

## Supplementary Materials

**Table S1.** Background data of patients in the treatment and no treatment groups.

	Treatment group	No treatment group	<i>p</i> -Value
Number	96	31	
Age (years old)	69.6 (25.4–87.0)	73.0 (40.4–86.7)	0.189
Men	78 (81.3%)	24 (77.4%)	0.641
HBV	14 (14.6%)	5 (16.1%)	0.834
HCV	52 (54.2%)	17 (54.8%)	0.948
HBV+HCV	3 (3.1%)	0 (0.0%)	0.319
Alcoholic	13 (13.5%)	2 (6.5%)	0.288
NASH	8 (8.3%)	4 (12.9%)	0.449
Others	6 (6.3%)	3 (9.7%)	0.518
FIB-4 index	4.85 (0.48–27.8)	7.73 (1.44–39.5)	0.145
Child–Pugh score	5.5 (5 – 11)	8 (5 –13)	<0.001
ALBI score	–2.35 (–3.26 to –0.81)	–1.59 (–2.87 to –0.62)	<0.001
AFP (ng/mL)	107 (1–671940)	204 (1–245405)	0.818
DCP (mAU/mL)	506 (10–1084600)	1261 (22–562056)	0.040
Frequency of multiple intrahepatic HCC	70 (72.9%)	25 (80.6%)	0.389
Maximum size of intrahepatic HCC (mm)	38 (0–154)	58 (0–140)	0.003
Vascular invasion	55 (57.3%)	25 (80.6%)	0.019
Hepatic TNM	3 (0–4)	4 (0–4)	0.013
Performance status	0 (0–4)	0 (0–2)	0.665
Bone metastasis alone	32 (33.3%)	4 (12.9%)	0.028
Lung metastasis alone	13 (13.5%)	12 (38.7%)	0.002
Lymph node metastasis alone	16 (16.7%)	13 (41.9%)	0.004
another organ metastasis	5 (5.2%)	0 (0.0%)	0.195
Multiple metastases	30 (31.3%)	2 (6.5%)	0.006

AFP,  $\alpha$ -fetoprotein; DCP, des- $\gamma$ -carboxy prothrombin; HBV, hepatitis B virus; HCV, hepatitis C virus ; NASH, nonalcoholic steatohepatitis ; TNM, tumor-node-metastasis.

**Table S2.** Contents of TKI and conventional therapies.

	TKI group			Non-TKI group		p-Value
	TKI alone	TKI plus conventional therapies	Use of pembrolizumab or ramucirumab	Conventional therapies	TKI use before extrahepatic metastases	
n	29	36	2 (excluded)	25	4 (excluded)	
SOR	24	17	1	0	4	0.003 <sup>a)</sup>
LEN	4	12	0	0	0	0.069 <sup>a)</sup>
		7				
Multiple TKIs	1 SOR+LEN (1)	SOR+REG (1) SOR+LEN (5) SOR+REG+LEN (1)	1 SOR+REG (1)	0	0	0.051 <sup>a)</sup>
TACE/TAI		11		11		0.282 <sup>b)</sup>
RT		12		7		0.658 <sup>b)</sup>
TACE/TAI +RT		9		2		0.089 <sup>b)</sup>
other		4		5		0.336 <sup>b)</sup>

LEN, lenvatinib; REG, regorafenib; RT, radiation therapy; SOR, sorafenib; TACE, transcatheter arterial chemoembolization; TAI, transhepatic arterial infusion; other includes surgical resection and oral UFT (tegafur/uracil); TKI, Tyrosine kinase inhibitor. a) Comparison of TKI between TKI alone and TKI plus conventional therapies. b) Comparison of conventional therapies between TKI group and non-TKI group.

**Table S3.** Background data of patients in TKI and non-TKI groups.

	TKI group	Non-TKI group	p-Value
Number	65	25	
Age (years old)	70.3 (25.4–85.9)	69.7 (49.6–87.0)	0.961
Men	54 (83.1%)	19 (76.0%)	0.442
FIB4-index	4.77 (0.48–27.8)	4.97 (1.74–25.7)	0.121
Child–Pugh score	5 (5–11)	6 (5–10)	0.021
ALBI score	–2.41 (–3.25 to –0.90)	–2.03 (–3.26 to –0.81)	0.016
AFP (ng/mL)	63 (1–128650)	403 (2–671940)	0.140
DCP (mAU/mL)	395 (10–1084600)	1932 (16–562056)	0.077
Frequency of multiple intrahepatic HCC	45 (69.2%)	20 (80.0%)	0.307
Maximum size of intrahepatic HCC (mm)	35 (0–154)	41 (0–138)	0.114
Vascular invasion	30 (46.2%)	19 (76.0%)	0.011
Hepatic TNM	3 (0–4)	4 (0–4)	0.008
Performance status	0 (0–3)	0 (0–4)	0.250

AFP,  $\alpha$ -fetoprotein; DCP, des- $\gamma$ -carboxy prothrombin; TKI, Tyrosine kinase inhibitor; TNM, tumor-node-metastasis. .

**Table S4.** Background data of patients who started TKI after diagnosis of metastases.

	TKI group	Non-TKI group	p-Value
Number	56	25	
Age (years old)	70.0 (45.9–85.9)	69.7 (49.6–87.0)	0.862
Men	46 (82.1%)	19 (76.0%)	0.521
FIB-4 index	4.19 (0.48–18.0)	4.97 (1.74–25.7)	0.076
Child–Pugh score	5 (5–11)	6 (5–10)	0.035
ALBI score	–2.42 (–3.25 to –0.90)	–2.03 (–3.26 to –0.81)	0.016
AFP (ng/mL)	84 (1–128650)	403 (2–671940)	0.142
DCP (mAU/mL)	442 (10–1084600)	1932 (16–562056)	0.125
Frequency of multiple intrahepatic HCC	38 (67.9%)	20 (80.0%)	0.263
Maximum size of intrahepatic HCC (mm)	35 (0–154)	41 (0–138)	0.123
Vascular invasion	26 (46.4%)	19 (76.0%)	0.013
Hepatic TNM	3 (0–4)	4 (0–4)	0.009
Performance status	0 (0–3)	0 (0–4)	0.214

AFP,  $\alpha$ -fetoprotein; DCP, des- $\gamma$ -carboxy prothrombin; TKI, Tyrosine kinase inhibitor; TNM, tumor-node-metastasis.

**Table S5.** Background data of Child-Pugh A and B patients who started TKI after diagnosis of metastases.

	Child-Pugh A			Child-Pugh B		
	TKI	Non-TKI	P-value	TKI	Non-TKI	P-value
Number	46	15		9	9	
Age (years old)	69.6 (45.9–85.9)	75.5 (61.8–83.4)	0.115	73.9 (51.9–83.4)	63.7 (49.6–87.0)	0.301
Men	37 (80.4%)	11 (73.3%)	0.560	8 (88.9%)	7 (77.8%)	0.527
FIB-4 index	3.75 (0.48–18.0)	4.43 (1.74–14.3)	0.303	6.95 (3.75–17.2)	12.3 (3.58–25.7)	0.174
ALBI score	–2.49 (–3.25 to –1.83)	–2.38 (–3.26 to –1.65)	0.182	–1.92 (–2.21 to –1.19)	–1.77 (–2.44 to –0.90)	0.640
AFP (ng/mL)	57 (1–128650)	155 (4–369127)	0.248	504 (2–123578)	577 (2–671940)	0.659
DCP (mAU/mL)	352 (10–1084600)	166 (16–562056)	0.541	575 (23–82003)	5952 (24–45363)	0.825
Frequency of multiple intrahepatic HCC	30 (65.2%)	10 (66.7%)	0.918	7 (77.8%)	9 (100%)	0.134
Maximum size of intrahepatic HCC (mm)	26 (0–154)	41 (0–125)	0.322	52 (0–127)	53 (24–138)	0.750
Vascular invasion	19 (41.3%)	10 (66.7%)	0.088	6 (66.7%)	8 (88.9%)	0.257
Hepatic TNM	3 (0–4)	3 (0–4)	0.144	3 (0–4)	4 (3–4)	0.048
Performance status	0 (0–3)	0 (0–4)	0.736	0 (0–0)	0 (0–3)	0.066

AFP,  $\alpha$ -fetoprotein; DCP, des- $\gamma$ -carboxy prothrombin; TKI, Tyrosine kinase inhibitor; TNM, tumor-node-metastasis.

**Table S6.** Background data of patients who meet the REFLECT criteria (REFLECT IN) and do not meet the criteria (REFLECT OUT).

	REFLECT IN			REFLECT OUT		
	TKI	TKI plus conventional	p-value	TKI	TKI plus conventional	p-value
Number	14	21		15	15	
Age (years old)	72.2 (25.4–84.2)	69.1 (49.9–80.9)	0.893	71.1 (51.9–85.9)	67.5 (57.4–85.1)	0.788
Men	12 (85.7%)	16 (76.2%)	0.490	13 (86.7%)	13 (86.7%)	1.000
FIB4-index	3.81 (1.56–8.3)	3.60 (1.84–8.52)	0.731	8.63 (0.95–18.0)	6.29 (0.48–25.7)	0.443
Child–Pugh score	5 (5–6)	5 (5–6)	0.213	6 (5–11)	5 (5–8)	0.145
ALBI score	–2.61 (–3.14 to –2.14)	–2.50 (–3.25 to –1.83)	0.730	–1.86 (–3.20 to –0.90)	–2.41 (–3.02 to –1.19)	0.086
AFP (ng/mL)	79 (1–127956)	14 (1–2132)	0.252	504 (2–128650)	70 (1–123578)	0.372
DCP (mAU/mL)	30 (10–5061)	216 (15–9129)	0.029	1832 (10–1084600)	464 (21–63989)	0.089
Frequency of multiple intrahepatic HCC	10 (71.4%)	12 (57.1%)	0.392	11 (73.3%)	12 (80.0%)	0.666
Maximum size of intrahepatic HCC (mm)	23 (0–57)	14 (0–78)	0.804	63 (25–154)	35 (0–120)	0.008
Vascular invasion	4 (28.6%)	4 (19.0%)	0.511	13 (86.7%)	9 (60.0%)	0.099
Hepatic TNM	3 (0–4)	2 (0–4)	0.593	4 (2–4)	3 (0–4)	0.139
Performance status	0 (0–1)	0 (0–1)	0.331	0 (0–3)	0 (0–2)	0.544
HCC occupation ≥50% of the liver	0 (0%)	0 (0%)	-	4 (26.7%)	1 (6.7%)	0.142
Bile duct invasion	0 (0%)	0 (0%)	-	3 (20.0%)	3 (20.0%)	1.000
Main portal vein invasion (Vp4)	0 (0%)	0 (0%)	-	1 (6.7%)	0 (0%)	0.309
Sorafenib	12	13	0.126	12	4	0.003
Lenvatinib	2	5	0.384	2	7	0.046
Multiple TKI	0	3	0.139	1	4	0.142

AFP,  $\alpha$ -fetoprotein; DCP, des- $\gamma$ -carboxy prothrombin; TKI, Tyrosine kinase inhibitor; TNM, tumor-node-metastasis.

**Table S7.** Background data of patients with lung or bone metastases.

	Bone metastasis alone	Lung metastasis alone	p-value
Number	32	13	
Age (years old)	69.7 (56.3–85.9)	67.1 (25.4–83.7)	0.582
Men	27 (84.4%)	11 (84.6%)	0.984
FIB-4 index	5.84 (0.95–27.8)	5.30 (1.56–25.6)	1.000
Child–Pugh score	6 (5–9)	6 (5–7)	0.925
ALBI score	–2.26 (–3.25 to –1.09)	–2.47 (–3.20 to –1.45)	0.903
AFP (ng/mL)	128 (1–36917)	247 (3–671940)	0.367
DCP (mAU/mL)	1545 (21–1084600)	4059 (10–43699)	0.802
Frequency of multiple intrahepatic HCC	24 (75.0%)	11 (84.6%)	0.482
Maximum size of intrahepatic HCC (mm)	43 (0–154)	41 (0–138)	0.573
Vascular invasion	20 (62.5%)	8 (61.5%)	0.952
Hepatic TNM	4 (0–4)	4 (0–4)	0.674

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Performance status	0 (0–4)	0 (0–2)	0.428
TKI use	23 (71.9%)	10 (76.9%)	0.729

AFP,  $\alpha$ -fetoprotein; DCP, des- $\gamma$ -carboxy prothrombin; TKI, Tyrosine kinase inhibitor; TNM, tumor-node-metastasis.