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ORIGINAL RESEARCH

Tolerability and Effectiveness of Regorafenib Treatment in Patients with Unresectable Hepatocellular Carcinoma: Real-World Data from the United States

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Introduction: While several systemic therapies are available for unresectable hepatocellular carcinoma (uHCC), there is a lack of granular real-world evidence to support the efficacy and safety of these therapies. The REFINE study evaluated safety and effectiveness of regorafenib in a global population under real-world practice conditions. This sub-analysis describes the safety and effectiveness of regorafenib among the United States (US) subset of patients in the REFINE study relative to patients in the non-US subset.

Materials and Methods: REFINE was an international, prospective, multicenter observational study. Eligible patients were those with uHCC for whom a decision to treat with regorafenib had already been made. The primary study endpoint was the frequency of documented treatment-emergent adverse events (TEAEs). Additional endpoints included overall survival and progression-free survival. Groups were compared descriptively.

Results: Of 1005 patients, 65 were from the US and 940 were from other countries. 91% of patients in the US subset (n=59) and 92% in the non-US subset (n=862) experienced ≥1 TEAE. Common adverse events (AEs) included gastrointestinal disorders, fatigue, and hand-foot skin reaction. Median overall survival for patients in the US subset was 11.4 months (interquartile range [IQR]: 4.7–25.4) and 13.2 months (IQR: 5.8–26.3) in the non-US subset. Median progression-free survival was 3.4 months (IQR: 2.4–6.1) for patients in the US subset and 3.9 months (IQR: 2.2–8.5) in the non-US subset.

Conclusion: Regorafenib was associated with similar safety and effectiveness outcomes for patients in the US and non-US subsets of the REFINE study. Differences in the incidence of certain AEs may be due to differences in treatment management between study sites or baseline disease status. These findings are consistent with the phase 3 RESORCE trial and corroborate the safety and effectiveness of regorafenib as a subsequent-line treatment in US patients with uHCC.

Keywords: hepatocellular carcinoma, regorafenib, sorafenib, observational study

Introduction

Hepatocellular carcinoma (HCC) is the most common form of liver cancer.[1] Each year, there are approximately 36,000 new cases and 28,000 deaths due to liver cancer in the United States (US),[2] of which an estimated 90% are due to HCC.[1] Common risk factors for HCC include alcohol-use disorder, hepatitis B, hepatitis C, and metabolic dysfunction-associated steatohepatitis.[3,4]

Treatment recommendations for HCC are dependent on stage of detection. For many patients, HCC is not detected until it has reached an intermediate (Barcelona Clinic Liver Cancer [BCLC]-B) or advanced stage (BCLC-C) that is ineligible for surgical intervention or non-systemic anti-cancer therapies.[3,5] For patients with unresectable HCC (uHCC),

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systemic therapies such as atezolizumab + bevacizumab, durvalumab + tremelimumab, sorafenib, or lenvatinib are approved first-line options.[6] Until 2017, sorafenib was the only first-line treatment option for uHCC, demonstrating a statistically significant overall survival benefit compared with placebo in two phase 3 randomized, placebo-controlled trials.[7,8] However, there were no approved second-line therapies following radiological or clinical disease progression that occurred during sorafenib treatment.

To fill this evidence gap, the RESORCE (REgorafenib after SORafenib in patients with hepatoCEllular carcinoma) trial was conducted from 2013 to 2015.[9] This trial was a post-authorization safety study that was requested by the European Medicines Agency and sought to evaluate the safety and efficacy of regorafenib following sorafenib treatment. The results of the RESORCE trial indicated that, compared with placebo, regorafenib was associated with clinically and statistically significant overall survival prolongation for patients with uHCC who have progressed during first-line sorafenib therapy (hazard ratio [HR] = 0.63; 95% confidence interval [CI]: 0.50–0.79).[9] In addition, the safety profile of regorafenib was consistent with previous clinical trials,[9–12] and adverse events (AEs) leading to treatment discontinuation were relatively low.[9]

The REFINE study – an international, multicenter observational study – sought to build on the results of the RESORCE trial by evaluating the safety and effectiveness of regorafenib as a subsequent-line therapy in patients with uHCC under real-world practice conditions. This approach also permitted the inclusion of a broader patient population than may have been included in the RESORCE trial. The results of the REFINE study were consistent with those of the RESORCE trial and corroborated the safety and effectiveness of regorafenib in a real-world setting.[13] No new safety signals were identified in the REFINE study, and overall survival time was similar to the RESORCE trial.

As treatment outcomes may differ across settings, regions, and contexts, the objective of this sub-analysis was to describe the real-world safety and effectiveness of regorafenib for the US subset of patients in the REFINE study relative to patients in the non-US subset.

Materials and Methods

Study Design and Population

The REFINE study was an international, prospective, multicenter, observational study. Patients were recruited from across Asia, Europe, Latin America, the Middle East, North Africa, and North America, and were treated according to the local standard of care. Data from patients in the US subset were analyzed separately to permit comparisons between the US and non-US regions.

Eligibility Criteria

Patients with uHCC, and for whom a decision to treat with regorafenib had already been made before enrollment, were eligible to participate in the REFINE study if they met the criteria for regorafenib use according to local health authority-approved product information. Patients who participated in another investigational program with interventions outside of standard of care were excluded, as were patients who had previously been treated with regorafenib.

Study Endpoints

The primary study endpoint was the safety of regorafenib in patients with uHCC, defined as the frequency of documented treatment-emergent adverse events (TEAEs). TEAEs referred to any events that arose or worsened after initiating regorafenib until 30 days after last dose. Drug-related TEAEs referred to any TEAEs that were specifically related to regorafenib. TEAEs were classified by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 category, term, and worst CTCAE grade, and by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), preferred term (PT), and worst CTCAE grade.

Secondary endpoints were: overall survival (measured in days from start of treatment to date of death for any reason); progression-free survival (measured in days from start of treatment to date of first observed radiological or clinical disease progression); time to radiological or clinical progression (whichever was earlier, measured in days from start of

treatment to date of first documented disease progression); best overall tumor response; and duration of regorafenib treatment (measured in days from start of treatment to permanent discontinuation of regorafenib).

Tertiary endpoints were: duration of prior sorafenib treatment (measured in days from start of sorafenib treatment to date of permanent discontinuation of sorafenib); reasons for sorafenib discontinuation; response to sorafenib treatment; overall survival (measured in days from the start of sorafenib treatment to date of death due to any cause); frequency of adverse reactions experienced during treatment with sorafenib; and time from discontinuation of sorafenib to start of regorafenib.

Data Collection

Patients were screened and enrolled between December 22, 2017 and January 30, 2020, and the observation period ran from December 22, 2017 to March 15, 2022. Patients were observed from initiation of regorafenib therapy until disease progression, premature discontinuation, withdrawal of consent, death, or the end of the study (after at least 24 months of observation). Data were collected on AEs, patient demographics, baseline clinical characteristics, and treatment outcomes. Demographic and clinical data were collected from medical records or from interviewing patients. Treatment-related data were collected during the initial visit and during follow-up visits that occurred over the course of routine clinical care.

Statistical Analyses

Descriptive statistics were generated for all study variables for the overall study population and for the US subset. Categorical data are presented as counts and percentages. Continuous data are presented as mean, standard deviation (SD), median, and interquartile range (IQR). Kaplan–Meier estimates and curves were generated for time-to-event variables such as overall survival, progression-free survival, and time to progression. Data are presented descriptively for both the US and non-US subsets. Where 95% CIs are presented, these CIs are exploratory and have not been adjusted for multiple hypothesis testing.

Results

Baseline Demographics

The REFINE study comprised a total of 1005 patients, 65 of whom were from the US and 940 from countries other than the US. The majority of patients in the non-US subset (n=557, 59%) were from Asia (ie, China, Japan, Korea, Taiwan, and Thailand). Demographic information for both subsets is presented in Table 1. The majority of patients were male in both the US subset (n=51, 79%) and the non-US subset (n=784, 83%). The median age in the US subset was slightly younger (64 years, range: 49–86 years) than in the non-US subset (66 years; range: 21–94 years).

Table 1 Baseline Characteristics of Patients with uHCC Treated with Regorafenib as a Subsequent-Line Anti-Cancer Therapy

Characteristics	US Patients (n=65)	Non-US Patients (n=940)
Duration of observation (weeks)		
Median (Q1, Q3)	41.57 (21.29, 84.43)	41.00 (18.57, 80.71)
Information collection period (weeks)		
Median (Q1, Q3)	49.71 (22.43, 92.86)	44.36 (20.79, 86.79)
Age (years)		
Median (range)	64 (49–86)	66 (21–94)

(*Continued*)

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Table 1 (Continued).

Characteristics	US Patients (n=65)	Non-US Patients (n=940)
Sex, male, n (%)	51 (78.5)	784 (83.4)
Race, n (%)		
White	43 (66.2)	211 (22.4)
Black or African American	16 (24.6)	4 (0.4)
Asian	3 (4.6)	564 (60.0)
Unknown/not reported	3 (4.6)	161 (17.1)
Etiology, n (%)		
Alcohol use	22 (33.8)	228 (24.3)
Hepatitis C	34 (52.3)	208 (22.1)
Hepatitis B	3 (4.6)	379 (40.3)
Metabolic dysfunction-associated steatohepatitis	6 (9.2)	60 (6.4)
Genetic or metabolic reasons	1 (1.5)	28 (3.0)
Other	2 (3.1)	27 (2.9)
Unknown	9 (13.8)	100 (10.6)
Missing	2 (3.1)	24 (2.6)
Albumin-bilirubin grade, n (%)		
Grade 1	12 (18.5)	306 (32.6)
Grade 2	36 (55.4)	444 (47.2)
Grade 3	6 (9.2)	31 (3.3)
Missing	11 (16.9)	159 (16.9)
Child–Pugh classification, n (%)		
A	23 (35.4)	595 (63.3)
B	6 (9.2)	117 (12.4)
C	1 (1.5)	4 (0.4)
Not evaluable	2 (3.1)	24 (2.6)
Missing	33 (50.8)	200 (21.3)
ECOG PS, n (%)		
0/1	45 (69.2)	784 (83.4)
≥2	1 (1.5)	59 (6.3)
Missing	19 (29.2)	97 (10.3)

(*Continued*)

Table 1 (Continued).

Characteristics	US Patients (n=65)	Non-US Patients (n=940)
BCLC stage, n (%)		
0 (Very early stage)	0	2 (0.2)
A (Early stage)	2 (3.1)	11 (1.2)
B (Intermediate stage)	11 (16.9)	122 (13.0)
C (Advanced stage)	35 (53.8)	590 (62.8)
D (End-stage)	1 (1.5)	18 (1.9)
Missing	16 (24.6)	197 (21.0)
Metastases at study entry, n (%)		
Yes	31 (47.7)	560 (59.6)
No	34 (52.3)	379 (40.3)
Extrahepatic spread to lymph nodes, n (%)		
Yes	20 (64.5)	252 (45.0)
No	11 (35.5)	306 (54.6)
Missing	0	2 (0.4)
Distant extrahepatic spread, n (%)		
Yes	26 (83.9)	466 (83.2)
No	5 (16.1)	92 (16.4)
Missing	0	2 (0.4)
Location of metastasis, n (%)		
Adrenal gland	5 (16.1)	65 (11.6)
Bone	9 (29.0)	123 (22.0)
Brain	0	5 (0.9)
Gastrointestinal tract	0	6 (1.1)
Lung	13 (41.9)	274 (48.9)
Lymph node	6 (19.4)	178 (31.8)
Peritoneum	2 (6.5)	69 (12.3)
Spinal	4 (12.9)	10 (1.8)
Other	5 (16.1)	49 (8.8)
Vascular invasion, n (%)		
No	43 (66.2)	612 (65.1)
Yes	22 (33.8)	324 (34.5)
Missing	0	4 (0.4)

(*Continued*)

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Table 1 (Continued).

Characteristics	US Patients (n=65)	Non-US Patients (n=940)
Specification of vascular invasion, n (%)		
Number of patients (100%)	22	324
Hepatic vein invasion	7 (31.8)	72 (22.2)
Portal vein thrombosis	16 (72.7)	263 (81.2)
Lack of portal blood flow	1 (4.5)	8 (2.5)
Missing	0	3 (0.9)
Details of thrombosis, n (%)		
Number of patients (100%)	16	263
Segmental portal vein	3 (18.8)	77 (29.3)
Lobar portal vein	5 (31.3)	68 (25.9)
Portal vein trunk	5 (31.3)	78 (29.7)
Missing	3 (18.8)	40 (15.2)
Liver lesions, n (%)		
Yes	61 (93.8)	786 (83.6)
No	4 (6.2)	153 (16.3)
Missing	0	1 (0.1)
Total number of countable liver lesions		
Mean (SD)	3.9 (6.4)	4.6 (6.0)
Missing	0	69
Longest diameter of liver lesions ≥10 mm or 0.39 inches (cm)		
Number of patients (100%)	52	680
Mean (SD)	7.3 (6.2)	5.3 (4.0)
Missing	9	106
Alpha fetoprotein level, n (%)		
<400 ng/mL	21/35 (60.0)	374/626 (59.7)
≥400 ng/mL	14/35 (40.0)	252/626 (40.3)

Note: Baseline characteristics collected at the study entry.
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; Q, quartile; SD, standard deviation; uHCC, unresectable hepatocellular carcinoma; US, United States.

Baseline Clinical Characteristics

Patients' baseline clinical characteristics are presented in Table 1. Among patients in the US subset, HCC was most commonly associated with hepatitis C (n=34, 52%), alcohol use (n=22, 34%), and metabolic dysfunction-associated steatohepatitis (n=6, 9%). By contrast, among patients in the non-US subset, the most common etiology for HCC was hepatitis B, which accounted for 40% (n=379) of all cases, compared with 5% (n=3) of cases in the US subset. The

largest proportion of patients in both the US subset (n=36, 55%) and the non-US subset (n=444, 47%) had an albumin-bilirubin grade of 2.

Using BCLC staging, the majority of patients in both the US subset (n=35, 54%) and the non-US subset (n=590, 63%) were classified as being in an advanced stage of disease (ie, BCLC-C) at the time of study entry. However, BCLC stages were not available for 25% of patients (n=16) in the US subset and 21% of patients (n=197) in the non-US subset.

Using the Child–Pugh score, fewer patients in the US subset (n=23, 35%) were classified as Class A at the time of study entry than in the non-US subset (n=595, 63%). Child–Pugh scores were not available for 51% of patients (n=33) in the US subset and 21% (n=200) in the non-US subset at the time of study entry.

A smaller proportion of patients in the US subset (n=45, 69%) than the non-US subset (n=784, 83%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 at the time of study entry. ECOG performance status was not available for 29% of patients (n=19) in the US subset and 10% of patients (n=97) in the non-US subset.

At the time of study entry, a smaller proportion of patients in the US subset (n=31, 48%) than the non-US subset (n=560, 60%) had metastases. Sites of metastases are presented in Table 1.

Baseline Treatment Characteristics

Baseline treatment characteristics are presented in Table 2. Fewer patients in the US subset (n=57, 88%) than the non-US subset (n=908, 97%) had a history of prior treatment with sorafenib. The majority of patients in both the US subset (n=46, 71%) and the non-US subset (n=802, 85%) received regorafenib as a second-line treatment, while 28% of patients in the US subset (n=18) and 14% of patients in the non-US subset (n=127) received regorafenib as a third-line treatment. A smaller proportion of patients (n=2, 3%) in the US subset had a history of prior systemic therapy other than sorafenib compared with the non-US subset (n=65, 7%).

Table 2 Treatment Characteristics of Patients with uHCC Treated with Regorafenib as a Subsequent-Line Anti-Cancer Therapy

Treatment Characteristics	US Patients (n=65)	Non-US Patients (n=940)
Time between diagnosis of uHCC and start of regorafenib (months)		
Median (Q1, Q3)	16.98 (8.84, 33.80)	25.26 (11.10, 47.11)
Time since most recent progression/relapse to start of regorafenib		
Median (Q1, Q3)	1.22 (0.62, 3.78)	0.59 (0.23, 1.31)
Treatment line, n (%)		
Regorafenib as first-line treatment	1 (1.5)	11 (1.2)
Regorafenib as second-line treatment	46 (70.8)	802 (85.3)
Regorafenib as ≥ third-line treatment	18 (27.7)	127 (13.5)
Patients with prior sorafenib therapy, n (%)		
Yes	57 (87.7)	908 (96.6)
Patients with prior multikinase inhibitor other than sorafenib, n (%)		
Yes	8 (12.3)	57 (6.1)
Patients with prior immune checkpoint inhibitor, n (%)		
Yes	16 (24.6)	81 (8.6)

(*Continued*)

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Table 2 (Continued).

Treatment Characteristics	US Patients (n=65)	Non-US Patients (n=940)
Patients with other prior immunotherapy, n (%)		
Yes	2 (3.1)	5 (0.5)
Patients with other prior systemic therapy, n (%)		
Yes	2 (3.1)	65 (6.9)
Any prior non-systemic anti-cancer therapy, n (%)		
Yes	37 (56.9)	709 (75.4)
Prior procedures, n (%)		
Hepatectomy, partial	2 (3.1)	193 (20.5)
Hepatic artery infusion	0	44 (4.7)
Percutaneous ethanol injection	1 (1.5)	40 (4.3)
Thermal ablation	11 (16.9)	228 (24.3)
Transarterial chemoembolization	27 (41.5)	557 (59.3)
Transplantation	4 (6.2)	20 (2.1)
Other	7 (10.8)	77 (8.2)
Embolization agents used, n (%)		
Gelatin foam	1 (1.5)	169 (18.0)
Microspheres	16 (24.6)	120 (12.8)
Lipiodol	5 (7.7)	425 (45.2)
Any prior radiotherapy, n (%)		
Yes	18 (27.7)	232 (24.7)
Type of radiotherapy, n (%)		
Brachytherapy	2 (3.1)	23 (2.4)
External-beam radiation therapy	4 (6.2)	57 (6.1)
Gamma knife	0	11 (1.2)
Stereotactic	5 (7.7)	51 (5.4)
Transarterial radioembolization	5 (7.7)	23 (2.4)
Other	4 (6.2)	72 (7.7)

Abbreviations: Q, quartile; uHCC, unresectable hepatocellular carcinoma; US, United States.

The majority of patients in both the US subset (n=37, 57%) and the non-US subset (n=709, 75%) had received some form of non-systemic anti-cancer therapy before study entry. Transarterial chemoembolization was the most common prior non-systemic anti-cancer therapy received by patients in both groups but was reported less commonly by patients in the US subset (n=27, 42%) than patients in the non-US subset (n=557, 59%). A further 17% of patients in the US subset (n=11) and 24% in the non-US subset (n=228) had received thermal ablation. Partial hepatectomy was more common in the non-US subset, where it was received by 21% of patients (n=193) compared with 3% of patients in the US subset (n=2).

Approximately one-quarter of patients in both the US subset (n=18, 28%) and the non-US subset (n=232, 25%) received prior radiotherapy. In the US subset, 8% of patients (n=5) had received transarterial radioembolization, compared with 2% of patients in the non-US subset (n=23).

Characteristics of Patients in the US Subset with Prior Sorafenib Treatment

Among patients in the US subset, 57 (88%) were previously treated with sorafenib (Supplementary Table 1). Of these patients, 30% (n=17) were classified as Child–Pugh Class A at the time of initial treatment with sorafenib, and the majority (n=34, 60%) had an ECOG performance score of 0 or 1. Nearly one-third (n=18, 32%) of patients who had received prior sorafenib treatment were classified as BCLC-C at the time of initial treatment with sorafenib, indicating advanced-stage disease.

The median time between initial diagnosis of uHCC and initiation of sorafenib treatment was 4.6 months (IQR: 1.5–22.0) and the median sorafenib treatment duration was 4.1 months (IQR: 2.7–7.6). The median initial daily sorafenib dose for patients in this subgroup was 800 mg (IQR: 400–800) and 44% of patients in this subgroup (n=25) had their initial dose changed over the course of treatment.

Over half of patients (n=30, 53%) in this subgroup experienced sorafenib-related side effects (Supplementary Table 2). Common AEs included fatigue (n=17, 30%), diarrhea (n=14, 25%), hand-foot skin reaction (HFSR; n=14, 25%), decreased appetite (n=7, 12%), and secondary hypertension (n=4, 7%). The main reason for discontinuation of sorafenib treatment was disease progression/relapse (n=36, 63%) followed by AEs (n=10, 18%) and switching to another treatment (n=9, 16%) (Supplementary Table 1).

Most patients in this subgroup (n=47, 83%) demonstrated tumor progression during treatment with sorafenib, and the majority of patients (n=29, 51%) demonstrated progression of the target lesion (Table 3). The median time from start of treatment to tumor progression during or after sorafenib treatment was 3.66 months.

Characteristics of Patients in the US Subset with Prior Systemic Anti-Cancer Treatment Other Than Sorafenib Treatment

Among patients in the US subset who had a history of prior treatment with systemic anti-cancer therapies other than sorafenib (n=24, 37%), 54% (n=13) had previously received nivolumab and 29% (n=7) had previously received lenvatinib (Supplementary Table 3).

Table 3 Treatment Responses in Patients in the US Subset Previously Treated with Sorafenib

Prior Sorafenib Treatment, n (%)	**US (n=57)**
Complete response	2 (3.5)
Partial response	1 (1.8)
Stable disease	8 (14.0)
Progressive disease by clinical judgment	12 (21.1)
Progressive disease by response assessment criteria	25 (43.9)
Unknown	6 (10.5)
Not evaluable	3 (5.3)
Tumor progression during or after treatment with sorafenib, n (%)	
Yes	47 (82.5)
No	10 (17.5)

(*Continued*)

Table 3 (Continued).

Prior Sorafenib Treatment, n (%)	US (n=57)
Type of progression (multiple responses), n (%)	
New lesion	19 (33.3)
New vascular invasion	5 (8.8)
Progression of target lesion	29 (50.9)
Missing	10 (17.5)
Location of progression, n (%)	
Liver	9 (15.8)
Extrahepatic	10 (17.5)
Missing	38 (66.7)
Radiologically confirmed progression, n (%)	
Yes	44 (77.2)
No	3 (5.3)
Missing	10 (17.5)

Abbreviation: US, United States.

Less than half of patients in this subgroup (n=10, 42%) experienced treatment-related side effects with these other agents (Supplementary Table 4). These side effects included fatigue (n=6, 25%), rash (n=3, 13%), diarrhea (n=2, 8%), peripheral swelling (n=2, 8%), and HFSR (n=1, 4%). The most common reasons for discontinuation of therapies other than sorafenib were progression or relapse of HCC (n=15, 63%) and switching to other treatments (n=8, 33%) (Supplementary Table 3).

Tumor progression was documented in 84% of patients in this subgroup (n=20) (Supplementary Table 5). The most common type of tumor progression was progression of the target lesion (n=17, 71%).

Safety Profile of Regorafenib Treatment

The majority of patients in both the US subset (n=59, 91%; 95% CI: 81.0–96.5) and the non-US subset (n=862, 92%; 95% CI: 89.8–93.4) experienced at least one TEAE (Table 4). A larger proportion of patients in the US subset (n=43, 66%) than in the non-US subset (n=497, 53%) reported TEAEs of CTCAE grade 3 or higher. A larger proportion of patients in the US subset (n=29, 45%) than the non-US subset (n=345, 37%) reported serious TEAEs. Over one-quarter of patients (n=19, 29%) in the US subset and 31% of patients (n=292) in the non-US subset experienced TEAEs that led to permanent discontinuation of regorafenib. Eight patients in the US subset (12%) and 138 patients in the non-US subset (15%) died as a result of a TEAE (Grade 5).

Commonly reported TEAEs for both subsets included gastrointestinal disorders (US subset: n=30, 46%; non-US subset: n=506, 54%), fatigue (US subset: n=17, 26%; non-US subset: n=183, 20%), decreased appetite (US subset: n=11, 17%; non-US subset: n=166, 18%), and HFSR (US subset: n=8, 12%; non-US subset: n=321, 34%). The full list of TEAEs is presented in Supplementary Table 6.

Drug-related TEAEs were reported by fewer patients in the US subset (n=45, 69%; 95% CI: 56.6–80.1) than in the non-US subset (n=701, 75%; 95% CI: 33.6–39.9; Table 4). Grade 3 drug-related TEAEs were the worst grade experienced by 26% of patients in the US subset (n=17) and 25% of patients in the non-US subset (n=232). In the US subset, 19% of patients (n=12) experienced a drug-related TEAE that led to permanent discontinuation of regorafenib, compared with 16% of patients (n=149) in the non-US subset. No patients in the US subset and <1% of patients (n=7) in

Table 4 Incidence of TEAEs and Drug-Related TEAEs in Regorafenib-Treated Patients

TEAE Summary	US (n=65)	Non-US (n=940)
Any TEAE, n (%)	59 (90.8) (95% CI: 81.0–96.5)	862 (91.7) (95% CI: 89.8–93.4)
Grade 1	7 (10.8)	97 (10.3)
Grade 2	7 (10.8)	261 (27.8)
Grade 3	33 (50.8)	315 (33.5)
Grade 4	2 (3.1)	44 (4.7)
Grade 5 (death)	8 (12.3)	138 (14.7)
Not gradable	2 (3.1)	5 (0.5)
Missing	0	2 (0.2)
Serious TEAE, n (%)	29 (44.6) (95% CI: 32.3–57.5)	345 (36.7) (95% CI: 33.6–39.9)
TEAE leading to dose modification[a], n (%)	25 (38.5)	425 (45.2)
TEAE leading to dose reduction, n (%)	5 (7.7)	259 (27.6)
TEAE leading to permanent discontinuation of regorafenib, n (%)	19 (29.2)	292 (31.1)
Any drug-related[b] TEAE, n (%)	45 (69.2) (95% CI: 56.6–81.1)	701 (74.6) (95% CI: 71.7–77.3)
Grade 1	14 (21.5)	142 (15.1)
Grade 2	12 (18.5)	298 (31.7)
Grade 3	17 (26.2)	232 (24.7)
Grade 4	0	12 (1.3)
Grade 5 (death)	0	7 (0.7)
Not gradable	2 (3.1)	8 (0.9)
Missing	0	2 (0.2)
Serious drug-related TEAE, n (%)	5 (7.7) (95% CI: 2.5–17.1)	85 (9.0) (95% CI: 7.3–11.1)
Drug-related TEAE leading to dose modification[a], n (%)	21 (32.3)	351 (37.3)
Drug-related TEAE leading to dose reduction, n (%)	4 (6.2)	228 (24.3)
Drug-related TEAE leading to permanent discontinuation of regorafenib, n (%)	12 (18.5)	149 (15.9)

Notes: [a]Modifications include interruptions and reductions; [b]Drug-related: related to regorafenib.
Abbreviations: TEAE, treatment-emergent adverse event; US, United States.

the non-US subset died as the result of a drug-related TEAE. Common drug-related TEAEs included diarrhea (US subset: n=9, 14%; non-US subset: 249, 27%), HFSR (US subset: n=8, 12%, non-US subset: n=301, 32%), and fatigue (US subset: n=12, 19%; non-US subset: n=139, 15%) (Supplementary Table 6).

Response to Regorafenib Treatment

Treatment responses to regorafenib are presented in Table 5. The disease control rate was 38% (n=25; 95% CI: 26.7–51.4) in the US subset and 54% (n=499; 95% CI: 50.3–56.8) in the non-US subset. By contrast, 35% of patients

Table 5 Overall Regorafenib Treatment Response

Response Categories n (%, 95% CI)	US (n=65)	Non-US (n=932)
Complete response	3 (4.62)	20 (2.15)
Partial response	9 (13.85)	106 (11.37)
Stable disease	13 (20.00)	373 (40.02)
Progressive disease	23 (35.38)	247 (26.50)
Overall response rate (complete response + partial response)	12 (18.46)	126 (13.52)
Disease control rate (complete response + partial response + stable disease)	25 (38.46)	499 (53.54)

Abbreviations: CI, confidence interval; US, United States.

(n=23; 95% CI: 23.9–48.2) in the US subset and 27% of patients (n=247; 95% CI: 23.7–29.5) in the non-US subset experienced progressive disease as their best response. These unadjusted CIs suggest no significant differences between subgroups.

Among patients in the US subset, the most common reasons for regorafenib discontinuation were AEs (n=27, 42%) and disease progression (n=25, 39%) (Supplementary Table 7). Of the 57 patients who had received prior treatment with sorafenib, 98% discontinued regorafenib treatment. The most common reasons for regorafenib treatment discontinuation among this subgroup were AEs (40%) and progressive disease (40%).

Overall Survival

The median overall survival from start of regorafenib until death for patients in the US subset was 11.4 months (95% CI: 8.4–18.0) compared with 13.2 months (95% CI: 11.7–14.9) in the non-US subset (Table 6). The median progression-free survival was 3.4 months (IQR: 2.4–6.1) for patients in the US subset and 3.9 months (IQR: 2.2–8.5) in the non-US subset. The median overall survival from time of prior sorafenib initiation in the US subset was 25.4 months.

Discussion

In this evaluation of real-world safety and effectiveness outcomes, regorafenib was associated with similar overall survival and progression-free survival for patients in both the US and non-US subsets of the REFINE study. Among patients in the US subset who had previously received sorafenib, overall survival and progression-free survival were similar to that seen in the US and non-US subsets. Similar TEAE types and severity were reported between the US and non-US subsets, and reported TEAEs were also similar to those reported in the RESORCE trial (eg, HFSR, fatigue, diarrhea).[9] Moreover, overall survival from sorafenib initiation was nearly identical to overall survival from first-line therapy among patients in the RESORCE trial (25.4 months in REFINE vs 26 months in RESORCE).

As HCC etiology and baseline characteristics of patients in the non-US subset may differ from those in the US subset, this sub-analysis helps to address these concerns and may offer useful insights for clinicians working in the US context and provide insights for the design of future global second-line studies in advanced HCC. While overall rates of TEAEs were similar between patients in the US and non-US subsets, some differences were observed. A lower proportion of patients in the US subset experienced HFSR, which may be due to racial differences or differences in approaches to treatment or side-effect management between physicians in the US and elsewhere.[14] Differences were also noted between the US subset and the non-US subset in terms of overall survival and progression-free survival. This may be explained by the larger proportion of patients in the US subset who had documented extrahepatic spread and liver lesions at the time of study enrollment, or by the larger proportion of patients in the US subset who received regorafenib as a later-line therapy. There were also differences between the US and non-US subsets in terms of the etiology of HCC. The large number of patients in the non-US subset whose liver cancer was attributed to hepatitis B is reflective of the higher burden of hepatitis B in settings outside the US.[15]

Table 6 Overall Treatment Effectiveness of Regorafenib in Patients in the US and Non-US Subsets

Variable	US (n=65)	Non-US (n=940)
Overall survival		
Events, n (%)	47 (72.3)	585 (62.2)
Censored, n (%)	18 (27.7)	355 (37.8)
Median (months)	11.4	13.2
95% CI	8.4–18.0	11.7–14.9
	US (n=65)	**Non-US (n=932)**
Progression-free survival		
Events, n (%)	60 (92.3)	813 (87.2)
Censored, n (%)	5 (7.7)	119 (12.8)
Median (months)	3.4	3.9
95% CI	2.9–4.4	3.6–4.2
	US (n=65)	**Non-US (n=932)**
Treatment duration		
Events, n (%)	61 (93.8)	868 (92.3)
Censored, n (%)	4 (6.2)	72 (7.7)
Median (months)	3.1	3.8
95% CI	2.6–3.8	3.4–4.2
Subset of patients with prior sorafenib treatment		
Overall survival	**US (n=57)**	**Non-US (n=908)**
Events, n (%)	43 (75.4)	565 (62.2)
Censored, n (%)	14 (24.6)	343 (37.8)
Median (months)	11.4	13.2
95% CI	8.3–18.0	12.0–15.0
Progression-free survival	**US (n=57)**	**Non-US (n=900)**
Events, n (%)	54 (94.7)	789 (87.7)
Censored, n (%)	3 (5.3)	111 (12.3)
Median (months)	3.3	3.9
95% CI	2.8–4.3	3.6–4.2
Overall survival from start of prior sorafenib	**US (n=57)**	
Events, n (%)	43 (75.4)	
Censored, n (%)	14 (24.6)	
Median (months)	25.4	
95% CI	15.9–30.1	

Abbreviations: CI, confidence interval; US, United States.

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As the treatment landscape for HCC becomes more diverse, including two recently approved first-line immunotherapies for HCC,[16,17] there is a need for real-world evidence that can help to inform clinicians' treatment decisions for second-line options. Since the RESORCE trial, several second-line therapies have been approved for use following treatment with sorafenib, including cabozantinib,[18] pembrolizumab,[19] ramucirumab,[20] and nivolumab + ipilimumab.[21] In randomized, phase 3, placebo-controlled clinical trials,[22,23] these treatments demonstrated improvements in overall survival for patients who had been previously treated with sorafenib. The results of the current study build on the existing evidence base and suggest that treatment with regorafenib with or without prior sorafenib treatment is effective and does not introduce any additional safety concerns in a real-world clinical setting. Future research should seek to further evaluate the safety of regorafenib and other first-line treatments as a subsequent-line therapy, with a particular focus on AE management and resolution to maintain patient quality of life.

Limitations

The limitations of this global study primarily arise from the observational nature of the research. High rates of missing data such as those seen in the BCLC, Child–Pugh, and ECOG performance status scores are a challenge specific to real-world data. In this case, the missing Child–Pugh and ECOG data may be due in part to the fact that these scores are not routinely collected in real-world settings like they are in clinical trials. In addition, assessment of response and intervals were based on physician practice and interpretation.

The observational nature of this study means that it may also be vulnerable to selection bias and differences in treatment and reporting standards between study sites. To reduce this risk, physicians were encouraged to sample consecutive patients. Nonetheless, the results of this study must be interpreted carefully.

As this study was descriptive in nature, CIs generated to compare the US and non-US subsets were not adjusted for multiple hypothesis testing, limiting our ability to draw conclusions about statistical differences between the two subsets. Furthermore, this small sample size limits our ability to draw specific conclusions about the effectiveness of regorafenib as a subsequent-line treatment in the broader US HCC population.

Finally, the treatment landscape for HCC has changed since this study was conducted. Increasingly, patients receive immuno-oncology therapies first-line instead of systemic therapies. Additional real-world datasets should evaluate the effectiveness of regorafenib as a subsequent-line therapy following immuno-oncology treatment.

Conclusion

The diverse HCC treatment landscape underscores the importance of real-world evidence to help clinicians decide what treatment option is best for their patients. This sub-analysis of the REFINE study demonstrates comparable TEAEs, overall survival and progression-free survival between US and non-US subsets, as well as consistent findings with the RESORCE trial. These findings provide further real-world evidence supporting the safety and effectiveness of regorafenib as a treatment in US patients with uHCC.

Abbreviations

AE, adverse event; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HFSR, hand-foot skin reaction; HR, hazard ratio; IQR, interquartile range; IRB, Institutional Review Board; KM, Kaplan–Meier; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SD, standard deviation; SOC, System Organ Class; TEAE, treatment-emergent adverse event; uHCC, unresectable hepatocellular carcinoma; US, United States.

Data Sharing Statement

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, timepoint, and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in patients for medicines and indications

approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal.

Data access will be granted to anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Ethics Approval

Institutional Review Board (IRB) approval for this analysis was obtained from the WCG IRB, Washington USA (IRB #20172750). This trial complies with the Declaration of Helsinki (2013 revision). All patients provided written informed consent. This trial is registered with ClinicalTrials.gov (NCT03289273).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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