

# Efficacy and Safety of Lenvatinib for Patients With Advanced Hepatocellular Carcinoma: A Retrospective, Real-world Study Conducted in Japan

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**Abstract.** *Aim:* We evaluated real-world efficacy and toxicity of lenvatinib in 142 patients with advanced hepatocellular carcinoma (HCC) at six tertiary referral centres. *Patients and Methods:* The patients with advanced HCC treated with lenvatinib were grouped into two categories based on REFLECT criteria for analysis of efficacy and safety. The primary endpoint was progression-free survival (PFS). *Results:* The objective response rate (ORR) at week 12 of therapy was 41.5%, with a median PFS of 176 days. Child–Pugh score of 5 points, the presence of extrahepatic metastasis and adverse effects grade 2 or higher were considered independent factors associated with both better PFS and ORR. The ORR for patients who fulfilled the REFLECT inclusion criteria was significantly higher than that for those who did not. However, no significant differences in PFS were observed between the two groups. The incidence rate of adverse effects grade 3 or higher was 40.1%, which was similar for the two groups. *Conclusion:* Lenvatinib is safe and effective for patients, whether or not they satisfy REFLECT criteria. The result warrants replication in a larger study.

Lenvatinib is recognised as a prerequisite for the successful treatment of advanced hepatocellular carcinoma (HCC) (1). In a recent phase 3, multinational, randomised, non-inferiority trial (REFLECT), lenvatinib was shown to be non-inferior to sorafenib with respect to overall survival and led to significant improvements in progression-free survival (PFS) compared with sorafenib as first-line systemic therapy for advanced HCC (2). Lenvatinib is a pan-receptor tyrosine kinase inhibitor (TKI) that targets vascular endothelial growth factor receptors 1 to 3, fibroblast growth factor receptors 1 to 4, platelet-derived growth factor receptor  $\alpha$ , c-KIT and receptor tyrosine kinases (3). However, TKIs have been associated with serious adverse effects (AEs) (4). The United States Food and Drug Administration has approved a variety of drugs for the treatment of HCC, including multi-kinase inhibitors, immune checkpoint inhibitors and combinations with standard chemotherapeutic drugs (5). Bevacizumab combined with atezolizumab is now recommended as first-line treatment for patients with advanced HCC as a result of consensus statements and recommendations by the Japan Society of Hepatology 2021 updated version (5). The efficacy and tolerability of lenvatinib as second-line treatment for advanced HCC remains unknown and may address an important aspect of HCC treatment (6). In the present study, we evaluated the real-world efficacy and toxicity of lenvatinib in patients with advanced HCC.

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**Key Words:** Lenvatinib, tyrosine kinase inhibitor, hepatocellular carcinoma, Child–Pugh, adverse events, progression-free survival, objective response.

## Patients and Methods

*Study design and patients.* In this multi-centre retrospective study, lenvatinib (Lenvima®; Eisai Co., Ltd., Tokyo, Japan) was administered orally to 190 patients with unresectable HCC from March 2018 to March 2020. This retrospective study was conducted at six institutions including Nara and Osaka, Japan, namely Nara

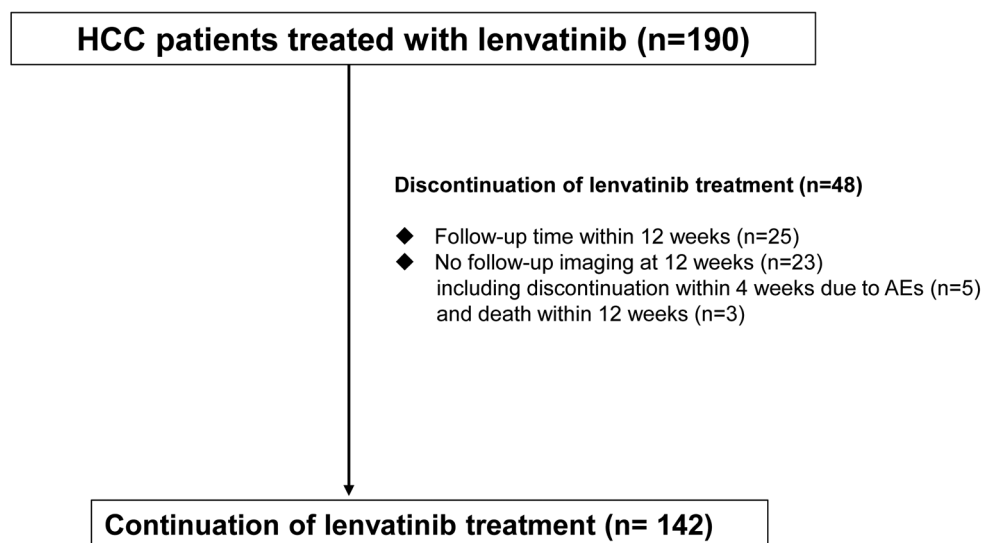


Figure 1. Flow chart showing patient enrolment in the study.

Medical University Hospital (n=79), Tenri Hospital (n=40), Nara Prefecture General Medical Center (n=34), Kindai University Nara Hospital (n=25), Osaka Bell Land General Hospital (n=10), Nara Prefecture Seiwa Medical Center (n=2). Of 190 patients, 48 patients were excluded because they had a follow-up time of less than 12 weeks (n=25) or did not undergo computed tomography examination at 12 months after treatment initiation (n=23), five of whom discontinued lenvatinib within 4 weeks because of AEs and three patients died within 12 weeks. In total, 142 patients with HCC were enrolled in the study (Figure 1). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee of Nara Medical University (Nara-med, 070-0056 approved on 13 February 2018). All patients provided written informed consent before the interview and a venous blood specimen.

**Protocol.** The dose of lenvatinib was based on body weight and was initially administered at 12 mg/day for those weighing 60 kg or more and 8 mg/day for those weighing less than 60 kg. For those with Child–Pugh grade B, 8 mg for those weighing 60 kg or more and 4 mg for those weighing less than 60 kg was administered once daily. Data for factors age, sex, background liver disease, aetiology, Child–Pugh score (CPS) and grade, Eastern Cooperative Oncology Group performance status (ECOG PS) and alpha-fetoprotein and des-gamma-carboxyprothrombin (DCP), number of hepatic lesions and their maximum diameter, tumour, node, metastasis (TNM) stage, initial dose, dose modification and prior treatment at baseline were obtained from medical records and radiological images.

**Diagnosis and evaluation of treatment response.** Treatment response was evaluated using the modified response evaluation criteria in solid tumours (mRECIST) (7). Lenvatinib was continued until the emergence of progressive disease, occurrence of unmanageable AEs or if a patient wished to discontinue treatment at their discretion. The objective response rate (ORR), PFS and disease control rate (DCR) were evaluated. The efficacy of lenvatinib was evaluated among

patients who did and did not fulfill the REFLECT trial inclusion criteria. The REFLECT trial criteria included patients who had one or more measurable target lesions based on mRECIST (7) (lesions previously treated with radiotherapy or locoregional therapy had to show radiographic evidence of disease progression to be deemed target lesions), Barcelona Clinic Liver Cancer stage B or C, (8) Child–Pugh class A, and an ECOG PS of 0 or 1. All eligible patients had controlled blood pressure ( $\leq 150/90$  mmHg), adequate liver function (albumin  $\geq 2.8$  g/dl, bilirubin  $\leq 3.0$  mg/dl, and aspartate aminotransferase, alkaline phosphatase, and alanine aminotransferase  $\leq 5$  times the upper limit of normal), and adequate bone marrow (haemoglobin  $\geq 8.5$  g/dl, platelet count  $\geq 75 \times 10^9/l$ , and absolute neutrophil count  $\geq 1.5 \times 10^9/l$ ).

All procedures involving human participants were based on the ethical guidelines of the Medical Ethics Committee of Nara Medical University (Nara-med, 063-0191 approved on 15 December 2015) and the Declaration of Helsinki principles. All enrolled patients voluntarily provided informed consent to participate in this study.

**Safety assessment.** Patients were evaluated every 2–4 weeks during lenvatinib therapy using laboratory tests and physical examinations for tolerability assessment, including ECOG PS, vital signs, physical findings, laboratory tests and urinalysis. Grades of AEs complied with the Common Terminology Criteria for Adverse Events version 4.0 (9). Patients that developed grade 3 or more or intolerable AEs had an adjustment of lenvatinib dose or treatment was interrupted according to the manufacturer’s instructions until the conditions before the start of treatment or recovery to grade 1 or lower was achieved.

**Statistical analysis.** The data are expressed as the median  $\pm$  interquartile range. The baseline characteristics between groups were compared using the Mann–Whitney *U*-test. Univariate and multivariate Cox regression analyses were used to identify the factors associated with PFS. Logistic regression analysis was performed for assessing the factors that affected the ORR. Kaplan–Meier plots of

the medians with 95% confidence intervals (CIs) were used for estimating PFS. The censoring date was defined as the date of the last follow-up. The median PFS was estimated using Kaplan–Meier plots of medians with 95% CIs, with the progression date defined according to mRECIST and the censoring date defined as the date of last radiological assessment without progression. All statistical analyses were conducted using the Statistical Package for the Social Sciences version 25 statistical software (IBM, Armonk, NY, USA). Values of  $p < 0.05$  were considered statistically significant.

## Results

**Patient characteristics.** This was a retrospective multi-centre study that enrolled patients who were administered lenvatinib for advanced HCC between March 2018 and March 2020. The baseline characteristics of the 142 HCC patients are summarised in Table I. The median age was 75 years (range=39-90 years) and 115 of the patients (81.0%) were male. Hepatitis C was the most common aetiology of HCC ( $n=47$ , 33.1%). The other patients had HBV ( $n=24$ , 16.9%), alcohol-related liver disease ( $n=31$ , 21.8%), non-alcoholic fatty liver disease ( $n=29$ , 20.4%) or autoimmune liver disease ( $n=11$ , 7.7%). The majority of those were classified with Child–Pugh score 5 or 6 [ $n=65$  (45.8%) and  $n=46$  (32.4%), respectively], at the time of lenvatinib administration. Thirty-eight patients (26.8%) had extrahepatic metastasis, with the most common metastatic site being the lymph nodes ( $n=21$ , 14.9%). This study included 19 (38.0%) patients with macrovascular invasion. Median serum alpha-fetoprotein and DCP levels were 34.5 ng/ml (range=0.8-364407 ng/ml) and 629 mAU/ml (range=9-511314 mAU/ml), respectively. Thirty-eight patients (26.8%) had extrahepatic metastasis including the lymph nodes ( $n=21$ , 14.8%). Of the 20 patients who had received prior systemic therapy, sorafenib and regorafenib had been administered to 14 (9.9%) and six (4.2%) patients, respectively.

In total, 44 (31.0%) patients in this study did not fulfil the REFLECT inclusion criteria (history of TKI in 20; Child–Pugh grade B in 31; bile duct invasion, in 3; and main portal trunk invasion in 3). Furthermore, the patients who did not fulfil REFLECT inclusion criteria exhibited a significantly higher CPS, more advanced stage, higher tumour number and higher rate of portal vein invasion, bile duct invasion, extrahepatic metastasis and prior TKI therapy compared with those who fulfilled the REFLECT inclusion criteria (Table I).

**Factors associated with treatment response.** A univariate logistic regression analysis demonstrated that the proportions of patients under 75 years old, with CPS of 5 points, Child–Pugh-A, DCP level  $< 600$  mAU/ml, no vascular invasion, presence of extrahepatic metastasis and AEs grade 1 or 2, were significantly higher in the group with an objective response compared with those in the group with stable or progressive disease (Table II). A multivariate logistic regression analysis

revealed that a CPS of 5 points [hazard ratio (HR)=0.341, 95% CI=0.1310-0.886;  $p=0.0273$ ], DCP level  $< 600$  mAU/ml (HR=0.171, 95% CI=0.0675-0.432;  $p < 0.01$ ), the presence of extrahepatic metastasis (HR=2.690, 95% CI=1.0100-7.220;  $p=0.048$ ) and AEs of grade 2 or more (HR=0.205, 95% CI=0.0833-0.504;  $p < 0.01$ ) were independent factors significantly associated with treatment response (Table III).

**Factors associated with PFS.** Overall, the median PFS was 176 days (95% CI=134-234 days) (Figure 2). Patients who fulfilled the REFLECT inclusion criteria tended to have a longer PFS compared with patients who did not (176 vs. 130 days; HR=0.92, 95% CI=0.51-1.69;  $p=0.0501$ ). Univariable analysis indicated that CPS of 5 points (HR=2.114, 95% CI=1.437-3.111;  $p < 0.01$ ), three or fewer tumours (HR=1.496, 95% CI=1.027-2.179;  $p=0.03574$ ), DCP level  $< 600$  mAU/ml (HR=1.638, 95% CI=1.126-2.383;  $p < 0.01$ ), no vascular invasion (HR=1.61, 95% CI=1.058-2.456;  $p=0.02636$ ), the presence of extrahepatic metastasis (HR=0.6174, 95% CI=0.3973-0.9596;  $p=0.03208$ ) and AEs of grade 2 or less (HR=1.57, 95% CI=1.083-2.291;  $p=0.01757$ ) were independent factors associated with favourable PFS (Table IV). In a multivariate analysis, a CPS of 5 points (HR=2.1860, 95% CI=1.3910-3.4360;  $p < 0.01$ ), the presence of extrahepatic metastasis (HR=0.5856, 95% CI=0.3731-0.9193;  $p=0.02003$ ) and AEs of grade 2 or less (HR=1.7560, 95% CI=1.1890-2.5930;  $p < 0.01$ ) were identified as factors associated with a favourable PFS. A Kaplan–Meier survival analysis showed that the median PFS was significantly longer in patients with a CPS of 5 points compared with those with a CPS of 6 points or more (245 vs. 130 days,  $p < 0.01$ ; Figure 3A). The median PFS tended to be longer in patients with fewer tumours (235 days vs. 80 days for those with  $\leq 3$  vs.  $\geq 4$ ,  $p=0.0338$ ; Figure 3B); patients with DCP  $< 600$  mAU/ml (252 vs. 135 days,  $p < 0.01$ ; Figure 3C); patients with vascular invasion (191 vs. 127 days;  $p=0.0244$ ; Figure 3D); patients with extrahepatic metastasis (348 vs. 156 days;  $p=0.0298$ ; Figure 3E) and patients with AEs grade 2 or less (240 vs. 127 days;  $p=0.0162$ ; Figure 3F).

**Treatment response and PFS in patients according to REFLECT inclusion criteria.** Response rates at week 12 after treatment initiation with lenvatinib were evaluated. Of the 142 patients, nine (6.3%), 50 (35.2%), 49 (34.5%) and 34 (24.0%) showed a CR, PR, SD and PD, respectively (Table V). The ORR and DCR were 41.5% and 76.0%, respectively. The ORR was significantly higher in patients who fulfilled the REFLECT criteria compared with those who did not (49.0% vs. 25.0%,  $p < 0.01$ ). No significant differences in DCR were observed between the two groups ( $p=0.201$ ) (79.6% vs. 68.2%).

Furthermore, the ORR was similar for patients with and without prior TKI therapy (21.4% vs. 43.8%,  $p=0.154$ ); Child–

Table I. Characteristics of study patients with hepatocellular carcinoma.

Characteristic	Subgroup	REFLECT criteria			p-Value
		Overall cohort (n=142)	Fulfilled (n=98)	Not fulfilled (n=44)	
Age, years	Median (range)	75 (39-90)	76 (39-90)	72 (52-88)	0.0584
Gender, n (%)	Male	115 (80.99%)	78 (79.59%)	37 (84.09%)	0.646
	Female	27 (19.01%)	20 (20.41%)	7 (15.91%)	
Etiology, n (%)	HBV	24 (16.90%)	19 (19.39%)	5 (11.36%)	0.109
	HCV	47 (33.10%)	34 (34.69%)	13 (29.55%)	
	ArLD	29 (20.42%)	14 (14.29%)	15 (34.10%)	
	NASH	31 (21.83%)	22 (22.45%)	9 (20.45%)	
	other	11 (7.75%)	9 (9.18%)	2 (4.54%)	
Child Pugh score, n (%)	5	65 (45.77%)	56 (57.14%)	9 (20.45%)	<0.01
	6	46 (32.39%)	42 (42.86%)	4 (9.10%)	
	7	18 (12.68%)	0 (0%)	18 (40.91%)	
	8	11 (7.75%)	0 (0%)	11 (25.0%)	
	9	2 (1.41%)	0 (0%)	2 (4.54%)	
Body weight, kg	Median (range)	60.5 (34.2-97.0)	61.0 (34.2-91.0)	60.0 (40.7-97.0)	0.786
Dose, n (%)	12 mg	37 (26.06%)	32 (32.65%)	8 (18.19%)	0.154
	8 mg	89 (62.67%)	60 (61.23%)	31 (70.45%)	
	4 mg	16 (11.27%)	6 (6.12%)	5 (11.36%)	
ECOG PS, n (%)	0	131 (92.25%)	91 (92.86%)	40 (90.91%)	0.739
	1	11 (7.75%)	7 (7.14%)	4 (9.09%)	
TNM stage, n (%)	I	0 (0%)	0 (0%)	0 (0%)	0.0189
	II	14 (9.86%)	10 (10.20%)	4 (9.10%)	
	III	67 (47.18%)	54 (55.10%)	13 (29.55%)	
	IVA	23 (16.20%)	14 (14.29%)	9 (20.45%)	
	IVB	38 (26.76%)	20 (20.41%)	18 (40.90%)	
Portal vein invasion, n (%)	Absent	129 (90.85%)	94 (95.92%)	35 (79.55%)	<0.01
	Vp2	4 (2.82%)	2 (2.04%)	2 (4.55%)	
	Vp3	6 (4.22%)	2 (2.04%)	4 (9.09%)	
	Vp4	3 (2.11%)	0 (%)	3 (6.81%)	
Inferior vena cava invasion, n (%)	Absent	133 (93.66%)	92 (93.88%)	41 (93.18%)	>0.99
	Present	9 (6.34%)	6 (6.12%)	3 (6.82%)	
Bile duct invasion, n (%)	Absent	139 (97.89%)	98 (100%)	41 (93.18%)	<0.01
	Present	3 (2.11%)	0 (0%)	3 (6.82%)	
Lymph node metastasis, n (%)	Absent	121 (85.21%)	86 (87.76%)	35 (79.55%)	0.211
	Present	21 (14.79%)	12 (12.24%)	9 (20.45%)	
Extrahepatic metastasis, n (%)	Absent	104 (73.24%)	78 (79.59%)	26 (59.10%)	0.0141
	Present	38 (26.76%)	20 (20.41%)	18 (40.90%)	
Maximum intrahepatic tumor size, cm	Median (range)	4.0 (0.5-18.0)	3.9 (0.5-18)	4.5 (1-12)	0.801
Number of intrahepatic lesions	Median (range)	4 (1-20)	3.5 (0-20)	8 (1-20)	<0.01
AFP, ng/ml	Median (range)	34.5 (0.8-364407)	30.0 (0.8-339510)	48.2 (1.9-364407)	0.409
DCP, mAU/ml	Median (range)	629 (9-511314)	558.5 (9-395936)	705.5 (14-511314)	0.1582
Prior treatment					
Surgery, n (%)	Absent	90 (63.38%)	60 (61.22%)	30 (68.18%)	0.457
	Present	52 (36.62%)	38 (38.78%)	14 (31.82%)	
RFA, n (%)	Absent	76 (53.52%)	57 (58.16%)	18 (40.90%)	0.051
	Present	66 (46.48%)	41 (41.84%)	26 (59.10%)	
TACE, n (%)	Absent	53 (37.32%)	35 (35.71%)	18 (40.90%)	0.578
	Present	89 (62.68%)	63 (64.29%)	26 (59.10%)	
Hepatic arterial infusion, n (%)	Absent	123 (86.62%)	84 (85.71%)	39 (88.64%)	0.792
	Present	19 (13.38%)	14 (14.29%)	5 (11.36%)	
Sorafenib or regorafenib, n (%)	Absent	128 (90.14%)	98 (100%)	24 (54.55%)	<0.01
	Present	14 (9.86%)	0 (0%)	20 (45.45%)	

AFP: Alpha fetoprotein; ArLD: alcohol-related liver disease; DCP: *des*-gamma-carboxy prothrombin; ECOG PS: Eastern Cooperative Oncology Group performance status score; NASH: non-alcoholic fatty liver disease; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization.

Table II. Analysis of factors associated with objective response (complete plus partial responses) in patients with advanced hepatocellular carcinoma treated with lenvatinib.

Variable	Subgroup	Objective response, n (%)			p-Value
		Total	No (n=83)	Yes (n=59)	
Gender	Male	115 (80.99%)	65 (78.31%)	50 (84.75%)	0.338
	Female	27 (19.01%)	18 (23.69%)	9 (15.25%)	
Age	<75 Years	66 (46.48%)	33 (39.76%)	33 (55.93%)	0.0627
	≥75 Years	76 (53.52%)	50 (60.24%)	26 (44.07%)	
Etiology	Viral	71 (50.0%)	39 (46.99%)	32 (52.24%)	0.395
	Nonviral	71 (50.0%)	44 (53.01%)	27 (45.76%)	
Child–Pugh score	5	65 (45.77%)	29 (34.94%)	36 (61.02%)	<0.01
	6	77 (54.23%)	54 (65.06%)	23 (38.98%)	
Child–Pugh grade	A	111 (78.17%)	60 (72.29%)	51 (86.44%)	0.0483
	B	31 (21.83%)	23 (27.71%)	8 (13.56%)	
Tumor number	≤3	63 (44.37%)	34 (40.96%)	29 (49.15%)	0.392
	≥4	79 (55.63%)	49 (59.04%)	30 (50.85%)	
Tumor size	<5 cm	87 (61.27%)	50 (60.24%)	37 (62.71%)	0.862
	≥5 cm	55 (38.73%)	33 (39.76%)	22 (37.29%)	
AFP ng/ml	<40 ng/ml	74 (50.11%)	39 (46.99%)	35 (59.32%)	0.174
	≥40 ng/ml	68 (47.89%)	44 (53.01%)	24 (40.68%)	
DCP	<600 mAU/ml	68 (47.89%)	28 (33.73%)	40 (67.80%)	<0.01
	≥600 mAU/ml	74 (52.11%)	55 (66.27%)	19 (32.20%)	
Vascular invasion	Absent	107 (75.35%)	55 (66.27%)	52 (88.14%)	<0.01
	Present	35 (24.65%)	28 (33.73%)	7 (11.86%)	
Lymph node metastasis	Absent	121 (85.21%)	70 (84.34%)	51 (86.44%)	0.728
	Present	21 (14.79%)	13 (15.67%)	8 (13.56%)	
Extrahepatic metastasis	Absent	104 (73.24%)	66 (79.52%)	38 (64.41%)	0.0472
	Present	38 (26.76%)	17 (20.48%)	21 (35.59%)	
TNM stage	II, III	81 (57.04%)	46 (55.42%)	35 (59.32%)	0.644
	IVA, IVB	61 (42.96%)	37 (44.58%)	24 (40.68%)	
Previous treatment history	Absent	27 (19.01%)	16 (19.28%)	11 (18.64%)	0.925
	Present	115 (80.99%)	67 (80.72%)	48 (81.36%)	
TACE history	Absent	53 (37.32%)	32 (38.55%)	21 (35.59%)	0.719
	Present	89 (62.68%)	51 (61.45%)	38 (64.41%)	
TKI therapy	Absent	128 (90.14%)	72 (86.75%)	56 (94.92%)	0.121
	Present	14 (9.86%)	11 (13.25%)	3 (5.08%)	
Dose reduction at initiation of lenvatinib	Absent	90 (63.38%)	53 (63.86%)	37 (62.71%)	0.889
	Present	52 (36.62%)	30 (36.14%)	22 (37.29%)	
Dosage reduction after initiation of lenvatinib	Absent	107 (75.35%)	66 (79.52%)	41 (69.49%)	0.174
	Present	35 (24.65%)	17 (20.48%)	18 (30.51%)	
Adverse effects	≤Grade 2	97 (68.31%)	53 (63.86%)	44 (74.58%)	<0.01
	≥Grade 3	45 (31.69%)	30 (36.14%)	15 (25.42%)	

AFP: Alpha fetoprotein; ArLD: alcohol-related liver disease; DCP: *des*-gamma-carboxy prothrombin; NASH: non-alcoholic fatty liver disease; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization; TKI: tyrosine kinase inhibitor.

Pugh A versus Child–Pugh B (45.8% vs. 56.0%,  $p=0.102$ ); and patients with and without main portal trunk invasion (33.3% vs. 41.7%,  $p>0.99$ ). The DCR was also similar for patients when compared by these factors (Table VI).

A Kaplan–Meier analysis showed that the median PFS tended to be longer in patients who fulfilled the REFLECT inclusion criteria compared with patients who did not (178 vs. 130 days; HR=0.67, 95% CI=0.4469–1.004,  $p=0.0501$ ; Figure 4A) and in patients with Child–Pugh A versus Child–Pugh B (median PFS 177 days and 153 days,  $p=0.0946$ ;

Figure 4B). The median PFS was similar for patients regardless of main portal trunk invasion (176 days with and 49 days without,  $p=0.492$ ; Figure 4C) and prior TKI therapy (177 days with and 176 days without,  $p=0.478$ ; Figure 4D).

**Adverse events.** Lenvatinib-related AEs are summarised in Table VII. The overall incidences of drug related AEs of any grade and of grade 3 or more were 97.2% (in 138 out of 142 patients) and 40.1% (in 57 out of 142 patients), respectively. The most frequent lenvatinib-related AEs grade 3 or more

Table III. Multivariate analysis of objective response at 12 weeks in patients with advanced hepatocellular carcinoma treated with lenvatinib.

Variable	Comparator vs. referent (HR=1)	Odds ratio	95% CI	p-Value
Age	<75 vs. ≥75 Years	0.495	0.2100-1.170	0.109
Child–Pugh score	6 vs. 5	0.341	0.1310-0.886	0.0273
DCP	≥600 vs. <600 mAU/ml	0.171	0.0675-0.432	<0.01
Vascular invasion	Present vs. absent	0.414	0.1360-1.260	0.120
Extrahepatic metastasis	Present vs. absent	2.690	1.0100-7.220	0.048
Adverse effects	≥grade 3 vs. ≤grade 2	0.205	0.0833-0.504	<0.01

CI: Confidence interval; DCP: *des*-gamma-carboxy prothrombin.

were hypertension (13.4%), general fatigue (12.0%), proteinuria (7.0%) and hepatic encephalopathy (7.0%).

Lenvatinib-related AEs were assessed according to whether patients met REFLECT inclusion criteria. The most commonly reported AEs were appetite loss (44.9%), hypertension (39.8%), proteinuria (33.7%) and hypothyroidism (27.6%) in those who fulfilled the REFLECT inclusion criteria. Appetite loss (59.1%), general fatigue (43.2%), diarrhoea (27.3%) and hypothyroidism (25.0%) were the most frequent observed in those who did not (Table VIII). The prevalence of proteinuria and general fatigue was significantly higher and lower, respectively, in those who fulfilled the inclusion criteria compared with those who did not ( $p=0.0426$  and  $p=0.0161$ ). There were no significant differences in grade 3 or more AEs between the two groups (Table IX).

## Discussion

The treatment sequence after immune checkpoint inhibitor plus TKI combination therapy remains an important issue considering that standard second-line options include several TKIs, such as lenvatinib.

We compared the real-world efficacy and safety of lenvatinib between patients who did and did not fulfil the REFLECT inclusion criteria. Of these, 31.0% (44/142) of the included patients with advanced HCC did not fulfil the REFLECT trial inclusion criteria. In summary, the early response rates and tolerability were favourable and they were similar for patients who fulfilled the REFLECT inclusion criteria and those who did not. PFS was longer in the REFLECT trial compared with patients who fulfilled the REFLECT inclusion criteria in this study (7.3 vs. 5.9 months). This may be explained by the fact that a greater proportion of patients who fulfilled the REFLECT criteria in this study had a CPS of 6 points [42.9% (42/98) vs. 22.5% (107/475)], previous transarterial chemoembolization [64.3% (63/98) vs. 51.5% (246/478)] and were significantly older (76 vs. 63 years) (data not shown).

The results of randomised controlled trials revealed that side-effects can enhance treatment response through

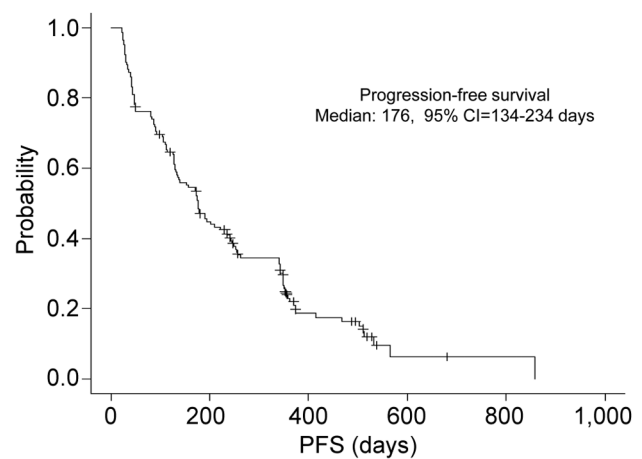


Figure 2. Kaplan–Meier analysis of progression-free survival in 142 patients treated with lenvatinib. Median progression-free survival was 176 days (95% confidence interval=134-234 days).

expectancy effects (10). We have shown that AEs of grade 2 or less are significant independent factors associated with both higher ORR and longer PFS times. Our findings are consistent with those of Ohki *et al.* who showed that AEs were negatively associated with PFS in patients with HCC treated with lenvatinib (11). In contrast, AEs have been shown to be a positive predictor of overall survival in patients with HCC treated with lenvatinib (12, 13). In addition, the development of dermatological adverse events was shown to be associated with better survival in patients with HCC treated with sorafenib (14). This indicates that the relationship between treatment efficacy and AEs for lenvatinib therapy remains controversial. Our findings reinforce the fact that less serious AEs might predict favourable treatment response and longer survival in patients with advanced HCC treated with lenvatinib. Furthermore, the recommended daily dose of lenvatinib should be administered as long as a clinical benefit is observed without serious AEs to improve the response rate, efficacy and tolerability of lenvatinib.

Table IV. Analysis of factors associated with progression-free survival in patients with advanced hepatocellular carcinoma treated with lenvatinib.

Variable	Comparator vs. referent (HR=1)	Univariate Cox hazard analysis			Multivariate Cox hazard analysis		
		HR	95% CI	p-Value	HR	95% CI	p-Value
Gender	Male vs. female	1.435	0.912-2.257	0.1184			
Age	<75 vs. ≥75 Years	1.289	0.891-1.865	0.1779			
Etiology	Viral vs. nonviral	0.9577	0.6628-1.384	0.8178			
Child-Pugh score	5 vs. 6	2.114	1.437-3.111	<0.01	2.1860	1.3910-3.4360	<0.01
Child-Pugh grade	A vs. B	1.473	0.9311-2.33	0.09797			
Tumor number	≤3 vs. ≥4	1.496	1.027-2.179	0.03574	1.1390	0.7681-1.6900	0.5165
Tumor size	<5 vs. ≥5 cm	1.162	0.7974-1.693	0.4349			
AFP	<40 vs. ≥40 ng/ml	1.388	0.9601-2.007	0.08122	1.1810	0.7857-1.7760	0.4234
DCP	<600 vs. ≥600 mAU/ml	1.638	1.126-2.383	<0.01	1.247	0.6715-2.3160	0.4844
Vascular invasion	Absent vs. present	1.61	1.058-2.456	0.02636	1.325	0.8346-2.103	0.2329
Lymph node metastasis	Absent vs. Present	1.155	0.6878-1.939	0.5861			
Extrahepatic metastasis	Absent vs. Present	0.6174	0.3973-0.9596	0.03208	0.5856	0.3731-0.9193	0.02003
TNM stage	II, III vs. IVA, IVB	0.9988	0.6879-1.45	0.9948			
Previous treatment history	Absent vs. present	0.8933	0.5439-1.467	0.656			
TACE history	Absent vs. present	0.8602	0.5846-1.266	0.4446			
TKI therapy	Absent vs. present	1.242	0.6804-2.266	0.4806			
Dose reduction at initiation of lenvatinib	Absent vs. present	0.7938	0.5372-1.173	0.2464			
Dosage reduction after initiation of lenvatinib	Absent vs. present	0.8151	0.534-1.244	0.3434			
Adverse effects	Grade ≤2 vs. ≥3	1.57	1.083-2.291	0.01757	1.7560	1.1890-2.5930	<0.01

AFP: Alpha fetoprotein; DCP: *des*-gamma-carboxy prothrombin; TACE: transcatheter arterial chemoembolization; TKI: tyrosine kinase inhibitor; TNM: tumor node metastasis.

Table V. Response to lenvatinib therapy according to fulfilment of REFLECT criteria.

Treatment response	REFLECT criteria, n (%)			
	Overall cohort (n=142)	Fulfilled (n=98)	Not fulfilled (n=44)	p-Value
Complete response	9 (6.3%)	8 (8.2%)	1 (2.3%)	0.274
Partial response	50 (35.2%)	40 (40.8%)	10 (22.7%)	0.039
Stable disease	49 (34.5%)	30 (30.6%)	19 (43.2%)	0.182
Progressive disease	34 (23.9%)	20 (20.4%)	14 (31.8%)	0.201
Objective response rate	59 (41.5%)	48 (49.0%)	11 (25.0%)	<0.01
Disease control rate	108 (76.1%)	78 (79.6%)	30 (68.2%)	0.201

Comparing the efficacy of lenvatinib according to the REFLECT inclusion criteria, the ORR in our study was higher in patients with HCC who fulfilled the REFLECT trial inclusion criteria compared with those who did not. Patients who fulfilled the criteria tended to have a longer PFS compared with patients who did not, although the difference was not statistically significant. Goh *et al.* demonstrated that patients who fulfilled the REFLECT eligibility criteria had better DCR and overall survival than those of patients who did not (15). In contrast, Sho *et al.* demonstrated that the efficacy was similar regardless of

REFLECT inclusion criteria (16, 17). This may have resulted from differences in factors for patients who did not fulfil the REFLECT inclusion criteria. These findings suggest that lenvatinib is more effective in patients who fulfil the REFLECT inclusion criteria *versus* those who do not. Nevertheless, the results indicate that further investigation is warranted to confirm these findings.

This study had some limitations. The study was retrospective and some information was missing because of its retrospective nature. The observation period was short and limited to 12 weeks. In addition, the characteristics of

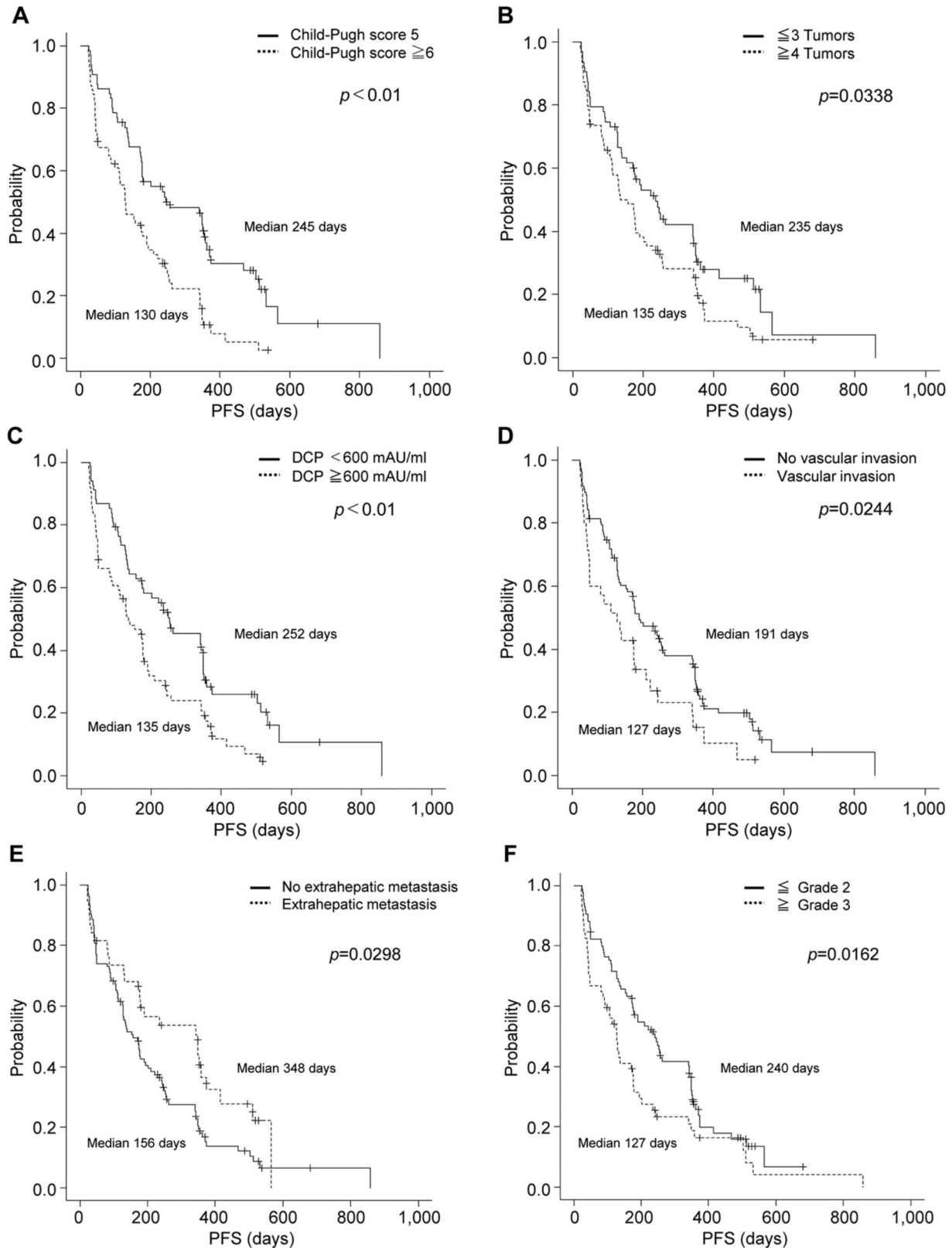


Figure 3. Kaplan–Meier analysis of progression-free survival in 142 patients with hepatocellular carcinoma treated with lenvatinib stratified by Child–Pugh score (A), tumour number (B), des-gamma-carboxy prothrombin (DCP) level (C), vascular invasion (D), extrahepatic metastasis (E) and adverse effects (F).

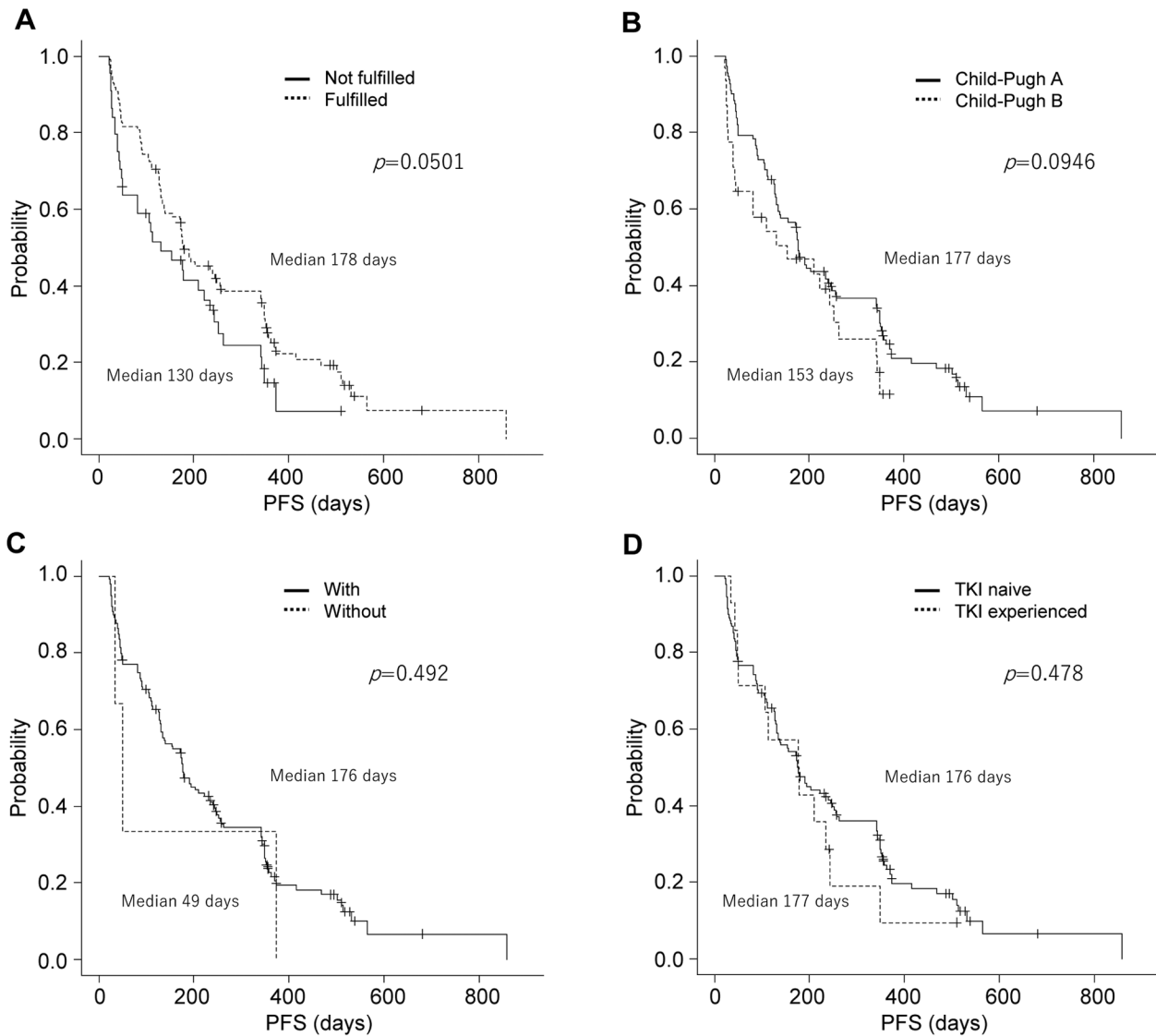


Figure 4. Kaplan-Meier analysis of progression-free survival in 142 patients with hepatocellular carcinoma treated with lenvatinib stratified by the REFLECT trial eligibility criteria (A), Child-Pugh grade (B), main portal trunk invasion (Vp4) (C) and prior tyrosine kinase inhibitor (TKI) therapy (D).

patients who did not meet the REFLECT inclusion trial were varied. Therefore, prospective studies with large cohorts and long observation periods are required to validate these results

In conclusion, we verified the treatment response and tolerability toward AEs arising in patients with HCC treated with lenvatinib. This real-world study demonstrated that lenvatinib provides a high early response rate and favourable tolerability for advanced HCC in patients regardless of fulfilling the REFLECT trial inclusion criteria. Lenvatinib has the potential to become an appropriate post-treatment agent following therapy with atezolizumab and bevacizumab.

### Conflicts of Interest

The Authors declare they have no conflicts of interest.

### Authors' Contributions

Conceptualization: H. Kinoshita; investigation: A. Okano, and M. Ohana, D. Kinoshita, T. Kawasaki, Y. Aihara, T. Nakatani, H. Kinoshita, T. Ann, K. Saito, M. Yoshida; data curation: N. Shimozato; writing – original draft preparation: N. Shimozato and T. Namisaki; writing – review and editing: T. Namisaki and H. Yoshiji. All Authors read and approved the article.

Table VI. Response to lenvatinib therapy according to tyrosine kinase inhibitor (TKI) experience, Child–Pugh class and main portal trunk invasion (Vp4).

	Treatment response		p-Value
	Objective response rate	Disease control rate	
<b>TKI</b>			
Naïve (n=128)	43.8%	76.7%	0.154
Experienced (n=14)	21.4%	71.4%	0.743
<b>Child–Pugh class</b>			
A (n=111)	45.9%	76.6%	0.102
B (n=31)	25.8%	74.2%	0.814
<b>Vp4 status</b>			
Absent (n=139)	41.7%	77.0%	>0.99
Present (n=3)	33.3%	33.3%	0.142

Table VII. Frequency of adverse events during lenvatinib treatment.

Adverse event	Any grade, n (%)	Grade ≥3, n (%)
Hypertension	51 (35.9%)	19 (13.4%)
Proteinuria	47 (33.1%)	10 (7.0%)
Hand–foot syndrome	31 (21.8%)	4 (2.8%)
Skin rash	10 (7.0%)	1 (0.7%)
Diarrhea	30 (20.4%)	4 (2.8%)
Appetite loss	72 (50.7%)	8 (5.6%)
Bone marrow suppression	14 (9.9%)	5 (3.5%)
Liver dysfunction	6 (4.2%)	0 (0%)
Hepatic encephalopathy	12 (8.5%)	10 (7.0%)
General fatigue	63 (44.4%)	17 (12.0%)
Hypothyroidism	38 (26.8%)	0 (0%)
Bleeding	6 (4.2%)	3 (2.1%)

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Table VIII. All adverse events according to fulfilment of REFLECT criteria.

	REFLECT criteria, n (%)		p-Value
	Fulfilled (n=98)	Not fulfilled (n=44)	
Hypertension	39 (39.8%)	10 (22.7%)	0.0571
Proteinuria	33 (33.7%)	7 (15.9%)	0.0426
Hand–foot syndrome	23 (23.5%)	6 (13.6%)	0.26
Skin rash	9 (9.2%)	2 (4.5%)	0.503
Diarrhea	15 (15.3%)	12 (27.3%)	0.108
Appetite loss	44 (44.9%)	26 (59.1%)	0.147
Bone marrow suppression	12 (12.2%)	1 (2.3%)	0.0645
Liver dysfunction	3 (3.1%)	3 (6.8%)	0.374
Liver failure	6 (6.1%)	5 (11.4%)	0.316
General fatigue	22 (22.4%)	19 (43.2%)	0.0161
Hypothyroidism	27 (27.6%)	11 (25.0%)	0.839
Bleeding	5 (5.1%)	2 (4.5%)	>0.99

Table IX. Grade 3 or higher adverse events according to fulfilment of REFLECT criteria.

	REFLECT criteria, n (%)		p-Value
	Fulfilled (n=40)	Not fulfilled (n=17)	
Hypertension	21 (52.5%)	5 (29.4%)	0.149
Proteinuria	14 (35.0%)	3 (17.6%)	0.224
Hand–foot syndrome	9 (22.5%)	2 (11.8%)	0.476
Skin rash	2 (5.0%)	2 (11.8%)	0.575
Diarrhea	6 (15.0%)	4 (23.5%)	0.484
Appetite loss	20 (50.0%)	11 (64.7%)	0.389
Bone marrow suppression	8 (20.0%)	0 (0%)	0.0899
Liver dysfunction	1 (2.5%)	1 (5.9%)	0.511
Liver failure	6 (15%)	3 (17.6%)	>0.99
General fatigue	17 (42.5%)	9 (52.9%)	0.566
Hypothyroidism	9 (22.5%)	4 (23.5%)	>0.99
Bleeding	3 (7.5%)	1 (5.9%)	>0.99

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