Supplementary Online Content

Yoon SM, Ryoo B-Y, Lee SJ, et al. Efficacy and safety of transarterial chemoembolization plus external beam radiotherapy vs sorafenib in hepatocellular carcinoma with macroscopic vascular invasion: a randomized trial. *JAMA Oncol.* Published online March 15, 2018. doi:10.1001/jamaoncol.2017.5847

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Baseline Characteristics of the Patients

Characteristics	Sorafenib (n = 45)	TACE+RT (n = 45)	*P*-value
Age, years, median (range)	55 (33 – 82)	55 (42 – 77)	0.15
Sex, no. (%)			0.76
Male	39 (86.7%)	38 (84.4%)	
Female	6 (13.3%)	7 (15.6%)	
Child-Pugh class A, no. (%)	45 (100%)	45 (100%)	>0.99
Albumin, g/dL, median (IQR)	3.5 (3.3 – 3.8)	3.5 (3.3 – 3.9)	0.49
Total bilirubin, mg/dL, median (IQR)	0.7 (0.6 – 1.0)	0.7 (0.6 – 1.0)	0.64
ECOG performance status, no. (%)			0.53
0	22 (48.9%)	19 (42.2%)	
1	23 (51.1%)	26 (57.8%)	
Cause of disease, no. (%)			0.39
Hepatitis B virus infection	40 (88.9%)	36 (80.0%)	
Hepatitis C virus infection	0	1 (2.2%)	
Others	5 (11.1%)	8 (17.8%)	
Tumor size, maximum, cm, median (IQR)	9.6 (7.0 - 11.8)	9.8 (8.0 – 12.8)	0.89
Tumor number, no. (%)			0.07
Single	13 (28.9%)	6 (13.3%)	
Multiple	32 (71.1%)	39 (86.7%)	
Tumor extent, no. (%)			0.21
Unilobar involvement	27 (60.0%)	21 (46.7%)	
Bilobar involvement	18 (40.0%)	24 (53.3%)	
Level of vascular invasion, no. (%)			0.95
Unilateral PV	27 (60.0%)	26 (57.8%)	
Bilateral or main PV	16 (35.6%)	17 (37.8%)	
Unilateral PV+HV/IVC	1 (2.2%)	1 (2.2%)	
Bilateral PV+HV/IVC	1 (2.2%)	1 (2.2%)	
Bile duct invasion, no. (%)			0.04
No	45 (100.0%)	41 (91.1%)	
Yes	0	4 (8.9%)	
Alpha-fetoprotein, ng/mL, median (IQR)	667 (36 – 51,138)	1496 (78 – 37,736)	0.86
PIVKA-II, mAU/mL, median (IQR)	2,426 (111 – 13,775)	2,266 (150 – 16,339)	0.98

ECOG, Eastern Cooperative Oncology Group; HV, hepatic vein; IQR, inter-quartile range; IVC, inferior vena cava; PIVKA-II, protein induced by vitamin K absence or antagonist; PV, portal vein; RT, external beam radiation therapy; TACE, transarterial chemoembolization.

eTable 2. Characteristics of Patients at Baseline vs Treatment Crossover on Disease Progression in 24 Weeks

	Sorafenib			TACE+RT		
Characteristics	**Baseline (n = 34)**	**At crossover (n = 34)**	***P*-value (paired)**	**Baseline (n = 9)**	**At crossover (n = 9)**	***P*-value (paired)**
Failure patterns at the time of treatment cross-over						
Intrahepatic progression		24 (70.6%)			3 (33.3%)	
Extrahepatic metastasis		0			1 (11.1%)	
Both (intrahepatic + extrahepatic)		10 (29.4%)			5 (55.6%)	
Characteristics						
Child-Pugh class A, no. (%)	34 (100%)	24 (70.6%)	0.01	9 (100%)	7 (77.8%)	0.47
Albumin, g/dL, median (IQR)	3.6 (3.3 – 3.8)	3.3 (2.9 – 3.7)	0.04	3.5 (3.3 – 3.7)	3.0 (2.8 – 3.2)	0.01
Total bilirubin, mg/dL, median (IQR)	0.8 (0.5 – 1.0)	0.8 (0.5 – 1.2)	0.08	0.8 (0.6 – 1.0)	0.9 (0.8 – 1.5)	0.11
ECOG performance status, no. (%)			0.05			>0.99
0	17 (50%)	25 (73.5%)		3 (33.3%)	2 (22.2%)	
1	17 (50%)	9 (26.4%)		6 (66.7%)	7 (77.8%)	
Alpha-fetoprotein, $\log_{10}$ ng/mL, median (IQR)	2.61 (1.56 – 4.06)	2.79 (1.68 – 4.63)	0.44	1.88 (1.15 – 4.39)	2.15 (1.05 – 4.55)	0.86

IQR, inter-quartile range; ECOG, Eastern Cooperative Oncology Group; TACE, transarterial chemoembolization; RT, external beam radiation therapy.

eTable 3. Radiologic Response Evaluation Between the Primary and Secondary Radiologic Reviews in 24 Weeks

Within 24 weeks		Secondary central review			Total
		Non-PD	PD	Not Evaluable*	
Primary review	Non-PD	24	4†	NA	28
	PD	0	55	NA	55
	Not Evaluable*	NA	NA	7	7
Total		24	59	7	90

The discordance rate between primary and central radiologic reviews among evaluable patients was 4.8% (4/83), which was not statistically significant (*P*=0.13 by McNemar test).
PD, progressive disease.
*Not evaluable, due to death without radiologic disease progression or early study termination by withdrawal or adverse event.
†The detailed reasons of discordance were summarized in Supplementary Table 4.

eTable 4. Details of Discordance Between Primary and Secondary Central Radiologic Reviews

Case No.	Treatment group	Weeks after randomization	Primary review	Secondary central review	Reasons of discordance
31	TACE+RT	24	Stable disease	Progressive disease	A new small lesion in contralateral liver lobe was counted as PD
40	TACE+RT	24	Stable disease	Progressive disease	Multiple new small lesions in contralateral liver lobe was counted as PD
80	TACE+RT	24	Stable disease	Progressive disease	A new small lesion in contralateral liver lobe was counted as PD
88	TACE+RT	24	Stable disease	Progressive disease	Multiple new small lesions in contralateral liver lobe was counted as PD

eTable 5. Changes in Alpha-Fetoprotein (AFP) at Weeks 12 and 24 by Treatment Groups

	Sorafenib					TACE+RT				
	Baseline (n=45)	**At week 12 (n=39)**	**At week 24 (n=31)**	***P*-value***	***P*-value†**	**Baseline (n=45)**	**At week 12 (n=45)**	**At week 24 (n=38)**	***P*-value***	***P*-value†**
AFP, ng/mL	667 (36-51,138)	646 (48-33,815)	153 (45-1,840)	0.21	0.40	1,496 (78-37,736)	163 (14-2,398)	85 (8-590)	0.54	0.049
AFP, $\log_{10}$ ng/mL	2.82 (1.55-4.68)	2.81 (1.68-4.53)	2.18 (1.65-3.27)	0.19	0.68	3.18 (1.89-4.58)	2.21 (1.14-3.38)	1.92 (0.91-2.77)	<0.001	<0.001

Expressed as median (IQR).
*Between baseline and week 12
†Between baseline and week 24

eTable 6. Treatment-Emergent Adverse Events in the Safety Population

Adverse event category*	Sorafenib (n = 44)	TACE+RT (n = 45)	*P* Value
Patient number	44†	45	
Any adverse events	41 (93.2%)	41 (91.1%)	>0.99
Adverse events ≥ Grade 3	12 (27.3%)	7 (15.6%)	0.18
Serious adverse events	5‡ (11.4%)	5§ (11.1%)	0.97
Discontinuation due to adverse event	1‖	0	0.49
Dose reduction due to adverse event	6¶	0	0.01

*Patients are counted once for each category.
†By modified intention-to-treat analysis excepting a patient who withdrew consent before the treatment in the sorafenib group.
‡Skin rash, abdominal pain, abdominal distension, liver abscess, and hepatic encephalopathy.
§Cisplatin anaphylactoid reaction, grade 4 liver enzyme elevation, hyperbilirubinemia, and two bilomas.
‖Severe mucositis.
¶hand-foot syndrome, hypertension, and abdominal pain.

eTable 7. Adverse Event Categories in the Safety Population

	Sorafenib group (n = 44)*				TACE+RT group (n = 45)			
NCI-CTCAE Grade	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Anorexia	4 (9.1%)	3 (6.8%)	1 (2.3%)	0	18 (40.0%)	4 (8.9%)	0	0
Fatigue	5 (11.4%)	0	0	0	6 (13.3%)	3 (6.7%)	0	0
Fever	0	0	0	0	13 (28.9%)	3 (6.7%)	0	0
Nausea	12 (27.3)	2 (4.5%)	0	0	29 (64.4%)	3 (6.7%)	0	0
Diarrhea	12 (27.3%)	4 (9.1%)	2 (4.5%)	0	2 (4.4%)	1 (2.2%)	1 (2.2%)	0
Abdominal pain	9 (20.5%)	4 (9.1%)	1 (2.3%)	0	22 (48.9%)	13 (28.9%)	1 (2.2%)	0
Constipation	0	0	0	0	1 (2.2%)	0	0	0
Hand-foot syndrome	14 (31.8%)	9 (20.5%)	2 (4.5%)	0	0	0	0	0
Skin rash	4 (9.1%)	4 (9.1%)	0	0	0	0	0	0
Hypertension	3 (6.8%)	7 (15.9%)	4 (9.1%)	0	0	0	0	0
Mucositis	2 (4.5%)	2 (4.5%)	1 (2.3%)	0	0	0	0	0
Hoarseness	4 (9.1%)	2 (4.5%)	0	0	0	0	0	0
AST/ALT increase	0	0	3 (6.8%)	0	0	0	5 (11.1%)	1 (2.2%)
Bilirubin increase	0	1 (2.3%)	0	0	0	0	1 (2.2%)	0
Non-classic RILD	0	0	0	0	12 (26.7%)	0	0	0

*By modified intention-to-treat analysis excepting a patient who withdrew consent before the treatment in the sorafenib group.
ALT, alanine transaminase; AST, aspartate transaminase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03; RILD, radiation-induced liver disease; RT, radiotherapy; TACE, transarterial chemoembolization.

eTable 8. Exposure to Sorafenib, Transarterial Chemoembolization, and Radiation in 24 Weeks

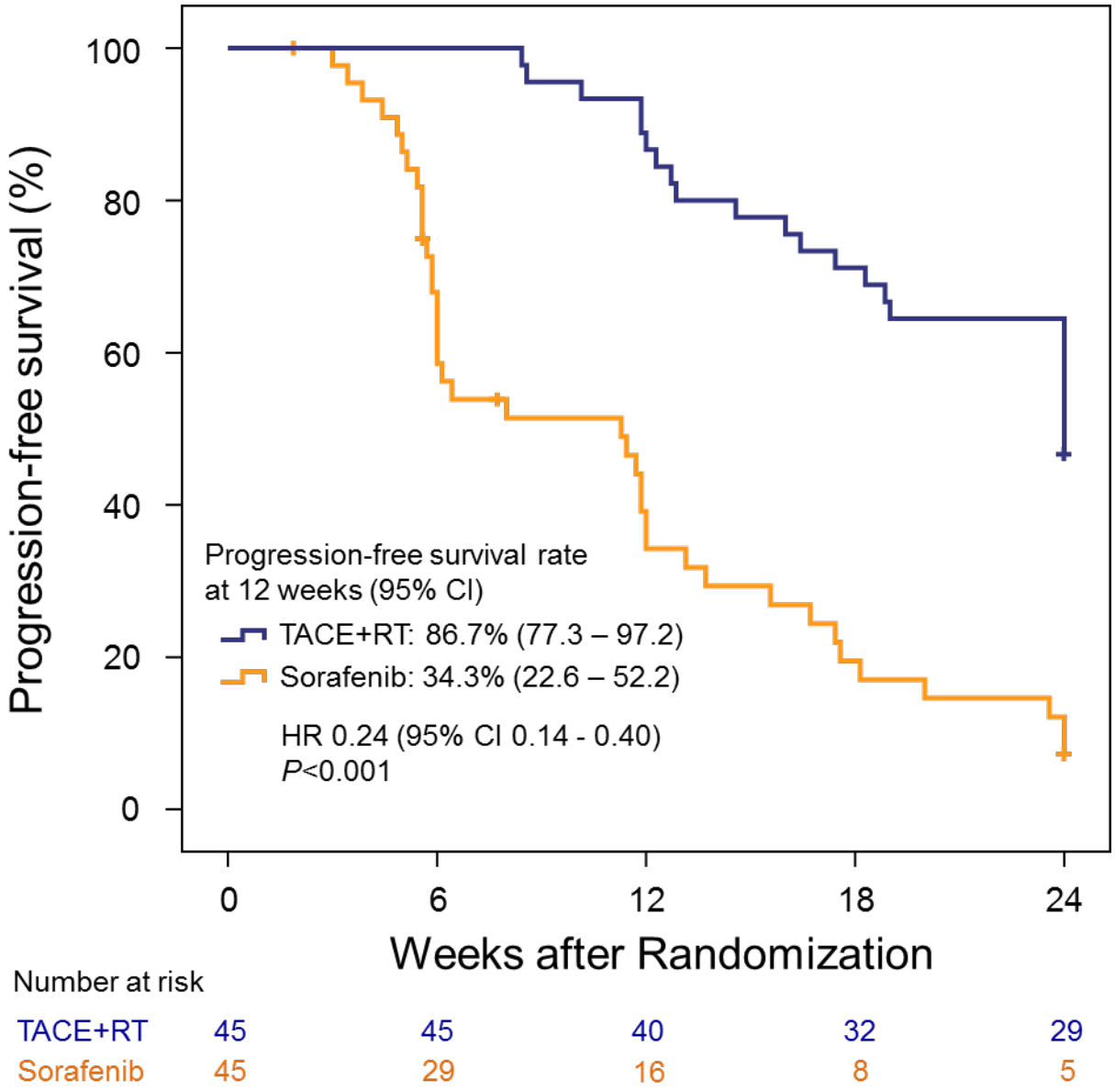
Characteristics	Sorafenib (n = 44)
Duration of treatment (weeks)	
Mean (SD)	10.7 (7.1)
Median (IQR)	6.6 (5.8 – 16.6)
Actual daily dose* (mg/day)	
Mean (SD)	739 (110)
Median (IQR)	800 (730 – 800)
Percent of planned dose (%)	
Mean (SD)	92.4 (13.8)
Median (IQR)	100 (91.2 – 100)
Dose modifications	14 (31.8%)
Dose interruption	12 (27.3%)
Dose reduction	6 (13.6%)
Characteristics	**TACE+RT (n = 45)**
Number of TACE procedures	
1	2 (4.4%)
2	2 (4.4%)
3	12 (26.7%)
4	29 (64.5%)
Mean (SD)	3.5 (0.9)
Median (IQR)	4 (3 – 4)
Interval between 1st TACE and RT start (days)	
Mean (SD)	15.6 (2.9)
Median (IQR)	15 (13 – 19)
Radiation dose	
20 Gy†	1 (2.2%)
30 Gy	9 (20.0%)
35 Gy	12 (26.7%)
40 Gy	7 (15.5%)
45 Gy	16 (35.6%)
Mean (SD)	38 Gy (6.4)
Median (IQR)	40 Gy (35 – 45)
Fraction size	
2.5 Gy	30 (66.7%)
3.0 Gy	15 (33.3%)

SD, standard deviation; IQR, inter-quartile range; TACE, transarterial chemoembolization; RT, external beam radiation therapy.

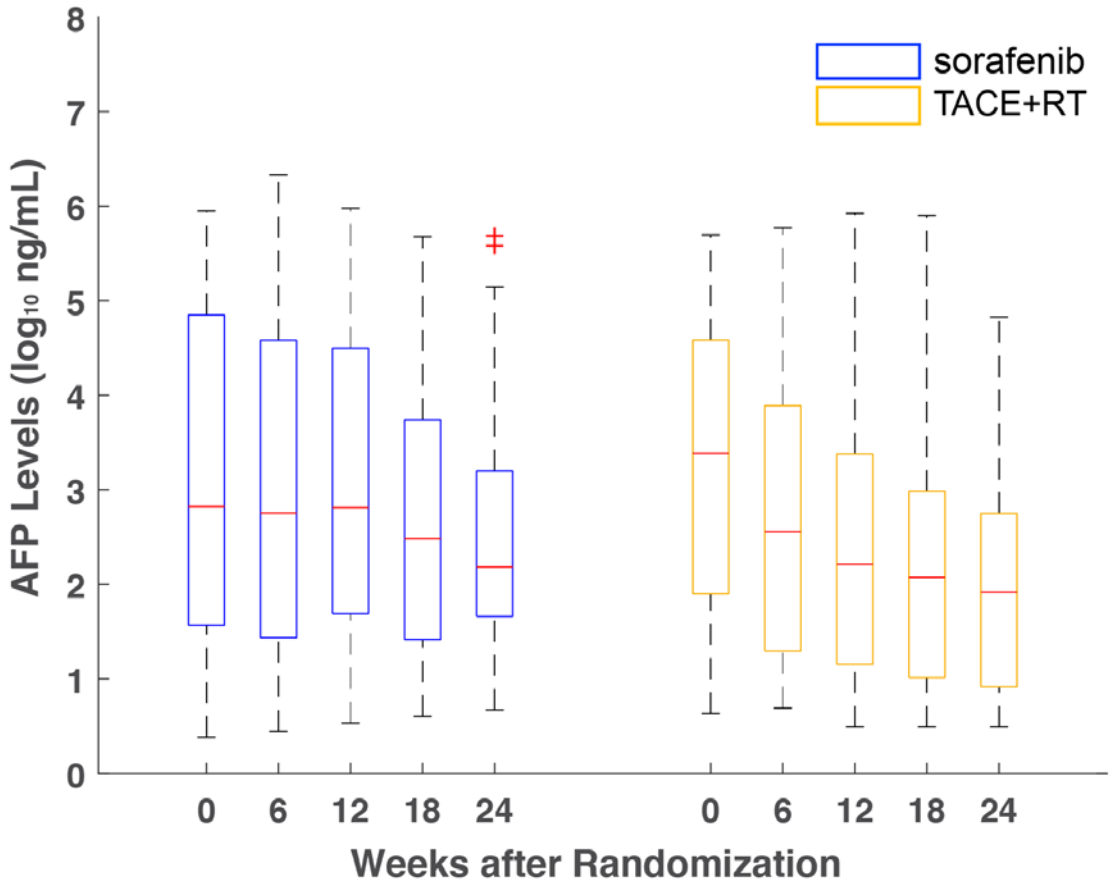
*Assessed by returned pill counts and patient survey

†Planned radiation dose was not delivered, because of the deteriorated patient's performance status.

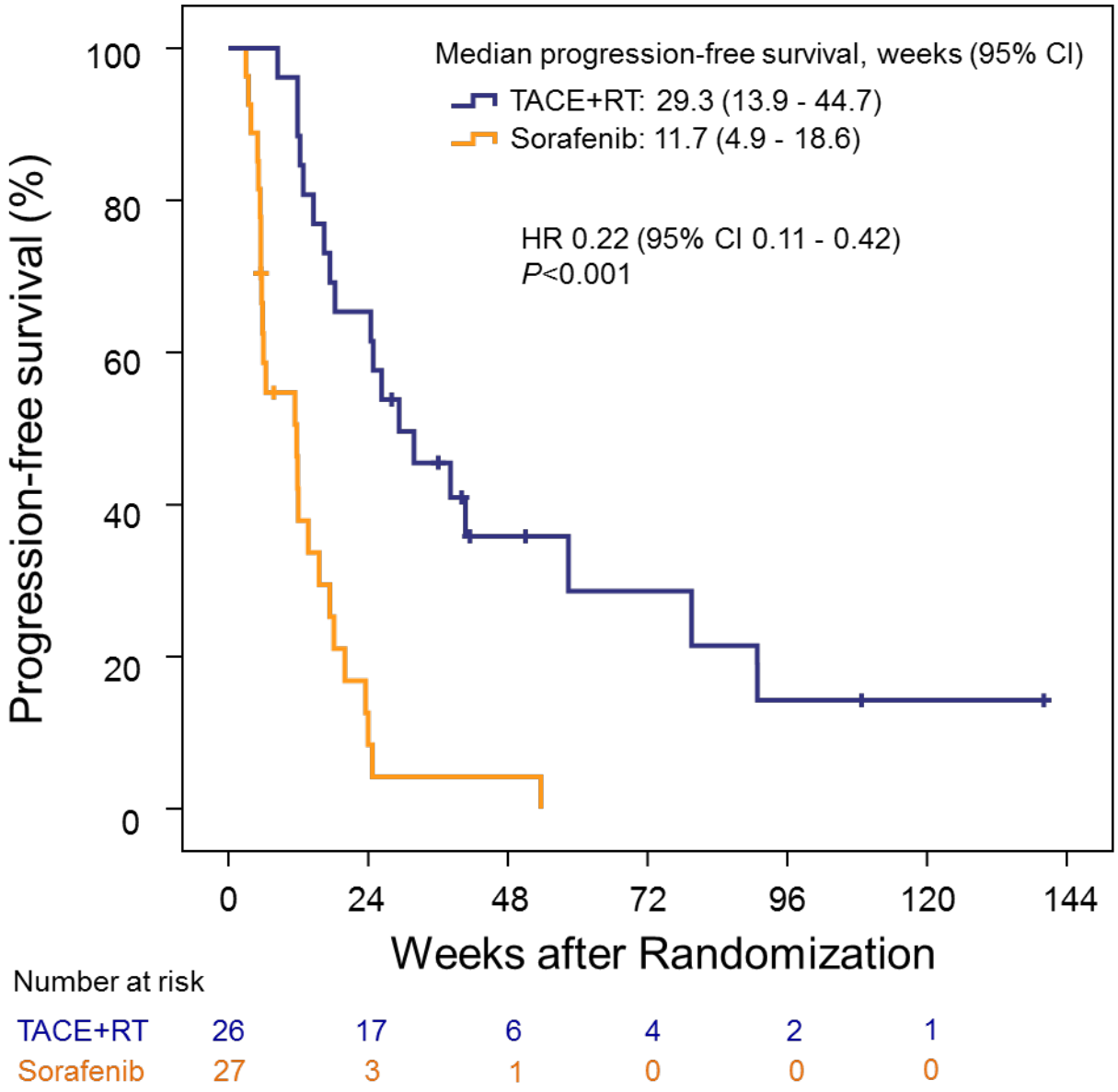
eFigure 1. Estimated Progression-Free Survival Rate in 24 Weeks by Secondary Central Radiologic Reviews



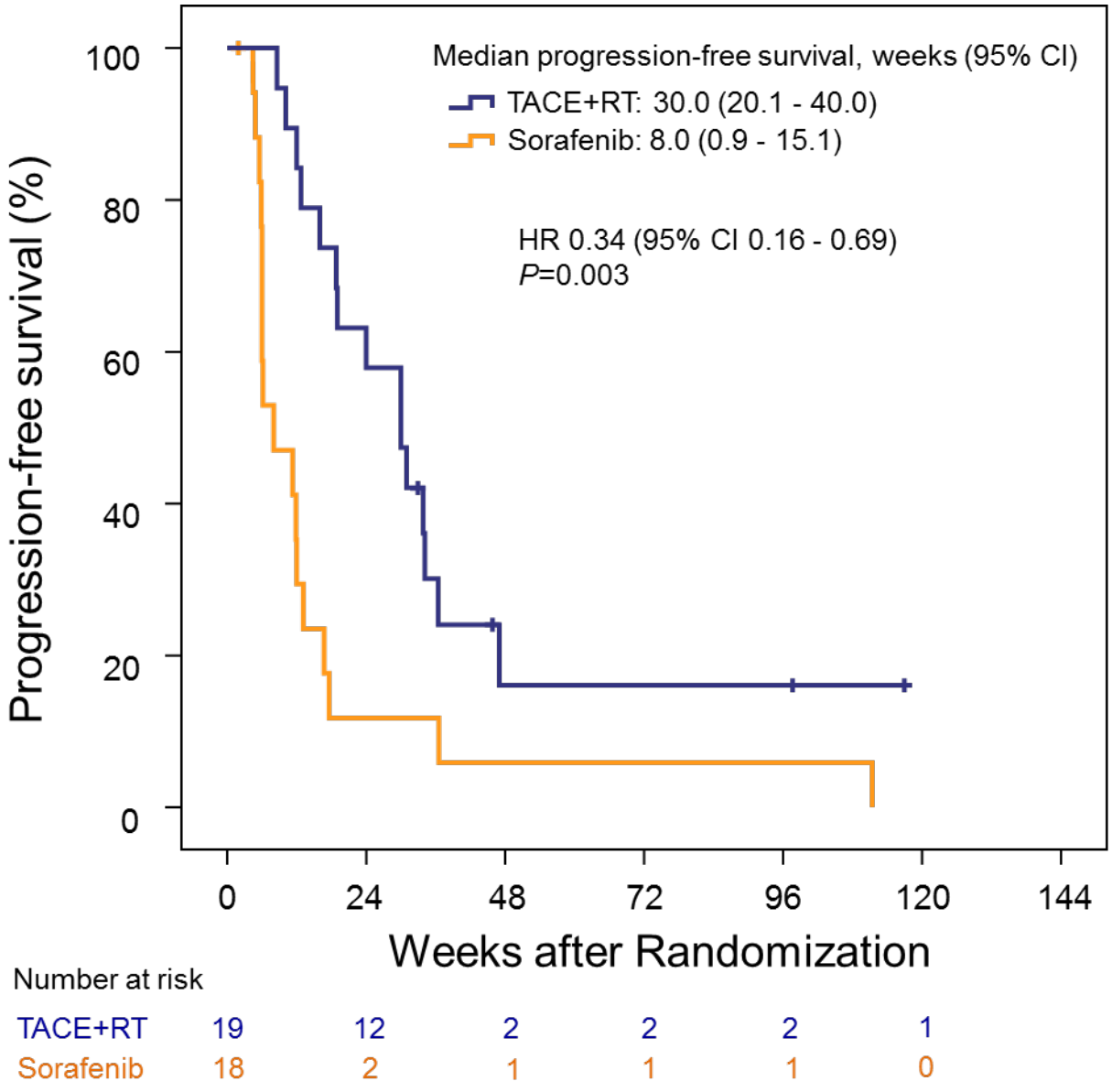
eFigure 2. Changes in Alpha-Fetoprotein (AFP) Levels in 24 Weeks by Treatment Groups



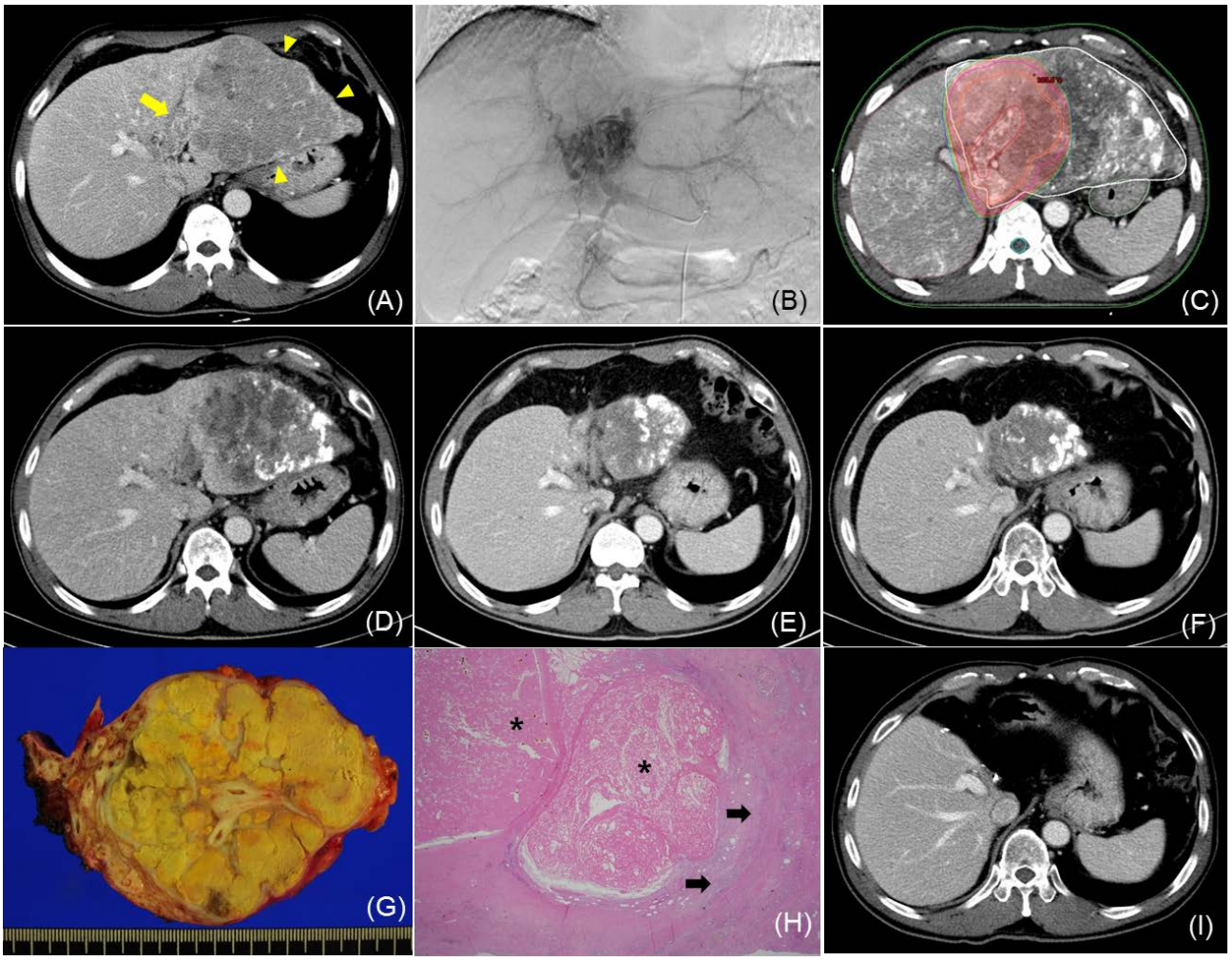
eFigure 3. Estimated Progression-Free Survival During Follow-up
A. Patients with HCC and unilateral portal vein invasion



B. Patients with HCC and multiple vascular invasion



eFigure 4. A Representative Case of a 52-Year-Old Man With Hepatocellular Carcinoma (HCC) With Portal Vein Tumor Thrombus (PVTT) Who Was Assigned to the Combined Transarterial Chemoembolization (TACE) Plus Radiotherapy (RT) Group



(A) Computed tomography (CT) scan at diagnosis, showing a 14-cm HCC in the left lobe (yellow triangles) and PVTT in the left portal vein (yellow arrow). (B) Celiac arteriogram for TACE, showing a diffuse tumor staining in the left of the liver. (C) Twelve days after TACE, RT for PVTT and a 2-cm margin into the contiguous HCC was performed with a total dose of 40 Gy in 16 fractions. (D) CT scan at week 12. (E) Follow-up CT scan at week 24. (F) At 36 weeks after randomization, the patient showed partial tumor response after receiving a total of 6 TACE procedures. (G) At week 40, left hepatectomy was performed. On the examination of the gross specimen, a 7.5 x 5.5 x 5.0 cm sized tumor was observed. (H) On microscopic examination, residual tumor cells (Edmondson-Steiner grade III/III) were found focally (black arrow); however, the majority (99%) of the tumor consisted of necrotic tissue (black asterisk) (original magnification, x 12.5). (I) By the last follow-up at 140 weeks, no recurrence was observed on liver-dynamic CT scan.