SUPPLEMENTARY MATERIALS

First-in-Human Safety and Efficacy Study on Combination of High-Intensity Focused Ultrasound Sonication and Micellar Nanoparticle-Encapsulated Epirubicin, K-912; a Novel Sonodynamic Therapy for the Treatment of Refractory Abdominal Cancers

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Table S1 Inclusion and exclusion criteria
Table S2 Dose escalation criteria

Table S1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Male or female patients aged 20 to 75 years diagnosed with refractory cancer including pancreatic cancer, biliary tract cancer, bone tumors including bone metastases detectable by ultrasonography • Patients for whom conventional local treatments were not applicable or had not been effective • Patients whose tumor could be evaluated by ultrasonography, computed tomography, or magnetic resonance imaging • Patients in whom HIFU the sonication convergence site was secured • Patients who met the following o Neutrophils ≥ 1500/mm^3 o Platelets ≥ 100000/mm^3 o Hemoglobin ≥ 9.0 g/dL o Creatinine ≤ 1.5mg/dL o AST ≤ 120 IU/l o ALT ≤ 120 IU/l o Total bilirubin ≤ 3mg/dL (in cases of pancreatic cancer and biliary tract cancer) within two weeks prior to enrollment • Eastern Cooperative Oncology Group (ECOG) performance status was 0 – 1 • Patients who were expected to survive for ≥ 12 weeks.	• Patients who had, or were suspected of having, malignancy in other organs • Patients who had a treatment history of radiotherapy • Patients who had a treatment history of chemotherapy within one month before registration • Patients who had a treatment history of HIFU within two months before registration • Patients who were expected to have difficulty achieving hemostasis due to treatments such as antiplatelet therapy, anticoagulation therapy, or similar treatments • Patients who had gastrointestinal infiltration • Patients who had obstructive jaundice (allowed after jaundice reduction) • If the tumor was adjacent to the inferior vena cava, tumor embolus was present in the inferior vena cava (allowed if the area was avoided) • If the tumor was adjacent to the aorta and calcification lesions were present in the aorta (allowed if the area was avoided) • Patients who had cystic components in pancreatic cancer • Patients who had been using anthracycline anti-tumor agents • Patients who had a history of severe drug hypersensitivity • Patients who were allergic to contrast agent • Patients who had severe brain disease, lung disease (interstitial pneumonia and pulmonary fibrosis confirmed by imaging) • Patients who had a history of congestive heart failure, symptomatic coronary artery disease,

Inclusion criteria	Exclusion criteria
	arrhythmia poorly controlled with medication, myocardial infarction or unstable angina pectoris within 6 months before registration • Patients who had active infectious diseases requiring systemic treatment • Patients who were pregnant or might become pregnant during treatment • Patients found by the investigator to be unsuitable

Table S2 Dose escalation criteria

Cohort	K-912 (mg/m^2)	HIFU Power (W)	Number of Patients	Step up criteria				AEs				Total Number of Patients
				AEs	Action	AEs	Action	Cohort 1	Cohort 2	Cohort 3	Cohort 4	
1	30	75	3	0/3	Proceed to cohort 2	-	-	0/3	-	-	-	3
				1/3	Add 3 patients	0/3	Proceed to cohort 2	1/6	-	-	-	6
						1 - 3/3	30 mg/m^2 + 75 W is intolerable, K-912 is reduced by 50% and resumed at 15 mg/m^2 + 75 W	2 - 4/6	-	-	-	6
				2 - 3/3	30 mg/m^2 + 75 W is intolerable. K-912 is reduced by 50% and resumed at 15 mg/m^2 + 75 W	-	-	2 - 3/3	-	-	-	3
2	30	150	3	0/3	Proceed to cohort 3	-	-	0/3, 1/6	0/3	-	-	6 - 9
				1/3	Add 3 patients	0/3	Proceed to cohort 3	0/3, 1/6	1/6	-	-	9 - 12
						1 - 3/3	30 mg/m^2 + 150 W is intolerable. MTD: 30 mg/m^2 + 75 W	0/3, 1/6	2 - 4/6	-	-	9 - 12
				2 - 3/3	30 mg/m^2 + 150 W is intolerable. MTD: 30 mg/m^2 + 75 W	-	-	0/3, 1/6	2 - 3/3	-	-	6 - 9

Cohort	K-912 (mg/m^2)	HIFU Power (W)	Number of Patients	Step up criteria				AEs				Total Number of Patients
				AEs	Action	AEs	Action	Cohort 1	Cohort 2	Cohort 3	Cohort 4	
3	80	75	3	0/3	Proceed to cohort 4	-	-	0/3, 1/6	0/3, 1/6	0/3	-	9 - 15
				1/3	Add 3 patients	0/3	Proceed to cohort 4	0/3, 1/6	0/3, 1/6	1/6	-	12 - 18
						1-3/3	$80\ mg/m^2$ + 75 W is intolerable. MTD: $30\ mg/m^2$ + 150 W	0/3, 1/6	0/3, 1/6	2 - 4/6	-	12 - 18
				2 - 3/3	$80\ mg/m^2$ + 75 W is intolerable. MTD: $30\ mg/m^2$ + 150 W	-	-	0/3, 1/6	0/3, 1/6	2 - 3/3	-	9 - 15
4	80	150	3	0/3	MTD: $80\ mg/m^2$ + 150 W	-	-	0/3, 1/6	0/3, 1/6	0/3, 1/6	0/3	12 - 21
				1/3	Add 3 patients	0/3	MTD: $80\ mg/m^2$+ 150 W	0/3, 1/6	0/3, 1/6	0/3, 1/6	1/6	15 - 24
						1-3/3	$80\ mg/m^2$ + 150 W is intolerable. MTD: $80\ mg/m^2$ + 75 W	0/3, 1/6	0/3, 1/6	0/3, 1/6	2 - 4/6	15 - 24
				2 - 3/3	$80\ mg/m^2$ + 150 W is intolerable. MTD: $80\ mg/m^2$ + 75 W	-	-	0/3, 1/6	0/3, 1/6	0/3, 1/6	2 - 3/3	12 - 21

AE, adverse event; HIFU, high-intensity focused ultrasound; MTD, maximum tolerated dose