Impact of bodyweight-based starting doses on the safety and efficacy of lenvatinib in primarily Japanese patients with hepatocellular carcinoma

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Abstract
Aim: The phase III REFLECT study utilized bodyweight-based lenvatinib dosing in patients with unresectable hepatocellular carcinoma, based on results of the phase II Study 202. This post hoc analysis compared efficacy and safety in patients with lower and higher bodyweights.

Methods: This comparison included patients from Study 202 (Japanese, \( n = 43 \); Korean, \( n = 3 \)) and Japanese patients from REFLECT (\( n = 81 \)) who received lenvatinib. In Study 202, all patients received a starting dose of lenvatinib 12 mg/day; in REFLECT, patients received starting doses based on bodyweight (patients <60 kg, 8 mg/day; \( \geq 60 \) kg, 12 mg/day). Safety and efficacy were assessed in both studies according to bodyweight.

Results: In Study 202, treatment-related, treatment-emergent adverse events (TEAEs) led to dose reductions in 80.8% and 55.0% of patients in the lower and higher bodyweight groups, respectively. In REFLECT, treatment-related TEAEs led to dose reductions in 52.5% and 70.7% of patients in the 8 and 12 mg groups, respectively. In Study 202, median overall survival (OS) was 16.2 months (95% confidence interval [CI], 9.8–25.1) and 21.3 months (95% CI, 10.1–not estimable) in the lower and higher bodyweight groups, respectively. In REFLECT, median OS was 15.8 months (95% CI, 10.4–27.6) and 18.2 months (95% CI, 11.3–26.9) in the 8 and 12 mg groups, respectively.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; CR, complete response; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; HCC, hepatocellular carcinoma; IR, independent imaging review; MPVI, microscopic portal vein invasion; mRECIST, modified RECIST; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; TEAE, treatment-emergent adverse event; TTP, time to progression; uHCC, unresectable hepatocellular carcinoma.

ClinicalTrials.gov numbers: Study 202: NCT00946153; REFLECT: NCT01761266.

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INTRODUCTION
Hepatocellular carcinoma has a high fatality rate. In 2021, the global estimate of incident cases of HCC was approximately 900,000, and approximately 830,000 deaths were anticipated. Many anticancer drugs are metabolized in the liver, and therefore liver impairment due to cancer or underlying etiologies can present challenges for determining the optimal dose for patients with HCC.

Recommended first-line systemic therapies for HCC include atezolizumab plus bevacizumab, sorafenib monotherapy, and lenvatinib monotherapy. Lenvatinib is approved for the treatment of patients with uHCC in over 70 countries, including Japan, the United States, Europe, and Asia. Lenvatinib is a multikinase inhibitor targeting vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet-derived growth factor receptor alpha, and RET and KIT proto-oncogenes.

To assess optimal dosing of lenvatinib in the treatment of patients with uHCC, efficacy and safety have been investigated irrespective of bodyweight in the phase II Study 202 and by bodyweight in the phase III REFLECT study (Table S1). In Study 202, all patients (Japanese, n = 43; Korean, n = 3) received a starting dose of lenvatinib 12 mg/day for treatment of uHCC. Exploratory analyses revealed that median bodyweight was lower among patients who required early-dose withdrawal or reduction than in patients who did not. Correlations between early-dose reductions or withdrawals and bodyweight in Study 202 led to implementation of bodyweight-adjusted dosing of lenvatinib in the phase III REFLECT study for patients with uHCC. In REFLECT, patients with bodyweights of less than 60 kg received a starting dose of lenvatinib 8 mg/day and those with bodyweights of 60 kg or more received a starting dose of lenvatinib 12 mg/day.

The impact of bodyweight-adjusted dosing was assessed in a subanalysis of REFLECT that compared efficacy and safety between patients treated with starting doses of lenvatinib 8 mg/day and 12 mg/day. In this analysis, lenvatinib efficacy was comparable between the two starting-dose groups. Moreover, no notable safety differences were observed between these two starting-dose groups.

Although safety in patients with lower bodyweights (<60 kg) was expected to improve by reducing the lenvatinib starting dose from 12 mg/day to 8 mg/day, the differences in efficacy and safety of bodyweight-adjusted dosing versus standard dosing among patients with lower bodyweight have yet to be determined. Herein we compare the safety and efficacy of lenvatinib in Asian patients (mostly Japanese) in Study 202 (lenvatinib 12 mg/day irrespective of bodyweight) and in Japanese patients from REFLECT (dose adjusted by bodyweight, <60 kg vs. ≥60 kg). As Study 202 was undertaken primarily in Japanese patients, this analysis used the Japanese subset of patients in REFLECT for a more relevant comparison.

METHODS

Patients
Eligibility criteria for Study 202 and REFLECT have been published previously. Briefly, in Study 202, patients were 20–80 years old, with a histologically or clinically confirmed diagnosis of advanced HCC, at least one measurable target lesion by RECIST version 1.1, and adequate organ function. Similarly, in REFLECT, patients (≥18 years old) were required to have a confirmed diagnosis of advanced HCC, at least one measurable target lesion by mRECIST, and adequate organ function. Written informed consent was provided by all patients in both studies before undergoing any study-specific procedures. The study protocols were approved by the relevant institutional ethics review boards and were carried out in accordance with the principles of the World Medical Association Declaration of Helsinki.

Study design
Study 202 was an open-label phase I/II study to determine the safety and efficacy of lenvatinib in patients with advanced HCC. Results of the study have been published. The primary objective of the phase II expansion was to evaluate the efficacy (TTP) and safety of lenvatinib at the recommended dose (lenvatinib, 12 mg/day orally) in patients with advanced HCC and Child–Pugh scores of 5–6 (Class A). Secondary objectives included evaluation of antitumor efficacy by ORR and disease control rate using mRECIST, as well as OS.

REFLECT was a multicenter, randomized, open-label, phase III study that compared the efficacy and safety of lenvatinib versus sorafenib as first-line treatment for patients with uHCC. In this study, dosing of oral lenvatinib was adjusted by bodyweight. Patients with bodyweights of less than 60 kg received a starting dose of lenvatinib 8 mg/day and those with bodyweights of 60 kg or more received a starting dose of lenvatinib 12 mg/day. Results of this study have been
presented. The primary objective of REFLECT was to compare OS between patients who received lenvatinib or sorafenib. Secondary objectives included assessment of PFS, TTP, and ORR using mRECIST, as well as safety and tolerability.

**Post hoc subgroup analyses**

To assess the impact of bodyweight-based lenvatinib dosing in patients with uHCC, post hoc analyses were undertaken among patients treated with lenvatinib. From Study 202, 46 patients (Japanese, n = 43; Korean, n = 3) who received lenvatinib were included in these analyses. From REFLECT, Japanese patients (n = 81) who received lenvatinib were included in these analyses. Analyses in Study 202 compared patients with lower bodyweights (<60 kg) who received a starting dose of lenvatinib 12 mg/day versus those with higher bodyweights (≥60 kg) who received a starting dose of lenvatinib 12 mg/day. The Japanese patients in REFLECT who received a starting dose of lenvatinib 8 mg/day (bodyweight <60 kg) were compared with patients who received a starting dose of 12 mg/day (bodyweight ≥60 kg). Side-by-side comparisons examined the impact of changing the lenvatinib starting dose from 12 mg/day to 8 mg/day in patients with bodyweights less than 60 kg. Analyses of lenvatinib exposure, safety, OS, PFS, and ORR were included. Tumor responses were assessed by IIR using mRECIST as well as RECIST version 1.1.

**Statistical methods**

Patients in Study 202 were grouped by bodyweight (<60 kg or ≥60 kg). The subset of Japanese patients in REFLECT were grouped by starting dose (8 mg or 12 mg), determined by bodyweight stratification (<60 kg or ≥60 kg). The same statistical methods used for the primary and secondary analyses in REFLECT were applied for the post hoc subgroup analyses.

**RESULTS**

**Patient baseline characteristics**

Patient baseline characteristics are summarized in Table 1. Overall, patient numbers were similar between groups in Study 202 (lower bodyweight group, n = 26; higher bodyweight group, n = 20) and the Japanese population of REFLECT (lenvatinib 8 mg group, n = 40; lenvatinib 12 mg group, n = 41), and there were similarities between the lower bodyweight group in Study 202 and the lenvatinib 8 mg starting-dose group of REFLECT. In Study 202, median patient age was 71.0 years in the lower bodyweight group and, in REFLECT, median patient age was 72.0 years in the lenvatinib 8 mg starting-dose group. All (13 of 13) of the women in Study 202 were in the lower bodyweight group, and 11 of 16 women in the Japanese subpopulation of REFLECT were in the lenvatinib 8 mg group. Most patients in both studies had a baseline ECOG PS of 0 (Study 202, 84.6% in the lower bodyweight group; REFLECT, 92.5% in the lenvatinib 8 mg group). In REFLECT, 60.0% of patients in the lenvatinib 8 mg starting-dose group and 63.4% of patients in the lenvatinib 12 mg starting-dose group had baseline α-fetoprotein levels less than 200 ng/ml. In Study 202, 46.2% of patients in the lower bodyweight group and 75.0% of patients in the higher bodyweight group had α-fetoprotein levels less than 200 ng/ml.

**Study-drug exposure**

In Study 202, median duration of lenvatinib treatment was 5.8 months (range, 0.1–36.0 months) in the lower bodyweight group and 9.4 months (range, 0.5–22.2 months) in the higher bodyweight group. Median lenvatinib dose intensity was 6.5 mg/day/patient (range, 3.6–12.0 mg/day/patient) in the lower bodyweight group and 9.1 mg/day/patient (range, 4.3–12.0 mg/day/patient) in the higher bodyweight group. The mean percentage of the planned lenvatinib starting dose was 57.0% (SD, 21.22) in the lower bodyweight group and 78.6% (SD, 19.33) in the higher bodyweight group. In the Japanese population in REFLECT, median duration of lenvatinib treatment was 5.7 months in both starting-dose groups (8 mg group range, 0.5–24.6 months; 12 mg group range, 0.6–35.0 months). Median lenvatinib dose intensity was 7.2 mg/day/patient (range, 2.1–8.0 mg/day/patient) in the 8 mg starting-dose group and 8.8 mg/day/patient (range, 1.7–12.1 mg/day/patient) in the 12 mg starting-dose group. The mean percentage of the planned lenvatinib starting dose was 79.1% (SD, 23.55) in the 8 mg starting-dose group and 70.7% (SD 25.46) in the 12 mg starting-dose group.

**Safety**

In all groups assessed in Study 202 and REFLECT, most patients experienced at least one treatment-related TEAE (Table 2). In Study 202, 96.2% of patients in the lower bodyweight group and 95.0% of patients in the higher bodyweight group experienced at least one treatment-related TEAE, and 84.6% and 90.0% of patients, respectively, experienced at least one treatment-related TEAE of grade 3 or higher. In the Japanese population of REFLECT, all patients in both groups experienced at least one treatment-related TEAE; 55.0% of patients in the lenvatinib 8 mg starting-dose group and 70.7% of patients in the 12 mg starting-dose group experienced at least one treatment-related TEAE of grade 3 or higher. In Study 202, rates of treatment-related SAEs were higher in the lower bodyweight group (46.2%) compared with the higher bodyweight group (10.0%). In REFLECT, 15.0% of patients in the lenvatinib 8 mg starting-dose group and 22.0% of patients in the 12 mg starting-dose group had at least one treatment-related SAE (Table 2). In Study 202, among patients in the lower bodyweight group, 80.8% had at least one treatment-related TEAE that led to lenvatinib dose reduction; in the higher
bodyweight group, only 55.0% of patients had treatment-related TEAEs leading to dose reduction (Table 2). In REFLECT, 52.5% of patients in the lenvatinib 8 mg starting-dose group and 70.7% of patients in the 12 mg starting-dose group had at least one treatment-related TEAE that led to dose reduction (Table 2).

The most frequent treatment-related TEAEs in both studies included palmar-plantar erythrodysesthesia syndrome, hypertension, decreased appetite, and proteinuria. The most common treatment-related TEAE of grade 3 or higher in both studies was hypertension. Among patients in both studies, the most common treatment-related TEAEs that led to dose reduction were fatigue, decreased appetite, and palmar-plantar erythrodysesthesia syndrome (Table S2).

### TABLE 1  Demographic and other baseline characteristics

| Characteristic          | Study 202 Reflect (Japanese population) |
|-------------------------|----------------------------------------|
|                         | Lenvatinib 12 mg (bodyweight <60 kg) (n = 26) | Lenvatinib 12 mg (bodyweight ≥60 kg) (n = 20) | Lenvatinib 8 mg (n = 40) | Lenvatinib 12 mg (n = 41) |
| Median age, years (range) | 71.0 (37.0–80.0) | 61.0 (45.0–79.0) | 72.0 (55–86) | 70.0 (35–82) |
| Sex, n (%)               |                                        |                                        |                          |                          |
| Male                    | 13 (50.0)                              | 20 (100.0)                             | 29 (72.5)               | 36 (87.8)               |
| Female                  | 13 (50.0)                              | 0                                      | 11 (27.5)               | 5 (12.2)                |
| Median bodyweight, kg (range) | 53.1 (42.8–57.9) | 71.5 (60.1–85.5) | 52.9 (39–60) | 69.3 (60–92) |
| Bodyweight, n (%)       |                                        |                                        |                          |                          |
| <60 kg                  | 26 (100.0)                             | 0                                      | 40 (100.0)              | 1 (2.4)                 |
| ≥60 kg                  | 0                                      | 20 (100.0)                             | 0                        | 40 (97.6)               |
| ECOG PS, n (%)          |                                        |                                        |                          |                          |
| 0                       | 22 (84.6)                              | 16 (80.0)                              | 37 (92.5)               | 39 (95.1)               |
| 1                       | 4 (15.4)                               | 4 (20.0)                               | 3 (7.5)                 | 2 (4.9)                 |
| Child–Pugh score, n (%) |                                        |                                        |                          |                          |
| 5                       | 24 (92.3)                              | 15 (75.0)                              | 25 (62.5)               | 33 (80.5)               |
| 6                       | 2 (7.7)                                | 4 (20.0)                               | 15 (37.5)               | 8 (19.5)                |
| 7                       | 0                                      | 1 (5.0)                                | 0                        | 0                        |
| MPVI, extrahepatic spread, or both, n (%) |                               |                                        |                          |                          |
| Yes                     | 16 (61.5)                              | 8 (40.0)                               | 21 (52.5)               | 28 (68.3)               |
| No                      | 10 (38.5)                              | 12 (60.0)                              | 19 (47.5)               | 13 (31.7)               |
| BCLC stage, n (%)       |                                        |                                        |                          |                          |
| B                       | 9 (34.6)                               | 10 (50.0)                              | 18 (45.0)               | 13 (31.7)               |
| C                       | 17 (65.4)                              | 10 (50.0)                              | 22 (55.0)               | 28 (68.3)               |
| Etiology, n (%)         |                                        |                                        |                          |                          |
| Hepatitis B virus       | 4 (15.4)                               | 11 (55.0)                              | 9 (22.5)                | 14 (34.1)               |
| Hepatitis C virus       | 18 (69.2)                              | 9 (45.0)                               | 27 (67.5)               | 10 (24.4)               |
| Alcohol                 | 1 (3.8)                                | 1 (5.0)                                | 2 (5.0)                 | 8 (19.5)                |
| Other                   | 3 (11.5)                               | 0                                      | 2 (5.0)                 | 3 (7.3)                 |
| Unknown                 | 0                                      | 0                                      | 0 (0.0)                 | 6 (14.6)                |
| Baseline α-fetoprotein, n (%) |                               |                                        |                          |                          |
| <200 ng/ml              | 12 (46.2)                              | 15 (75.0)                              | 24 (60.0)               | 26 (63.4)               |
| ≥200 ng/ml              | 13 (50.0)                              | 5 (25.0)                               | 16 (40.0)               | 15 (36.6)               |
| Missing                 | 1 (3.8)                                | 0                                      | 0                        | 0                        |

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; MPVI, microscopic portal vein invasion.
TABLE 2  Summary of adverse events

| Parameter, n (%)                      | Study 202 Lenvatinib 12 mg (bodyweight <60 kg) (n = 26) |  |  | Study 202 Lenvatinib 12 mg (bodyweight ≥60 kg) (n = 20) |  |  | REFLECT (Japanese population) Lenvatinib 8 mg (n = 40) | Lenvatinib 12 mg (n = 41) |
|--------------------------------------|--------------------------------------------------------|---|---|--------------------------------------------------------|---|---|--------------------------------------------------------|--------------------------|
| Any treatment-related TEAE           | 25 (96.2)                                              | 19 (95.0) | 40 (100.0) | 41 (100.0)                                             |  |  |  |  |
| Any grade ≥3 treatment-related TEAE  | 22 (84.6)                                              | 18 (90.0) | 22 (55.0) | 29 (70.7)                                              |  |  |  |  |
| Any treatment-related SAE            | 12 (46.2)                                              | 2 (10.0)  | 6 (15.0)  | 9 (22.0)                                               |  |  |  |  |
| Patients with treatment-related TEAE leading to: |  |  |  |  |  |  |  |  |
| Study-drug withdrawal                | 6 (23.1)                                               | 4 (20.0)  | 5 (12.5)  | 4 (9.8)                                                |  |  |  |  |
| Study-drug dose reduction            | 21 (80.8)                                              | 11 (55.0) | 21 (52.5) | 29 (70.7)                                              |  |  |  |  |
| Study-drug interruption              | 12 (46.2)                                              | 8 (40.0)  | 24 (60.0) | 22 (53.7)                                              |  |  |  |  |
| Study-drug dose reduction or interruption | 22 (84.6) | 13 (65.0) | 27 (67.5) | 32 (78.0)                                              |  |  |  |  |

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

TABLE 3  Most common (≥20% in either bodyweight group in Study 202) treatment-related TEAEs

| Preferred term, n (%)                      | Study 202 Lenvatinib 12 mg (bodyweight <60 kg) (n = 26) |  |  | Study 202 Lenvatinib 12 mg (bodyweight ≥60 kg) (n = 20) |  |  | REFLECT (Japanese population) Lenvatinib 8 mg (n = 40) | Lenvatinib 12 mg (n = 41) |
|--------------------------------------------|--------------------------------------------------------|---|---|--------------------------------------------------------|---|---|--------------------------------------------------------|--------------------------|
| Grade                                      | Any grade  | Grade ≥3 | Any grade  | Grade ≥3 | Any grade  | Grade ≥3 | Any grade  | Grade ≥3 |
| Any treatment-related TEAE                | 25 (96.2)  | 22 (84.6) | 19 (95.0)  | 18 (90.0) | 40 (100.0) | 22 (55.0) | 22 (55.0) | 29 (70.7) |
| Hypertension                              | 18 (69.2)  | 11 (42.3) | 17 (85.0)  | 14 (70.0) | 20 (50.0)  | 11 (27.5) | 20 (48.8) | 15 (36.6) |
| Proteinuria                               | 17 (65.4)  | 4 (15.4)  | 10 (50.0)  | 5 (25.0)  | 15 (37.5)  | 0        | 22 (53.7) | 7 (17.1)  |
| Decreased appetite                        | 16 (61.5)  | 1 (3.8)   | 10 (50.0)  | 0        | 18 (45.0)  | 3 (7.5)  | 21 (51.2) | 3 (7.3)   |
| Palmar-plantar erythrodysesthesia syndrome | 13 (50.0)  | 2 (7.7)   | 15 (75.0)  | 1 (5.0)   | 17 (42.5)  | 2 (5.0)  | 25 (61.0) | 4 (9.8)   |
| Diarrhea                                  | 12 (46.2)  | 4 (15.4)  | 4 (20.0)   | 0        | 14 (35.0)  | 1 (2.5)  | 16 (39.0) | 2 (4.9)   |
| Fatigue                                   | 12 (46.2)  | 0        | 10 (50.0)  | 0        | 5 (12.5)   | 0        | 7 (17.1)  | 0        |
| Thrombocytopenia                          | 10 (38.5)  | 5 (19.2)  | 6 (30.0)   | 5 (25.0)  | 1 (2.5)    | 1 (2.5)  | 1 (2.4)   | 0        |
| Peripheral edema                          | 9 (34.6)   | 0        | 6 (30.0)   | 0        | 9 (22.5)   | 0        | 9 (22.0)  | 1 (2.4)   |
| Hypothyroidism                            | 9 (34.6)   | 0        | 1 (5.0)    | 0        | 14 (35.0)  | 0        | 19 (46.3) | 0        |
| Dysphonia                                 | 8 (30.8)   | 0        | 8 (40.0)   | 0        | 18 (45.0)  | 0        | 17 (41.5) | 0        |
| Decreased weight                          | 8 (30.8)   | 0        | 4 (20.0)   | 1 (5.0)   | 8 (20.0)   | 2 (5.0)  | 8 (19.5)  | 2 (4.9)   |
| Constipation                              | 8 (30.8)   | 0        | 6 (30.0)   | 0        | 1 (2.5)    | 0        | 6 (14.6)  | 0        |
| Neutropenia                               | 7 (26.9)   | 2 (7.7)  | 5 (25.0)   | 0        | 0         | 0        | 1 (2.4)   | 1 (2.4)   |
| Blood urine present                       | 7 (26.9)   | 0        | 2 (10.0)   | 0        | 0         | 0        | 0         | 0        |
| Nausea                                    | 7 (26.9)   | 1 (3.8)  | 8 (40.0)   | 0        | 7 (17.5)   | 0        | 5 (12.2)  | 0        |
| Rash                                      | 7 (26.9)   | 0        | 5 (25.0)   | 0        | 3 (7.5)    | 0        | 4 (9.8)   | 0        |
| Stomatitis                                | 6 (23.1)   | 0        | 5 (25.0)   | 0        | 4 (10.0)   | 0        | 10 (24.4) | 0        |
| Increased blood thyroid-stimulating hormone | 4 (15.4)   | 0        | 8 (40.0)   | 0        | 3 (7.5)    | 0        | 4 (9.8)   | 0        |
| Vomiting                                  | 4 (15.4)   | 1 (3.8)  | 5 (25.0)   | 0        | 4 (10.0)   | 0        | 3 (7.3)   | 0        |

Abbreviation: TEAE, treatment-emergent adverse event.
FIGURE 1  Kaplan–Meier curves of overall survival (OS) and progression-free survival (PFS) (by independent imaging review using modified Response Evaluation Criteria in Solid Tumors) among patients with hepatocellular carcinoma treated with lenvatinib, drawn from Study 202 (a, b) and REFLECT (c, d), by starting dose based on bodyweight. CI, confidence interval; NE, not estimable.
Efficacy

In Study 202, median OS was 16.2 months (95% CI, 9.8–25.1) in the lower bodyweight group and 21.3 months (95% CI, 10.1–not estimable) in the higher bodyweight group (Figure 1a). When assessed by IIR using mRECIST in Study 202, PFS was 5.6 months (95% CI, 3.7–7.5) in the lower bodyweight group and 9.2 months (95% CI, 5.5–12.8) in the higher bodyweight group (Figure 1b). In Study 202, ORR assessed by IIR using mRECIST among patients in the lower bodyweight group was 30.8% (95% CI, 13.0–48.5) and 45.0% (95% CI, 23.2–66.8) in the higher bodyweight group (Table 4). The ORRs assessed by IIR using RECIST version 1.1 were 19.2% (95% CI, 4.1–34.4) and 30.0% (95% CI, 9.9–50.1) in the lower and higher bodyweight groups, respectively.

In the Japanese population in REFLECT, median OS was 15.8 months (95% CI, 10.4–27.6) in the lenvatinib 8 mg starting-dose group and 18.2 months (95% CI, 11.3–26.9) in the 12 mg starting-dose group (Figure 1c). Progression-free survival as assessed by IIR using mRECIST was 9.1 months (95% CI, 3.6–11.2) in the lenvatinib 8 mg starting-dose group and 7.2 months (95% CI, 5.4–9.2) in the 12 mg starting-dose group (Figure 1d). The ORRs assessed by IIR using mRECIST for patients in the lenvatinib 8 and 12 mg starting-dose groups were 55.0% (95% CI, 39.6–70.4) and 39.0% (95% CI, 24.1–54.0), respectively (Table 4). The ORRs assessed by IIR using RECIST version 1.1 were 25.0% (95% CI, 11.6–38.4) and 24.4% (95% CI, 11.3–37.5) for the lenvatinib 8 and 12 mg starting-dose groups, respectively.

DISCUSSION

The recommended starting dose of lenvatinib for uHCC is 12 mg/day in patients with bodyweights of 60 kg or more and 8 mg/day in patients with bodyweights less than 60 kg. These doses were suggested based on the findings of Study 202 and a population pharmacokinetics analysis and further confirmed in the pivotal phase III REFLECT study. Although post hoc analyses indicated that the bodyweight-based dosing in REFLECT provided comparable efficacy between starting-dose groups, the current analysis provides a comparison between patients with lower bodyweights who received a starting dose of lenvatinib 12 mg/day in Study 202 and those who received a starting dose of 8 mg/day in REFLECT. This analysis focuses specifically on patients from the Japanese subgroup in REFLECT to present a more relevant comparison with the predominantly Japanese population in Study 202.

### Table 4

Summary of tumor responses

| Parameter | Study 202 | REFLECT (Japanese population) |
|-----------|-----------|-------------------------------|
|           | Lenvatinib 12 mg (bodyweight <60 kg) (n = 26) | Lenvatinib 12 mg (bodyweight ≥60 kg) (n = 20) | Lenvatinib 8 mg (n = 40) | Lenvatinib 12 mg (n = 41) |
| mRECIST, by IIR | | | | |
| ORR, % (95% CI) | 30.8 (13.0–48.5) | 45.0 (23.2–66.8) | 55.0 (39.6–70.4) | 39.0 (24.1–54.0) |
| CR, n (%) | 0 | 0 | 1 (2.5) | 1 (2.4) |
| PR, n (%) | 8 (30.8) | 9 (45.0) | 21 (52.5) | 15 (36.6) |
| SD, n (%) | 11 (42.3) | 8 (40.0) | 12 (30.0) | 14 (34.1) |
| PD, n (%) | 5 (19.2) | 1 (5.0) | 4 (10.0) | 9 (22.0) |
| NE, n (%) | 2 (7.7) | 2 (10.0) | 2 (5.0) | 2 (4.9) |
| DCRa (%) (95% CI) | 73.1 (56.0–90.1) | 85.0 (69.4–100.0) | 85.0 (73.9–96.1) | 73.2 (59.6–86.7) |
| RECIST version 1.1, by IIR | | | | |
| ORR, % (95% CI) | 19.2 (4.1–34.4) | 30.0 (9.9–50.1) | 25.0 (11.6–38.4) | 24.4 (11.3–37.5) |
| CR, n (%) | 0 | 0 | 0 | 1 (2.4) |
| PR, n (%) | 5 (19.2) | 6 (30.0) | 10 (25.0) | 9 (22.0) |
| SD, n (%) | 14 (53.8) | 11 (55.0) | 23 (57.5) | 20 (48.8) |
| PD, n (%) | 5 (19.2) | 1 (5.0) | 5 (12.5) | 9 (22.0) |
| NE, n (%) | 2 (7.7) | 2 (10.0) | 2 (5.0) | 2 (4.9) |
| DCRa (%) (95% CI) | 73.1 (56.0–90.1) | 85.0 (69.4–100.0) | 82.5 (70.7–94.3) | 73.2 (59.6–86.7) |

Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; IIR, independent imaging review; mRECIST, modified RECIST; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

aProportion of patients with CR + PR + SD.
Patients in the lower bodyweight group in Study 202 had lower lenvatinib exposure compared with patients in the higher bodyweight group, while exposure was similar between the dosing groups in REFLECT. In Study 202, median lenvatinib dose intensity was 6.5 mg/day/patient in the lower bodyweight group and 9.1 mg/day/patient in the higher bodyweight group. In REFLECT, median lenvatinib dose intensity was 7.2 mg/day/patient in the 8 mg starting-dose group and 8.8 mg/day/patient in the 12-mg starting-dose group. Median duration of lenvatinib treatment was 5.7 months in both starting-dose groups in REFLECT; in Study 202, median duration of lenvatinib treatment was 5.8 months in the lower bodyweight group and 9.4 months in the higher bodyweight group.

In the lenvatinib 8 mg starting-dose group of REFLECT, median OS was 15.8 months (95% CI, 10.4–27.6), and ORR was 55.0% (95% CI, 39.6–70.4) per mRECIST by IIR and 25.0% (95% CI, 11.6–38.4) per RECIST version 1.1 by IIR. In the lenvatinib 12 mg starting-dose group, median OS was 18.2 months (95% CI, 11.3–26.9), and ORR was 39.0% (95% CI, 24.1–54.0) per mRECIST by IIR and 24.4% (95% CI, 11.3–37.5) per RECIST version 1.1 by IIR. It appears that safety and treatment exposure could be improved without compromising efficacy in patients with bodyweights less than 60 kg who receive lenvatinib 8 mg/day, supporting the use of bodyweight-based lenvatinib dosing in patients with uHCC.

In Study 202, toxicity appeared to be worse among patients in the lower bodyweight group versus the higher bodyweight group. Among patients in the lower bodyweight group, the rate of treatment-related TEAEs leading to lenvatinib dose reduction was 80.8%, and to lenvatinib dose reduction or interruption was 84.6%. Among patients in the higher bodyweight group, the rate of treatment-related TEAEs leading to lenvatinib dose reduction was 55.0%, and to lenvatinib dose reduction or interruption was 65.0%. However, in REFLECT, safety was generally comparable in the lenvatinib 8 mg and the 12 mg starting-dose groups. Treatment-related TEAEs led to dose reduction in 52.5% of patients and to dose reduction or interruption in 67.5% of patients in the lenvatinib 8 mg starting-dose group; in the 12 mg starting-dose group, treatment-related TEAEs led to dose reduction in 70.7% of patients and to dose reduction or interruption in 78.0% of patients. Although rates of treatment-related TEAEs leading to lenvatinib dose reduction or interruption may appear higher in the 12 mg starting-dose group of REFLECT than in the higher bodyweight group of Study 202, patient numbers are small, and caution should be used in directly comparing trials, as differences between study cohorts (e.g., age, microscopic portal vein invasion, Barcelona Clinic Liver Cancer status, and α-fetoprotein levels) could impact results.

When assessing specific treatment-related TEAEs, some interesting patterns were seen. In Study 202, several treatment-related TEAEs had a higher incidence in the lower bodyweight group compared with the higher bodyweight group; these included hypothyroidism (34.6% vs. 5.0%), diarrhea (46.2% vs. 20.0%), blood urine present (26.9% vs. 10.0%), proteinuria (65.4% vs. 50.0%), decreased appetite (61.5% vs. 50.0%), and decreased weight (30.8% vs. 20.0%). However, in REFLECT, incidences of the following specific treatment-related TEAEs were lower in the lenvatinib 8 mg starting-dose group or similar between the 8 and 12 mg starting-dose groups (8 vs. 12 mg): hypothyroidism (35.0% vs. 46.3%), diarrhea (35.0% vs. 39.0%), blood urine present (0% in both groups); proteinuria (37.5% vs. 53.7%), decreased appetite (45.0% vs. 51.2%), and decreased weight (20.0% vs. 19.5%). Although caution should be used when comparing clinical studies, as differences in results could stem from differences in patient populations or other factors, these data suggest that the increased incidences of these treatment-related TEAEs in patients with lower bodyweights compared with patients with higher bodyweights appear to be mitigated when bodyweight-based lenvatinib dosing is used. Given that these TEAEs could potentially impact quality of life and thus adherence to lenvatinib treatment, these findings strongly support bodyweight-based dosing in patients with uHCC. Comparison of lenvatinib dosing groups within REFLECT revealed that incidences of both hypothyroidism and proteinuria were higher in the 12 mg starting-dose group compared with the 8 mg starting-dose group (hypothyroidism, 46.3% vs. 35.0%; proteinuria, 53.7% vs. 37.5%); however, the exact reason for and clinical significance of this is unclear, and caution should be used when interpreting these results due to the limited number of patients in the Japanese subgroup. Several treatment-related TEAEs—specifically, thrombocytopenia, peripheral edema, neutropenia, and rash—did not display noticeable differences between groups in either Study 202 or REFLECT. Therefore, bodyweight-based dosing of lenvatinib did not appear to impact these treatment-related TEAEs.

These data are supported by a pooled analysis of lenvatinib pharmacokinetics, which included data from Study 202. This assessment included 8761 observations from a total of 452 individuals, including healthy participants and patients with a variety of tumor types. In this pharmacokinetic model, both clearance and volume of lenvatinib increased with higher bodyweight. A correlation was observed between the dose-normalized area under the curve and bodyweight, which was stronger in patients with HCC (R = −0.6803) than in those with solid tumors (R = −0.3273). This study also found that the lenvatinib area under the curve (based on the starting dose as a linear function) was a better predictor than any other parameter tested for the probability of adverse events leading to dose modifications during the first treatment cycle.

The current analysis has several limitations, namely, that direct comparisons between clinical trials are not recommended due to differences in study cohorts and inclusion/exclusion criteria. We have attempted to address this concern by not statistically comparing Study 202 with REFLECT, instead presenting the data side by side. Moreover, as REFLECT implemented bodyweight-based dosing, doses can be directly compared within that study. The current assessment is limited by the nature of the post hoc analyses and by the small number of patients included. Additionally, there are some differences in patient backgrounds, both between and within the two studies. Study 202 had a greater proportion of patients with an ECOG PS of 1 than did
REFLECT. In Study 202, 46.2% of patients in the lower bodyweight group had baseline α-fetoprotein levels less than 200 ng/ml compared with 75.0% in the higher bodyweight group; in REFLECT, 60.0% and 63.4% of patients in the lenvatinib 8 and 12 mg starting-dose groups, respectively, had baseline α-fetoprotein levels less than 200 ng/ml. It is possible that efficacy could be confounded in patients with lower α-fetoprotein levels, impacting data interpretation. Although age might impact toxicity, the numbers of overall patients in Study 202 and of Japanese patients in REFLECT are limited, thus the number of patients in each group would be too small to discern meaningful data if divided into further subgroups by age within the bodyweight groups. Moreover, age is likely to be confounded with bodyweight, as older patients tend to have lower bodyweights, making it difficult to differentiate the impact of age on lenvatinib exposure and treatment-related TEAEs within this analysis.

This analysis focuses on Japanese patients (with three Korean patients included in Study 202), and it is possible that these results might not generalize to a more global population. However, a review of published works on lenvatinib metabolism found no differences in pharmacokinetics or pharmacodynamics between Japanese patients and non-Japanese patients and concluded that race has no effect on apparent oral clearance. Additionally, the Japanese subgroup of patients from the lenvatinib arm in REFLECT had a higher percentage of patients with bodyweights less than 60 kg (51%) than the general population of patients from the lenvatinib arm in REFLECT (32%). Thus, the results of this analysis might be particularly relevant in Japanese patients. Furthermore, incidences of the most common adverse events are mainly higher in the Japanese population in REFLECT compared with the global REFLECT population. For these reasons, the most appropriate way to explore the safety implications of lenvatinib in patients with bodyweights less than 60 kg was to compare the patients in Study 202 with the Japanese population in REFLECT.

Although many targeted anticancer therapies approved for various indications use the maximum tolerated dose as the recommended dose, our findings suggest that, in some indications, dose adjustment by weight could reduce toxicity. This is particularly relevant in HCC because many anticancer treatments are metabolized in the liver. Liver impairment due to HCC and cirrhosis could impact the pharmacokinetic properties of these drugs and thereby increase toxicity and/or decrease efficacy. Therefore, starting-dose selection in patients with uHCC is crucial. To our knowledge, REFLECT was the first phase III trial of a kinase inhibitor in patients with uHCC that utilized bodyweight-based dosing. The current assessment is unique in that it explores the impact of bodyweight in both a phase II study and the phase III study that implemented bodyweight-based dosing based on results from that phase II study. These data further support the approved dosing regimen of lenvatinib in uHCC, specifically suggesting that safety is improved without compromising efficacy in patients with uHCC with lower bodyweights (<60 kg) when the starting dose is reduced from lenvatinib 12 mg/day to 8 mg/day.

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CONFLICT OF INTEREST
Takuji Okusaka reports research funding from AstraZeneca, Bristol Myers Squibb, and MSD. Masatoshi Kudo reports honoraria from Eisai, Bayer, MSD, Bristol Myers Squibb, EA Pharma, Eli Lilly, and Chugai Pharmaceutical; research funding from Eisai, Takeda, Otsuka, Taiho, EA Pharma, Gilead Sciences, AbbVie, Sumitomo Dainippon Pharma, Chugai Pharmaceutical, and Ono Pharmaceutical; and employment/leadership position/advisory role for Eisai, Ono Pharmaceutical, MSD, Bristol Myers Squibb, and Roche. Masafumi Ikeda reports honoraria from Bayer, Eisai, Eli Lilly Japan, Chugai Pharmaceutical, and Takeda; and research funding from AstraZeneca, Eisai, Eli Lilly Japan, MSD, Chugai Pharmaceutical, Bayer, Bristol Myers Squibb, Merck Serono, and Takeda. Michiko Sugawara and Toshiyuki Tamai are employees of Eisai Co., Ltd. Min Ren and Kenichi Saito are employees of Eisai Inc. Hiromitsu Kumada reports honoraria from MSD, Sumitomo Dainippon Pharma, AbbVie, Gilead Sciences, and Eisai. Kenji Ikeda and Kiwamu Okita declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT
The data will not be available for sharing at this time because the data are commercially confidential. However, Eisai will consider written requests to share the data on a case-by-case basis.

PREVIOUS PRESENTATIONS
Limited data from this manuscript were previously included in an abstract published at the American Society for Clinical Oncology virtual meeting, June 4–8, 2021.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.

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