Supporting Information

Article Title

Safety and effectiveness of lenvatinib in patients with unresectable hepatocellular carcinoma in real-world clinical practice: an observational post-marketing study in Japan

Journal

Drugs - Real World Outcomes

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Table S1. Assessment schedule

Assessments	Enrollment	CRF 1		CRF 2	
		Pre-dose	Month 3	Month 6	Month 12
Consent/Registration	x				
Patient background	x	x			
Treatment status			x		x
Concomitant therapy/medications for HCC			x		x
Medications for hepatic encephalopathy[a]			x		x
Tumor response by imaging data[b]			x[d]	x[d]	x[d]
Survival outcome			x		x
Child-Pugh score		x	x[d]	x[d]	x[d]
Laboratory tests[c]		Assessed from pre-dose to the end of 12-month observation (or discontinuation), if performed			
Adverse event			Assessed from the start to the end of 12-month observation (or discontinuation)		

x = performed

Data were collected using the two CRFs: 1) from the start of dosing to 3 months and 2) from 3 to 12 months after treatment initiation.

[a]Medications for prevention of hepatic encephalopathy; medications considered as a risk for hepatic encephalopathy-related adverse events (diuretics and analgesics); and medications requiring precautions for co-administration with lenvatinib (P-gp inhibitors and CYP3A/P-gp inducers)

[b]Best overall response during each time period (i.e., from the start of dosing to 3 months, 3 to 6 months, and 6 to 12 months after treatment initiation)

[c]Once the treatment was initiated, only laboratory tests related to adverse events were evaluated

[d]Only if assessments were performed

CRF, case report form; HCC, hepatocellular carcinoma

Table S2. Factors associated with the long treatment duration[a] identified in multivariate logistic regression analysis

Variable	Category	OR (95% CI)	P-value
ECOG PS	0	reference	
	≥1	0.429 (0.277–0.664)	<0.001
Portal vein invasion	No	reference	
	Yes	0.506 (0.325–0.789)	0.002
HAIC	No	reference	
	Yes	3.091 (1.596–5.986)	<0.001
mALBI grade	1	reference	
	2a	0.751 (0.476–1.185)	0.218
	≥2b	0.436 (0.283–0.670)	<0.001
eGFR (mL/min/1.73m^2)	≥45	reference	
	<45	0.477 (0.266–0.855)	0.012
AFP level (ng/mL)	<200	reference	
	≥200	0.560 (0.384–0.818)	0.002
Concomitant therapy/medications for HCC	No	reference	
	Yes	4.588 (2.654–7.933)	<0.001

[a]The duration longer than the median treatment duration of the population (177 days) was defined as the long treatment period.

OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HAIC, hepatic arterial infusion chemotherapy; mALBI grade, modified albumin-bilirubin grade; eGFR, estimated glomerular filtration rate; AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma

Table S3. Factors associated with the incidence of ADRs that led to treatment discontinuation, identified in multivariate logistic regression analysis

Variable	Category	OR (95% CI)	P-value
Sex	Male	reference	
	Female	1.850 (1.201–2.849)	0.005
ECOG PS	0	reference	
	≥1	2.043 (1.345–3.102)	<0.001
Previous TKI therapy	No	reference	
	Yes	0.533 (0.324–0.877)	0.013
Previous TACE procedures (times)	No	reference	
	<3	1.482 (0.899–2.443)	0.123
	≥3	2.164 (1.331–3.518)	0.001
mALBI grade	1	reference	
	2a	1.624 (0.999–2.641)	0.050
	≥2b	2.023 (1.284–3.187)	0.002
Concomitant therapy/medications for HCC	No	reference	
	Yes	0.581 (0.343–0.986)	0.044

ADR, adverse drug reaction; OR, odds ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; TKI, tyrosine kinase inhibitor; TACE, transcatheter arterial chemoembolization; mALBI grade, modified albumin-bilirubin grade; HCC, hepatocellular carcinoma

Table S4. Factors associated with the occurrence of hepatic encephalopathy, identified in multivariate logistic regression analysis

Variable	Category	OR (95% CI)	P-value
Extrahepatic lesions	No	reference	
	Yes	0.355 (0.134–0.939)	0.036
mALBI grade	1	reference	
	2a	2.161 (0.411–11.347)	0.362
	≥2b	5.568 (1.241–24.991)	0.024
Medications for prevention of hepatic encephalopathy	No	reference	
	Yes	11.736 (5.303–25.973)	<0.001

OR, odds ratio; CI, confidence interval; mALBI grade, modified albumin-bilirubin grade

Table S5. Factors associated with the achievement of objective response[a] identified in multivariate logistic regression analysis

Variable	Category	OR (95% CI)	P-value
Extrahepatic lesions	Yes	reference	
	No	0.542 (0.342–0.859)	0.009
mALBI grade	1	reference	
	2a	0.484 (0.291–0.808)	0.005
	≥2b	0.431 (0.263–0.708)	<0.001

[a]Objective response was defined as complete response and partial response.

OR, odds ratio; CI, confidence interval; mALBI grade, modified albumin-bilirubin grade