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Baseline Liver Function and Outcomes in the Phase 3 REFLECT Study in Patients With Unresectable Hepatocellular Carcinoma Treated With Lenvatinib or Sorafenib: Assessment of Overall Survival, Progression-free Survival, Objective Response Rate and Safety

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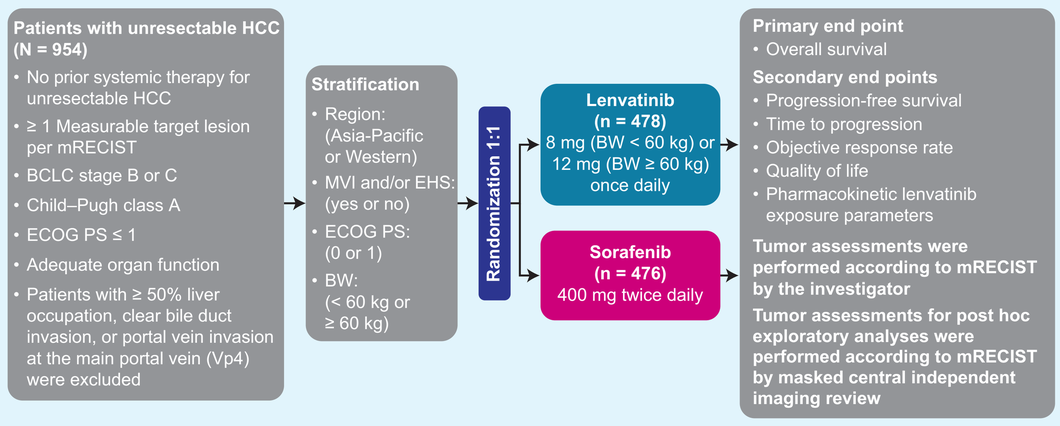
INTRODUCTION

- Underlying liver function affects prognosis in patients with hepatocellular carcinoma (HCC), and several markers of liver function have been identified as independent markers of poor prognosis:[1]
  - Child–Pugh score and albumin–bilirubin (ALBI) grade are 2 measures that have been reported to be prognostic indicators in patients with HCC.[2]
  - Child–Pugh score, originally used to estimate mortality risk for patients undergoing surgery for bleeding esophageal varices, has since been developed as a prognostic indicator for patients with chronic liver disease and cirrhosis.[2,3]
- Lenvatinib is a multikinase inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT.[4–7] It is approved in multiple countries for first-line treatment of unresectable HCC (uHCC).[8,9]
- In the phase 3 randomized, multicenter, open-label, noninferiority REFLECT study, lenvatinib demonstrated noninferiority to sorafenib in the first-line treatment of patients with uHCC:[10]
  - The median overall survival (OS) for patients who received lenvatinib was 13.6 months (95% confidence interval [CI] 12.1–14.9), and for patients who received sorafenib, the median OS was 12.3 months (95% CI 10.4–13.9); hazard ratio (HR) 0.92 (95% CI 0.79–1.06).
- In this post hoc analysis, we report the efficacy and safety outcomes for patients in REFLECT, stratified by baseline liver function.

METHODS

- This post hoc retrospective analysis includes patients who took part in REFLECT. Details of REFLECT methodology have been previously published[10] (**Figure 1**).

Figure 1. Study Design of REFLECT



BCLC, Barcelona Clinic Liver Cancer; BW, body weight; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; HCC, hepatocellular carcinoma; mRECIST, modified Response Evaluation Criteria In Solid Tumors; MVI, macroscopic portal vein invasion.

- For this analysis, efficacy and safety outcomes for patients were stratified by baseline liver function (ALBI grade 1 or 2, or Child–Pugh score 5 or 6):
  - Efficacy analyses included OS, progression-free survival (PFS), objective response rate (ORR), and time to deterioration to Child–Pugh class B.
  - For OS and PFS, medians were estimated with the Kaplan–Meier method and each HR was estimated using a Cox model.
  - For ORR, 95% CIs were calculated using asymptotic normal approximation.
  - For time to deterioration to Child–Pugh class B, medians were estimated with the Kaplan-Meier method and 95% CIs were constructed with a generalized Brookmeyer and Crowley method.
  - Tumor responses were assessed by independent imaging review per modified Response Evaluation Criteria In Solid Tumors (mRECIST).

RESULTS

Patient Disposition

- Of the 954 patients with uHCC enrolled in REFLECT, 478 were randomized to lenvatinib and 476 were randomized to sorafenib.
- Baseline liver function is summarized in **Table 1**.
  - Fewer patients with ALBI grade 1 (66.5%), and more patients with ALBI grade 2 (33.1%), received lenvatinib compared with sorafenib (ALBI grade 1, 71.4%; ALBI grade 2, 28.2%).

Table 1. Baseline Liver Function in Patients Randomized to Lenvatinib or Sorafenib

Parameter, n[a] (%)	Lenvatinib (n = 478)	Sorafenib (n = 476)
Baseline ALBI grade		
1	318 (66.5)	340 (71.4)
2	158 (33.1)	134 (28.2)
Baseline Child–Pugh score		
5	368 (77.0)	357 (75.0)
6	107 (22.4)	114 (23.9)

[a]Only patients with ALBI grade 1 or 2 and Child–Pugh score 5 or 6 were included in the analysis.
ALBI, albumin–bilirubin.

Efficacy

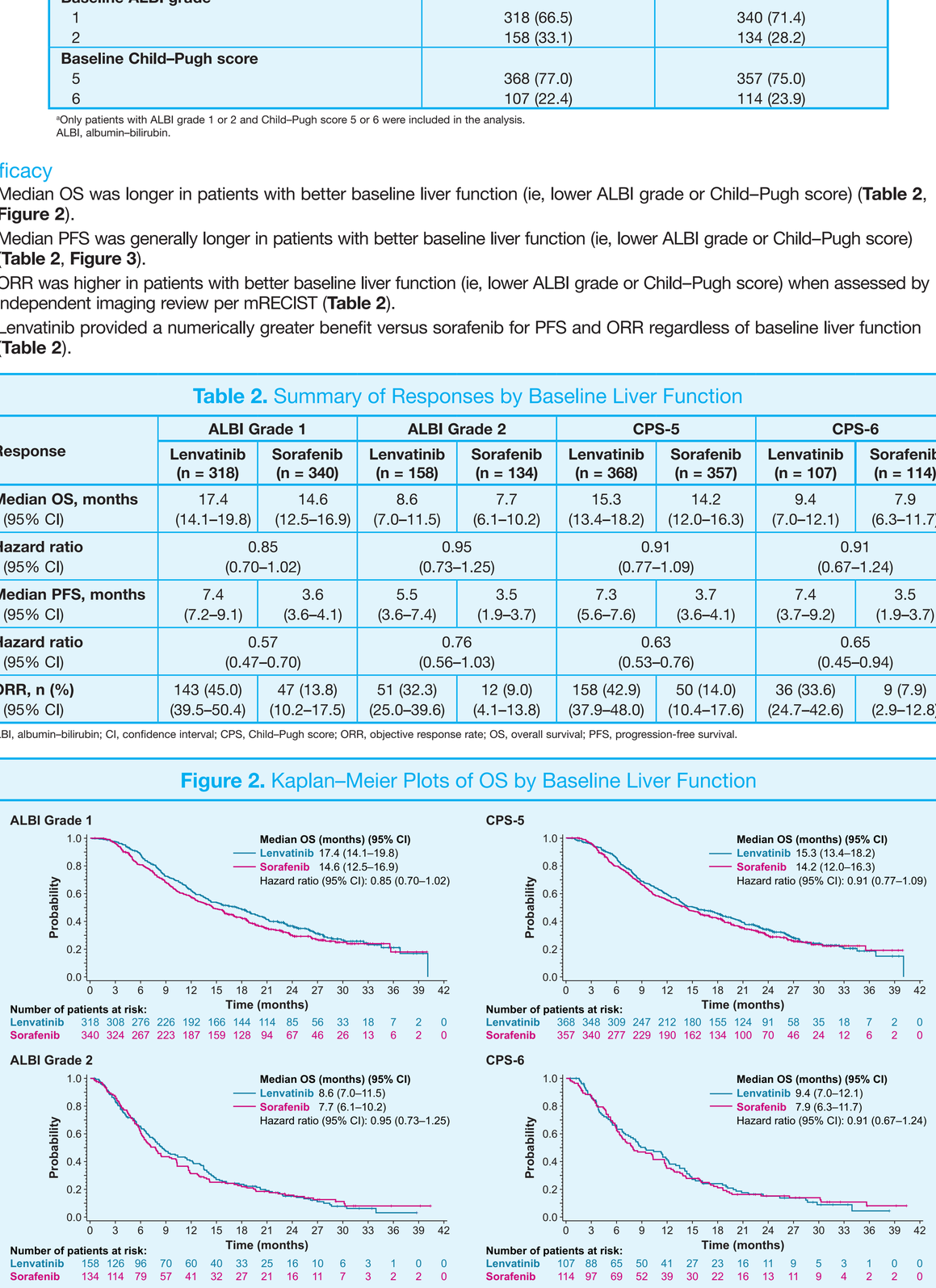
- Median OS was longer in patients with better baseline liver function (ie, lower ALBI grade or Child–Pugh score) (**Table 2**, **Figure 2**).
- Median PFS was generally longer in patients with better baseline liver function (ie, lower ALBI grade or Child–Pugh score) (**Table 2**, **Figure 3**).
- ORR was higher in patients with better baseline liver function (ie, lower ALBI grade or Child–Pugh score) when assessed by independent imaging review per mRECIST (**Table 2**).
- Lenvatinib provided a numerically greater benefit versus sorafenib for PFS and ORR regardless of baseline liver function (**Table 2**).

Table 2. Summary of Responses by Baseline Liver Function

Response	ALBI Grade 1		ALBI Grade 2		CPS-5		CPS-6	
	Lenvatinib (n = 318)	Sorafenib (n = 340)	Lenvatinib (n = 158)	Sorafenib (n = 134)	Lenvatinib (n = 368)	Sorafenib (n = 357)	Lenvatinib (n = 107)	Sorafenib (n = 114)
Median OS, months (95% CI)	17.4 (14.1–19.8)	14.6 (12.5–16.9)	8.6 (7.0–11.5)	7.7 (6.1–10.2)	15.3 (13.4–18.2)	14.2 (12.0–16.3)	9.4 (7.0–12.1)	7.9 (6.3–11.7)
Hazard ratio (95% CI)	0.85 (0.70–1.02)		0.95 (0.73–1.25)		0.91 (0.77–1.09)		0.91 (0.67–1.24)	
Median PFS, months (95% CI)	7.4 (7.2–9.1)	3.6 (3.6–4.1)	5.5 (3.6–7.4)	3.5 (1.9–3.7)	7.3 (5.6–7.6)	3.7 (3.6–4.1)	7.4 (3.7–9.2)	3.5 (1.9–3.7)
Hazard ratio (95% CI)	0.57 (0.47–0.70)		0.76 (0.56–1.03)		0.63 (0.53–0.76)		0.65 (0.45–0.94)	
ORR, n (%) (95% CI)	143 (45.0) (39.5–50.4)	47 (13.8) (10.2–17.5)	51 (32.3) (25.0–39.6)	12 (9.0) (4.1–13.8)	158 (42.9) (37.9–48.0)	50 (14.0) (10.4–17.6)	36 (33.6) (24.7–42.6)	9 (7.9) (2.9–12.8)

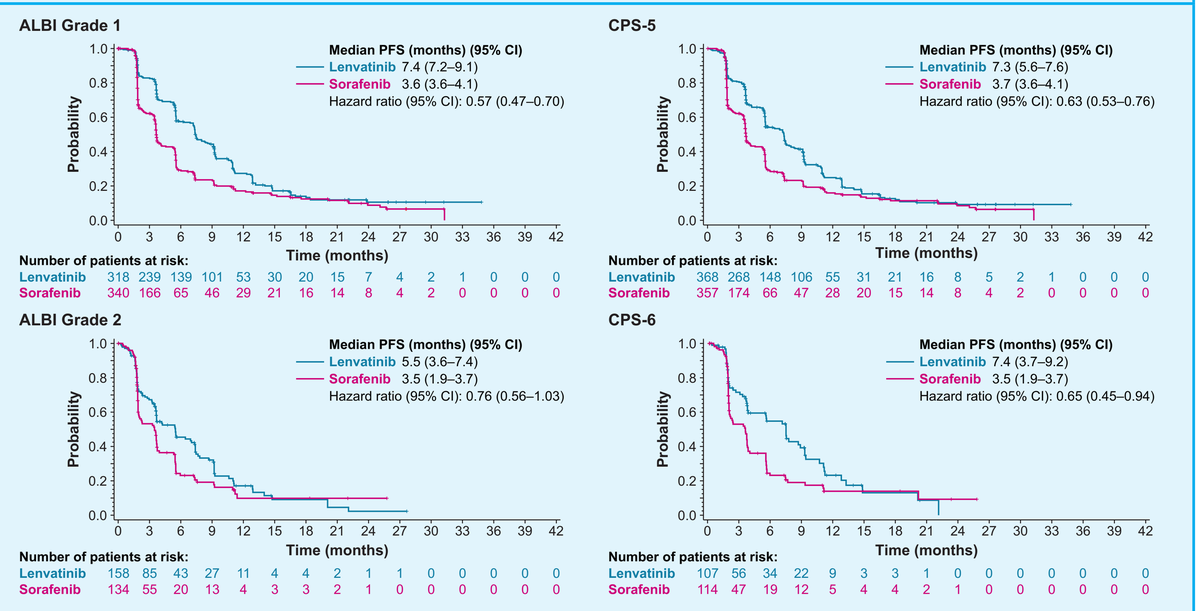
ALBI, albumin–bilirubin; CI, confidence interval; CPS, Child–Pugh score; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Figure 2. Kaplan–Meier Plots of OS by Baseline Liver Function



ALBI, albumin–bilirubin; CI, confidence interval; CPS, Child–Pugh score; OS, overall survival.

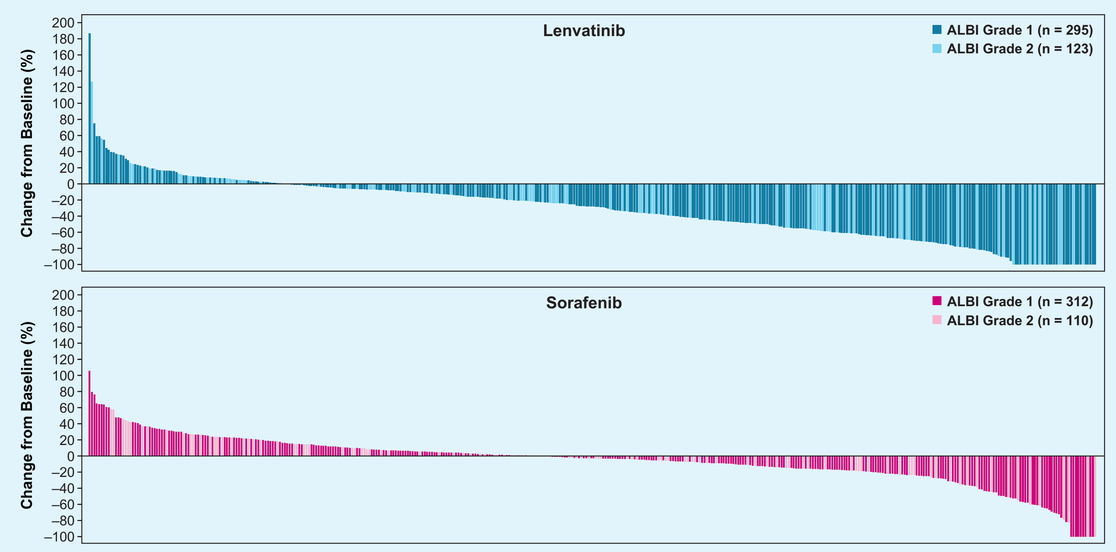
Figure 3. Kaplan–Meier Plots of PFS by Baseline Liver Function (by Independent Imaging Review; Using mRECIST)



ALBI, albumin–bilirubin; CI, confidence interval; CPS, Child–Pugh score; mRECIST, modified Response Evaluation Criteria In Solid Tumors; PFS, progression-free survival.

- Percentage changes in the sums of diameters of target lesions at postbaseline nadir are shown in **Figure 4** (by independent imaging review; using mRECIST).

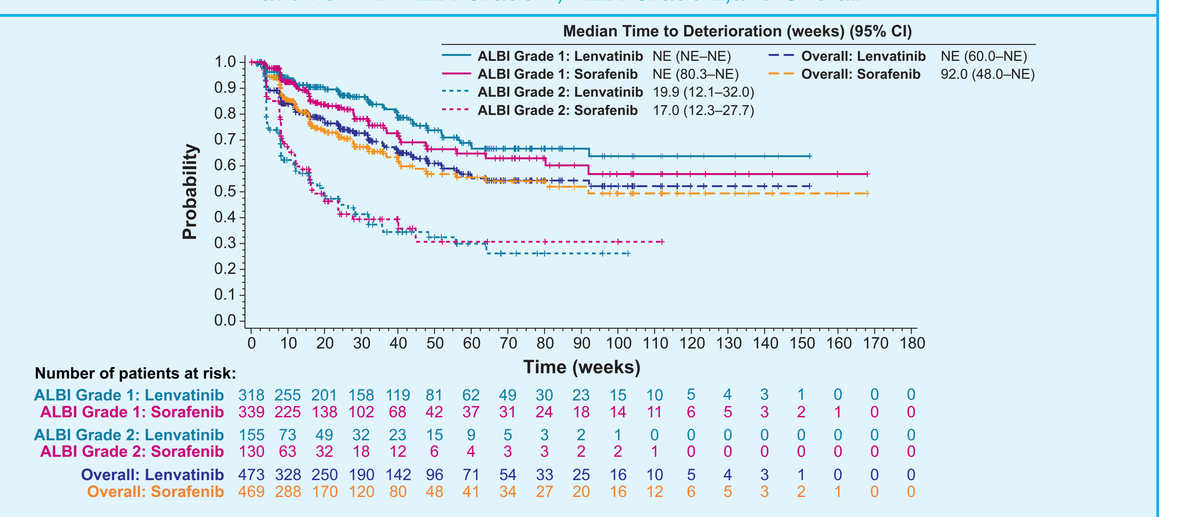
Figure 4. Percentage Changes in the Sums of Diameters of Target Lesions at Postbaseline Nadir for Patients Treated With Lenvatinib or Sorafenib (by Independent Imaging Review; Using mRECIST)



ALBI, albumin–bilirubin; mRECIST, modified Response Evaluation Criteria In Solid Tumors.

- In patients with ALBI grade 1, the median time to deterioration to Child–Pugh class B was not reached in either treatment arm (**Figure 5**).

Figure 5. Time to Deterioration to Child–Pugh Class B[a] in Patients With ALBI Grade 1, ALBI Grade 2,and Overall



[a]Time to deterioration from baseline Child–Pugh class to Child–Pugh class B was determined by Child–Pugh scores assessed at baseline, day 1 of cycle 2 to end of treatment, and the off-treatment visit.
ALBI, albumin–bilirubin; CI, confidence interval; NE, not estimable.

Safety

- With lenvatinib treatment, rates of treatment-emergent adverse events (TEAEs) grade ≥ 3 were lower in patients with better baseline liver function (ie, lower ALBI grade or Child–Pugh score):
  - ALBI grade 1, 69.5% of patients versus ALBI grade 2, 86.1% of patients.
  - Child–Pugh score 5, 71.6% of patients versus Child–Pugh score 6, 86.0% of patients.
- Study-drug withdrawal due to treatment-related TEAEs occurred less frequently in patients with better baseline liver function (ie, lower ALBI grade or Child–Pugh score):
  - Lenvatinib was withdrawn in 6.6% of patients with ALBI grade 1 versus 13.3% of patients with ALBI grade 2, and in 7.9% of those with Child–Pugh score 5 versus 12.1% with Child–Pugh score 6.
- Dose reductions due to treatment-related TEAEs occurred at similar rates irrespective of baseline liver function (ie, lower ALBI grade or Child–Pugh score):
  - Lenvatinib dose was reduced in 35.5% of patients with ALBI grade 1 versus 39.9% of patients with ALBI grade 2, and in 36.6% of those with Child–Pugh score 5 versus 39.3% with Child–Pugh score 6.

CONCLUSIONS

- This post hoc retrospective analysis suggests that baseline ALBI grade (for OS, PFS, and ORR) and Child–Pugh score (for ORR) may be prognostic for improved efficacy with lenvatinib and sorafenib treatment in patients with uHCC:
  - Baseline liver function may also be linked to safety outcomes in patients treated with lenvatinib.
- Lenvatinib provided a trend toward better PFS and ORR, regardless of baseline liver function; the efficacy of lenvatinib appeared greater in patients with better baseline liver function (ALBI grade 1 or Child–Pugh score 5).
- Despite more patients having a baseline ALBI score of 2 in the lenvatinib group compared with the sorafenib group, lenvatinib treatment resulted in better ORR and PFS and noninferior OS.
- To achieve better efficacy with lenvatinib (or sorafenib) treatment, it may be important to treat patients before baseline liver function deteriorates.

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