics (SAF, N=1005)

Parameter		
Time between initial diagnosis of uHCC and start of regorafenib [months]		
n	950	
Mean ± SD	35.92 ± 36.52	
Median	24.72	
Min	0.1	
Max	287.6	
Missing	55	
Time since most recent progression/relapse to start of regorafenib [months]		
n	982	
Mean ± SD	1.50 ± 3.68	
Median	0.62	
Min	0.0	
Max	60.4	
Missing	23	
Etiology of HCC (multiple responses)	**n**	**(%)**
Alcohol use	250	(24.9%)
Genetic / metabolic	29	(2.9%)
Hepatitis B	382	(38.0%)
Hepatitis C	242	(24.1%)
Nonalcoholic steatohepatitis (NASH)	66	(6.6%)
Unknown	109	(10.8%)
Other[a]	29	(2.9%)
Missing	26	(2.6%)
Location of progression (multiple responses)	**n**	**(%)**
New intrahepatic lesion(s)	304	(30.2%)
Growth of existing intrahepatic lesion(s)	558	(55.5%)
New extrahepatic lesion(s)	194	(19.3%)
Growth of existing extrahepatic lesion(s)	261	(26.0%)
Missing	26	(2.6%)
Type of assessment	**n**	**(%)**
Measurement proven	836	(83.2%)
Clinical judgement	92	(9.2%)
Pathology proven	12	(1.2%)
Measurement and pathology proven	46	(4.6%)
Unknown	3	(0.3%)
Missing	16	(1.6%)

Parameter		
TNM stage (AJCC, 7th edition) at initial diagnosis	**n**	**(%)**
Stage I	160	(15.9%)
Stage II	180	(17.9%)
Stage III A	143	(14.2%)
Stage III B	95	(9.5%)
Stage III C	24	(2.4%)
Stage IV A	69	(6.9%)
Stage IV B	100	(10.0%)
Unknown	223	(22.2%)
Missing	11	(1.1%)
Grading (AJCC, 7th edition) at initial diagnosis	**n**	**(%)**
G1, well differentiated	125	(12.4%)
G2, moderately differentiated	219	(21.8%)
G3, poorly differentiated	88	(8.8%)
G4, undifferentiated	7	(0.7%)
GX, grade cannot be assessed	484	(48.2%)
Missing	82	(8.2%)
BCLC at initial diagnosis	**n**	**(%)**
0 (very early stage)	19	(1.9%)
A (early stage)	165	(16.4%)
B (intermediate stage)	204	(20.3%)
C (advanced stage)	206	(20.5%)
D (end-stage)	5	(0.5%)
Missing	406	(40.4%)
Child-Pugh score at initial diagnosis	**n**	**(%)**
5	394	(39.2%)
6	74	(7.4%)
7	21	(2.1%)
8	16	(1.6%)
9	7	(0.7%)
10	4	(0.4%)
11	2	(0.2%)
Missing	487	(48.5%)
Child-Pugh classification at initial diagnosis	**n**	**(%)**
A	478	(47.6%)
B	44	(4.4%)
C	6	(0.6%)
Not evaluable	15	(1.5%)
Missing	462	(46.0%)
ECOG status at initial diagnosis	**n**	**(%)**
0 - Fully active	344	(34.2%)
1 - Restricted active	142	(14.1%)
2 - Ambulatory and capable of all self-care	14	(1.4%)
3 - Capable of limited self-care	2	(0.2%)
Missing	503	(50.0%)

Parameter		
TNM stage (AJCC, 7th edition) at study entry	**n**	**(%)**
Stage I	20	(2.0%)
Stage II	101	(10.0%)
Stage III A	115	(11.4%)
Stage III B	113	(11.2%)
Stage III C	32	(3.2%)
Stage IV A	99	(9.9%)
Stage IV B	491	(48.9%)
Missing	34	(3.4%)
BCLC at study entry	**n**	**(%)**
0 (very early stage)	2	(0.2%)
A (early stage)	13	(1.3%)
B (intermediate stage)	133	(13.2%)
C (advanced stage)	625	(62.2%)
D (end-stage)	19	(1.9%)
Missing	213	(21.2%)
Child-Pugh score at study entry	**n**	**(%)**
5	419	(41.7%)
6	194	(19.3%)
7	84	(8.4%)
8	27	(2.7%)
9	12	(1.2%)
10	5	(0.5%)
Missing	264	(26.3%)
Child-Pugh classification at study entry	**n**	**(%)**
A	618	(61.5%)
B	123	(12.2%)
C	5	(0.5%)
Not evaluable	26	(2.6%)
Missing	233	(23.2%)
ALBI Grade at baseline[b]	**n**	**(%)**
Grade 1	318	(31.6%)
Grade 2	480	(47.8%)
Grade 3	37	(3.7%)
Missing	170	(16.9%)
ECOG status at study entry	**n**	**(%)**
0 - Fully active	416	(41.4%)
1 - Restricted active	413	(41.1%)
2 - Ambulatory and capable of all self-care	47	(4.7%)
3 - Capable of limited self-care	12	(1.2%)
4 - Completely disabled	1	(<0.1%)
Missing	116	(11.5%)
Tumor morphology at study entry	n	(%)
Uninodular & extension ≤50%	138	(13.7%)
Multinodular & extension ≤50%	497	(49.5%)
Massive or extension >50%	105	(10.4%)
Unknown	259	(25.8%)
Missing	6	(0.6%)

Parameter		
Metastases at study entry	**n**	**(%)**
No	413	(41.1%)
Yes	591	(58.8%)
Missing	1	(<0.1%)
Liver lesions at study entry	**n**	**(%)**
No	157	(15.6%)
Yes	847	(84.3%)
Missing	1	(<0.1%)
Vascular invasion at study entry	**n**	**(%)**
No	655	(65.2%)
Yes	346	(34.4%)
Missing	4	(0.4%)

a: Patients with other etiology are listed in Table 14.5 / 3
b: ALBI grade is calculated according to Johnson et al (2014), for details on the calculation see Annex 1, SAP.
AJCC: American Joint Committee on Cancer, ALBI: albumin-bilirubin, BCLC: Barcelona Clinic Liver Cancer, ECOG: Eastern Cooperative Oncology Group, HCC: hepatocellular carcinoma, Max: maximum, Min: minimum, N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set, SAP: statistical analysis plan, SD: standard deviation, TNM: tumor, node, metastasis, uHCC: unresectable hepatocellular carcinoma
Source: Table 14.1 / 18 and Table 14.1 / 31

The mean ± SD time between initial uHCC diagnosis and start of treatment with regorafenib was 35.92 ± 36.52 months (median: 24.72 months). The mean ± SD time since most recent progression/relapse to start of treatment with regorafenib was 1.50 ± 3.68 months (median: 0.62 months).

The etiology of HCC was most commonly reported as hepatitis B (38.0%), followed by alcohol use (24.9%) and hepatitis C (24.1%). For more than half of patients (55.5%) the location of the progression was growth of existing intrahepatic lesion(s). For the vast majority of assessments (83.2%) the type of assessment was reported as “measurement proven”.

At initial diagnosis, almost half of patients (47.6%) had a Child-Pugh classification of A and 4.4% of patients had a Child-Pugh classification of B, although for another 46.0% of patients this information was missing. At study entry, almost two-thirds of patients (61.5%) were reported to have a Child-Pugh classification of A and 12.2% of patients had a Child-Pugh classification of B, with a smaller proportion (23.2% of patients) having missing values.

Additionally, the ALBI grade at baseline was calculated (for details on the calculation see Annex 1, SAP). Slightly less than half of patients (47.8%) were categorized into ALBI Grade 2, followed by Grade 1 (31.6%) and Grade 3 (3.7%). ALBI grade at baseline by region (Asia/non-Asia) is presented in Table 14.1 / 32 and by initial dose level in Table 14.1 / 33. A cross-table of Child-Pugh Classification by ALBI grade at baseline is presented in Table 14.1 / 34 for the SAF and in Table 14.1 / 35 for the SSAF.

Patients most frequently had an ECOG status at initial diagnosis of 0 (fully active) (34.2%), followed by 1 (restricted active) (14.1%), although for half of the patients (50.0%) this information was missing. At study entry, the proportion of patients with ECOG status of 0 (fully active) (41.4%) was similar to the proportion of patients with ECOG status of 1 (restricted active) (41.1%). Few patients had ECOG status 2 (ambulatory and capable of all self-care) and 3 (capable of limited self-

care) at study entry (4.7% and 1.2%, respectively), with a smaller proportion (11.5%) having missing values.

At initial diagnosis, patients were most commonly classified as C (advanced stage) (20.5%) and B (intermediate stage) (20.3%), however a large proportion of patients (40.4%) was missing the BCLC assessment. According to the BCLC assessments at study entry, almost two-thirds of patients (62.2%) were classified as C (advanced stage) and 13.2% were classified as B (intermediate stage). For 21.2% this information was missing.

For almost half of patients (48.2%) the American Joint Committee on Cancer (AJCC) grading at initial diagnosis was GX (could not be assessed), followed by G2 (moderately differentiated) (21.8%).

In terms of tumor, node, metastasis (TNM) stage at initial diagnosis, patients most frequently fell into the lower stages (Stage I: 15.9% of patients, Stage II: 17.9% of patients, and Stage III A: 14.2% of patients), although the TNM stage at initial diagnosis was unknown for 22.2% of patients. At study entry, almost half of patients (48.9%) were reported with TNM Stage IV B, with markedly smaller proportions classified into the lower stages compared to initial diagnosis.

At study entry, the tumor morphology was assessed as “multinodular & extension ≤50%” for almost half of patients (49.5%). Metastases at study entry were reported for 58.8% of patients, liver lesions for 84.3% of patients and vascular invasion for 34.4% of patients.

There were no major differences regarding baseline cancer characteristics in sorafenib-pretreated patients (SSAF) compared to the SAF (Table 14.1 / 21).

At study entry, extrahepatic spread to nearby lymph nodes (N1) was observed in 272 patients (46.0%) and distant extrahepatic spread (M1) was observed in the vast majority of patients (492 patients, 83.2%). Most patients (344 patients, 58.2%) had 1 metastatic site, followed by 2 metastatic sites (174 patients, 29.4%). Only 59 patients (10.0%) had 3 metastatic sites and 14 patients (2.4%) had >3 metastatic sites at study entry. The most common location of metastasis was lung (287 patients, 48.6%), followed by lymph node (184 patients 31.1%), bone (132 patients, 22.3%), liver (106 patients, 17.9%), peritoneum (71 patients, 12.0%), and adrenal gland (70 patients, 11.8%). The remaining metastases occurred in less than 10% of patients (multiple responses possible, Table 14.1 / 22). Patients with other locations of metastases at study entry are listed in Table 14.5 / 4.

Among the 778 patients with countable liver lesions at study entry, the mean ± SD number of liver lesions was 4.6 ± 6.0 (median: 3.0), the lesion count was missing for 69 patients (Table 14.1 / 25).

Of the 346 patients with vascular invasion, the specification for 279 patients (80.6%) was portal vein thrombosis, of which 83 patients (29.7%) had invasion in the portal vein trunk, 80 patients (28.7%) in segmental portal vein, and 73 patients (26.2%) in lobar portal vein. For the remaining patients with vascular invasion, the specification was hepatic vein invasion (79 patients, 22.8%) and lack of portal blood flow (9 patients, 2.6%). This information was missing for 3 patients (0.9%) (Table 14.1 / 28).

Stratifications for baseline cancer characteristics are presented in the TLF in Annex 1. Baseline cancer characteristics stratified by region (Asia/non-Asia) are presented in Table 14.1 / 19 and by initial dose level in Table 14.1 / 20. Metastases at study entry by region (Asia/non-Asia) are presented in Table 14.1 / 23 and by initial dose level in Table 14.1 / 24. Lesions at study entry by

region (Asia/non-Asia) are presented in Table 14.1 / 26 and by initial dose level in Table 14.1 / 27. Vascular invasion at study entry by region (Asia/non-Asia) is presented in Table 14.1 / 29 and by initial dose level in Table 14.1 / 30.

10.2.2 Prior and concomitant diseases

Prior and concomitant diseases were categorized by indication according to the MedDRA coding system (version 25) using SOCs and PTs.

10.2.2.1 Prior diseases

Prior diseases were defined as medical findings that were not present anymore at the time of study inclusion. A total of 871 patients (86.7%) had any prior disease. The most common prior diseases in the SAF by PT (≥3% of patients) (Table 14.1 / 45, Table 14.1 / 48) were:

- Gastrointestinal disorders (418 patients, 41.6%)
  - Varices oesophageal (150 patient, 14.9%)
  - Gastrointestinal ulcer (68 patients, 6.8%)
  - Gastrooesophageal reflux disease (52 patients, 5.2%)
  - Ascites (59 patients, 5.9%)
  - Upper gastrointestinal haemorrhage (33 patients, 3.3%)
  - Diarrhoea (31 patients, 3.1%)
- Metabolism and nutrition disorders (400 patients, 39.8%)
  - Type 2 diabetes mellitus (276 patients, 27.5%)
  - Hyperlipidaemia (36 patients, 3.6%)
  - Decreased appetite (31 patients, 3.1%)
- Infections and infestations (364 patients, 36.2%)
  - Hepatitis B (132 patients, 13.1%)
  - Chronic hepatitis B (107 patients, 10.6%)
  - Hepatitis C (41 patients, 4.1%)
  - Chronic hepatitis C (33 patients, 3.3%)
- Hepatobiliary disorders (241 patients, 24.0%)
  - Hepatic cirrhosis (152 patients, 15.1%)
- Respiratory, thoracic and mediastinal disorders (126 patients, 12.5%)
  - Chronic obstructive pulmonary disease (38 patients, 3.8%)
- Cardiac disorders (121 patients, 12.0%)
  - Atrial fibrillation (35 patients, 3.5%)
- Vascular disorders (114 patients, 11.3%)
  - Hypertension (60 patients, 6.0%)

- Blood and lymphatic system disorders (79 patients, 7.9%)
    - Anaemia (42 patients, 4.2%)
- Reproductive system and breast disorders (71 patients, 7.1%)
    - Benign prostatic hyperplasia (53 patients, 5.3%)
- Endocrine disorders (51 patients, 5.1%)
    - Hypothyroidism (33 patients, 3.3%)

Prior diseases by region (Asia/non-Asia) are presented in Table 14.1 / 46 and by initial dose level in Table 14.1 / 47.

10.2.2.2 Concomitant diseases

At the time of inclusion, a total of 565 patients (56.2%) had any concomitant disease (Table 14.1 / 49, Table 14.1 / 52). These included:

- Vascular disorders (504 patients, 50.1%)
    - Hypertension (502 patients, 50.0%)
    - Phlebitis (2 patients, 0.2%)
- Gastrointestinal disorders (111 patients, 11.0%)
    - Ascites (108 patients, 10.7%)
    - Lower gastrointestinal haemorrhage (2 patients, 0.2%)
    - Upper gastrointestinal haemorrhage (1 patient, <0.1%)
- Nervous system disorders (14 patients, 1.4%)
    - Encephalopathy (13 patients, 1.3%)
    - Cerebral haemorrhage (1 patient, <0.1%)

Concomitant diseases by region (Asia/non-Asia) are presented in Table 14.1 / 50 and by initial dose level in Table 14.1 / 51.

10.2.3 Prior and concomitant therapies and medications

10.2.3.1 Prior and concomitant systemic anti-cancer therapy

10.2.3.1.1 Prior systemic anti-cancer therapy with sorafenib

For 872 patients of the 965 patients with prior sorafenib therapy (SSAF), the mean ± SD time from initial diagnosis to start of sorafenib treatment was 25.40 ± 34.94 months (median: 11.73 months). These data were missing for the remaining 93 patients. The mean ± SD duration of prior sorafenib treatment reported for 904 patients was 8.86 ± 11.08 months (median: 4.93 months). For the majority of patients (761 patients, 78.9%), progression, recurrence/relapse of HCC was the reason for discontinuation of this therapy, followed by switch to other treatment (89 patients, 9.2%), and adverse event/toxicity (82 patients, 8.5%) (Table 14.1.2 / 2). Other reasons for discontinuation are listed in Table 14.5 / 5.

The most common initial daily dose of sorafenib in patients with prior sorafenib therapy (SSAF) was 800 mg (605 patients, 62.7%), followed by 400 mg (305 patients, 31.6%), with the mean ± SD initial daily dose being 654.1 ± 197.3 mg (reported for 952 patients, median 800.0 mg). The most common last daily dose was 800 mg (399 patients, 41.3%), followed by 400 mg (381 patients, 39.5%), with the mean ± SD last daily dose being 577.6 ± 207.4 mg (reported for 947 patients, median 600.0 mg). Further dosing information for patients with prior sorafenib treatment is presented in Table 14.1.2 / 2, by region (Asia/non-Asia) in Table 14.1.2 / 3 and by initial dose level in Table 14.1.2 / 4.

At initial sorafenib treatment, the BCLC assessment was mainly C (advanced stage) (399 patients, 41.3%), followed by B (intermediate stage) (128 patients, 13.3%), although this information was missing for 409 patients (42.4%). The TNM stage was mainly Stage IV B (210 patients, 21.8%), followed by Stage III A (85 patients, 8.8%), and Stage II (80 patients, 8.3%), however this information was missing for 426 patients (44.1%). The ECOG status was mainly 0 (fully active) (397 patients, 41.1%), followed by 1 (restricted active) (196 patients, 20.3%), and it was missing for 346 patients (35.9%). The Child-Pugh classification was A for most patients (541 patients, 56.1%), followed by B (40 patients, 4.1%), although this information was missing for 368 patients (38.1%) (Table 14.1.2 / 1).

With regard to best response, the largest proportions of patients with prior sorafenib therapy (SSAF) reported stable disease (342 patients, 35.4%) or progressive disease by response assessment criteria (334 patients, 34.6%), followed by progressive disease by clinical judgement (95 patients, 9.8%). Complete response was only reported in 12 patients (1.2%) and partial response in 85 patients (8.8%). For the vast majority (884 patients, 91.6%), tumor progression during or after sorafenib treatment was reported. For most patients, this was specified as progression of target lesion (607 patients, 62.9%), followed by new lesion (341 patients, 35.3%). For 39 patients (4.0%), new vascular invasion was reported, and for 85 patients this information was missing (multiple responses were possible) (Table 14.1.2 / 5).

Over three-quarters of patients with prior sorafenib therapy (SSAF) (749 patients, 77.6%) experienced sorafenib related side effects. At the MedDRA PT level these were most frequently palmar-plantar erythrodysaesthesia syndrome (475 patients, 49.2%), diarrhoea (352 patients, 36.5%), fatigue (261 patients, 27.0%), secondary hypertension (190 patients, 19.7%), decreased appetite (158 patients, 16.4%), proteinuria (66 patients, 6.8%), and alopecia (58 patients, 6.0%). The remaining PTs occurred in <5% of patients (Table 14.1.2 / 6). The sorafenib related side effects by worst grade are presented in Table 14.1.2 / 7.

A total of 366 patients with prior sorafenib therapy (37.9%) experienced sorafenib related side effects resulting in dose modification. At the MedDRA PT level these were most commonly palmar-plantar erythrodysaesthesia syndrome (197 patients, 20.4%), diarrhoea (97 patients, 10.1%), and fatigue (62 patients, 6.4%). The remaining PTs occurred in <5% of patients (Table 14.1.2 / 8). A total of 91 patients with prior sorafenib therapy (9.4%) experienced sorafenib related side effects resulting in treatment withdrawal. At the MedDRA PT level these were most commonly palmar-plantar erythrodysaesthesia syndrome (34 patients, 3.5%), followed by diarrhoea (25 patients, 2.6%), and fatigue (19 patients, 2.0%). The remaining PTs occurred in less than 1% of patients (Table 14.1.2 / 9).

10.2.3.1.2 Prior and concomitant systemic anti-cancer therapy other than sorafenib

A total of 200 patients had treatment with prior systemic anti-cancer therapy other than sorafenib, most commonly nivolumab (47 patients, 23.5%), followed by lenvatinib (40 patients, 20.0%), pembrolizumab (20 patients, 10.0%), cabozantinib, and fluorouracil (11 patients each, 5.5%). The remaining therapies were reported in <5% of patients each. The main reason for discontinuation among patients with prior systemic anti-cancer therapy other than sorafenib was progression/recurrence/relapse of HCC (134 patients, 67.0%) followed by switch to other treatment (45 patients, 22.5%). Other reasons for discontinuation are listed in Table 14.5 / 6. Further information on prior systemic anti-cancer therapy other than sorafenib is presented in Table 14.1.3 / 1, and by region (Asia/non-Asia) in Table 14.1.3 / 2.

With regard to best response, the highest proportions of patients with prior systemic anti-cancer therapy other than sorafenib reported stable disease (71 patients, 37.2%) and progressive disease by response assessment criteria (56 patients, 29.3%). Complete response was reported in 6 patients (3.1%) and partial response in 27 patients (14.1%). A treatment summary including progression information is presented in Table 14.1.3 / 3.

Almost half of patients with prior systemic anti-cancer therapy other than sorafenib (92 patients, 46.0%) experienced related side effects before switching to regorafenib. At the MedDRA PT level these were most commonly fatigue (29 patients, 14.5%), rash, diarrhoea (26 patients each, 13.0%), palmar-plantar erythrodysaesthesia syndrome (14 patients, 7.0%), and decreased appetite (11 patients, 5.5%). The remaining PTs occurred in <5% of patients (Table 14.1.3 / 4). The related side effects by worst grade are presented in Table 14.1.3 / 5 and by the resulting dose modifications and withdrawn treatments are presented in Table 14.1.3 / 6 and Table 14.1.3 / 7, respectively.

A total of 59 patients (5.9%) were reported to have concomitant systemic anti-cancer therapy. The most common concomitant treatments were monoclonal antibodies (12 patients, 1.2%) and lenvatinib (11 patients, 1.1%). The remaining treatments were reported in <1% each (Table 14.1.3 / 8). This information is presented by region (Asia/non-Asia) in Table 14.1.3 / 9.

10.2.3.1.3 Treatment lines of prior systemic anti-cancer therapy

A summary of systemic prior anti-cancer therapy for the SAF is shown in Table 10.

Table 10: Overview of regorafenib treatment lines and prior systemic anti-cancer therapies (SAF, N=1005)

Treatment Line[a]	n	(%)
Number of patients with regorafenib as first-line treatment[b]	12	(1.2%)
Number of patients with regorafenib as second-line treatment[c]	848	(84.4%)
Number of patients with regorafenib as ≥third-line treatment[d]	145	(14.4%)
Number of patients with prior sorafenib therapy	965	(96.0%)
Number of patients with prior multikinase inhibitor other than sorafenib	65	(6.5%)
Number of patients with prior immune checkpoint inhibitor	97	(9.7%)
Number of patients with prior other immunotherapy	7	(0.7%)
Number of patients with other prior systemic therapy	67	(6.7%)

a: Table includes parameters assigned by medical review
b: Patient with no prior systemic anti-cancer therapy
c: Patient with one line of prior systemic anti-cancer therapy
d: Patient with two or more prior systemic anti-cancer therapies
N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set
Source: Table 14.1.1 / 1

Regorafenib was given as a first-line treatment for only 12 patients (1.2%). Overall, the vast majority of patients (96.0%) had been previously treated with sorafenib. Prior treatment with other therapies were each observed in less than 10% of the population.

A total of 848 patients of the 1005 patients (84.4%) were treated with regorafenib as a second-line treatment. Of these, almost all patients (803 patients, 94.7%) were previously treated with sorafenib alone. In addition, 5 patients (0.6%) were previously treated with lenvatinib, while 3 patients each (0.4%) were treated with a combination of sorafenib and nivolumab, atezolizumab and bevacizumab, or pembrolizumab and lenvatinib. Other treatment lines before second-line treatment with regorafenib were observed in less than 3 patients (Table 14.1.1 / 3).

For the 145 patients (14.4%) with regorafenib as ≥third-line treatment, the most common prior treatment line was first sorafenib, then nivolumab in 22 patients (15.2%), followed by first lenvatinib, then sorafenib in 9 patients (6.2%), and first sorafenib, then lenvatinib in 8 patients (5.5%). Other treatment lines prior to ≥third-line treatment with regorafenib were observed in less than 5% of patients each (Table 14.1.1 / 3).

For all patients in the SAF, the mean ± SD time since most recent prior systemic anti-cancer therapy to treatment with regorafenib was 1.87 ± 5.83 months (median: 0.26 months) (Table 14.1.1 / 2).

10.2.3.2 Prior and concomitant non-systemic anti-cancer therapy

A summary of prior non-systemic anti-cancer therapies and best response for the SAF are shown in Table 11.

Table 11: Overview of prior non-systemic anti-cancer therapies and best response per patient (SAF, N=1005)

Treatment Line / Best Response	n	(%)
Number of patients with any prior non-systemic anti-cancer therapy	746	(74.2%)
Prior procedures		
TACE	584	(58.1%)
Radio-frequency ablation	239	(23.8%)
Hepatectomy, partial	195	(19.4%)
HAI	44	(4.4%)
PEI	41	(4.1%)
Transplantation	24	(2.4%)
Other[a]	84	(8.4%)
Best response to prior procedures[b]		
TACE	584	(100.0%)
Complete response	76	(13.0%)
Partial response	163	(27.9%)
Stable disease	164	(28.1%)
Progressive disease measurement proven	77	(13.2%)
Progressive disease by clinical judgement	22	(3.8%)
Unknown	80	(13.7%)
Missing	2	(0.3%)
Radio-frequency ablation	239	(100.0%)
Complete response	97	(40.6%)
Partial response	43	(18.0%)
Stable disease	45	(18.8%)
Progressive disease measurement proven	21	(8.8%)
Progressive disease by clinical judgement	4	(1.7%)
Unknown	28	(11.7%)
Missing	1	(0.4%)
HAI	44	(100.0%)
Partial response	19	(43.2%)
Stable disease	13	(29.5%)
Progressive disease measurement proven	6	(13.6%)
Progressive disease by clinical judgement	2	(4.5%)
Unknown	4	(9.1%)
PEI	41	(100.0%)
Complete response	12	(29.3%)
Partial response	7	(17.1%)
Stable disease	7	(17.1%)
Progressive disease measurement proven	4	(9.8%)
Progressive disease by clinical judgement	2	(4.9%)
Unknown	9	(22.0%)

a: Patients with other prior non-systemic anti-cancer therapies are listed in Table 14.5 / 7
b: Multiple responses possible
HAI: hepatic artery infusion, N: number of patients in analysis set, n: number of patients with observations, PEI: percutaneous ethanol injection, SAF: safety analysis set, TACE: transarterial chemoembolization
Source: Table 14.1.4 / 1 and Table 14.1.4 / 3

Almost three-quarters of patients (746 patients, 74.2%) received prior non-systemic anti-cancer therapy. For 741 patients (73.7%) the location of the prior non-systemic anti-cancer therapy was the liver, and for 52 patients (5.2%) another location was targeted (multiple responses possible, Table 14.1.4 / 1 and Table 14.5 / 8).

The most common prior non-systemic anti-cancer therapy was transarterial chemoembolization (TACE) (584 patients, 58.1%). Of these 584 patients, 76 patients (13.0%) showed complete response, 163 patients (27.9%) showed partial response, and 164 patients (28.1%) showed stable disease. The most common anti-cancer drug used for TACE (preferred drug name) was doxorubicin (271 patients, 27.0%) followed by epirubicin (142 patients, 14.1%). The remaining anti-cancer drugs used for TACE were used in less than 5% of patients (Table 14.1.4 / 1). This information is presented by region (Asia/non-Asia) in Table 14.1.4 / 2.

The next most common prior non-systemic anti-cancer therapy was radio-frequency ablation (239 patients, 23.8%). Of these 239 patients, 97 patients (40.6%) had complete response, 43 patients (18.0%) had partial response, and 45 patients (18.8%) had stable disease.

Of the 44 patients (4.4%) receiving prior hepatic artery infusion (HAI), 19 patients (43.2%) showed partial response and 13 patients (29.5%) showed stable disease. Complete response was reported for none of the patients with prior HAI (Table 14.1.4 / 3). The most common anti-cancer drug used for HAI (preferred drug name) was cisplatin (30 patients, 3.0%) followed by fluorouracil (14 patients, 1.4%). The remaining anti-cancer drugs used for HAI were used in less than 1% of patients (Table 14.1.4 / 1).

For the 41 patients (4.1%) receiving prior percutaneous ethanol injection (PEI), the best response was complete response for 12 patients (29.3%), partial response for 7 patients and stable disease for 7 patients (17.1% each).

The number of procedures per patient for each of these prior procedures is presented in Table 14.1.4 / 3.

Prior partial hepatectomy was conducted for 195 patients (19.4%) and transplantation for 24 patients (2.4%).

Prior non-systemic anti-cancer therapies by region (Asia/non-Asia) are presented in Table 14.1.4 / 2. Details on best response, number of procedures per patient, and type of prior non-systemic anti-cancer therapy are presented by region (Asia/non-Asia) in Table 14.1.4 / 4.

Any concomitant non-systemic anti-cancer therapy was reported for 89 patients (8.9%). The most common concomitant procedure was TACE (65 patients, 73.0%). Further information on concomitant non-systemic anti-cancer therapy is presented in Table 14.1.4 / 5, Table 14.5 / 9, and Table 14.5 / 10, and by region (Asia/non-Asia) in Table 14.1.4 / 6.

10.2.3.3 Prior and concomitant radiotherapy

A summary of prior radiotherapy for the SAF is shown in Table 12.

Table 12: Overview of prior radiotherapy and best response per patient (SAF, N=1005)

Treatment Line / Best Response	n	(%)
Number of patients with prior radiotherapy	250	(24.9%)
Prior procedures		
External beam radiation therapy	61	(6.1%)
Stereotactic	56	(5.6%)
Brachytherapy	25	(2.5%)
Transarterial radioembolization	28	(2.8%)
Gamma knife	11	(1.1%)
Other[a]	76	(7.6%)
Best response to prior procedures[b]		
External beam radiation therapy	61	(100.0%)
Complete response	3	(4.9%)
Partial response	19	(31.1%)
Stable disease	23	(37.7%)
Progressive disease measurement proven	5	(8.2%)
Unknown	11	(18.0%)
Stereotactic	56	(100.0%)
Complete response	12	(21.4%)
Partial response	10	(17.9%)
Stable disease	16	(28.6%)
Progressive disease measurement proven	11	(19.6%)
Progressive disease by clinical judgement	2	(3.6%)
Unknown	5	(8.9%)
Brachytherapy	25	(100.0%)
Partial response	3	(12.0%)
Stable disease	3	(12.0%)
Progressive disease measurement proven	2	(8.0%)
Progressive disease by clinical judgement	1	(4.0%)
Unknown	16	(64.0%)
Transarterial radioembolization	28	(100.0%)
Complete response	1	(3.6%)
Partial response	7	(25.0%)
Stable disease	8	(28.6%)
Progressive disease measurement proven	9	(32.1%)
Unknown	3	(10.7%)
Gamma knife	11	(100.0%)
Partial response	2	(18.2%)
Stable disease	2	(18.2%)
Progressive disease measurement proven	4	(36.4%)
Progressive disease by clinical judgement	1	(9.1%)
Unknown	2	(18.2%)

a: Patients with other prior radiotherapy are listed in Table 14.5 / 11
b: Multiple responses possible
N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set
Source: Table 14.1.5 / 1 and Table 14.1.5 / 3

Around a quarter of patients (24.9%) received prior radiotherapy, most commonly classified as other radiotherapy (76 patients, 7.6%). The next most common prior radiotherapy was external beam radiation therapy (61 patients, 6.1%). Of these 61 patients, 3 patients (4.9%) showed complete response, 19 patients (31.1%) showed partial response, and the largest proportion (23 patients, 37.7%) presented with stable disease. For the 56 patients (5.6%) receiving stereotactic therapy, 12 patients (21.4%) had complete response and 10 patients (17.9%) had partial response, although the most common best response was stable disease (16 patients, 28.6%). For the 25 patients (2.5%) receiving prior brachytherapy, the best response was unknown for almost two-thirds of these patients (64.0%); complete response was reported for none of the patients, and partial response and stable disease for 3 patients (12.0%) each. Of the 28 patients (2.8%) receiving transarterial radioembolization, 1 patient (3.6%) showed complete response and 7 patients (25.0%) showed partial response, although the most common responses were stable disease (8 patients, 28.6%) or progressive disease (measurement proven) (9 patients, 32.1%). For the 11 patients (1.1%) receiving prior gamma knife therapy, partial response and stable disease waere reported for 2 patients each (18.2%) and complete response was reported for none of the patients. The most frequently reported best response was progressive disease (measurement proven) for 4 patients (36.4%).

Type of prior radiotherapy and best response per patient by region (Asia/non-Asia) are presented in Table 14.1.5 / 2 and Table 14.1.5 / 4, respectively.

Concomitant radiotherapy was reported for 61 patients (6.1%), most commonly reported as stereotactic radiotherapy (18 patients, 1.8%), followed by other radiotherapy (16 patients, 1.6%), brachytherapy (11 patients, 1.1%), and external beam radiation therapy (9 patients, 0.9%) (Table 14.1.5 / 5). This information is presented by region (Asia/non-Asia) in Table 14.1.5 / 6 and a list of other concomitant radiotherapies is presented in Table 14.5 / 12.

10.2.3.4 Prior and concomitant medication

Medication coding was based on World Health Organization (WHO) Drug Dictionary (DD) version 09/2021.

Prior medication was defined as any medication with a start date earlier than start of regorafenib or medication for which the start date was missing.

More than half of the patients (589 patients, 58.6%) were reported to have used prior medication. Most common prior medications at the WHO Anatomical Therapeutic Chemical (Classification System) (ATC) Level 1 concerned mainly the cardiovascular system and alimentary tract and metabolism (321 patients each, 31.9%), followed by nervous system (149 patients, 14.8%), anti-infectives for systemic use (142 patients, 14.1%), and dermatologicals (114 patients, 11.3%). Less than 10% of patients had prior medications coded into each of the remaining WHO ATC Level 1 groups. Prior medications at the WHO ATC Level 2 are presented in Table 14.1.6 / 1.

Prior medication by region (Asia/non-Asia) is presented in Table 14.1.6 / 2.

Concomitant medication was defined as any medication with a stop date later than regorafenib start, with the stop date missing or classified as ongoing at the end of observation.

Almost three-quarters of the patients (748 patients, 74.4%) were reported to use concomitant medication. Most common concomitant medications at the WHO ATC Level 1 concerned the alimentary tract and metabolism (505 patients, 50.2%), followed by cardiovascular system (457 patients, 45.5%), dermatologicals (293 patients, 29.2%), nervous system (288 patients, 28.7%),

blood and blood forming organs (241 patients, 24.0%), anti-infectives for systemic use (249 patients, 24.8%), sensory organs (222 patients, 22.1%), various (219 patients, 21.8%), and respiratory system (208 patients, 20.7%). Less than 20% of patients had concomitant medications coded into each of the remaining WHO ATC Level 1 groups. Concomitant medications at the WHO ATC Level 2 are presented in Table 14.1.6 / 3.

Concomitant medication by region (Asia/non-Asia) is presented in Table 14.1.6 / 4.

10.2.4 Follow-up therapies

A total of 324 patients (32.2%) received systemic anti-cancer therapy after regorafenib. The most common of these therapies were lenvatinib (126 patients, 12.5%), cabozantinib (110 patients, 10.9%), nivolumab (52 patients, 5.2%), ramucirumab (37 patients, 3.7%), bevacizumab (17 patients, 1.7%), fluorouracil (15 patients, 1.5%), atezolizumab, sorafenib (14 patients each, 1.4%), atezolizumab combined with bevacizumab (13 patients, 1.3%), pembrolizumab (12 patients, 1.2%), cisplatin, and oxaliplatin (10 patients each, 1.0%) (Table 14.1.3 / 10). The remaining therapies were reported in <1% of patients. This information is also presented by region (Asia/non-Asia) in Table 14.1.3 / 11.

10.3 Outcome data

Patient demographic information and disease characteristics are presented in Section 10.2. The primary outcomes (safety parameters) are presented in Section 10.4.1, the secondary effectiveness outcomes of deaths and progression in Section 10.4.2.1, OS in Section 10.4.2.2, PFS in Section 10.4.2.3, TTP in Section 10.4.2.4, ORR in Section 10.4.2.5. The secondary objective of dosing is described in Section 10.4.2.6, and the tertiary objectives (prior sorafenib treatment and other therapies) in Section 10.4.3.

10.4 Main results

10.4.1 Analysis of primary outcome variable

The primary objective of this study was to evaluate the safety of regorafenib in patients with uHCC, including incidence of all TEAEs and dose modifications due to TEAEs in real-world practice conditions. TEAEs were defined as any event arising or worsening after start of regorafenib until 30 days after last intake.

10.4.1.1 Overview of treatment-emergent adverse events

A summary of TEAEs is presented in Table 13.

Table 13: Overall summary of patients with TEAEs (SAF, N=1005)

TEAE summary	n	(%)
Any TEAE	921	(91.6%)
Worst grade		
Grade 1	104	(10.3%)
Grade 2	268	(26.7%)
Grade 3	348	(34.6%)
Grade 4	46	(4.6%)
Grade 5 (death)	146	(14.5%)
Not gradable	7	(0.7%)
Missing	2	(0.2%)
Grade 1 or 2	372	(37.0%)
Grade 3 or 4	394	(39.2%)
Grade 3, 4 or 5	540	(53.7%)
Serious	374	(37.2%)
Leading to dose modification[a]	450	(44.8%)
Leading to dose reduction	264	(26.3%)
Leading to permanent discontinuation of study drug	311	(30.9%)
Any drug-related[b] TEAE	746	(74.2%)
Worst grade		
Grade 1	156	(15.5%)
Grade 2	310	(30.8%)
Grade 3	249	(24.8%)
Grade 4	12	(1.2%)
Grade 5 (death)	7	(0.7%)
Not gradable	10	(1.0%)
Missing	2	(0.2%)
Grade 1 or 2	466	(46.4%)
Grade 3 or 4	261	(26.0%)
Grade 3, 4 or 5	268	(26.7%)
Serious	90	(9.0%)
Leading to dose modification[a]	372	(37.0%)
Leading to dose reduction	232	(23.1%)
Leading to permanent discontinuation of study drug	161	(16.0%)

a: Modifications include interruptions and reductions
b: Drug-related: related to regorafenib
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake
N: number of patients in analysis set, n: number of patients with observations, SAF: safety analysis set, TEAE: treatment-emergent adverse event
Source: Table 14.2.1 / 1

Any TEAE was reported for 921 patients (91.6%). A total of 374 patients (37.2%) had TEAEs classified as serious, 450 patients (44.8%) had TEAEs leading to a dose modification and 311 patients (30.9%) had TEAEs leading to permanent discontinuation of regorafenib.

Any drug-related TEAE was reported for 746 patients (74.2%). A total of 90 patients (9.0%) had drug-related TEAEs classified as serious, 372 patients (37.0%) had drug-related TEAEs leading to a

dose modification and 161 patients (16.0%) had drug-related TEAEs leading to permanent discontinuation of regorafenib.

An overview of TEAEs by region (Asia/non-Asia) is presented in Table 14.2.1 / 2 and by initial dose level in Table 14.2.1 / 3.

The patient-based incidences of TEAEs by MedDRA SOC and PT are presented in Table 14.

Table 14: Patient-based incidences of TEAEs by MedDRA SOC and PT (SAF, N=1005, ≥1.0% of patients)

TEAE summary	n	(%)
Number of patients with TEAEs	921	(91.6%)
Blood and lymphatic system disorders	94	(9.4%)
Anaemia	60	(6.0%)
Thrombocytopenia	36	(3.6%)
Cardiac disorders	36	(3.6%)
Ear and labyrinth disorders	18	(1.8%)
Endocrine disorders	20	(2.0%)
Hypothyroidism	17	(1.7%)
Eye disorders	17	(1.7%)
Gastrointestinal disorders	536	(53.3%)
Diarrhoea	296	(29.5%)
Abdominal pain	114	(11.3%)
Nausea	80	(8.0%)
Constipation	71	(7.1%)
Ascites	64	(6.4%)
Vomiting	57	(5.7%)
Abdominal pain upper	36	(3.6%)
Stomatitis	29	(2.9%)
Abdominal distension	27	(2.7%)
Dyspepsia	15	(1.5%)
Upper gastrointestinal haemorrhage	13	(1.3%)
Melaena	12	(1.2%)
Oesophageal varices haemorrhage	12	(1.2%)
Dry mouth	11	(1.1%)
General disorders and administration site conditions	463	(46.1%)
Fatigue	200	(19.9%)
Asthenia	108	(10.7%)
Pyrexia	71	(7.1%)
Oedema peripheral	63	(6.3%)
Malaise	36	(3.6%)
Pain	30	(3.0%)
Chest pain	22	(2.2%)
Death	16	(1.6%)
Mucosal inflammation	16	(1.6%)
General physical health deterioration	12	(1.2%)
Oedema	11	(1.1%)

TEAE summary	n	(%)
Hepatobiliary disorders	118	(11.7%)
Hepatic failure	33	(3.3%)
Hepatic function abnormal	15	(1.5%)
Hyperbilirubinaemia	15	(1.5%)
Jaundice	10	(1.0%)
Infections and infestations	133	(13.2%)
Pneumonia	24	(2.4%)
Urinary tract infection	19	(1.9%)
Upper respiratory tract infection	12	(1.2%)
Sepsis	10	(1.0%)
Injury, poisoning and procedural complications	60	(6.0%)
Off label use	31	(3.1%)
Product use in unapproved indication	29	(2.9%)
Investigations	186	(18.5%)
Blood bilirubin increased	59	(5.9%)
Aspartate aminotransferase increased	46	(4.6%)
Alanine aminotransferase increased	42	(4.2%)
Weight decreased	38	(3.8%)
Platelet count decreased	20	(2.0%)
Blood alkaline phosphatase increased	17	(1.7%)
Blood creatinine increased	12	(1.2%)
Metabolism and nutrition disorders	250	(24.9%)
Decreased appetite	177	(17.6%)
Hypoalbuminaemia	31	(3.1%)
Hypokalaemia	18	(1.8%)
Hyperkalaemia	17	(1.7%)
Hyponatraemia	13	(1.3%)
Musculoskeletal and connective tissue disorders	143	(14.2%)
Back pain	37	(3.7%)
Arthralgia	28	(2.8%)
Muscle spasms	28	(2.8%)
Muscular weakness	22	(2.2%)
Pain in extremity	22	(2.2%)
Myalgia	10	(1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	50	(5.0%)
Hepatocellular carcinoma	35	(3.5%)
Nervous system disorders	141	(14.0%)
Hepatic encephalopathy	31	(3.1%)
Dizziness	30	(3.0%)
Headache	21	(2.1%)
Encephalopathy	13	(1.3%)
Psychiatric disorders	52	(5.2%)
Insomnia	30	(3.0%)
Renal and urinary disorders	56	(5.6%)
Acute kidney injury	18	(1.8%)
Proteinuria	10	(1.0%)
Reproductive system and breast disorders	10	(1.0%)

TEAE summary	n	(%)
Respiratory, thoracic and mediastinal disorders	186	(18.5%)
Dysphonia	65	(6.5%)
Dyspnoea	50	(5.0%)
Cough	34	(3.4%)
Pleural effusion	14	(1.4%)
Epistaxis	12	(1.2%)
Skin and subcutaneous tissue disorders	423	(42.1%)
Palmar-plantar erythrodysaesthesia syndrome	329	(32.7%)
Rash	30	(3.0%)
Alopecia	27	(2.7%)
Pruritus	27	(2.7%)
Rash maculo-papular	11	(1.1%)
Vascular disorders	134	(13.3%)
Hypertension	115	(11.4%)

Event coding was based on MedDRA version 25
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake.
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients with observations, PT: preferred term, SAF: safety analysis set, SOC: system organ class, TEAE: treatment-emergent adverse event
Source: Table 14.2.3 / 1

A total of 921 patients (91.6%) experienced any TEAE. At the PT level, TEAEs that occurred in ≥5% of patients were palmar-plantar erythrodysaesthesia syndrome (329 patients, 32.7%), diarrhoea (296 patients, 29.5%), fatigue (200 patients, 19.9%), decreased appetite (177 patients, 17.6%), hypertension (115 patients, 11.4%), abdominal pain (114 patients, 11.3%), asthenia (108 patients, 10.7%), nausea (80 patients, 8.0%), constipation, pyrexia (71 patients each, 7.1%), dysphonia (65 patients, 6.5%), ascites (64 patients, 6.4%) oedema peripheral (63 patients, 6.3%), anaemia (60 patients, 6.0%), blood bilirubin increased (59 patients, 5.9%), vomiting (57 patients, 5.7%), and dyspnoea (50 patients, 5.0%) (Table 14.2.3 / 5). An overview of patient-based incidence of TEAEs by region (Asia/non-Asia) is presented in Table 14.2.3 / 2 and by initial dose level in Table 14.2.3 / 3.

When assessing the patient-based incidence of TEAEs by worst CTCAE grade, most of these events were classified as worst grade Grade 3 (348 patients, 34.6%), followed by Grade 2 (268 patients, 26.7%), Grade 5 (146 patients, 14.5%), Grade 1 (104 patients, 10.3%), and Grade 4 (46 patients, 4.6%). TEAEs by worst CTCAE grade were not gradable for 7 patients (0.7%). At the MedDRA PT level, all Grade 4 events occurred in less than 3 patients except for hepatic failure (7 patients, 0.7%), hepatic encephalopathy, (6 patients, 0.6%), sepsis (4 patients, 0.4%), ascites, dyspnoea, gastrointestinal haemorrhage, and hyponatraemia (3 patients each, 0.3%). At the PT level, the most common Grade 5 events were hepatocellular carcinoma (29 patients, 2.9%), hepatic failure (19 patients, 1.9%), death (16 patients, 1.6%), multiple organ dysfunction syndrome, pneumonia (7 patients each, 0.7%), acute kidney injury (6 patients, 0.6%), upper gastrointestinal haemorrhage, general physical health deterioration, respiratory failure (4 patients each, 0.4%), cardiac arrest, hepatic encephalopathy, malignant neoplasm progression, and myocardial infarction (3 patients each, 0.3%). All other Grade 4 and Grade 5 events occurred in less than 3 patients (Table 14.2.4 / 1). The patient-based incidences of TEAEs by worst CTCAE grade 3 to 5 are presented in Table 14.2.3 / 4.

Within the first 56 days of regorafenib treatment (corresponding to 2 theoretical cycles of regorafenib), TEAEs were most commonly classified as worst grade Grade 2 (320 patients, 31.8%), followed by worst grade Grade 3 (231 patients, 23.0%), Grade 1 (180 patients, 17.9%), Grade 5 (50 patients, 5.0%), and Grade 4 (23 patients, 2.3%) (Table 14.2.4 / 2). At the PT level, the most common worst grade Grade 4 TEAEs were hepatic encephalopathy (5 patients, 0.5%), and sepsis (3 patients, 0.3%), with all other TEAEs occurring in less than 3 patients. For worst grade Grade 5 TEAEs at the PT level, the most common were hepatocellular carcinoma (13 patients, 1.3%), death (7 patients, 0.7%), hepatic failure (6 patients, 0.6%), and general physical health deterioration (3 patients, 0.3%). Within this time frame, TEAEs by worst grade were not gradable for 9 patients (0.9%) (Table 14.2.4 / 2).

Within the first 84 days (corresponding to 3 theoretical cycles) of regorafenib treatment, TEAEs were most commonly classified as worst grade Grade 2 (316 patients, 31.4%), followed by worst grade Grade 3 (289 patients, 28.8%), Grade 1 (163 patients, 16.2%), Grade 5 (61 patients, 6.1%), and Grade 4 (26 patients, 2.6%). At the PT level, the most common worst grade Grade 4 TEAEs were hepatic encephalopathy (5 patients, 0.5%) and sepsis (3 patients, 0.3%), with all other TEAEs occurring in less than 3 patients each. For worst grade Grade 5 TEAEs at the PT level, the most common were hepatocellular carcinoma (15 patients, 1.5%), death (8 patients, 0.8%), hepatic failure (7 patients, 0.7%), general physical health deterioration, and malignant neoplasm progression (3 patients each, 0.3%). During this time frame, TEAEs by worst grade were not gradable for 8 patients (0.8%) (Table 14.2.4 / 3).

Cross-tables of patient-based incidences of TEAEs are presented by worst grade and region (Asia / non-Asia) in Table 14.2.4 / 4 and by time frame after regorafenib start, worst grade and region (Asia / non-Asia) in Table 14.2.4 / 5 and Table 14.2.4 / 6, by worst grade and initial dose level in Table 14.2.4 / 7, and by time frame after regorafenib start, worst grade and initial dose in Table 14.2.4 / 8 and Table 14.2.4 / 9.

The TEAEs were also tabulated by NCI CTCAE term, in addition to MedDRA SOC/PT. By NCI CTCAE term, the most frequent TEAEs were palmar-plantar erythrodysesthesia syndrome (330 patients, 32.8%), diarrhoea (296 patients, 29.5%), fatigue (295 patients, 29.4%), anorexia (176 patients, 17.5%), abdominal pain (131 patients, 13.0%), no code in CTCAE (86 patients, 8.6%), nausea (80 patients, 8.0%), blood bilirubin increased (78 patients, 7.8%), hypertension (117 patients, 11.6%), constipation (73 patients, 7.3%), fever (71 patients, 7.1%), anemia (62 patients, 6.2%), ascites, edema limbs (61 patients each, 6.1%), vomiting (59 patients, 5.9%), and dyspnea (52 patients, 5.2%). The remaining events occurred in <5% of patients. By worst CTCAE grade, the most frequently reported Grade 4 events were hepatic failure (8 patients, 0.8%), hepatobiliary disorders – other, specify (7 patients, 0.7%), dynspnea, sepsis (4 patients each, 0.4%), blood bilirubin increased, hyponatremia, and upper gastrointestinal hemorrhage (3 patients each, 0.3%). The most frequent Grade 5 events were neoplasms benign, malignant and unspecified (incl cysts and polyps) – other, specify (27 patients, 2.7%), hepatic failure (24 patients, 2.4%), death not otherwise specified (NOS) (15 patients, 1.5%), hepatobiliary disorders – other, specify (8 patients, 0.8%), lung infection, multi-organ failure (7 patients each, 0.7%), acute kidney injury (6 patients, 0.6%), general disorders and administration site conditions – other, specify, no code in CTCAE, respiratory failure, upper gastrointestinal hemorrhage (5 patients each, 0.5%), cardiac arrest, renal and urinary disorders – other, specify, and sepsis (4 patients each, 0.4%). The remaining events occurred in less than 3 patients (Table 14.2.2 / 1). This information is also provided by region in Table 14.2.2 / 2 and by initial dose level in Table 14.2.2 / 3.

Two patients experienced the event of COVID-19 infection, and 1 patient experienced COVID-19 pneumonia (Listing 14.2.6 / 1). The case of COVID-19 pneumonia was classified as serious, and one case of COVID-19 led to dose interruption of regorafenib (Table 14.2.3 / 9, Table 14.2.3 / 18).

When analyzing the patient-based incidences of TEAEs among the 91 sorafenib intolerant patients (defined as patients with side effects leading to discontinuation of prior sorafenib therapy), any TEAEs were reported for 85 of 91 patients (93.4%). The most common TEAEs were diarrhoea (25 patients, 27.5%), palmar-plantar erythrodysaesthesia syndrome (23 patients, 25.3%), asthenia (17 patients, 18.7%), decreased appetite (16 patients, 17.6%), abdominal pain (13 patients, 14.3%), hypertension (11 patients, 12.1%), fatigue, pyrexia, weight decreased (7 patients each, 7.7%), arthralgia, constipation, dyspnoea, hepatic failure, and rash (5 patients each, 5.5%). The remaining TEAEs occurred in <5% of patients. By worst grade, most events were classified as worst grade Grade 3 (34 patients, 37.4%), followed by Grade 2 (20 patients, 22.0%), Grade 5 (18 patients, 19.8%), Grade 1 (8 patients, 8.8%), and Grade 4 (4 patients (4.4%). At the PT level, the only Grade 4 events that occurred in more than 1 patient were gastrointestinal haemorrhage and hepatic failure (2 patients each, 2.2%). The only worst grade Grade 5 events that occurred in more than 1 patient were hepatocellular carcinoma and hepatic failure (3 patients each, 3.3%) (Table 14.2.5 / 1).

When assessing the occurrence of TEAEs over each theoretical cycle (4-week time interval) for TEAEs with incidence rates ≥5% of patients, events for all PTs occurred generally more in earlier cycles. For all PTs, the greatest number of patients with events were reported in cycle 1. Most patients experienced their first TEAE within 8 weeks (2 cycles) after starting regorafenib. After cycle 5, most PTs occurred in ≤5 patients each, with a few exceptions: constipation occurred in 5 patients in cycle 6, decreased appetite occurred in 7 patients in cycle 6 and 7, diarrhoea occurred in 6 patients in cycle 6, and fatigue occurred in 7 patients in cycle 6 (Table 14.2.1 / 4).

10.4.1.2 Incidence rates of drug-related treatment-emergent adverse events

The patient-based incidence rates of drug-related TEAEs by MedDRA SOC and PT are presented in Table 15.

Table 15: Patient-based incidences of drug-related TEAEs by MedDRA SOC and PT (SAF, N=1005, ≥1.0% of patients)

TEAE summary	n	(%)
Number of patients with drug-related TEAEs	746	(74.2%)
Blood and lymphatic system disorders	43	(4.3%)
Anaemia	23	(2.3%)
Thrombocytopenia	20	(2.0%)
Endocrine disorders	13	(1.3%)
Hypothyroidism	12	(1.2%)
Gastrointestinal disorders	371	(36.9%)
Diarrhoea	258	(25.7%)
Nausea	51	(5.1%)
Abdominal pain	41	(4.1%)
Stomatitis	27	(2.7%)
Vomiting	25	(2.5%)
Constipation	23	(2.3%)
Abdominal pain upper	10	(1.0%)
General disorders and administration site conditions	296	(29.5%)
Fatigue	151	(15.0%)
Asthenia	91	(9.1%)
Pyrexia	26	(2.6%)
Malaise	26	(2.6%)
Mucosal inflammation	15	(1.5%)
Oedema peripheral	11	(1.1%)
Hepatobiliary disorders	37	(3.7%)
Hepatic function abnormal	11	(1.1%)
Hyperbilirubinaemia	10	(1.0%)
Infections and infestations	18	(1.8%)
Injury, poisoning and procedural complications	34	(3.4%)
Off label use	31	(3.1%)
Product use in unapproved indication	29	(2.9%)
Investigations	104	(10.3%)
Blood bilirubin increased	27	(2.7%)
Weight decreased	29	(2.9%)
Alanine aminotransferase increased	17	(1.7%)
Aspartate aminotransferase increased	17	(1.7%)
Metabolism and nutrition disorders	155	(15.4%)
Decreased appetite	133	(13.2%)
Hypoalbuminaemia	10	(1.0%)
Musculoskeletal and connective tissue disorders	44	(4.4%)
Muscle spasms	14	(1.4%)
Pain in extremity	10	(1.0%)

TEAE summary	n	(%)
Nervous system disorders	59	(5.9%)
Dizziness	11	(1.1%)
Hepatic encephalopathy	11	(1.1%)
Psychiatric disorders	13	(1.3%)
Renal and urinary disorders	15	(1.5%)
Respiratory, thoracic and mediastinal disorders	83	(8.3%)
Dysphonia	52	(5.2%)
Dyspnoea	10	(1.0%)
Skin and subcutaneous tissue disorders	379	(37.7%)
Palmar-plantar erythrodysaesthesia syndrome	309	(30.7%)
Alopecia	24	(2.4%)
Rash	24	(2.4%)
Pruritus	16	(1.6%)
Vascular disorders	102	(10.1%)
Hypertension	96	(9.6%)

Event coding was based on MedDRA version 25
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients with observations, PT: preferred term, SAF: safety analysis set, SOC: system organ class, TEAE: treatment-emergent adverse event
Source: Table 14.2.3 / 6

A total of 746 patients (74.2%) experienced drug-related TEAEs. At the PT level, drug-related TEAEs that occurred in ≥5% of patients were palmar-plantar erythrodysaesthesia syndrome (309 patients, 30.7%), diarrhoea (258 patients, 25.7%), fatigue (151 patients, 15.0%), decreased appetite (133 patients, 13.2%), hypertension (96 patients, 9.6%), asthenia (91 patients, 9.1%), dysphonia (52 patients, 5.2%), and nausea (51 patients, 5.1%). Patient-based incidence of drug-related TEAEs is presented by region (Asia/non-Asia) in Table 14.2.3 / 7, and by initial dose level in Table 14.2.3 / 8.

When assessing the patient-based incidence of drug-related TEAEs by worst CTCAE grade, most of these events were classified as worst grade Grade 2 (310 patients, 30.8%), followed by Grade 3 (249 patients, 24.8%), and Grade 1 (156 patients, 15.5%). Only 12 patients (1.2%) had events classified as Grade 4 and only 7 patients (0.7%) had events in Grade 5. At PT level, the only Grade 4 events that occurred in more than 1 patient were hepatic encephalopathy and hyponatraemia (2 patients each, 0.2%). The only Grade 5 event that occurred in more than 1 patient was hepatic failure (3 patients, 0.3%). For 10 patients (1.0%) these events were not gradable (Table 14.2.4 / 10).

Within the first 56 days (corresponding to 2 theoretical cycles) of regorafenib treatment, drug-related TEAEs were classified most frequently as worst grade Grade 2 (295 patients, 29.4%), followed by Grade 1 (188 patients, 18.7%), and Grade 3 (157 patients, 15.6%). Only few patients had events classified as Grade 4 (4 patients, 0.4%) and Grade 5 (3 patients, 0.3%) (Table 14.2.4 / 11). Within the first 84 days (corresponding to 3 theoretical cycles) of regorafenib treatment, drug-related TEAEs were classified most frequently as Grade 2 (304 patients, 30.2%), followed by Grade 3 (189 patients, 18.8%) and Grade 1 (179 patients, 17.8%). Only few patients (0.5%) had events classified as Grade 4 (5 patients, 0.5%) and Grade 5 (3 patients, 0.3%) (Table 14.2.4 / 12). During both time frames, the only Grade 4 event that occurred in more than 1 patient

was hepatic encephalopathy (2 patients, 0.2%), all Grade 5 events occurred in single patients only. Also during both time frames, 11 patients (1.1%) had non-gradable events.

Cross-tables of patient-based incidence of drug-related TEAEs are presented by worst grade and region (Asia / non-Asia) in Table 14.2.4 / 13, by time frame after regorafenib start, worst grade and region (Asia / non-Asia) in Table 14.2.4 / 14 and Table 14.2.4 / 15, by worst grade and initial dose level in Table 14.2.4 / 16, and by time frame after regorafenib start, worst grade and initial dose in Table 14.2.4 / 17 and Table 14.2.4 / 18.

By NCI CTCAE term, the most frequent drug-related TEAEs were palmar-plantar erythrodysesthesia syndrome (310 patients, 30.8%), diarrhoea (258 patients, 25.7%), fatigue (233 patients, 23.2%), anorexia (133 patients, 13.2%), hypertension (98 patients, 9.8%), no code in CTCAE (60 patients, 6.0%), and nausea (51 patients, 5.1%). The remaining events occurred in <5% of patients. By worst CTCAE grade, the only Grade 4 events reported in more than 1 patient were hepatic failure, hyponatremia, and platelet count decreased (2 patients each, 0.2%). The only Grade 5 event occurring in more than 1 patient was hepatic failure (4 patients, 0.4%) (Table 14.2.2 / 4). This information is also provided by region in Table 14.2.2 / 5 and by initial dose level in Table 14.2.2 / 6.

When analyzing the patient-based incidences of drug-related TEAEs among sorafenib intolerant patients (defined as patients with side effects leading to discontinuation of prior sorafenib therapy), drug-related TEAEs were reported for 67 of 91 patients (73.6%). The most common PTs were diarrhoea, palmar-plantar erythrodysaesthesia syndrome (23 patients each, 25.3%), asthenia (15 patients, 16.5%), decreased appetite (13 patients, 14.3%), hypertension (10 patients, 11.0%), abdominal pain (8 patients, 8.8%), weight decreased (6 patients, 6.6%), constipation, and rash (5 patients each, 5.5%). The remaining TEAEs occurred in <5% of patients. By worst grade, events were most frequently classified as Grade 3 or Grade 2 (27 patients each, 29.7%), followed by Grade 1 (12 patients, 13.2%). No drug-related TEAEs in sorafenib intolerant patients were classified as worst grade Grade 4 or Grade 5 (Table 14.2.5 / 2).

10.4.1.3 Incidence rates of treatment-emergent serious adverse events

The patient-based incidence rates of TESAEs by MedDRA SOC and PT are presented in Table 16.

Table 16: Patient-based incidences of TESAEs by MedDRA SOC and PT (SAF, N=1005, ≥1.0% of patients)

TEAE summary	n	(%)
Number of patients with TESAEs	374	(37.2%)
Cardiac disorders	21	(2.1%)
Gastrointestinal disorders	105	(10.4%)
Abdominal pain	22	(2.2%)
Ascites	22	(2.2%)
Oesophageal varices haemorrhage	12	(1.2%)
General disorders and administration site conditions	61	(6.1%)
Death	16	(1.6%)
Hepatobiliary disorders	65	(6.5%)
Hepatic failure	29	(2.9%)
Infections and infestations	64	(6.4%)
Pneumonia	19	(1.9%)

TEAE summary	n	(%)
Injury, poisoning and procedural complications	11	(1.1%)
Investigations	12	(1.2%)
Metabolism and nutrition disorders	28	(2.8%)
Musculoskeletal and connective tissue disorders	13	(1.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	45	(4.5%)
Hepatocellular carcinoma	35	(3.5%)
Nervous system disorders	50	(5.0%)
Hepatic encephalopathy	21	(2.1%)
Renal and urinary disorders	23	(2.3%)
Acute kidney injury	14	(1.4%)
Respiratory, thoracic and mediastinal disorders	33	(3.3%)
Dyspnoea	12	(1.2%)

Event coding was based on MedDRA version 25
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients with observations, PT: preferred term, SAF: safety analysis set, SOC: system organ class, TEAE: treatment-emergent adverse event, TESAE: treatment-emergent serious adverse event
Source: Table 14.2.3 / 9

A total of 374 patients (37.2%) experienced any TESAEs. At the PT level, the most common TESAEs were hepatocellular carcinoma (35 patients, 3.5%), hepatic failure (29 patients, 2.9%), abdominal pain, ascites (22 patients each, 2.2%), hepatic encephalopathy (21 patients, 2.1%), pneumonia (19 patients, 1.9%), death (16 patients, 1.6%), acute kidney injury (14 patients, 1.4%), dyspnoea, and oesophageal varices haemorrhage (12 patients each, 1.2%). All other events occurred in less than 1% of patients. Patient-based incidences of TESAEs are presented by region (Asia/non-Asia) in Table 14.2.3 / 10 and by initial dose level in Table 14.2.3 / 11.

When assessing the patient-based incidence of TESAEs by worst CTCAE grade, these events were most commonly classified as worst grade Grade 3 (174 patients, 17.3%), followed by Grade 5 (146 patients, 14.5%), Grade 4 (40 patients, 4.0%), Grade 2 (10 patients, 1.0%), and Grade 1 (2 patients, 0.2%). At the PT level, the most frequently reported Grade 4 events were hepatic failure (7 patients, 0.7%), hepatic encephalopathy (6 patients each, 0.6%), sepsis (4 patients, 0.4%), ascites, gastrointestinal haemorrhage, and dyspnoea (3 patients each, 3.3%). The most frequent Grade 5 events were hepatocellular carcinoma (29 patients, 2.9%), hepatic failure (19 patients, 1.9%), death (16 patients, 1.6%), pneumonia (7 patients, 0.7%), multiple organ dysfunction syndrome (7 patients each, 0.7%), acute kidney injury (6 patients, 0.6%), general physical health deterioration, upper gastrointestinal haemorrhage, respiratory failure (4 patients each, 0.4%), cardiac arrest, hepatic encephalopathy, malignant neoplasm progression, and myocardial infarction (3 patients each, 0.3%). All other Grade 4 and Grade 5 events occurred in less than 3 patients. For 1 patient (0.1%) TESAEs by worst grade were not gradable (Table 14.2.4 / 19).

By NCI CTCAE term, the most frequent TESAEs were hepatic failure (41 patients, 4.1%), neoplasms benign, malignant and unspecified (incl cysts and polyps) (35 patients, 3.5%), hepatobiliary disorders – other, specify (25 patients, 2.5%), abdominal pain (24 patients, 2.4%), and lung infection (21 patients, 2.1%), ascites(19 patients, 1.9%), acute kidney injury, death NOS, upper gastrointestinal hemorrhage (15 patient, 1.5%), no code in CTCAE (14 patients, 1.4%), encephalopathy, sepsis (13 patients each, 1.3%), dyspnea, esophageal varices (12 patients each,

1.2%), general disorders and administration site conditions – other, specify (11 patients, 1.1%), fatigue, and gastric hemorrhage (10 patients each, 1.0%). The remaining events occurred in <1% of patients. By worst CTCAE grade, the most frequently reported Grade 4 events were hepatic failure (8 patients, 0.8%), hepatobiliary disorders – other, specify (7 patients, 0.7%), dyspnea, sepsis (4 patients each, 0.4%), blood bilirubin increased, and upper gastrointestinal hemorrhage (3 patients each, 0.3%). The most frequent Grade 5 events were neoplasms benign, malignant and unspecified (incl cysts and polyps) (27 patients, 2.7%), hepatic failure (24 patients, 2.4%), death NOS (15 patients, 1.5%), hepatobiliary disorders – other, specify (8 patients, 0.8%), lung infection, multi-organ failure (7 patients each, 0.7%), acute kidney injury (6 patients, 0.6%), general disorders and administration site conditions – other, specify, no code in CTCAE, respiratory failure, upper gastrointestinal hemorrhage (5 patients each, 0.5%), cardiac arrest, renal and urinary disorders – other, specify, and sepsis (4 patients each, 0.4%). All other events occurred in less than 3 patients (Table 14.2.2 / 7). This information is also provided by region in Table 14.2.2 / 8 and by initial dose level in Table 14.2.2 / 9.

10.4.1.4 Incidence rates of drug-related treatment-emergent serious adverse events

A total of 90 patients (9.0%) experienced drug-related TESAEs. By PT, the most frequent drug-related TESAEs were hepatic encephalopathy (10 patients, 1.0%), decreased appetite, hepatic failure (5 patients, 0.5%), blood bilirubin increased, fatigue, palmar-plantar erythrodysaesthesia syndrome, upper gastrointestinal haemorrhage (4 patients each, 0.4%), abdominal pain, diarrhoea, hepatocellular carcinoma, and oesophageal varices haemorrhage (3 patients each, 0.3%). All other drug-related TESAEs occurred in less than 3 patients (Table 14.2.3 / 12). Patient-based incidence of drug-related TESAEs is presented by region (Asia/non-Asia) in Table 14.2.3 / 13, and by initial dose level in Table 14.2.3 / 14.

When assessing the patient-based incidence of drug-related TESAEs by worst CTCAE grade, these events were most frequently classified as worst grade Grade 3 (64 patients, 6.4%). Only few patients had events classified as Grade 2 (9 patients, 0.9%), Grade 4 (8 patients, 0.8%), Grade 5 (7 patients, 0.7%), and Grade 1 (2 patients, 0.2%). The Grade 4 drug-related TESAEs were hepatic encephalopathy (2 patients, 0.2%), blood bilirubin increased, general physical condition abnormal, hypokalaemia, oesophageal varices haemorrhage, pain, and upper gastrointestinal haemorrhage (1 patient each, <0.1%). The Grade 5 drug-related TESAEs were hepatic failure (3 patients, 0.3%), blood bilirubin increased, hepatic function abnormal, hepatocellular carcinoma, and upper gastrointestinal haemorrhage (1 patient each, <0.1%) (Table 14.2.4 / 20).

By NCI CTCAE term, the most frequent drug-related TESAEs were hepatic failure (9 patients, 0.9%), fatigue (6 patient, 0.6%), anorexia, hepatobiliary disorders – other, specify, upper gastrointestinal hemorrhage (5 patients each, 0.5%), palmar-plantar erythrodysesthesia (4 patients, 0.4%), abdominal pain, blood bilirubin increased, diarrhea, encephalopathy, and no code in CTCAE (3 patients each, 0.3%). By worst CTCAE grade, the only Grade 4 and Grade 5 event occurring in more than 1 patient was hepatic failure (Grade 4: 2 patients, 0.2%, Grade 5: 4 patients, 0.4%). The remaining events occurred in less than 3 patients (Table 14.2.2 / 10). This information is also provided by region in Table 14.2.2 / 11 and by initial dose level in Table 14.2.2 / 12.

10.4.1.5 Treatment-emergent adverse events leading to dose reduction

The patient-based incidence rates of TEAEs leading to dose reduction by MedDRA SOC and PT are presented in Table 17.

Table 17: Patient-based incidences of TEAEs leading to dose reduction by MedDRA SOC and PT (SAF, N=1005, ≥1.0% of patients)

TEAE summary	n	(%)
Number of patients with TEAEs leading to dose reduction	264	(26.3%)
Gastrointestinal disorders	87	(8.7%)
Diarrhoea	50	(5.0%)
Nausea	12	(1.2%)
Abdominal pain	12	(1.2%)
General disorders and administration site conditions	74	(7.4%)
Fatigue	33	(3.3%)
Asthenia	27	(2.7%)
Investigations	18	(1.8%)
Metabolism and nutrition disorders	24	(2.4%)
Decreased appetite	20	(2.0%)
Musculoskeletal and connective tissue disorders	13	(1.3%)
Nervous system disorders	10	(1.0%)
Skin and subcutaneous tissue disorders	107	(10.6%)
Palmar-plantar erythrodysaesthesia syndrome	97	(9.7%)
Vascular disorders	14	(1.4%)
Hypertension	14	(1.4%)

Event coding was based on MedDRA version 25
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients with observations, PT: preferred term, SAF: safety analysis set, SOC: system organ class, TEAE: treatment-emergent adverse event.
Source: Table 14.2.3 / 15

A total of 264 patients (26.3%) experienced any TEAEs leading to dose reduction. At the PT level, the most common TEAEs leading to dose reduction were palmar-plantar erythrodysaesthesia syndrome (97 patients, 9.7%), diarrhoea (50 patients, 5.0%), fatigue (33 patients, 3.3%), asthenia (27 patients, 2.7%), decreased appetite (20 patients, 2.0%), hypertension (14 patients, 1.4%), abdominal pain, and nausea (12 patients, 1.2%). Patient-based incidence of TEAEs leading to dose reduction are presented by region (Asia/non-Asia) in Table 14.2.3 / 16, and by initial dose level in Table 14.2.3 / 17.

When assessing the patient-based incidence of TEAEs leading to dose reduction by worst CTCAE grade, these events were most frequently classified as worst grade Grade 2 (152 patients, 15.1%), followed by Grade 3 (55 patients, 5.5%), and Grade 1 (54 patients, 5.4%). Only 1 patient each (0.1%) had an event classified as worst grade Grade 4 (PT: cardiac failure) and Grade 5 (PT: hepatic failure) (Table 14.2.4 / 21).

Within the first 56 days (corresponding to 2 theoretical cycles) of regorafenib treatment, the most frequently reported TEAEs leading to dose reduction were classified as Grade 2 (113 patients, 11.2%), followed by Grade 1 (46 patients, 4.6%) and Grade 3 (35 patients, 3.5%) (Table 14.2.4 / 22). Within the first 84 days (corresponding to 3 theoretical cycles) of regorafenib treatment, the TEAEs leading to dose reduction were most frequently classified as Grade 2 (131 patients, 13.0%), followed by Grade 1 (47 patients, 4.7%) and Grade 3 (39 patients, 3.9%)

(Table 14.2.4 / 23). During both time frames, only 1 patient each (0.1%) had an event classified as worst grade Grade 4 (PT: cardiac failure) and Grade 5 (PT: hepatic failure).

Cross-tables of patient-based incidence of TEAEs leading to dose reduction are presented by worst grade and region (Asia / non-Asia) in Table 14.2.4 / 24 and by time frame after regorafenib start, worst grade and region (Asia / non-Asia) in Table 14.2.4 / 25 and Table 14.2.4 / 26, and by worst grade and initial dose level in Table 14.2.4 / 27, and by time frame after regorafenib start, worst grade and initial dose in Table 14.2.4 / 28 and Table 14.2.4 / 29.

By NCI CTCAE term, the most frequent TEAEs leading to dose reduction were palmar-plantar erythrodysesthesia syndrome (96 patients, 9.6%), fatigue (55 patients, 5.5%), diarrhea (50 patients, 5.0%), and anorexia (21 patients, 2.1%). The remaining events occurred in <2% of patients. By worst CTCAE grade, no Grade 4 or Grade 5 event occurred in more than 1 patient (Table 14.2.2 / 13). This information is also provided by region in Table 14.2.2 / 14 and by initial dose level in Table 14.2.2 / 15.

10.4.1.6 Treatment-emergent adverse events leading to dose interruption

The patient-based incidence rates of TEAEs leading to dose interruption by MedDRA SOC and PT are presented in Table 18.

Table 18: Patient-based incidences of TEAEs leading to dose interruption by MedDRA SOC and PT (SAF, N=1005, ≥1.0% of patients)

TEAE summary	n	(%)
Number of patients with TEAEs leading to dose interruption	271	(27.0%)
Blood and lymphatic system disorders	11	(1.1%)
Gastrointestinal disorders	76	(7.6%)
Diarrhoea	42	(4.2%)
Abdominal pain	11	(1.1%)
General disorders and administration site conditions	71	(7.1%)
Fatigue	27	(2.7%)
Pyrexia	19	(1.9%)
Asthenia	14	(1.4%)
Malaise	11	(1.1%)
Hepatobiliary disorders	24	(2.4%)
Infections and infestations	25	(2.5%)
Investigations	33	(3.3%)
Blood bilirubin increased	16	(1.6%)
Metabolism and nutrition disorders	35	(3.5%)
Decreased appetite	24	(2.4%)
Musculoskeletal and connective tissue disorders	11	(1.1%)
Nervous system disorders	22	(2.2%)
Renal and urinary disorders	11	(1.1%)
Respiratory, thoracic and mediastinal disorders	21	(2.1%)
Dyspnoea	11	(1.1%)
Skin and subcutaneous tissue disorders	63	(6.3%)
Palmar-plantar erythrodysaesthesia syndrome	48	(4.8%)

TEAE summary	n	(%)
Vascular disorders	13	(1.3%)
Hypertension	12	(1.2%)

Event coding was based on MedDRA version 25
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients with observations, PT: preferred term, SAF: safety analysis set, SOC: system organ class, TEAE: treatment-emergent adverse event.
Source: Table 14.2.3 / 18

A total of 271 patients (27.0%) experienced any TEAEs leading to dose interruption. At the PT level, the most common TEAEs leading to dose interruption were palmar-plantar erythrodysaesthesia syndrome (48 patients, 4.8%), diarrhoea (42 patients, 4.2%), fatigue (27 patients, 2.7%), and decreased appetite (24 patients, 2.4%), pyrexia (19 patients, 1.9%), blood bilirubin increased (16 patients, 1.6%), asthenia (14 patients, 1.4%), hypertension (12 patients, 1.2%), abdominal pain, dyspnoea, and malaise (11 patients each, 1.1%). Patient-based incidence of TEAEs leading to dose interruption are presented by region (Asia/non-Asia) in Table 14.2.3 / 19 and by initial dose level in Table 14.2.3 / 20.

When assessing the patient-based incidence of TEAEs leading to dose interruption by worst CTCAE grade, these events were most frequently classified as Grade 3 (132 patients, 13.1%), followed by Grade 2 (95 patients, 9.5%), Grade 1 (29 patients, 2.9%), and Grade 4 (12 patients, 1.2%). Only 2 patients (0.2%) had an event classified as worst grade Grade 5 (PT: hepatic failure). The only Grade 4 event that occurred in more than 1 patient was pneumonia (2 patients, 0.2%), and the only Grade 5 event that occurred in more than 1 patient was hepatic failure (2 patients, 0.2%). For 1 patient (<0.1%) the events were non-gradable by worst grade (Table 14.2.4 / 30).

Within the first 56 days (corresponding to 2 theoretical cycles) of regorafenib treatment, the most frequently reported TEAEs leading to dose interruption were classified as Grade 2 (75 patients, 7.5%), followed by Grade 3 (73 patients, 7.3%) and Grade 1 (24 patients, 2.4%) (Table 14.2.4 / 31). Within the first 84 days (corresponding to 3 theoretical cycles) of regorafenib treatment, the most commonly reported TEAEs leading to dose interruption were classified as Grade 3 (94 patients, 9.4%), followed by Grade 2 (80 patients, 8.0%) and Grade 1 (26 patients, 2.6%) (Table 14.2.4 / 32). During both times frames, only 1 patient (0.1%) experienced a Grade 4 event (PT: respiratory failure). Also during both time frames, these events were non-gradable for 1 patient (0.1%).

Cross-tables of patient-based incidence of TEAEs leading to dose interruption are presented by worst grade and region (Asia / non-Asia) in Table 14.2.4 / 33 and by time frame after regorafenib start, worst grade and region (Asia / non-Asia) in Table 14.2.4 / 34 and Table 14.2.4 / 35, and by worst grade and initial dose level in Table 14.2.4 / 36, and by time frame after regorafenib start, worst grade and initial dose in Table 14.2.4 / 37 and Table 14.2.4 / 38.

By NCI CTCAE term, the most frequent TEAEs leading to dose interruption were palmar-plantar erythrodysesthesia syndrome (49 patients, 4.9%), diarrhea (42 patients, 4.2%), fatigue (41 patients, 4.1%), anorexia (24 patients, 2.4%), and blood bilirubin increased (21 patients, 2.1%). The remaining events occurred in <2% of patients. By worst CTCAE grade, the only Grade 4 event occurring in more than 1 patient was lung infection (2 patients, 0.2%), and the only Grade 5 event occurring in more than 1 patient was hepatic failure (2 patients, 0.2%) (Table 14.2.2 / 16). This

information is also provided by region in Table 14.2.2 / 17 and by initial dose level in Table 14.2.2 / 18.

10.4.1.7 Treatment-emergent adverse events leading to permanent discontinuation of treatment

The patient-based incidence rates of TEAEs leading to permanent discontinuation of regorafenib by MedDRA SOC and PT are presented in Table 19.

Table 19: Patient-based incidences of TEAEs leading to permanent discontinuation of regorafenib by MedDRA SOC and PT (SAF, N=1005, ≥1.0% of patients)

TEAE summary	n	(%)
Number of patients with TEAEs leading to permanent discontinuation of regorafenib	311	(30.9%)
Gastrointestinal disorders	77	(7.7%)
Diarrhoea	17	(1.7%)
Ascites	13	(1.3%)
Abdominal pain	12	(1.2%)
General disorders and administration site conditions	61	(6.1%)
Fatigue	23	(2.3%)
Asthenia	11	(1.1%)
Hepatobiliary disorders	41	(4.1%)
Hepatic failure	16	(1.6%)
Infections and infestations	14	(1.4%)
Investigations	34	(3.4%)
Blood bilirubin increased	12	(1.2%)
Metabolism and nutrition disorders	38	(3.8%)
Decreased appetite	25	(2.5%)
Musculoskeletal and connective tissue disorders	10	(1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10	(1.0%)
Nervous system disorders	20	(2.0%)
Hepatic encephalopathy	11	(1.1%)
Renal and urinary disorders	11	(1.1%)
Respiratory, thoracic and mediastinal disorders	15	(1.5%)
Skin and subcutaneous tissue disorders	37	(3.7%)
Palmar-plantar erythrodysaesthesia syndrome	25	(2.5%)

Event coding was based on MedDRA version 25
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients with observations, PT: preferred term, SAF: safety analysis set, SOC: system organ class, TEAE: treatment-emergent adverse event.
Source: Table 14.2.3 / 21

A total of 311 patients (30.9%) experienced any TEAEs leading to permanent discontinuation of regorafenib. At the PT level, the most frequently reported TEAEs leading to permanent discontinuation of regorafenib were decreased appetite, palmar-plantar erythrodysaesthesia syndrome (25 patients each, 2.5%), fatigue (23 patients, 2.3%), diarrhoea (17 patients, 1.7%), hepatic failure (16 patients, 1.6%), ascites (13 patients, 1.3%), abdominal pain, blood bilirubin increased (12 patients each, 1.2%), asthenia, and hepatic encephalopathy (11 patients each, 1.1%).

Patient-based incidence of TEAEs leading to permanent discontinuation of regorafenib are presented by region (Asia/non-Asia) in Table 14.2.3 / 22 and by initial dose level in Table 14.2.3 / 23.

When assessing the patient-based incidence of TEAEs leading to permanent discontinuation of regorafenib by worst CTCAE grade, these events were most frequently classified as Grade 3 (130 patients, 12.9%), followed by Grade 2 (73 patients, 7.3%), Grade 4 (46 patients, 4.6%), Grade 5 (33 patients, 3.3%), and grade Grade 1 (24 patients, 2.4%). At the PT level, the most common Grade 4 events were hepatic failure (8 patients, 0.8%), hepatic encephalopathy (4 patients, 0.4%), and acute kidney injury (3 patients, 0.3%). The most common Grade 5 events were hepatic failure (7 patients, 0.7%), death, hepatocellular carcinoma, multiple organ dysfunction syndrome, and respiratory failure (3 patients each, 0.3%). All other Grade 4 and Grade 5 events occurred in less than 3 patients. For 3 patients (0.3%), events leading to permanent discontinuation of regorafenib were not gradable (Table 14.2.4 / 39).

Within the first 56 days (corresponding to 2 theoretical cycles) of regorafenib treatment, the most frequently reported TEAEs leading to permanent discontinuation of regorafenib were classified as Grade 3 (64 patients, 6.4%), followed by Grade 2 (45 patients, 4.5%), Grade 4 (20 patients, 2.0%), Grade 1 (14 patients, 1.4%), and Grade 5 (9 patients, 0.9%). At the PT level, the only Grade 4 events occurring in more than 1 patient were hepatic encephalopathy (3 patients, 0.3%), hepatic failure, and hepatocellular carcinoma (2 patients each, 0.2%). The only Grade 5 event occurring in more than 1 patient was hepatic failure (3 patients, 0.3%). For 1 patient, events during this time frame were not gradable (Table 14.2.4 /40). Within the first 84 days (corresponding to 3 theoretical cycles) of regorafenib treatment, the most frequently reported TEAEs leading to permanent discontinuation of regorafenib were classified as Grade 3 (83 patients, 8.3%), followed by Grade 2 (53 patients, 5.3%), Grade 4 (23 patients, 2.3%), Grade 1 (16 patients, 1.6%), and Grade 5 (14 patients, 1.4%). At the PT level, the only Grade 4 events occurring in more than 1 patient were hepatic encephalopathy, hepatic failure (3 patients each, 0.3%), hepatocellular carcinoma, and septic shock (2 patients each, 0.2%). The only Grade 5 events occurring in more than 1 patient were hepatic failure (3 patients, 0.3%) and malignant neoplasm progression (2 patients, 0.2%). For 2 patients, events during this time frame were not gradable (Table 14.2.4 / 41).

Cross-tables of patient-based incidence of TEAEs leading to permanent discontinuation of regorafenib are presented by worst grade and region (Asia/non-Asia) in Table 14.2.4 / 42, by time frame after regorafenib start, worst grade and region (Asia/non-Asia) in Table 14.2.4 / 43 and Table 14.2.4 / 44, by worst grade and initial dose level in Table 14.2.4 / 45, and by time frame after regorafenib start, worst grade and initial dose in Table 14.2.4 / 46 and Table 14.2.4 / 47.

By NCI CTCAE term, the most frequent TEAEs leading to permanent discontinuation were fatigue (34 patients, 3.4%), palmar-plantar erythrodysesthesia syndrome (26 patients, 2.6%), hepatic failure (25 patients, 2.5%), and anorexia (23 patients, 2.3%). The remaining events occurred in <2% of patients. By worst CTCAE grade, the most frequently reported Grade 4 events were hepatic failure (11 patients, 1.1%), acute kidney injury, blood bilirubin increased, hepatobiliary disorders – other, specify, sepsis, and upper gastrointestinal hemorrhage (3 patients each, 0.3%). The most frequent Grade 5 events were hepatic failure (8 patients, 0.8%), neoplasms benign, malignant and unspecified (incl cysts and polyps) – other, specify, hepatobiliary disorders – other, specify, respiratory failure (4 patients each, 0.4%), death NOS, and multi-organ failure (3 patients each, 0.3%). The remaining Grade 4 and Grade 5 events occurred in less than 3 patients (Table 14.2.2 / 19). This information is also provided by region in Table 14.2.2 / 20 and by initial dose level in Table 14.2.2 / 21.

10.4.1.8 Treatment-emergent adverse events with fatal outcome

The patient-based incidence rates of TEAEs with fatal outcome by MedDRA SOC and PT are presented in Table 20.

Table 20: Patient-based incidences of TEAEs with fatal outcome by MedDRA SOC and PT (SAF, N=1005)

TEAE summary	n	(%)
Number of patients with TEAEs with fatal outcome	163	(16.2%)
Cardiac disorders	9	(0.9%)
Cardiac arrest	3	(0.3%)
Myocardial infarction	3	(0.3%)
Cardiac failure	1	(<0.1%)
Cardio-respiratory arrest	1	(<0.1%)
Cardiovascular insufficiency	1	(<0.1%)
Gastrointestinal disorders	18	(1.8%)
Upper gastrointestinal haemorrhage	5	(0.5%)
Oesophageal varices haemorrhage	2	(0.2%)
Abdominal pain	1	(<0.1%)
Ascites	1	(<0.1%)
Enterocolitis	1	(<0.1%)
Gastrointestinal haemorrhage	1	(<0.1%)
Haemoperitoneum	1	(<0.1%)
Large intestinal haemorrhage	1	(<0.1%)
Melaena	1	(<0.1%)
Oesophageal haemorrhage	1	(<0.1%)
Small intestinal haemorrhage	1	(<0.1%)
Subileus	1	(<0.1%)
General disorders and administration site conditions	31	(3.1%)
Death	16	(1.6%)
Multiple organ dysfunction syndrome	7	(0.7%)
General physical health deterioration	6	(0.6%)
Fatigue	1	(<0.1%)
Oedema	1	(<0.1%)
Hepatobiliary disorders	34	(3.4%)
Hepatic failure	22	(2.2%)
Hepatic function abnormal	2	(0.2%)
Hepatic haemorrhage	2	(0.2%)
Hepatorenal syndrome	2	(0.2%)
Acute hepatic failure	1	(<0.1%)
Chronic hepatic failure	1	(<0.1%)
Cirrhosis alcoholic	1	(<0.1%)
Hepatic cirrhosis	1	(<0.1%)
Jaundice	1	(<0.1%)
Jaundice cholestatic	1	(<0.1%)

TEAE summary	n	(%)
Infections and infestations	12	(1.2%)
Pneumonia	7	(0.7%)
Sepsis	2	(0.2%)
Bacteraemia	1	(<0.1%)
Infective exacerbation of chronic obstructive airways disease	1	(<0.1%)
Septic shock	1	(<0.1%)
Urinary tract infection	1	(<0.1%)
Investigations	1	(<0.1%)
Alanine aminotransferase increased	1	(<0.1%)
Aspartate aminotransferase increased	1	(<0.1%)
Blood bilirubin increased	1	(<0.1%)
Metabolism and nutrition disorders	4	(0.4%)
Hypoalbuminaemia	2	(0.2%)
Metabolic acidosis	1	(<0.1%)
Tumour lysis syndrome	1	(<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38	(3.8%)
Hepatocellular carcinoma	32	(3.2%)
Malignant neoplasm progression	3	(0.3%)
Hepatic cancer	1	(<0.1%)
Liver carcinoma ruptured	1	(<0.1%)
Neoplasm progression	1	(<0.1%)
Nervous system disorders	7	(0.7%)
Hepatic encephalopathy	4	(0.4%)
Coma hepatic	2	(0.2%)
Coma	1	(<0.1%)
Subarachnoid haemorrhage	1	(<0.1%)
Renal and urinary disorders	9	(0.9%)
Acute kidney injury	6	(0.6%)
Renal failure	2	(0.2%)
Renal impairment	1	(<0.1%)
Respiratory, thoracic and mediastinal disorders	9	(0.9%)
Respiratory failure	5	(0.5%)
Pneumonitis	2	(0.2%)
Lower respiratory tract congestion	1	(<0.1%)
Pulmonary embolism	1	(<0.1%)
Surgical and medical procedures	1	(<0.1%)
Euthanasia	1	(<0.1%)
Vascular disorders	1	(<0.1%)
Haematoma	1	(<0.1%)

Event coding was based on MedDRA version 25
Treatment-emergent was defined as any event arising or worsening after start of regorafenib until 30 days after last intake
One additional event of death due to HCC was not included in this table, as it was not considered a TEAE
MedDRA: Medical Dictionary for Regulatory Activities, N: number of patients in analysis set, n: number of patients with observations, PT: preferred term, SAF: safety analysis set, SOC: system organ class, TEAE: treatment-emergent adverse event
Source: Table 14.2.3 / 24

A total of 163 patients (16.2%) experienced any TEAEs with a fatal outcome. At the PT level, the most common TEAEs with a fatal outcome were hepatocellular carcinoma (32 patients, 3.2%), hepatic failure (22 patients, 2.2%), and death (16 patients, 1.6%). Patient-based incidence of TEAEs with a fatal outcome are presented by region (Asia/non-Asia) in Table 14.2.3 / 25, and by initial dose level in Table 14.2.3 / 26.

TEAEs with fatal outcome by worst CTCAE grade are shown in Table 14.2.4 / 48.

By NCI CTCAE term, the most frequent TEAEs with fatal outcome were neoplasms benign, malignant and unspecified (incl cysts and polyps) – other, specify (31 patients, 3.1%) and hepatic failure (26 patients, 2.6%). By worst CTCAE grade, the most frequently reported Grade 5 events were also neoplasms benign, malignant and unspecified (incl cysts and polyps) – other, specify (27 patients, 2.7%) and hepatic failure (24 patients, 2.4%). The remaining Grade 5 events occurred in <2% of patients (Table 14.2.2 / 22). This information is also provided by region (Asia/non-Asia) in Table 14.2.2 / 23 and by initial dose level in Table 14.2.2 / 24.

10.4.1.9 Laboratory parameters

Laboratory abnormalities at baseline graded on the NCI CTCAE are presented in Table 21. Laboratory values at baseline without categorization are available in Table 14.1 / 36. Parameters with non-graded values (due to unavailable reference ranges) are displayed in Table 14.1 / 42, by region (Asia/non-Asia) in Table 14.1 / 43, and by initial dose level in Table 14.1 / 44.

Table 21: Laboratory abnormalities at baseline graded based on the NCI CTCAE (SAF, N_a=1005)

Laboratory abnormality[a] **Worst NCI CTCAE Grade**	**n**	**(%)**
Alanine aminotransferase increased (N_b=876)	334	(38.1%)
Grade 1	296	(33.8%)
Grade 2	26	(3.0%)
Grade 3	12	(1.4%)
Grade 3-4	12	(1.4%)
Alkaline phosphatase increased (N_b=792)	440	(55.6%)
Grade 1	350	(44.2%)
Grade 2	70	(8.8%)
Grade 3	19	(2.4%)
Grade 4	1	(0.1%)
Grade 3-4	20	(2.5%)
Anaemia (N_b=856)	87	(10.2%)
Grade 2	79	(9.2%)
Grade 3	8	(0.9%)
Grade 3-4	8	(0.9%)
Aspartate aminotransferase increased (N_b=853)	585	(68.6%)
Grade 1	494	(57.9%)
Grade 2	65	(7.6%)
Grade 3	26	(3.0%)
Grade 3-4	26	(3.0%)

Laboratory abnormality[a] **Worst NCI CTCAE Grade**	**n**	**(%)**
Blood bilirubin increased (N_b=865)	372	(43.0%)
Grade 1	92	(10.6%)
Grade 2	111	(12.8%)
Grade 3	151	(17.5%)
Grade 4	18	(2.1%)
Grade 3-4	169	(19.5%)
Hypoalbuminemia (N_b=841)	86	(10.2%)
Grade 2	84	(10.0%)
Grade 3	2	(0.2%)
Grade 3-4	2	(0.2%)
Hyponatremia (N_b=644)	10	(1.6%)
Grade 3	10	(1.6%)
Grade 3-4	10	(1.6%)
Lymphocyte count decreased (N_b=653)	189	(28.9%)
Grade 2	129	(19.8%)
Grade 3	60	(9.2%)
Grade 3-4	60	(9.2%)
Lymphocyte count increased (N_b=653)	10	(1.5%)
Grade 2	10	(1.5%)
Neutrophil count decreased (N_b=651)	37	(5.7%)
Grade 2	26	(4.0%)
Grade 3	3	(0.5%)
Grade 4	8	(1.2%)
Grade 3-4	11	(1.7%)
Platelet count decreased (N_b=853)	92	(10.8%)
Grade 2	69	(8.1%)
Grade 3	19	(2.2%)
Grade 4	4	(0.5%)
Grade 3-4	23	(2.7%)
White blood cell decreased (N_b=771)	74	(9.6%)
Grade 2	45	(5.8%)
Grade 3	12	(1.6%)
Grade 4	17	(2.2%)
Grade 3-4	29	(3.8%)

a: Only laboratory values (no clinical assessments) were used for the grading. The abnormalities of hypernatremia and leukocytosis did not occur. Denominator and rates for each parameter is the number of subjects with specific lab value and reference ranges available.

CTCAE: common terminology criteria adverse event, N_a: number of patients in analysis set, N_b: number of patients with specific lab value and reference ranges available, n: number of patients with observation, NCI: National Cancer Institute, SAF: safety analysis set

Source: Table 14.1 / 39

Of the 876 patients with alanine aminotransferase values and reference ranges available, 334 patients (38.1%) showed an increase in alanine aminotransferase at baseline, mainly Grade 1 (296 patients, 33.8%).

Alkaline phosphatase increase was observed for 440 patients (55.6%) of the 792 patients with alkaline phosphatase values and reference ranges available at baseline, mainly Grade 1 (350 patients, 44.2%).

Among 856 patients with hemoglobin values and reference ranges available, 87 patients (10.2%) showed anemia at baseline, with almost all categorized as Grade 2 (79 patients, 9.2%).

Of the 853 patients with aspartate aminotransferase values and reference ranges available, 585 patients (68.6%) showed an increase in aspartate aminotransferase at baseline, mainly classified as Grade 1 (494 patients, 57.9%).

Of the 865 patients with blood bilirubin values and reference ranges available, 372 patients (43.0%) showed an increase in blood bilirubin at baseline, with the largest proportion of patients categorized as Grade 3-4 (169 patients, 19.5%), followed by Grade 2 (111 patients, 12.8%) and Grade 1 (92 patients, 10.6%).

Hypoalbuminemia was observed for 86 patients of the 841 patients (10.2%) with albumin values and reference ranges available at baseline, whereby all but 2 cases were classified as Grade 2 (84 patients, 10.0%).

Only 10 of the 644 patients (1.6%) with sodium values and reference ranges available showed hyponatremia at baseline, all classified as Grade 3.

Of the 653 patients with lymphocyte count and reference range available, 189 patients (28.9%) showed a decrease in lymphocyte count at baseline, mainly classified as Grade 2 (129 patients, 19.8%). An increased lymphocyte count was only observed for 10 patients (1.5%), all of which were classified as Grade 2.

Neutrophil count was decreased for 37 of the 651 patients (5.7%) with neutrophil count and reference range available at baseline, mainly categorized as Grade 2 (26 patients, 4.0%).

Platelet count decrease was observed for 92 of the 853 patients (10.8%) with platelet count and reference range available at baseline, mainly categorized as Grade 2 (69 patients, 8.1%).

Of the 771 patients with white blood cell count and reference range available, 74 patients (9.6%) showed a decrease in white blood cell count at baseline, classified as Grade 2 (45 patients, 5.8%) or Grade 3-4 (29 patients, 3.8%).

Laboratory values at baseline by region (Asia/non-Asia) are presented in Table 14.1 / 37 and by initial dose level in Table 14.1 / 38. Laboratory abnormalities at baseline graded based on NCI CTCAE by region (Asia/non-Asia) are presented in Table 14.1 / 40 and by initial dose level in Table 14.1 / 41.

Laboratory values at baseline are shown in Table 22, and laboratory parameters at every follow-up visit including change from baseline at every follow-up visit are shown in Table 14.2.7 / 4. It should be noted that the time from baseline to each documented follow-up visit was variable. The median time from baseline was 5.40 weeks (n=682) to follow-up visit 1, 9.85 weeks (n=542) to visit 2, 14.00 weeks (n=415) to visit 3, and 18.00 weeks (n=311) to visit 4. These timings continued in a similar pattern until visit 28 (Table 14.2.7 / 1). Times from baseline to each follow-up visit are also shown by region and by initial dose level in Table 14.2.7 / 2 and Table 14.2.7 / 3, respectively.

Table 22: Laboratory parameters at baseline

Parameter	n	Mean	SD	Median	Min	Max
ALT [U/L]	879	47.86	42.31	37.00	5.0	530.0
Albumin [g/dL]	841	3.69	0.57	3.70	1.3	5.3
ALP [U/L]	793	231.29	218.21	160.00	28.0	1954.0
AFP [ng/mL]	661	6955.76	34486.11	155.00	0.0	735050.0
AST [U/L]	856	65.80	51.70	50.00	4.7	549.0
Bilirubin [mg/dL]	869	1.06	0.81	0.82	0.1	10.2
CRP [mg/dL]	316	2.14	3.12	0.85	0.0	17.9
Creatinine [mg/dL]	831	0.87	0.54	0.79	0.2	9.9
Erythrocytes [T/L]	653	4.20	0.73	4.18	2.0	7.4
GGT [U/L]	525	226.77	258.44	149.00	1.2	2914.0
Hematocrit [%]	701	38.01	5.74	38.00	22.1	59.7
Hemoglobin [g/dL]	856	12.64	2.06	12.70	6.2	19.6
LDH [U/L]	391	276.58	123.51	239.00	120.0	892.0
Leukocytes [Giga/L]	771	5.68	2.75	5.33	0.0	27.3
Lymphocytes [Giga/L]	653	1.23	0.82	1.09	0.0	8.7
Neutrophils [Giga/L]	651	3.87	2.16	3.45	0.0	19.5
Platelets [Giga/L]	853	163.09	89.87	145.00	9.3	630.0
Prothrombin [International normalized ratio]	630	1.13	0.22	1.09	0.8	2.9
Sodium [mmol/L]	644	138.52	3.57	139.00	121.0	149.0

Laboratory measures documented at initial visit collected after start of regorafenib were not considered as baseline.
ALT: Alanine aminotransferase, AFP: Alpha-fetoprotein, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, CRP: C-reactive protein, GGT: Gamma-glutamyl transferase, LDH: Lactate dehydrogenase, Max: Maximum, Min: Minimum, N: number of patients in analysis set, n: number of patients with observations, SAF: Safety analysis set, SD: Standard deviation
Source: Table 14.2.7 / 4

The median alanine aminotransferase (ALT) level was 37 U/L at baseline and remained largely stable, ranging between 31 U/L (n=66) at visit 11 and 43 U/L (n=28) at visit 17. The largest median change from baseline was -8 U/L (n=35) at visit 14. After visit 18, patient numbers were too small for meaningful conclusions.

The median albumin level was 3.70 g/dL at baseline and remained stable (3.60-3.78 g/dL) until visit 13. At visit 14, the median albumin level increased slightly (4.05 g/dL, n=38), but then decreased at visit 17 (3.50 g/dL, n=25). When looking at median changes from baseline, there was a slight decrease at all visits, with the largest decrease of -0.4 g/dL at visit 18 (n=22). After visit 18, patient numbers were too small for meaningful conclusions.

The median alkaline phosphatase (ALP) level was 160 U/L at baseline and varied slightly between 118 U/L (visit 15, n=29) and 165 U/L (visit 12, n=45) until visit 17, when documentation was available for less than 20 patients. When looking at median changes from baseline, there was a slight increase at most visits, with the largest change (before visit 17) of +12 U/L (n=24) at visit 16.

The median AFP level was 155 ng/mL at baseline and showed a tendency to decrease, although values were very variable (between 12.03 ng/mL at visit 16, n=21 and 155.00 ng/mL at baseline, n=661). After visit 17, patient numbers were too small for meaningful conclusions.

The median aspartate aminotransferase (AST) level was 50 U/L at baseline and remained largely stable, ranging between 39 U/L at visit 18 (n=22) and 50.0 U/L (n=856) at baseline. Median changes from baseline were only minor, with the largest change of +5 U/L (n=89) at visit 8. After visit 18, patient numbers were too small for meaningful conclusions.

The median bilirubin level was 0.82 mg/dL at baseline and remained largely stable, ranging between 0.73 mg/dL (n=32) at visit 16 and 1.00 mg/dL (n=722) at visit 1. When looking at median change from baseline, there was an increase at all visits, with the largest increase of 0.22 mg/dL at visit 10 (n=73). After visit 18, patient numbers were too small for meaningful conclusions.

The median C-reactive protein (CRP) level was 0.85 mg/dL at baseline and remained largely stable, ranging between 0.85 mg/dL at baseline (n=316), visit 3 (n=136), visit 6 (n=45), and visit 9 (n=21) and 1.30 mg/dL at visit 8 (n=23). After visit 9, patient numbers were too small for meaningful conclusions. The largest median change from baseline (until visit 9) was +0.30 mg/dL (n=43) at visit 5.

The median creatinine level was 0.79 mg/dL at baseline and remained stable (0.79-0.94 mg/dL). Median changes from baseline were very small at most visits. After visit 18, patient numbers were too small for meaningful conclusions.

The median erythrocyte count was 4.18 T/L at baseline and remained largely stable, ranging between 4.13 T/L (n=81) at visit 8 and 4.53 T/L (n=20) at visit 16. After visit 18, patient numbers were too small for meaningful conclusions.The largest median change from baseline (until visit 18) was -0.14 T/L (n=65) at visit 8.

The median gamma-glutamyl transferase (GGT) level was 149 U/L at baseline and showed a slight tendency to decrease, ranging between 91 U/L (n=24) at visit 14 and 160 U/L (n=60) at visit 8. After visit 14, patient numbers were too small for meaningful conclusions. When looking at median change from baseline, there was a decrease at most visits, with the largest change (until visit 14) of -13 U/L (n=17) at visit 13.

The median hematocrit was 38% at baseline and remained stable (37.65%-42.00%). The largest median change from baseline was -1.50% (n=67) at visit 8. After visit 18, patient numbers were too small for meaningful conclusions.

The median hemoglobin level was 12.7 g/dL at baseline and remained stable (12.6-13.4 g/dL). The largest median change from baseline was -0.4 g/dL (n=93) at visit 8. After visit 18, patient numbers were too small for meaningful conclusions.

The median lactate dehydrogenase (LDH) level was 239 U/L at baseline and remained largely stable, ranging between 217 U/L (n=39) at visit 8 and 255 U/L (n=22) at visit 11. After visit 11, patient numbers were too small for meaningful conclusions. The largest median change from baseline (until visit 11) was -22.5 U/L (n=26) at visit 8.

The median leukocyte count was 5.33 Giga/L at baseline and showed a slight tendency to increase, ranging between 5.25 Giga/L (n=25) at visit 17 and 6.20 Giga/L (n=220) at visit 5. After visit 18, patient numbers were too small for meaningful conclusions. When looking at median change from baseline, there was an increase at every visit, with the largest increase (until visit 18) of +1.16 Giga/L (n=24) at visit 15.

The median lymphocyte count was 1.09 Giga/L at baseline and remained stable (1.05-1.25 Giga/L). After visit 18, patient numbers were too small for meaningful conclusions. The largest median change from baseline (until visit 18) was -0.11 Giga/L (n=19) at visit 16.

The median neutrophil count was 3.45 Giga/L at baseline and showed a slight tendency to increase, ranging between 3.42 Giga/L (n=32) at visit 14 and 4.03 Giga/L (n=147) at visit 6. After visit 18, patient numbers were too small for meaningful conclusions. When looking at median change from baseline, there was an increase at all visits (until visit 18), with the largest change of +0.99 Giga/L (n=15) at visit 17.

The median platelet count was 145 Giga/L at baseline and remained stable (140-155 Giga/L). After visit 18, patient numbers were too small for meaningful conclusions. When looking at median change from baseline, the changes (until visit 18) ranged between -5 Giga/L and +7 Giga/L, with the exception of visit 17, where the change from baseline was +11.4 Giga/L (n=21).

The median prothrombin level (international normalized ratio) was 1.09 at baseline and remained stable (1.03-1.10). After visit 16, patient numbers were too small for meaningful conclusions. The largest median change from baseline (until visit 16) was +0.02 at visit 1 (n=408), visit 7 (n=69), and visit 12 (n=27).

The median sodium level was 139 mmol/L and remained stable. After visit 17, patient numbers were too small for meaningful conclusions. When looking at median change from baseline, there was no change (0.00 mol/L) at most visits (until visit 17).

Overall, no large changes were observed during earlier visits (Table 14.2.7 / 4). This information is also provided by region in Table 14.2.7 / 5 and by initial dose level in Table 14.2.7 / 6.

When tabulating these values by artificial follow-up intervals, the overall trends were similar. To obtain these intervals, visits were assigned to artificial time intervals to improve comparability, but it should be noted that these do not reflect actual time intervals (Table 14.2.7 / 7). Laboratory measures and changes from baseline by artificial follow-up intervals are also provided by region in Table 14.2.7 / 8 and by initial dose level in Table 14.2.7 / 9.

By worst CTCAE grade, most laboratory abnormalities were mainly categorized as Grade 1 to Grade 3 in week 1-4 (artificial time interval). Notably, increased blood bilirubin was classified as Grade 4 in 19 patients (of 217 patients with increased blood bilirubin), decreased neutrophil count was classified as Grade 4 in 4 patients (of 11 patients with decreased neutrophil count), decreased white blood cells were classified as Grade 4 in 5 patients (of 20 patients with decreased white blood cells), decreased platelet count was classified as Grade 4 in 2 patients (of 48 patients with decreased platelet count), and increased aspartate aminotransferase and hyponatremia were each Grade 4 in 1 patient (of 281 patients and 8 patients with this abnormality, respectively). These trends were largely similar in the following time intervals. A notable exception was decreased white blood cell count, which was classified as Grade 4 in 10 patients during week 9-12 (among 25 patients with decreased white blood cell count) (Table 14.2.7 / 10). This information is also provided by region in Table 14.2.7 / 11 and by initial dose level in Table 14.2.7 / 12.

10.4.2 Analysis of secondary outcome variables

The secondary objectives of this study were:

- To describe the effectiveness of regorafenib, including OS, PFS, TTP, and ORR
- To describe the patterns of regorafenib treatment, including actual doses, DOT, and other dosing parameters
- To describe patient characteristics, comorbidities, prior therapies, and assess their potential influence on treatment and outcomes under real-life conditions
- To describe the physicians' practice patterns, including regional differences in the management and treatment of uHCC under real-life conditions

A brief overview on effectiveness and dosing parameters is presented in the sections below, with the full results presented in Annex 1, TLF Section 14.3.1 for death and progression, Section 14.3.2 for OS, Section 14.3.3 for PFS and Section 14.3.4 for TTP, Section 14.3.5 for ORR, and Section 14.3.6 for exposure. A brief overview of patient characteristics, comorbidities and prior therapies is presented in Section 10.2. Output tables stratified by region (Asia/non-Asia) are provided in the TLF.

10.4.2.1 Deaths and progression

Of the SAF, a total of 151 patients (15.0%) died during or within 30 days of the last dose of regorafenib, and a total of 482 patients (48.0%) died after 30 days succeeding the last dose of regorafenib. In total, 633 patients died. The primary reason reported for cause of death was progressive disease (470 patients, 46.8%), followed by AE (71 patients, 7.1%), unknown (56 patients, 5.6%), liver disorder (18 patients, 1.8%), and other reason (17 patients, 1.7%). This information was missing for 1 patient (Table 14.3.1 / 1). Other primary causes of death are listed in Table 14.5 / 13. Information on summary of deaths by region (Asia/non-Asia) is presented in Table 14.3.1 / 2 and by initial dose in Table 14.3.1 / 3.

The mean ± SD follow-up time for the 373 censored patients (patients who were alive or patients whose death was not confirmed at the time of data cut-off) was 15.57 ± 11.17 months (median: 14.22 months). Further information is presented in Table 14.3.1 / 4, and by region (Asia/non-Asia) in Table 14.3.1 / 5 and by initial dose in Table 14.3.1 / 6.

During the observational period, almost two-thirds of patients (656 patients, 65.8%) were reported to have disease progression. This was measurement proven for 578 patients (88.1%) and assessed by clinical judgement for 78 patients (11.9%). Of these 656 patients, 182 patients (27.7%) had new metastases at first progression. The most frequent (>10%) locations of new metastases were lung (83 patients, 45.6%), lymph node (51 patients, 28.0%), bone (23 patients, 12.6%), liver (22 patients, 12.1%), and other (19 patients, 10.4%) (Table 14.3.1 / 7). Details on other location of new metastases at first progression are listed in Table 14.5 / 15. Further information, including radiological response and details on metastases and vascular invasion, is presented in Table 14.3.1 / 7, and by region (Asia/non-Asia) in Table 14.3.1 / 8 and by initial dose in Table 14.3.1 / 9. Details on other methods of determining radiological response are presented in Table 14.5 / 14.

10.4.2.2 Overall survival

The median OS for the observational period was 13.2 months (n=1005, 95% CI [11.6; 14.8]) (Table 14.3.2 / 9). The KM curve for OS of the SAF is presented in Figure 1.

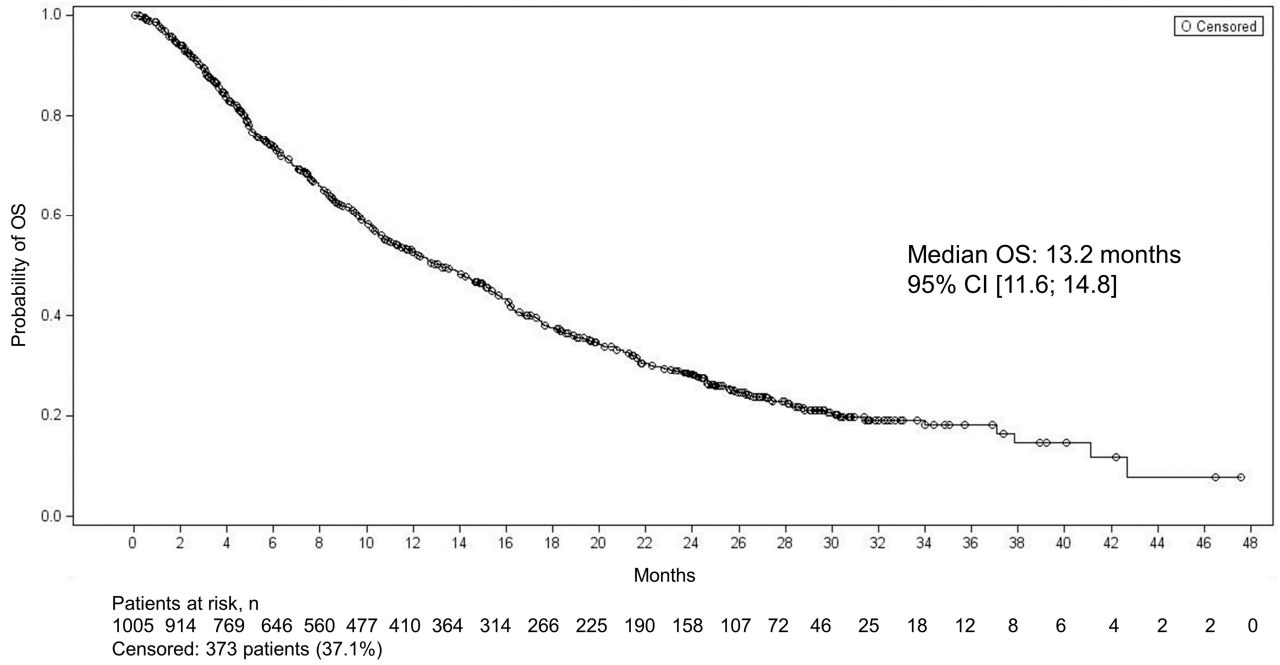

Figure 1. Kaplan-Meier curve for overall survival in months – SAF

CI: confidence interval, n: number of patients with observations, OS: overall survival, SAF: safety analysis set

Source: Figure 14.3.2 / 9, Table 14.3.2 / 9

When analyzing patients previously treated with sorafenib (SSAF), there was no major difference in OS compared to the total SAF, the median OS was 13.2 months (n=965, 95% CI [11.7; 14.9]) (Table 14.3.2 / 16). The KM curve for OS of the SSAF is shown in Figure 14.3.2 / 16.

By ALBI grade at baseline, the median OS for patients with Grade 1 was 20.2 months (n=318, 95% CI [17.4; 23.2]). For patients with Grade 2 the median OS was 10.2 months (n=480, 95% CI [8.7; 11.4]) and for patients with Grade 3 the median OS was 3.5 months (n=37, 95% CI [2.4; 6.3]) (Table 14.3.2 / 14 and Figure 14.3.2 / 14).

By Child-Pugh classification at baseline, the median OS was 15.5 months (n=618, 95% CI [13.9; 16.3]) for patients with Child-Pugh A and 6.3 months (n=123, 95% CI [4.9; 7.8]) for patients with Child-Pugh B. Data were available for only 5 patients with Child-Pugh C and not evaluable for 26 patients (Table 14.3.2 / 15 and Figure 14.3.2 / 15).

OS in months is also presented by region in Table 14.3.2 / 10, by initial dose level in Table 14.3.2 / 11, by treatment line in Table 14.3.2 / 12, and by prior use of immune checkpoint inhibitor in Table 14.3.2 / 13. The corresponding KM curves are shown in Figures 14.3.2 / 10 to 14.3.2 / 13. OS in days is provided in Tables 14.3.2 / 1 to 14.3.2 /8, and the corresponding KM curves are provided in Figures 14.3.2 / 1 to 14.3.2 / 8.

10.4.2.3 Progression-free survival

Most patients (873 patients, 87.6%) had an event of disease progression. The median PFS for the observational period was 3.9 months (n=997, 95% CI [3.6; 4.1]) (Table 14.3.3 / 6). The KM curve for PFS is presented in Figure 2.

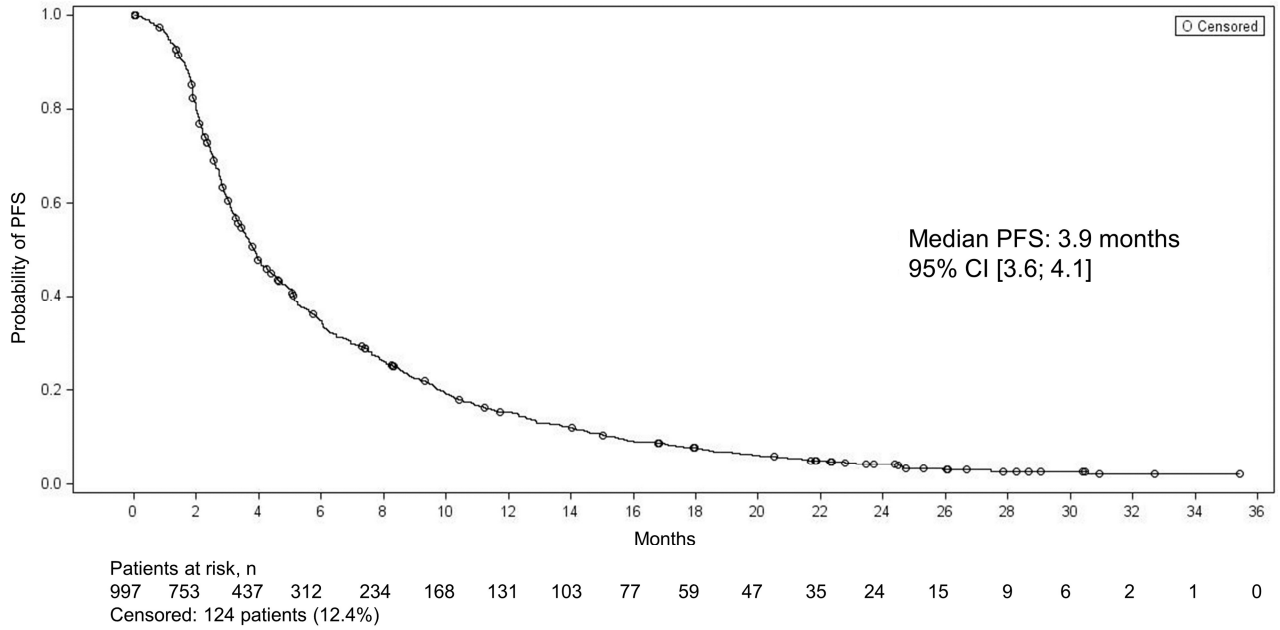

Figure 2. Kaplan-Meier curve for progression-free survival in months – SAF

CI: confidence interval, n: number of patients with observations, PFS: progression-free survival, SAF: safety analysis set
Source: Figure 14.3.3 / 6, Table 14.3.3 / 6

When analyzing patients previously treated with sorafenib (SSAF), there was no major difference in PFS compared to the total SAF, the median PFS was 3.9 months for 843 patients (88.1%) with disease progression (n=957, 95% CI [3.6; 4.1]) (Table 14.3.3 / 10). The KM curve for PFS of the SSAF is shown in Figure 14.3.3 / 10.

PFS in months is also presented by region in Table 14.3.3 / 7, by initial dose level in Table 14.3.3 / 8, and by prior use of immune checkpoint inhibitor in Table 14.3.3 / 9. The corresponding KM curves are shown in Figure 14.3.3 / 7, 14.3.3 / 8, and 14.3.3 / 9. PFS in days is provided in Tables 14.3.3 / 1 to 14.3.3 /5, and the corresponding KM curves are provided in Figures 14.3.3 / 1 to 14.3.3 / 5.

10.4.2.4 Time to progression

The median TTP for the observational period was 4.1 months (n=997, 95% CI [3.9; 4.6]) (Table 14.3.4 / 6). The KM curve for TTP is presented in Figure 3.

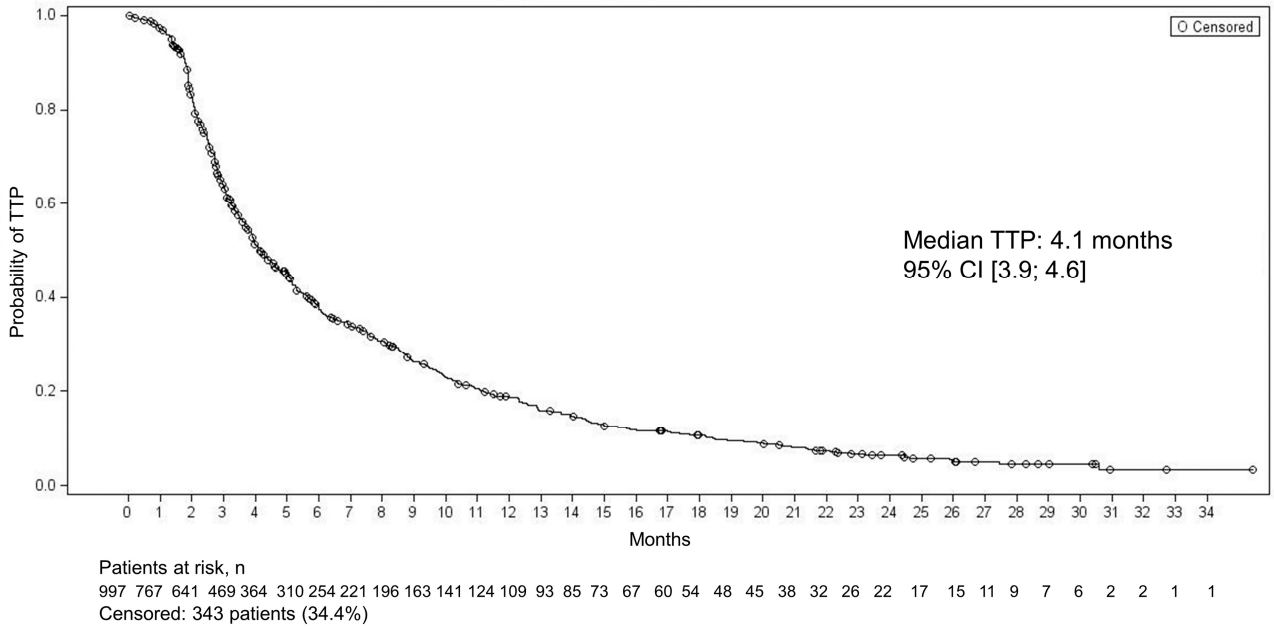

Figure 3. Kaplan-Meier curve for time to progression in months– SAF

CI: confidence interval, n: number of patients with observations, SAF: safety analysis set, TTP: time to progression
Source: Figure 14.3.4 / 6, Table 14.3.4 / 6

When analyzing patients previously treated with sorafenib (SSAF), there was no major difference in TTP compared to the total SAF, the median TTP was 4.1 months (n=957, 95% CI [3.9; 4.6]) (Table 14.3.4 / 10). The KM curve for TTP of the SSAF is shown in Figure 14.3.4 / 10.

TTP in months is also presented by region in Table 14.3.4 / 7, by initial dose level in Table 14.3.4 / 8, and by prior use of immune checkpoint inhibitor in Table 14.3.4 / 9. The corresponding KM curves are shown in Figure 14.3.4 / 7, 14.3.4 / 8, and 14.3.4 / 9. TTP in days is provided in Tables 14.3.4 / 1 to 14.3.4 /5, and the corresponding KM curves are provided in Figures 14.3.4 / 1 to 14.3.4 / 5.

10.4.2.5 Overall response rate

The best overall tumor response was stable disease for 386 patients (38.7%), progressive disease for 270 patients (27.1%), complete response for 23 patients (2.3%), and partial response for 115 patients (11.5%). The overall response rate, including patients with complete response and partial response, was 13.8%. It should be noted that patients with a baseline tumor assessment more than 16 weeks before start of regorafenib were excluded from this analysis (Table 14.3.5 / 1).

10.4.2.6 Exposure

Patients most commonly had an initial regorafenib daily dose of 160 mg (469 patients, 46.7%) or 80 mg (398 patients, 39.6%). Only 106 patients (10.5%) had 120 mg, 31 patients (3.1%) had 40 mg, and 1 patient (<0.1%) had 140 mg. Over half of the patients (574 patients, 57.1%) had any dose modification, which was a dose reduction for 409 patients (40.7%), a dose escalation for 233 patients (23.2%), a dose interruption for 315 patients (31.3%), and a dose restart for 184 patients (18.3%) (multiple responses were possible). Further details on dose modifications by initial dose level, including reasons for dose modifications, are presented in Table 14.3.6 / 1. Other reasons for dose modifications are listed in Table 14.5 / 16.

Among the sorafenib intolerant patients (defined as patients with side effects leading to discontinuation of prior sorafenib therapy), the most common initial dose level was 80 mg (45 patients, 49.5%), followed by 160 mg (29 patients, 31.9%) (Table 14.2.5 / 3).

The median DOT was 3.7 months (95% CI [3.3; 4.0]) (Table 14.3.4 / 2). DOT is also presented by region (Asia/non-Asia) in Table 14.3.6 / 3, by initial dose in Table 14.3.6 / 4, and by prior use of immune checkpoint inhibitor in Table 14.3.6 / 5.

Of the 936 patients (93.1%) who discontinued regorafenib treatment, the most common primary reason for discontinuation was progressive disease (428 patients, 42.6%) followed by AE (321 patients, 31.9%), physician decision (72 patients, 7.2%), and patient decision (65 patients, 6.5%). The remaining reasons were reported in ≤5% of patients each (Table 14.3.6 / 6), other reasons are listed in Table 14.5 / 17. This information is also presented by region (Asia/non-Asia) in Table 14.3.6 / 7 and by initial dose in Table 14.3.6 / 8.

Figures of the daily dose for patients by each initial dose are presented in Figures 14.3.6 / 1 to 14.3.6 / 5.

10.4.3 Analysis of tertiary outcome variables

The tertiary objective of this study was to describe sorafenib treatment and other therapies for HCC prior to regorafenib treatment including doses, DOT, best response, and reasons for discontinuation.

An overview of prior sorafenib treatment is presented in Section 10.2.3.1.1 and on other prior systemic therapies for HCC is presented in Section 10.2.3.1.2. An overview of prior non-systemic anti-cancer therapies is provided in Section 10.2.3.2 and on prior radiotherapy is provided in Section 10.2.3.3.The full results are presented in Annex 1, TLF Section 14.1.2 for prior sorafenib treatment, Section 14.1.3 for other prior systemic therapies, Section 14.1.4 for non-systemic anti-cancer therapies, and Section 14.1.5 for radiotherapy.

The median OS from start of prior sorafenib therapy for patients receiving regorafenib in second-line was 769 days (95% CI [732; 836]). More than half of the patients died (514 patients, 62.5%) (Table 14.4 / 1).

The median OS from start of other prior systemic anti-cancer therapy was 619 days (95% CI [383; 919]). In total, 13 of the 21 patients died (61.9%) (Table 14.4 / 2).

10.5 Other analyses

The time to deterioration (TTD) of ALBI grade is provided in Tables 14.2.8.1 / 1 to 14.2.8.1 / 8 and the corresponding Kaplan-Meier curves are shown in Figures 14.2.8.1 / 1 to 14.2.8.1 / 8. TTD of Child-Pugh class is provided in Tables 14.2.8.2 / 1 to 14.2.8.2 / 8 and Figures 14.2.8.2 / 1 to

14.2.8.2 / 8, and TTD of ECOG status in Tables 14.2.8.3 / 1 to 14.2.8.3 / 8 and Figures 14.2.8.3 / 1 to 14.2.8.3 / 8.

A listing and summary of patients who received regorafenib and would be predominantly excluded from second-line phase 3 trials were compiled in Table 14.6 / 1 and Table 14.6 / 2.

10.6 Adverse events/adverse reactions

The primary objectives of this study included assessing the incidence of TEAEs (collected up to 30 days after last administration). These results are presented in Section 10.4.1.

11 Discussion

11.1 Key results

11.1.1 Demographics and baseline characteristics

The SAF consisted of 1005 patients with a median observational period of 41.00 weeks. The median time between initial uHCC diagnosis and start of treatment with regorafenib was 24.72 months. The median time since most recent progression/relapse to start of treatment with regorafenib was 0.62 months. The COVID-19 pandemic resulted in study disruptions for 56 patients, most of which had remote visits.

The greatest proportions of patients were from Korea (16.9%), followed by Japan (14.5%), France (13.7%), Taiwan (13.5%), and China (10.0%). Of the remaining countries, each accounted for less than 10% of the SAF. The majority of patients (83.1%) were male. The mean ± SD age of patients was 65.2 ± 10.5 years.

Almost half of the patients (47.4%) reported former alcohol use, while only 11.3% of patients reported current alcohol use. For the current and former alcohol users, 22.6% reported light use while fairly equal proportions of patients reported moderate (18.0%) or heavy (16.0%) use. A total of 45.8% of patients reported never smoking cigarettes, with a large proportion of patients also reporting former cigarette use (37.5%). A total of 14.5% of patients were current cigarette users.

The **etiology of HCC** was most commonly reported as hepatitis B (38.0% of patients), followed by alcohol use (24.9%) and hepatitis C (24.1%). At start of regorafenib treatment, for more than half of patients (55.5%) the location of the progression was growth of existing intrahepatic lesion(s). Of the patients with metastases at study entry (58.8%), extrahepatic spread to nearby lymph nodes (N1) was observed in 46.0% of patients, while distant extrahepatic spread (M1) was observed in 83.2% of patients at study entry. Of these, 58.2% of patients had only 1 metastatic site. The most common location of metastasis was lung (48.6%), followed by lymph node (31.1%) and bone (22.3%). Among the 778 patients with countable liver lesions at study entry, the mean ± SD number of liver lesions was 4.6 ± 6.0 lesions.

A total of 86.7% of patients in the SAF had any **prior disease**. The most common patient-based prior diseases at the PT level were type 2 diabetes mellitus (27.5%), hepatic cirrhosis (15.1%), varices oesophageal (14.9%), hepatitis B (13.1%), and chronic hepatitis B (10.6%). The remaining PTs were reported in less than 10% of patients. At the time of inclusion, 56.2% of patients had any **concomitant disease.** At the PT level, the most common patient-based concomitant diseases included hypertension (50.0%) and ascites (10.7%), while the remaining PTs occurred in less than 2% of patients.

Around a quarter of patients (24.9%) received **prior radiotherapy**, while **concomitant radiotherapy** was reported for only 6.1% of patients.

A total of 58.6% of patients were reported to have used **prior medication**. Most common prior medications concerned the cardiovascular system and alimentary tract and metabolism (321 patients each, 31.9%), followed by nervous system (149 patients, 14.8%), anti-infectives for systemic use (142 patients, 14.1%), and dermatologicals (114 patients, 11.3%). Use of **concomitant medication** was reported in 74.4% of patients. Most common concomitant medications included medications for the alimentary tract and metabolism (505 patients, 50.2%), followed by cardiovascular system (457 patients, 45.5%), dermatologicals (293 patients, 29.2%), nervous system (288 patients, 28.7%),

blood and blood forming organs (241 patients, 24.0%), anti-infectives for systemic use (249 patients, 24.8%), sensory organs (222 patients, 22.1%), various (219 patients, 21.8%), and respiratory system (208 patients, 20.7%).

A total of 5.9% of patients in the SAF were reported to have **concomitant systemic anti-cancer therapy**. The most common concomitant treatments were monoclonal antibodies (1.2%) and lenvatinib (1.1%) A total of 32.2% of patients received **systemic anti-cancer therapy after regorafenib**. The most common of these therapies were lenvatinib (12.5% of patients) and cabozantinib (10.9% of patients).

Any **concomitant non-systemic anti-cancer therapy** was reported for 8.9% of patients in the SAF. The most common concomitant procedure was TACE (73.0% of these patients).

Almost all patients (96.0%) had been previously treated with sorafenib. Regorafenib was reported as a **first-line treatment** for only 1.2% of patients. A total of 84.4% of patients were treated with regorafenib as a **second-line treatment**. Of these patients, almost all (94.7%) were first treated with sorafenib. For the 14.4% of patients with regorafenib as **≥third-line treatment**, the most common prior treatment line was first sorafenib, then nivolumab in 15.2% of patients. The median time since the most recent prior systemic anti-cancer therapy before ≥third-line treatment with regorafenib was 0.26 months.

11.1.2 Analysis of primary outcome variables

The primary objective of this study was to evaluate the safety of regorafenib in patients with uHCC, including incidence of all TEAEs and dose modifications due to TEAEs in real-world practice conditions. TEAEs were defined as any event arising or worsening after start of regorafenib until 30 days after last intake.

The vast majority (91.6%) of patients in the SAF experienced any **TEAE**. At the MedDRA PT level, TEAEs that occurred in ≥5% of patients in the SAF were palmar-plantar erythrodysaesthesia syndrome (329 patients, 32.7%), diarrhoea (296 patients, 29.5%), fatigue (200 patients, 19.9%), decreased appetite (177 patients, 17.6%), hypertension (115 patients, 11.4%), abdominal pain (114 patients, 11.3%), asthenia (108 patients, 10.7%), nausea (80 patients, 8.0%), constipation, pyrexia (71 patients each, 7.1%), dysphonia (65 patients, 6.5%), ascites (64 patients, 6.4%) oedema peripheral (63 patients, 6.3%), anaemia (60 patients, 6.0%), blood bilirubin increased (59 patients, 5.9%), vomiting (57 patients, 5.7%), and dyspnoea (50 patients, 5.0%). When assessing the patient-based incidence of TEAEs by worst CTCAE grade, most of these events were classified as Grade 3 (348 patients, 34.6%), followed by Grade 2 (268 patients, 26.7%), Grade 5 (146 patients, 14.5%), Grade 1 (104 patients, 10.3%), and Grade 4 (46 patients, 4.6%). At the PT level, all Grade 4 events occurred in less than 3 patients except for hepatic failure (7 patients, 0.7%), hepatic encephalopathy, (6 patients, 0.6%), sepsis (4 patients, 0.4%), ascites, dyspnoea, gastrointestinal haemorrhage, and hyponatraemia (3 patients each, 0.3%). The most common Grade 5 events were hepatocellular carcinoma (29 patients, 2.9%), hepatic failure (19 patients, 1.9%), death (16 patients, 1.6%), multiple organ dysfunction syndrome, pneumonia (7 patients each, 0.7%), acute kidney injury (6 patients, 0.6%), upper gastrointestinal haemorrhage, general physical health deterioration, respiratory failure (4 patients each, 0.4%), cardiac arrest, hepatic encephalopathy, malignant neoplasm progression, and myocardial infarction (3 patients each, 0.3%).

By NCI CTCAE term, TEAEs occurring in ≥5% of patients were palmar-plantar erythrodysesthesia syndrome (330 patients, 32.8%), diarrhoea (296 patients, 29.5%), fatigue (295 patients, 29.4%),

anorexia (176 patients, 17.5%), abdominal pain (131 patients, 13.0%), no code in CTCAE (86 patients, 8.6%), nausea (80 patients, 8.0%), blood bilirubin increased (78 patients, 7.8%), hypertension (117 patients, 11.6%), constipation (73 patients, 7.3%), fever (71 patients, 7.1%), anemia (62 patients, 6.2%), ascites, edema limbs (61 patients each, 6.1%), vomiting (59 patients, 5.9%), and dyspnea (52 patients, 5.2%).

When analyzing the patient-based incidences of TEAEs among sorafenib intolerant patients, any TEAEs were reported for 93.4% of patients. The most frequently reported (≥5%) TEAEs were diarrhoea (25 patients, 27.5%), palmar-plantar erythrodysaesthesia syndrome (23 patients, 25.3%), asthenia (17 patients, 18.7%), decreased appetite (16 patients, 17.6%), abdominal pain (13 patients, 14.3%), hypertension (11 patients, 12.1%), fatigue, pyrexia, weight decreased (7 patients each, 7.7%), arthralgia, constipation, dyspnoea, hepatic failure, and rash (5 patients each, 5.5%).

When assessing the occurrence of TEAEs over each theoretical cycle (4-week time interval) for TEAEs with incidence rates ≥5% of patients, events for all PTs occurred generally more in earlier cycles. For all PTs, the greatest number of patients with events were reported in cycle 1. After cycle 5, most PTs occurred in ≤5 patients each.

Almost three-quarters of patients (74.2%) experienced any **drug-related TEAEs**. At the PT level, drug-related TEAEs that occurred in ≥5% of patients were palmar-plantar erythrodysaesthesia syndrome (309 patients, 30.7%), diarrhoea (258 patients, 25.7%), fatigue (151 patients, 15.0%), decreased appetite (133 patients, 13.2%), hypertension (96 patients, 9.6%), asthenia (91 patients, 9.1%), dysphonia (52 patients, 5.2%), and nausea (51 patients, 5.1%). When assessing the patient-based incidence of drug-related TEAEs by worst CTCAE grade, the only Grade 4 events that occurred in more than 1 patient were hepatic encephalopathy and hyponatraemia (2 patients each, 0.2%). The only Grade 5 event that occurred in more than 1 patient was in the PT hepatic failure (3 patients, 0.3%).

More than a third of patients (37.2%) experienced any **TESAEs**. At the PT level, TESAEs occurring in ≥1% of patients were hepatocellular carcinoma (35 patients, 3.5%), hepatic failure (29 patients, 2.9%), abdominal pain, ascites (22 patients each, 2.2%), hepatic encephalopathy (21 patients, 2.1%), pneumonia (19 patients, 1.9%), death (16 patients, 1.6%), acute kidney injury (14 patients, 1.4%), dyspnoea, and oesophageal varices haemorrhage (12 patients each, 1.2%). When assessing the patient-based incidence of TESAEs by worst CTCAE grade, the most common Grade 5 events were hepatocellular carcinoma (29 patients, 2.9%), hepatic failure (19 patients, 1.9%), and death (16 patients, 1.6%).

A total of 9.0% of patients experienced any **drug-related TESAEs**. By PT, the most frequent drug-related TESAEs (≥3 patients) were hepatic encephalopathy (10 patients, 1.0%), decreased appetite, hepatic failure (5 patients, 0.5%), blood bilirubin increased, fatigue, palmar-plantar erythrodysaesthesia syndrome, upper gastrointestinal haemorrhage (4 patients each, 0.4%), abdominal pain, diarrhoea, hepatocellular carcinoma, and oesophageal varices haemorrhage (3 patients each, 0.3%). By worst CTCAE grade, the only Grade 4 drug-related TESAEs that occurred in more than 1 patient was hepatic encephalopathy (2 patients, 0.2%) and the only Grade 5 drug-related TESAE that occurred in more than 1 patient was hepatic failure (3 patients, 0.3%).

Around a quarter (26.3%) of patients experienced any **TEAEs leading to dose reduction**. At the PT level, the most common (≥1%) TEAEs leading to dose reduction were palmar-plantar erythrodysaesthesia syndrome (97 patients, 9.7%), diarrhoea (50 patients, 5.0%), fatigue (33 patients, 3.3%), asthenia (27 patients, 2.7%), decreased appetite (20 patients, 2.0%),

hypertension (14 patients, 1.4%), abdominal pain, and nausea (12 patients, 1.2%). By worst CTCAE grade, only 1 patient each (0.1%) had an event classified as worst grade Grade 4 (PT: cardiac failure) and Grade 5 (PT: hepatic failure).

A total of 27.0% of patients experienced any **TEAEs leading to dose interruption**. At the PT level, the most common (≥1%) TEAEs leading to dose interruption were palmar-plantar erythrodysaesthesia syndrome (48 patients, 4.8%), diarrhoea (42 patients, 4.2%), fatigue (27 patients, 2.7%), decreased appetite (24 patients, 2.4%), pyrexia (19 patients, 1.9%), blood bilirubin increased (16 patients, 1.6%), asthenia (14 patients, 1.4%), hypertension (12 patients, 1.2%), abdominal pain, dyspnoea, and malaise (11 patients each, 1.1%). By worst CTCAE grade, the only Grade 4 event that occurred in more than 1 patient was pneumonia (2 patients, 0.2%), and the only Grade 5 event that occurred in more than 1 patient was hepatic failure (2 patients, 0.2%).

A total of 30.9% of patients experienced any **TEAEs leading to permanent discontinuation** of regorafenib. At the PT level, the most common (≥1%) TEAEs leading to permanent discontinuation of regorafenib were decreased appetite, palmar-plantar erythrodysaesthesia syndrome (25 patients each, 2.5%), fatigue (23 patients, 2.3%), diarrhoea (17 patients, 1.7%), hepatic failure (16 patients, 1.6%) ascites (13 patients, 1.3%), abdominal pain, blood bilirubin increased (12 patients each, 1.2%), asthenia, and hepatic encephalopathy (11 patients each, 1.1%). By worst CTCAE grade, the most common (≥3 patients) Grade 4 events were hepatic failure (8 patients, 0.8%), hepatic encephalopathy (4 patients, 0.4%), and acute kidney injury (3 patients, 0.3%). The most common Grade 5 events were hepatic failure (7 patients, 0.7%), death, hepatocellular carcinoma, multiple organ dysfunction syndrome, and respiratory failure (3 patients each, 0.3%).

A total of 16.2% of patients in the SAF experienced any **TEAEs with a fatal outcome**. At the PT level, the most common (≥1%) TEAEs with a fatal outcome were hepatocellular carcinoma (32 patients, 3.2%), hepatic failure (22 patients, 2.2%), and death (16 patients, 1.6%).

Most of the **laboratory values** (ALT, albumin, AST, bilirubin, CRP, creatinine, erythrocytes, hematocrit, hemoglobin, LDH, lymphocytes, platelets, prothrombin, and sodium) remained largely stable throughout the study. The median ALP level was 160 U/L at baseline and varied slightly between 118 U/L (visit 15, n=29) and 165 U/L (visit 19, n=45). The median AFP level was 155 ng/mL at baseline and showed a slight tendency to decrease, although values were very variable (between 8.7 ng/mL at visit 17, n=17 and 155.00 ng/mL at baseline, n=661). The median GGT level was 149 U/L at baseline and showed a slight tendency to decrease, ranging between 91 U/L (n=24) at visit 14 and 160 U/L (n=60) at visit 8. The median leukocyte count was 5.33 Giga/L at baseline and showed a slight tendency to increase, ranging between 5.25 Giga/L (n=25) at visit 17 and 6.20 Giga/L (n=220) at visit 5. The median neutrophil count was 3.45 Giga/L at baseline and showed a slight tendency to increase, ranging between 3.42 Giga/L (n=32) at visit 14 and 4.03 Giga/L (n=147) at visit 6.

11.1.3 Analysis of secondary outcome variables

The secondary objectives of this study were to describe the effectiveness of regorafenib, including OS, PFS, TTP, and ORR; to describe the patterns of regorafenib treatment, including actual doses, DOT, and other dosing parameters; to describe patient characteristics, comorbidities, and prior therapies (discussed in Section 11.1.1); and to describe the physicians' practice patterns under real-life conditions.

Regarding **death and progression**, 15.0% of patients in the SAF died during or within 30 days of the last dose of regorafenib, and 48.0% died after 30 days succeeding the last dose of regorafenib. Overall, 633 patients died. The primary cause of death was progressive disease (46.8%), followed by AE (7.1%), unknown (5.6%), liver disorder (1.8%), and other reason (1.7%). The median follow-up time for censored patients (patients who were alive or patients whose death was not confirmed at the time of data cut-off) was 14.22 months. During the observation period, almost two-thirds of patients (65.8%) were reported to have disease progression. Of these patients, 27.7% had new metastases at first progression.

The median **OS** for the observational period was 13.2 months (95% CI [11.6; 14.8]).

For **PFS**, most patients (87.6%) had an event of disease progression. The median PFS for the observation period was 3.9 months (95% CI [3.6; 4.1]).

The median **TTP** for the observational period was 4.1 months (95% CI [3.9; 4.6]).

The **ORR**, including patients with complete response and partial response, was 13.8%.

Regarding **exposure**, patients in the SAF most commonly had an initial regorafenib daily dose of 160 mg (46.7% of patients). Over half of the patients (57.1%) had any dose modification. The median DOT was 3.7 months (95% CI [3.3; 4.0]). For the 93.1% of patients who discontinued regorafenib treatment, the most common primary reason for discontinuation was progressive disease (42.6%) followed by AE (31.9%), physician decision (7.2%), and patient decision (6.5%).

11.1.4 Analysis of tertiary outcome variables

The tertiary objective of this study was to describe sorafenib treatment and other therapies for HCC prior to regorafenib treatment including doses, DOT, best response, and reasons for discontinuation.

For the SAF the median time since most recent **prior systemic anti-cancer therapy** to treatment with regorafenib was 0.26 months.

For patients with **prior sorafenib therapy**, the median time from initial diagnosis to start of sorafenib treatment was 11.73 months. The median duration of prior sorafenib treatment was 4.93 months. For the majority of these patients (79.0%), progression, recurrence/relapse of HCC was the reason for discontinuation of prior sorafenib therapy. The most common initial daily dose of sorafenib was 800 mg (62.7%), followed by 400 mg (31.6%), with the mean ± SD initial daily dose being 654.1 ± 197.3 mg (median 800.0 mg). The most common last daily dose was 800 mg (41.3%), followed by 400 mg (39.5%), with the mean ± SD last daily dose being 577.6 ± 207.4 mg (median 600.0 mg). The largest proportions of patients reported stable disease (342 patients, 35.4%) or progressive disease by response assessment criteria (334 patients, 34.6%). Over three-quarters of patients with prior sorafenib therapy (77.6%) experienced sorafenib related side effects. At the PT level these were most commonly (>10%) palmar-plantar erythrodysaesthesia syndrome (475 patients, 49.2%), diarrhoea (352 patients, 36.5%), fatigue (261 patients, 27.0%), secondary hypertension (190 patients, 19.7%), decreased appetite (158 patients, 16.4%). The median OS from start of prior sorafenib therapy was 769 days (95% CI [732; 836]).

A total of 200 patients had treatment with **prior systemic anti-cancer therapy other than sorafenib**, most commonly nivolumab (23.5% of these patients), followed by lenvatinib (20.0%). The main reason for discontinuation among patients with prior systemic anti-cancer therapy other than sorafenib was progression/recurrence/relapse of HCC (67.0% of these patients). The largest proportions of patients with prior systemic anti-cancer therapy other than sorafenib reported stable

disease (37.2%) and complete response with incomplete blood recovery (29.3%). Complete response was reported in 3.1% of patients and partial response in 14.1% of patients. Almost half of patients with other prior systemic anti-cancer therapy (46.0%) experienced related side effects before switching to regorafenib. At the PT level these were most commonly (>10%) fatigue (14.5%), rash, and diarrhoea (13.0% each).

A total of 74.2% of patients in the SAF received **prior non-systemic anti-cancer therapy**. For 73.7% of patients the location of the prior non-systemic anti-cancer therapy was the liver. The most common prior non-systemic anti-cancer therapy was TACE (58.1% of patients), followed by radio-frequency ablation (23.8%). Of the 584 patients with TACE, 13.0% showed complete response and 27.9% showed partial response, whereas the most common best response was stable disease (28.1%). Of the 239 patients with radio-frequency ablation, 40.6% had complete response and 18.0% had partial response.

A total of 24.9% of patients in the SAF received **prior radiotherapy**. The most common prior radiotherapy was classified as other radiotherapy (7.6%), followed by external beam radiation therapy (6.1%) and stereotactic radiotherapy (5.6%). For 4.9% of the 61 patients with external beam radiation therapy complete response was reported and slightly less than a third (31.1%) showed partial response, whereas more than a third (37.7%) presented with stable disease. For the 56 patients receiving stereotactic therapy, 21.4% of patients had complete response and 17.9% of patients had partial response, although the most common best response was stable disease (28.6%).

11.2 Limitations

This prospective observational cohort study collected data on the safety and effectiveness of regorafenib in patients with uHCC under real-life conditions that could be analyzed and disseminated in a timely manner. This study has limitations associated with all observational studies, including the lack of blinding and randomization, the heterogeneity of the patient population in terms of disease stage and pre-treatment status, and a high amount of missing data. Furthermore, this study is a single-arm cohort study without an active comparison group. Comparisons can only be performed with historical data from clinical or observational studies, which is prone to bias and confounding. Historical patient data collected with respect to prior sorafenib treatment or other treatments may be incomplete and/or differ relating to sorafenib use and standard of care in local practice. Historical data provided by patient interview is prone to errant recall.

Although the study included participants from a variety of geographic regions, there may be local limitations that reduce the representativeness of patients recruited, such as patient access to recruiting physicians (including differences in patient profile in specialized recruiting sites vs local general practice), regorafenib availability and reimbursement, and decisions relating to local standard of care. In addition, the sample size from Japan may result in comparative over-representation of this country with respect to other individual nations, as 150 patients were planned based on the Japanese protocol, and 146 patients were eventually included.

As all data collected in this study were part of routine clinical practice, the treating physician decided on the prescription of the respective medication and inclusion of the patient in the study. This may have influenced the patients' decisions and course of treatment, thereby introducing bias. Patients who discontinued the documentation during the observational period might have created an outcome bias. Also, as most examinations were not mandatory, this could lead to underreporting of certain events, although the proportion of missing data in this study was comparatively low. In addition, some patients might not have complete follow-up and/or the time might not be sufficient to

observe the development of events. Therefore, careful attention should be applied to the interpretation of the summary measures, as there could be potential underestimation of events.

11.3 Interpretation

It was previously demonstrated in the RESORCE study that regorafenib prolongs survival in patients with uHCC who have progressed on the first-line therapy of sorafenib. However, real-world data on the use of regorafenib as second-line after first-line treatment with sorafenib at the time of initiation of this study was limited. As such, the REFINE study has provided safety and effectiveness of treatment with regorafenib in a real-world setting across a broad range of patients.

The methodological as well as patient demographic and baseline disease differences must be considered when comparing results between these two studies. The RESORCE study only enrolled patients with HCC who tolerated sorafenib (≥400 mg/day for ≥20 of last 28 days of treatment), progressed on sorafenib, had a Child-Pugh A liver function (to avoid any confounding effects of impaired liver function), and had an ECOG status of 0 or 1 (3). In contrast, the population in the REFINE study was more heterogeneous, with 123 patients (12.2%) having Child-Pugh B liver function at study entry and 91 patients being sorafenib intolerant. The REFINE study also included patients with ECOG status at study entry of 2 (4.7%) and 3 (1.2%). Further, 14.4% of patients received regorafenib in ≥third-line, and due to the rapidly evolving treatment landscape, patients also received systemic treatments other than sorafenib (e.g., other TKIs or immunotherapy). In the RESORCE study, all patients received an initial regorafenib daily dose of 160 mg (3), whereas in the REFINE study only 46.7% of patients received this initial dose.

In the RESORCE study, TEAEs were reported in all regorafenib recipients and 44% of total patients had TESAEs. By worst CTCAE grade, most TEAEs were classified as Grade 3 (56%) (3). In the REFINE study, TEAEs were reported for 92% of patients and TESAEs for 37% of patients. By worst CTCAE grade, most TEAEs were graded as Grade 2 or Grade 3 (27% and 35%, respectively). In the RESORCE study, 68% of patients in the regorafenib group experienced TEAEs leading to interruptions or dose reductions and 25% discontinued due to TEAEs. For comparison, 45% of patients in the REFINE study had TEAEs leading to a dose modification (including interruptions and reductions) and 31% had TEAEs leading to permanent discontinuation of regorafenib. In the RESORCE study, 13% of patients in the regorafenib group experienced an event with fatal outcome, while in the REFINE study a slightly higher proportion of patients (16%) experienced any TEAE with a fatal outcome. However, it should be considered that the REFINE study included a broader patient population, with Child-Pugh classification B and C, with ECOG status 2 and 3, and receiving regorafenib in ≥third-line.

Drug-related TEAEs were reported for 93% of patients in the RESORCE study. The most common events were hand-foot skin reaction (PT: palmar-plantar erythrodysaesthesia syndrome) (52%), diarrhoea (33%), fatigue (29%), anorexia (24%), and hypertension (23%). Seven patients had drug-related Grade 5 TEAEs, which were reported as death not otherwise specified, encephalopathy, gastric perforation, general disorders and administrative site conditions, intracranial haemorrhage, myocardial infarction, and upper gastrointestinal haemorrhage (3). In the REFINE study, drug-related TEAEs were reported for 74% of patients, with the most common events being palmar-plantar erythrodysaesthesia syndrome (31%) and diarrhoea (26%). Seven patients had regorafenib-related Grade 5 TESAEs (<1%) in the context of underyling malignancy (HCC), impaired liver function (hepatic failure, hepatic function abnormal, and blood bilirubin increased), and hemorrhage

(upper gastrointestinal haemorrhage). Drug-related TESAEs were reported for 10.4% of patients in the RESORCE study and 9.0% of patients in the REFINE study (14).

In the REFINE study, most laboratory values remained stable, there was only a slight tendency to increase for leukocyte count and neutrophil count, and a slight tendency to decrease for GGT. AFP levels were very variable, which was similar in the RESORCE study (14).

The median OS for the observation period in the REFINE study was 13.2 months (95% CI [11.6; 14.8]), which was slightly longer than that observed for the treatment group in the RESORCE study, with 10.6 months (95% CI [9.1; 12.1]). The median PFS in the REFINE study was 3.9 months (95% CI [3.6; 4.1]), which was also slightly longer compared to 3.1 months (95% CI [2.8; 4.2]) in the RESORCE study (3). The median OS from start of prior sorafenib therapy in the REFINE study was 769 days (95%CI [732; 836], corresponding to approximately 26 months), which was similar to the RESORCE study, with 26.0 months (95% CI 22.6; 28.1]) (15).

REFINE evaluated a broader patient population compared with RESORCE and included patients with ECOG status ≥2, Child-Pugh classification B and C, intolerance to sorafenib, and those who had received prior immunotherapy, thus representing real-world patients with uHCC. The final results of the real-world REFINE study confirmed the safety and effectiveness of regorafenib in a broad population of patients with uHCC, consistent with the results from the RESORCE trial (14).

Overall, the results of this study confirm in a real-world setting that regorafenib provides improvement in patients with uHCC, with a safety profile comparable to regorafenib in other indications (4, 5).

11.4 Generalizability

The study allowed the enrollment of a heterogeneous patient population with regard to demographic and disease characteristics and, thus, the patient population in this study is assumed to reflect the real-life situation in patients with uHCC who are treated with regorafenib.

Patients were treated according to daily practice conditions with all decisions in terms of diagnostic procedures, treatments, management of the disease, and resource utilization fully dependent on mutual agreement between the patient and the attending physician, without interference by the study protocol. The observational design of the study allowed to collect real-life data, without influencing the physicians' treatment decisions.

Despite the COVID-19 pandemic happening during the time of this study, only 56 patients experienced COVID-19 related study disruptions and almost all of these patients had remote visits.

The large sample size enabled comprehensive characterization of the regorafenib safety profile of all treated patients, as well as analysis of safety and effectiveness among different patient subsets.

12 Other information

Not applicable.

13 Conclusion

This final analysis of the observational REFINE study assessed a more varied patient population than the phase 3 RESORCE trial, including a higher proportion of patients with ECOG performance status ≥1 and with Child-Pugh B liver function. Further, patients with prior treatments other than sorafenib, patients who were intolerant to sorafenib, and patients who received regorafenib in third-line or later were also included in REFINE. Almost all patients in REFINE received prior sorafenib treatment and most received only one prior line of therapy. Approximately half of the patients initiated regorafenib at the approved 160 mg dose, while almost two-fifths initiated at 80 mg. Most patients experienced their first TEAE within 8 weeks (2 cycles) after starting regorafenib. The incidences of TESAEs and TEAEs leading to dose modification were slightly lower than that reported in the RESORCE trial, while the incidences of TEAEs leading to permanent discontinuation and fatal TEAEs were slightly higher. The median OS, as well as the median PFS, was longer than that reported in the RESORCE trial.

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Appendices

Annex 1 List of stand-alone documents

Document name	Final version and date (if available)*
Study Protocol 19244_REFINE_OS Protocol_v3.0_2020-07-06	v3.0, 06 JUL 2020
Study Protocol Japan 19244_REFINE_OS Protocol_JP_v3.0_2020-06-07	v3.0, 06 JUL 2020
Validity Report 19244_REFINE_VDR_FA_v3_0_2022-09-16	v3.0, 16 SEP 2022
SAP 19244_REFINE_SAP_V2.0_2020-10-30	v2.0, 30 OCT 2020
TLF 19244_REFINE_FA_TLF_2_0_FINAL_2022_09_30	v2.0, 30 SEP 2022
Country Approval List	Available upon request
Site Investigator List	Available upon request

Annex 2 Additional information

Not applicable.

Annex 3 Signature Pages

This report is electronically signed in the study management system.

Title	REFINE: Regorafenib observational study in hepatocellular carcinoma
Report version and date	V1.0, 12 OCT 2022
IMPACT study number	19244
Study type / Study phase	Observational, Phase IV ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	EUPAS20981
Medicinal product	STIVARGA®, regorafenib
Study initiator and funder	Bayer AG, 51368 Leverkusen, Germany

The signatories confirm that they agree that the study was conducted under the conditions described in the protocol.

Signatories

PPD (OS Medical Expert)

PPD (OS Statistician)

PPD (Safety Lead)

PPD (Ops Ex & PM)

PPD (OS Conduct Responsible)