Supplementary Tables

Yttrium-90 radioembolization in combination with durvalumab for locally advanced unresectable hepatocellular carcinoma: A phase 1/2a trial

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Supplementary Table S1. Objective response determined by mRECIST in the per-protocol population

Parameter	N=23
Objective response, no. (%)	
Complete response	7 (30.4)
Partial response	13 (56.5)
Stable disease	2 (8.7)
Progressive disease	0 (0)
Not evaluable	1 (4.3)
Objective response rate (95% CI)	87.0% (66.4 to 97.2)
Disease control rate (95% CI)	95.7% (78.1 to 99.9)

Abbreviations: CI, confidence interval; mRECIST, modified RECIST.

Supplementary Table S2. Objective response determined by mRECIST according to BCLC stage in the intent-to-treat population

Parameter	BCLC stage B (N=8)	BCLC stage C (N=16)
Objective response, no. (%)		
Complete response	4 (50.0)	3 (18.8)
Partial response	3 (37.5)	10 (62.5)
Stable disease	0 (0)	2 (12.5)
Progressive disease	0 (0)	0 (0)
Not evaluable	1 (12.5)	1 (6.3)
Objective response rate (95% CI)	87.5% (47.4 to 99.7)	81.3% (54.4 to 96.0)
Disease control rate (95% CI)	87.5% (47.4 to 99.7)	93.8% (69.8 to 99.8)

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; mRECIST, modified RECIST.

Supplementary Table S3. Objective response determined by mRECIST according to BCLC stage in the per-protocol population

Parameter	BCLC stage B (N=7)	BCLC stage C (N=16)
Objective response, no. (%)		
Complete response	4 (57.1)	3 (18.8)
Partial response	3 (42.9)	10 (62.5)
Stable disease	0 (0)	2 (12.5)
Progressive disease	0 (0)	0 (0)
Not evaluable	0 (0)	1 (6.3)
Objective response rate (95% CI)	100% (59.0 to 100)	81.3% (54.4 to 96.0)
Disease control rate (95% CI)	100% (59.0 to 100)	93.8% (69.8 to 99.8)

Abbreviations: BCLC, Barcelona Clinic Liver Clinic; CI, confidence interval; mRECIST, modified RECIST.

Supplementary Table S4. Objective response determined by mRECIST according to etiology in the intent-to-treat population

Parameter	Hepatitis B (N=15)	Others (N=9)
Objective response, no. (%)		
Complete response	4 (26.7)	3 (33.3)
Partial response	9 (60.0)	4 (44.4)
Stable disease	1 (6.7)	1 (11.1)
Progressive disease	0 (0)	0 (0)
Not evaluable	1 (6.7)	1 (11.1)
Objective response rate (95% CI)	86.7% (59.5 to 98.3)	77.8% (40.0 to 97.2)
Disease control rate (95% CI)	93.3% (68.1 to 99.8)	89.9% (51.8 to 99.7)

Abbreviations: CI, confidence interval; mRECIST, modified RECIST.

Supplementary Table S5. Objective response determined by mRECIST according to etiology in the per-protocol population

Parameter	Hepatitis B (N=15)	Others (N=8)
Objective response, no. (%)		
Complete response	4 (26.7)	3 (37.5)
Partial response	9 (60.0)	4 (50.0)
Stable disease	1 (6.7)	1 (12.5)
Progressive disease	0 (0)	0 (0)
Not evaluable	1 (6.7)	0 (0)
Objective response rate (95% CI)	86.7% (59.5 to 98.3)	87.5% (47.4 to 99.7)
Disease control rate (95% CI)	93.3% (68.1 to 99.8)	100% (63.1 to 100)

Abbreviations: CI, confidence interval; mRECIST, modified RECIST.

Supplementary Table S6. Treatment-emergent adverse events and serious adverse events in the per-protocol population

Event	N=23				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Treatment-emergent adverse events, no. (%)					
Abdominal pain	1 (4.3)	3 (13.0)	2 (8.7)	0	0
Anemia	0	1 (4.3)	0	0	0
Anorexia	1 (4.3)	1 (4.3)	0	0	0
Aortic injury	0	0	0	0	1 (4.3)
Ascites	0	6 (26.1)	0	0	0
Aspartate aminotransferase increased	0	1 (4.3)	0	0	0
Back pain	0	2 (8.7)	0	0	0
Blood bilirubin increased	0	0	2 (8.7)	1 (4.3)	0
Chills	0	1 (4.3)	0	0	0
Chronic kidney disease	0	1 (4.3)	0	0	0
Constipation	1 (4.3)	0	0	0	0
Coronary atherosclerosis	0	0	1 (4.3)	0	0
Dyspepsia	0	1 (4.3)	0	0	0
Dyspnea	0	1 (4.3)	0	0	0
Edema peripheral	1 (4.3)	0	0	0	0
Fatigue	3 (13.0)	0	0	0	0
Fever	1 (4.3)	1 (4.3)	1 (4.3)	0	0
Hepatic failure	0	0	1 (4.3)	0	0
Herpes simplex reactivation	1 (4.3)	0	0	0	0
Herpes zoster	0	1 (4.3)	0	0	0
Hypercalcemia	0	1 (4.3)	1 (4.3)	0	0
Hyperkalemia	0	3 (13.0)	0	1 (4.3)	0
Hypertension	0	1 (4.3)	0	0	0
Hypocalcemia	0	1 (4.3)	0	0	0
Hypophosphatemia	0	1 (4.3)	0	0	0
Laryngeal hemorrhage	0	1 (4.3)	0	0	0
Muscle weakness lower limb	1 (4.3)	0	0	0	0
Nausea	1 (4.3)	0	0	0	0
Neutrophil count decreased	0	0	1 (4.3)	0	0
Oral dysesthesia	0	1 (4.3)	0	0	0
Osteoporosis	1 (4.3)	0	0	0	0
Pain in Extremity	1 (4.3)	3 (13.0)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	0	1 (4.3)	0	0	0
Paronychia	0	1 (4.3)	0	0	0
Pneumonitis	1 (4.3)	0	0	0	0
Rash	1 (4.3)	1 (4.3)	0	0	0
Upper gastrointestinal hemorrhage	0	0	1 (4.3)	0	0
Urinary tract obstruction	1 (4.3)	0	0	0	0
Urticaria	4 (17.4)	3 (13.0)	0	0	0
Treatment-emergent serious adverse events, no. (%)					
Abdominal pain	0	0	2 (8.7)	0	0
Aortic injury	0	0	0	0	1 (4.3)
Arterial thromboembolism	0	0	1 (4.3)	0	0
Fever	0	1 (4.3)	1 (4.3)	0	0
Hepatic failure	0	0	1 (4.3)	0	0

Hyperkalemia	0	0	0	1 (4.3)	0
Upper gastrointestinal hemorrhage	0	0	1 (4.3)	0	0

NOTE: Data are expressed as number (%).

Supplementary Table S7. Treatment-related adverse events and serious adverse events in the intent-to-treat population

Event	N=24				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Treatment-related adverse events, no. (%)					
Chills	0	1 (4.2)	0	0	0
Fever	0	0	1 (4.2)	0	0
Hyperkalemia	0	2 (8.3)	0	0	0
Nausea	1 (4.2)	0	0	0	0
Neutrophil count decreased	0	0	1 (4.2)	0	0
Palmar-plantar erythrodysesthesia syndrome	0	1 (4.2)	0	0	0
Pneumonitis	1 (4.2)	0	0	0	0
Rash	1 (4.2)	0	0	0	0
Urticaria	1 (4.2)	1 (4.2)	0	0	0
Treatment-related serious adverse events, no.	0	0	0	0	0

NOTE: Data are expressed as number (%).

Supplementary Table S8. Treatment-emergent adverse events and serious adverse events in the intent-to-treat population

Event	N=24				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Treatment-emergent adverse events, no. (%)					
Abdominal pain	1 (4.2)	3 (12.5)	2 (8.3)	0	0
Anemia	0	2 (8.3)	0	0	0
Anorexia	1 (4.2)	2 (8.3)	0	0	0
Aortic injury	0	0	0	0	1 (4.2)
Ascites	0	7 (29.2)	0	0	0
Aspartate aminotransferase increased	0	1 (4.2)	0	0	0
Back pain	0	2 (8.3)	0	0	0
Blood bilirubin increased	0	0	2 (8.3)	1 (4.2)	0
Chills	0	1 (4.2)	0	0	0
Chronic kidney disease	0	1 (4.2)	0	0	0
Constipation	1 (4.2)	0	0	0	0
Coronary atherosclerosis	0	0	1 (4.2)	0	0
Dyspepsia	0	1 (4.2)	0	0	0
Dyspnea	0	1 (4.2)	0	0	0
Edema peripheral	1 (4.2)	0	0	0	0
Fatigue	3 (12.5)	0	0	0	0
Fever	1 (4.2)	1 (4.2)	1 (4.2)	0	0
Hepatic failure	0	0	1 (4.2)	0	0
Herpes simplex reactivation	1 (4.2)	0	0	0	0
Herpes zoster	0	1 (4.2)	0	0	0
Hypercalcemia	0	1 (4.2)	1 (4.2)	0	0
Hyperkalemia	0	3 (12.5)	0	1 (4.2)	0
Hypertension	0	1 (4.2)	0	0	0
Hypocalcemia	0	1 (4.2)	0	0	0
Hypoalbuminemia	0	1 (4.2)	0	0	0
Hypophosphatemia	0	1 (4.2)	0	0	0
Laryngeal hemorrhage	0	1 (4.2)	0	0	0
Muscle weakness lower limb	1 (4.2)	0	0	0	0
Nausea	1 (4.2)	0	0	0	0
Neutrophil count decreased	0	0	1 (4.2)	0	0
Oral dysesthesia	0	1 (4.2)	0	0	0
Osteoporosis	1 (4.2)	0	0	0	0
Pain in Extremity	1 (4.2)	4 (16.7)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	0	1 (4.2)	0	0	0
Paronychia	0	1 (4.2)	0	0	0
Pneumonitis	1 (4.2)	0	0	0	0
Rash	1 (4.2)	1 (4.2)	0	0	0
Upper gastrointestinal hemorrhage	0	0	1 (4.2)	0	0
Urinary tract obstruction	1 (4.2)	0	0	0	0
Urticaria	4 (16.7)	3 (12.5)	0	0	0
Treatment-emergent serious adverse events, no. (%)					
Abdominal pain	0	0	2 (8.3)	0	0
Aortic injury	0	0	0	0	1 (4.2)
Arterial thromboembolism	0	0	1 (4.2)	0	0
Fever	0	1 (4.2)	1 (4.2)	0	0

Hepatic failure	0	0	1 (4.2)	0	0
Hyperkalemia	0	0	0	1 (4.2)	0
Upper gastrointestinal hemorrhage	0	0	1 (4.2)	0	0

NOTE: Data are expressed as number (%).

Supplementary Table S9. Representativeness of study participants

Cancer type(s)/subtype(s)/stage(s)/condition	Hepatocellular carcinoma
Considerations related to:	
Sex	In most countries, the incidence of hepatocellular carcinoma is 2- to 4-fold higher in male versus female patients (1,2). The 2016 age-adjusted incidence rate in males was 10.4/100,000, whereas the rate in females was 2.9/100,000 in the United States (2,3). In Europe, the age-adjusted incidence rate in males can be >4-fold higher than rate in females (2,3). In East and Southeast Asia, the highest incidence ratio of males to females is around 3.5 in 2020 for primary liver cancer (4).
Age	Incidence rate of hepatocellular carcinoma is directly correlated with age globally until approximately 75 years of age (2). In the United States, median age at diagnosis for male patients is 60 to 64 years, whereas median age for female patients is 65 to 69 years (3). In China and Taiwan, the median age of diagnosis was reported as 63 years (5). In South Korea, most male patients of primary liver cancer are diagnosed at ages 50 to 59 years, whereas most female patients are diagnosed at ages 70 to 79 years (6).
Race/ethnicity	In the United States, American Indians/Alaskan Natives had the highest incidence rate of hepatocellular carcinoma (11.4/100,000), followed by Hispanics (9.8/100,000), Asians/Pacific Islanders (9.1/100,000), non-Hispanic blacks (8.1/100,000), and non-Hispanic whites (4.6/100,000) (3). However, few studies have been conducted to compare racial variation in HCC within Asian populations.
Geography	In 2020, most hepatocellular carcinoma cases worldwide were reported in East and Southeast Asia (4). In 2020, the highest age-standardized incidence rates of liver cancer were observed in Eastern Asia (17.8/100,000), followed by Northern Africa (15.2/100,000), and South-Eastern Asia (13.7 /100,000 person-years) (1). The wide variability in incidence of hepatocellular carcinoma by geographical region, is largely related to the prevalence, and age at acquisition, of major risk factors (3).
Other considerations	The major risk factors of hepatocellular carcinoma are hepatitis B virus (HBV) and hepatitis C virus (HCV), excessive alcohol consumption, and non-alcoholic fatty liver disease (NAFLD) (3,4). In a Korean cohort study, the most common etiologies of hepatocellular carcinoma were HBV (62.2%), HCV (10.4%), and alcohol or unknown etiology (27.4%) (7).
Overall representativeness of this study	The distribution of male (21 [87.5%]) and female (3 [12.5%]) patients in our small pilot study reflects the male predominance in incidence of hepatocellular carcinoma. The age distribution of our study (median [interquartile range], 63 years [58.5 to 73]) is similar to the average age distribution of hepatocellular carcinoma in the literature, median age of 63.

	As our study was a single-center pilot study with a small sample size of 24 patients, our study population was limited our institution in South Korea.

Supplementary References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-249.
2. Petrick JL, Florio AA, Znaor A, Ruggieri D, Laversanne M, Alvarez CS, et al. International trends in hepatocellular carcinoma incidence, 1978-2012. Int J Cancer 2020;147:317-330.
3. McGlynn KA, Petrick JL, El-Serag HB. Epidemiology of hepatocellular carcinoma. Hepatology 2021;73:4-13.
4. Zhang CH, Cheng Y, Zhang S, Fan J, Gao Q. Changing epidemiology of hepatocellular carcinoma in Asia. Liver Int 2022;42:2029-2041.
5. Honda T, Miyaaki H, Ichikawa T, Taura N, Miuma S, Shibata H, et al. Clinical characteristics of hepatocellular carcinoma in elderly patients. Oncol Lett 2011;2:851-854.
6. Chon YE, Jeong SW, Jun DW. Hepatocellular carcinoma statistics in South Korea. Clin Mol Hepatol 2021;27:512-514.
7. Kim BH, Lim YS, Kim EY, Kong HJ, Won YJ, Han S, et al. Temporal improvement in survival of patients with hepatocellular carcinoma in a hepatitis B virus-endemic population. J Gastroenterol Hepatol 2018;33:475-483.