Sequential treatment with sorafenib followed by regorafenib in patients with unresectable hepatocellular carcinoma: Interim analysis of the observational REFINE study

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INTRODUCTION

- Regorafenib is an oral multikinase inhibitor approved for the treatment of patients with hepatocellular carcinoma (HCC) who previously received sorafenib[1,2]
- In the randomized, controlled, phase 3 RESORCE trial, regorafenib improved overall survival (OS) vs placebo in patients who had disease progression on prior sorafenib[3,4]
  - Median OS was 10.6 vs 7.8 months (hazard ratio 0.62; 95% confidence interval [CI] 0.50, 0.78; one-sided P<0.0001)
  - The most frequent grade 3 or 4 drug-related treatment-emergent adverse events (TEAEs) were hypertension, hand–foot skin reaction (HFSR; palmar–plantar erythrodysesthesia), increased blood bilirubin, and fatigue
  - Patients must have tolerated sorafenib (i.e. received sorafenib ≥400 mg daily for at least 20 of the 28 days before discontinuation) and received their last sorafenib dose within 10 weeks of randomization
- REFINE is an ongoing, prospective, observational, post-authorization safety study designed to evaluate the safety and effectiveness of regorafenib in patients with HCC in real-world practice
- A planned interim analysis of REFINE was carried out after the first 500 patients had been in the study for at least 4 months[5]

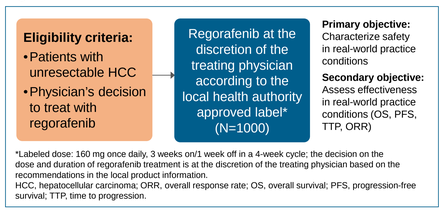
AIM

- To analyze patients included in the REFINE interim analysis who received prior sorafenib

METHODS

- REFINE (NCT03289273) is a prospective, observational study that is ongoing in countries across Europe, North America, Asia, Latin America, the Levant, the Middle East, and North Africa (**Figure 1**)
- The study recruited patients with unresectable HCC for whom the decision to treat with regorafenib was made prior to enrollment by the treating physician according to the local health authority approved label
- The primary objective is to evaluate safety, as assessed by the incidence of TEAEs, coded using the Medical Dictionary for Regulatory Activities and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03
- Secondary outcomes include OS and progression-free survival; tumor response and progression are assessed by the treating physician according to the local standard
- The frequency of assessments is not defined and occurs according to the treating physician's routine practice
- Data will be collected from approximately 1000 patients
- The cut-off date for the interim analysis was November 11, 2019

Figure 1. REFINE study design



*Labeled dose: 160 mg once daily, 3 weeks on/1 week off in a 4-week cycle; the decision on the dose and duration of regorafenib treatment is at the discretion of the treating physician based on the recommendations in the local product information.
HCC, hepatocellular carcinoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.

RESULTS

- Of the 500 patients enrolled and observed for ≥4 months, 498 received regorafenib and were evaluable
- Most patients (67%) had Child–Pugh class A liver disease; 11% and 1% had Child–Pugh class B and C disease, respectively (the Child–Pugh score was missing or not evaluable in 21% of patients)
- The proportions of patients with Eastern Cooperative Oncology Group performance status (ECOG PS) 0, 1, and 2–4 were 42%, 40%, and 5%, respectively (the ECOG PS was missing or not evaluable in 13% of patients)
- Most patients (98%; n=490) had received prior systemic therapy; 97% (n=482) had received prior sorafenib (**Table 1**)
- Regorafenib was second-line treatment in 81% of patients (n=403), third line or higher in 17% (n=87), and first line in 2% (n=8) (**Table 1**)
- Of the 403 patients who received regorafenib second line, 398 (99%) had received prior sorafenib
- Among all treated patients (N=498), 57% (n=286) initiated regorafenib at a daily dose of 160 mg, 13% (n=63) at 120 mg, 28% (n=141) at 80 mg, and 2% (n=8) at 40 mg

Table 1. Prior systemic anticancer therapy – all treated patients

n (%)	Regorafenib (N=498)
Prior systemic anticancer therapy	
Any	490 (98)
Sorafenib	482 (97)
Multikinase inhibitor other than sorafenib	18 (4)
Immune checkpoint inhibitor*	49 (10)
Other immunotherapy	2 (<1)
Other systemic therapy	43 (9)
Number of prior treatment lines before regorafenib	
0	8 (2)
1	403 (81)
≥2	87 (17)

*The most common immune checkpoint inhibitor received was nivolumab.

Prior sorafenib treatment

- Of the 482 patients who received sorafenib in any prior line of therapy:
  - The median duration of prior sorafenib was 4.8 months (interquartile range 2.5–9.6) (**Table 2**)
  - 45% of patients (n=216) had a last daily sorafenib dose of 800 mg (**Table 2**)
  - 8% of patients (n=40) had an adverse event leading to sorafenib discontinuation (defined as sorafenib-intolerant patients) (**Table 3**)
  - At study entry, the proportions of patients with Child–Pugh class A, B, and C liver disease were 67%, 12%, and 1%, respectively (**Table 4**)

Safety

- Among all regorafenib-treated patients (N=498), the most frequent TEAEs (any grade) were HFSR (30%), diarrhea (21%), fatigue (16%), and decreased appetite (14%)
- In sorafenib-intolerant patients, the most frequent TEAEs (any grade) with regorafenib were diarrhea, HFSR, abdominal pain, and decreased appetite (**Table 5**)

Table 2. Prior sorafenib treatment duration and dosing

	Regorafenib (n=482)*
Duration of prior sorafenib	
n	454
Median, months (IQR)	4.8 (2.5–9.6)
Initial daily dose of prior sorafenib (mg), n (%)	
200	10 (2)
400	134 (28)
600	5 (1)
800	327 (68)
Missing	6 (1)
Modifications to initial dose of prior sorafenib, n (%)	
Yes	235 (49)
No	238 (49)
Missing	9 (2)
Last daily dose of prior sorafenib (mg), n (%)	
100	1 (<1)
200	30 (6)
400	170 (35)
600	54 (11)
800	216 (45)
Missing	11 (2)
Primary reason for discontinuation of prior sorafenib, n (%)	
Progression, recurrence/relapse of HCC	367 (76)
Switch to other treatment	69 (14)
Adverse event/toxicity	32 (7)
Patient decision	4 (1)
Other	6 (1)
Missing	4 (1)

*Patients who received sorafenib at any time prior to treatment with regorafenib in REFINE.
HCC, hepatocellular carcinoma; IQR, interquartile range.

Table 3. Sorafenib-related adverse events during prior sorafenib

Sorafenib-related adverse event (any grade), n (%)	Regorafenib (n=482)*
Any	370 (77)
Most common	
HFSR	228 (47)
Diarrhea	168 (35)
Fatigue	116 (24)
Hypertension	101 (21)
Decreased appetite	73 (15)
Leading to sorafenib dose modification†	186 (39)
Leading to discontinuation of sorafenib‡	40 (8)

*Patients who received sorafenib at any time prior to treatment with regorafenib in REFINE; †Dose reduction or treatment interruption; ‡The most frequent adverse events leading to discontinuation were HFSR (n=16), diarrhea (n=11), and fatigue (n=11).
HFSR, hand–foot skin reaction.

Table 4. Child–Pugh class and ALBI grade at study entry in REFINE in patients who received prior sorafenib

n (%)	Regorafenib (n=482)*
Child–Pugh class	
A	324 (67)
B	56 (12)
C	4 (1)
Missing/not evaluable	98 (20)
ALBI grade	
1	165 (34)
2	254 (53)
3	18 (4)
Missing	45 (9)

*Patients who received sorafenib at any time prior to treatment with regorafenib in REFINE.
ALBI, albumin–bilirubin.

Table 5. TEAEs (any grade) during regorafenib treatment in sorafenib-intolerant patients

n (%)†	Regorafenib (n=40)*
Any TEAE	38 (95)
Diarrhea	10 (25)
HFSR	8 (20)
Abdominal pain	6 (15)
Decreased appetite	5 (13)
Fatigue	4 (10)
Hypertension	4 (10)

*Patients who discontinued sorafenib due to an adverse event prior to treatment with regorafenib in REFINE; †Individual events listed are those that occurred in ≥10% of patients.
HFSR, hand–foot skin reaction; TEAE, treatment-emergent adverse event.

Effectiveness

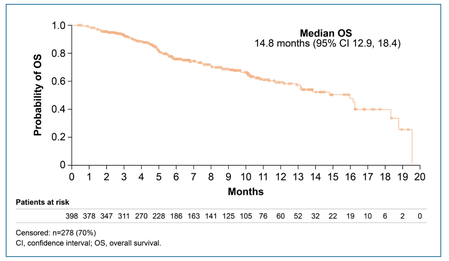
- Median OS was 14.8 months (95% CI 12.9, 18.4) in patients who received regorafenib as second-line treatment after sorafenib (**Table 6**, **Figure 2**)

Table 6. OS from the start of regorafenib by treatment line

Regorafenib	n	Censored, n (%)	Median OS (95% CI), months†
Any line*	498	343 (69)	13.2 (11.4, 16.3)
Any line after sorafenib	482	330 (68)	13.9 (11.4, 16.3)
Second line after sorafenib	398	278 (70)	14.8 (12.9, 18.4)
Third or higher line	87	54 (62)	8.3 (6.7, 12.3)

*Includes patients who received regorafenib first line (n=8) or second line after agents other than sorafenib (n=5); †From the start of regorafenib treatment.
CI, confidence interval; OS, overall survival.

Figure 2. OS from the start of regorafenib in patients who received regorafenib second line after sorafenib (n=398)



Censored: n=278 (70%)
CI, confidence interval; OS, overall survival.

- In patients who received prior sorafenib at any time (n=482), median OS (95% CI) from the start of regorafenib was 16.0 months (13.1, 18.8) in patients with Child–Pugh A disease and 8.0 months (5.2, not estimated) in patients with Child–Pugh B disease (**Table 7**)

Table 7. OS from the start of regorafenib by Child–Pugh class and ALBI grade at study entry in patients who received prior sorafenib*

	n	Censored, n (%)	Median OS (95% CI), months
Child–Pugh class†			
A	324	236 (73)	16.0 (13.1, 18.8)
B	56	32 (57)	8.0 (5.2, NE)
ALBI grade‡			
1	165	139 (84)	19.6 (14.8, 19.6)
2	254	158 (62)	10.5 (8.7, 16.0)
3	18	7 (39)	3.1 (1.6, 8.7)

*Patients who received sorafenib at any time prior to treatment with regorafenib in REFINE (n=482); †Patients with Child–Pugh class C (n=4) or missing/not evaluable data (n=98) are not shown; ‡Patients with missing ALBI grade (n=45) are not shown.
ALBI, albumin–bilirubin; CI, confidence interval; NE, not estimated; OS, overall survival.

CONCLUSIONS

- In this interim analysis of the observational REFINE study, most patients received regorafenib second line after sorafenib versus other lines of therapy
- Most patients who received regorafenib had tolerated prior sorafenib
  - Only 8% of patients who received prior sorafenib were sorafenib-intolerant
- The patient population is broader than that of the phase 3 RESORCE trial, reflecting the less stringent inclusion criteria of a real-world study; REFINE includes more patients with Child–Pugh B liver disease, and includes patients with ECOG PS ≥2 and sorafenib-intolerant patients[3]
- Despite the more varied patient population, the safety profile of regorafenib was consistent with that reported in RESORCE, with no unexpected safety signals[3]
- The effectiveness of regorafenib was consistent with the results of RESORCE[3]; median OS in patients who received regorafenib second line after sorafenib was longer than in RESORCE, but there was a high proportion of censored patients in this interim analysis
- In a preliminary analysis of OS, including a high percentage of censored patients, patients with Child–Pugh A liver disease receiving regorafenib as second- or later-line treatment after sorafenib were observed to have a longer median OS than reported in RESORCE[3]

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