Poster No. 317

Association Between Overall Survival and Adverse Events With Lenvatinib Treatment in Patients With Hepatocellular Carcinoma (REFLECT)

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INTRODUCTION

- Lenvatinib is a multikinase inhibitor of vascular endothelial growth factor (VEGF) receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor α, RET, and KIT.[1–3]
- In the phase 3, randomized, multicenter REFLECT study that compared lenvatinib with sorafenib in patients with first-line unresectable hepatocellular carcinoma (uHCC), lenvatinib demonstrated statistical confirmation of noninferiority in terms of overall survival (OS) (hazard ratio 0.92; 95% confidence interval: 0.79–1.06).[4]
  - In REFLECT, lenvatinib and sorafenib had distinct safety profiles.
  - The most common any-grade treatment-emergent adverse events (TEAEs) with lenvatinib were hypertension and diarrhea (**Table 1**).
  - Several TEAEs occurred more frequently in patients treated with lenvatinib versus sorafenib, including hypertension, proteinuria, dysphonia, and hypothyroidism (**Table 1**).

Table 1. Incidence Rates of Select TEAEs of Interest From REFLECT (Safety Analysis Set)[4]

	Lenvatinib (n = 476)		Sorafenib (n = 475)	
TEAEs	**Any grade n (%)**	**Grade ≥ 3 n (%)**	**Any grade n (%)**	**Grade ≥ 3 n (%)**
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (1)	57 (12)	0
Hypothyroidism	78 (16)	0	8 (2)	0

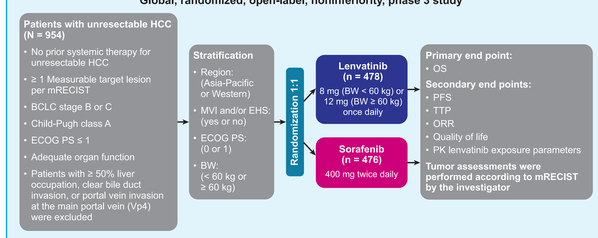
TEAE, treatment-emergent adverse event.

- Correlations between adverse events (AEs) and outcomes in clinical trials have been previously reported:
  - Skin toxicity, a common AE associated with epidermal growth factor inhibitors, has been positively correlated with a clinical benefit.[5]
  - Significantly improved outcomes have been observed in patients treated with sorafenib who developed hand-foot syndrome (HFS) compared with those who did not in both metastatic renal cancer cell carcinoma and HCC.[6,7]
    - HFS was also associated with improved OS in patients with HCC who were treated with regorafenib.[8]
  - Treatment-emergent hypertension was significantly correlated with improved efficacy outcomes,[9] and treatment-emergent diarrhea was associated with improved OS, in patients with radioiodine-refractory differentiated thyroid cancer treated with lenvatinib.[10]
    - Hypertension is an on-target effect of VEGF-signaling pathway inhibition.[11]
- In this post hoc analysis of REFLECT, we examined several AEs of interest of lenvatinib and potential correlations with OS.

METHODS

- REFLECT was a phase 3, global, randomized, open-label study of lenvatinib versus sorafenib in first-line uHCC (**Figure 1**)

Figure 1. REFLECT Study Design[4]



BCLC, Barcelona Clinic Liver Cancer; BW, bodyweight; 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; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; TTP, time to progression.

- AE management in REFLECT is summarized in **Table 2:**
  - Specific management plans were implemented for the management of hypertension and proteinuria.

Table 2. Recommended Dosage Reductions of Lenvatinib for Adverse Reactions[12]

Recommended Dosage Reductions of Lenvatinib for Adverse Reactions in HCC			
Indication	**First Dosage Reduction to:**	**Second Dosage Reduction to:**	**Third Dosage Reduction to:**
Body weight ≥ 60 kg	8 mg once daily	4 mg once daily	4 mg every other day
Body weight < 60 kg	4 mg once daily	4 mg every other day	Discontinue
Recommended Dosage Modifications for Lenvatinib for Adverse Reactions of Interest			
Adverse Reaction	**Severity[a]**	**Dose Modification for Lenvatinib**	
Hypertension	Grade 3	• Withhold for grade 3 that persists despite optimal antihypertensive therapy • Resume at reduced dose when hypertension is controlled at ≤ grade 2	
	Grade 4	• Permanently discontinue	
Proteinuria[b]	3.5 g or greater proteinuria in 24 hours	• Withhold until ≤ 3.4 g of proteinuria per 24 hours • For first occurrence, resume at same dose • For second through fourth occurrence, resume at a reduced dose • Permanently discontinue for nephrotic syndrome	
Nonhematological	Intolerable grade 2 or grade 3	• Interrupt until resolved to grade 0–1 or baseline • Resume at one-level reduced dose	

[a]Adverse event grades are based on Common Terminology Criteria for Adverse Events version 4.0.
[b]In REFLECT, management of proteinuria differs from what is stated in the lenvatinib package insert (ie, withhold until ≤ 2 grams of proteinuria per 24 hours).
HCC, hepatocellular carcinoma.

- For this post hoc exploratory analysis, patients who received lenvatinib were stratified by those who experienced the any-grade TEAE of interest versus those who did not.
- OS was analyzed using Kaplan-Meier estimates.
- *P* values are nominal and were not adjusted for multiplicity.

RESULTS

- In this post hoc analysis of REFLECT study outcomes, TEAEs including hypertension, diarrhea, proteinuria, and hypothyroidism were significantly associated with OS in patients with uHCC treated with lenvatinib (**Table 3**; **Figure 2 A–D**).
- No significant difference was found in OS between patients who did and did not develop dysphonia on lenvatinib (**Figure 2E**).

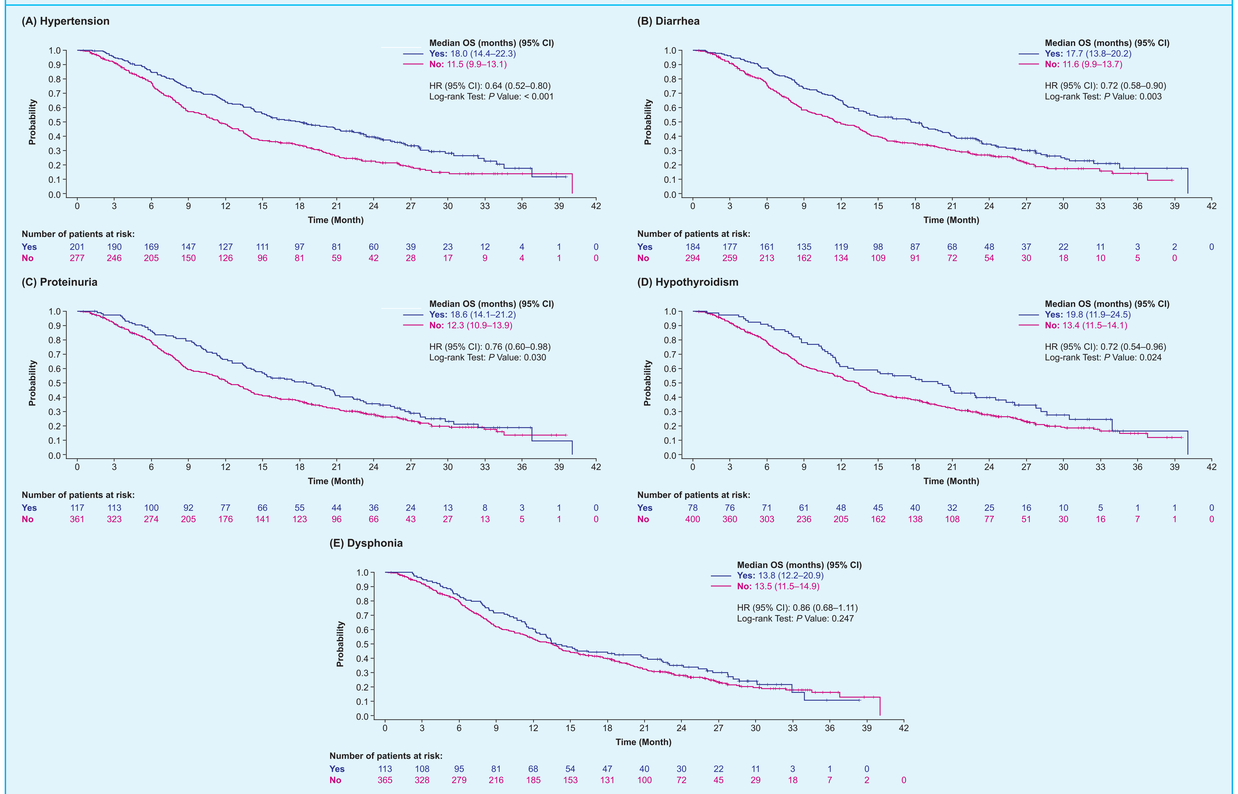
Table 3. TEAEs of Interest and OS Outcomes (Full Analysis Set)

	Lenvatinib (n = 478) n (%)				
Preferred Term	**TEAE**	**No TEAE**	**HR for OS**	**95% CI**	***P* Value**
Hypertension	201 (42)	277 (58)	0.64	0.52–0.80	< 0.001
Diarrhea	184 (38)	294 (62)	0.72	0.58–0.90	0.003
Proteinuria	117 (24)	361 (76)	0.76	0.60–0.98	0.030
Dysphonia	113 (24)	365 (76)	0.86	0.68–1.11	0.247
Hypothyroidism	78 (16)	400 (84)	0.72	0.54–0.96	0.024

CI, confidence interval; HR, hazard ratio; OS, overall survival; TEAE, treatment-emergent adverse event.

- To address a potential for lead-time bias, exploratory OS landmark analyses (at 28 and 56 days) were also performed to examine possible associations between OS and each TEAE of interest (data not shown). In these analyses, the associations observed between OS and treatment-emergent hypertension, proteinuria, or dysphonia were consistent with the analyses presented here. However, an association between OS and treatment-emergent diarrhea was not found in the landmark analysis, and a landmark analysis to examine the association between OS and treatment-emergent hypothyroidism was precluded due to limited sample size.

Figure 2. Kaplan-Meier Estimate of OS for Patients Treated With Lenvatinib, Stratified by AE Incidence for Each TEAE of Interest



AE, adverse event; CI, confidence interval; HR, hazard ratio; OS, overall survival; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Results of this post hoc exploratory analysis of the REFLECT study indicate that when patients with uHCC were treated with lenvatinib, the occurrences of hypertension, diarrhea, proteinuria, or hypothyroidism were associated with a longer OS.
- The occurrence of these AEs may serve as useful indicators for predicting benefit for patients receiving lenvatinib.
- Further research into the correlation between AEs and outcomes, as well as the possible confounding role of baseline characteristics, is warranted.

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