SUPPLEMENT

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Supplemental Appendix 2. Hyaluronan Affinity Histochemistry Assay

Halozyme and Ventana Medical Systems, Inc. (VMSI), co-developed the hyaluronan affinity histochemistry assay. Halozyme's recombinant TSG-6-ΔHep-Fc hyaluronan binding probe (fusion of Tumor necrosis factor-Stimulated Gene 6 protein with mutationally inactivated heparin-binding sequence and the Fc portion of human IgG1) was modified to include a rabbit Fc region for use with VMSI's detection system on the VENTANA BenchMark ULTRA automated staining platform.[1,2] The hyaluronan scoring method was based on the percentage of hyaluronan staining (at any staining intensity above background) in the extracellular matrix over the entire tumor sample surface. Patients with a score of ≥50% were categorized as hyaluronan high and were eligible for enrollment into the study, while those with a score <50% were hyaluronan low and were not eligible for enrollment. The scoring algorithm has been verified by inter- and intra-reader precision studies and supported in clinical studies.[2,3]

1. Jadin L, Huang L, Wei G, et al: Characterization of a novel recombinant hyaluronan binding protein for tissue hyaluronan detection. J Histochem Cytochem 62:672-683, 2014

2. Pu J, Aldrich C, Zhu J, et al: Hyaluronan assessment in tumor microenvironment using new affinity histochemistry assay and scoring method. J Clin Oncol 35:Abstract e23196, 2017

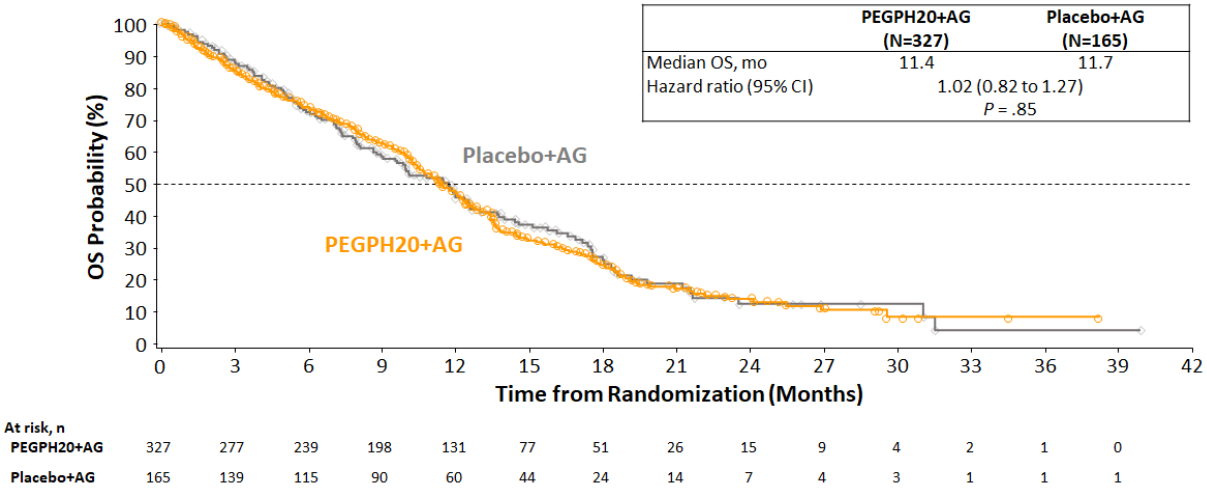
3. Hingorani SR, Zheng L, Bullock AJ, et al: HALO 202: randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J Clin Oncol 36:359-366, 2018

Supplemental Table S1. Subsequent Anticancer Therapy

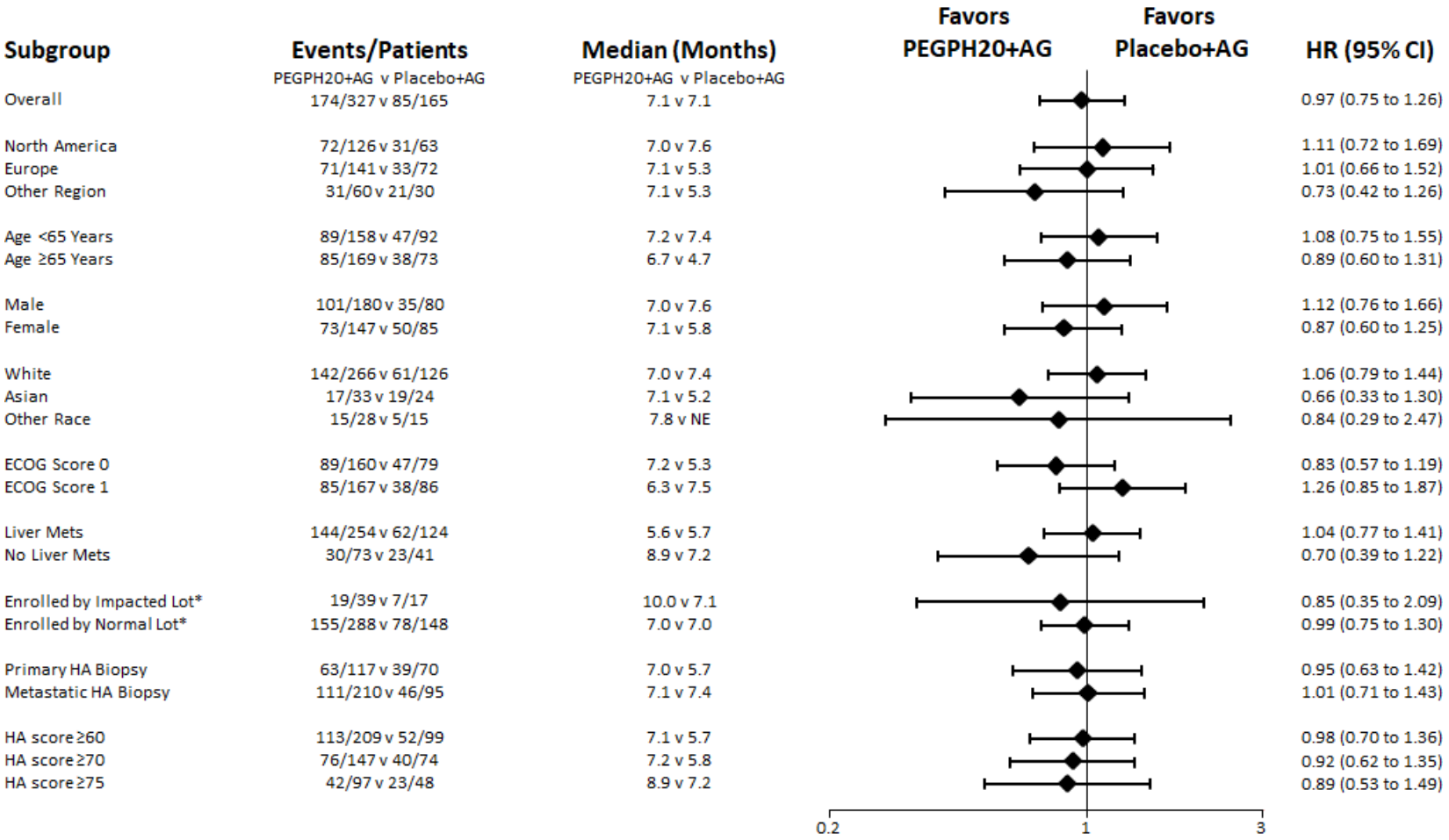
	PEGPH20 + AG (N = 327)	**Placebo + AG (N = 165)**
Any subsequent anticancer therapy, n (%)	168 (51.4)	87 (52.7)
Fluorouracil	102 (31.2)	63 (38.2)
Oxaliplatin	81 (24.8)	48 (29.1)
Irinotecan	64 (19.6)	42 (25.5)
Folinic acid	66 (20.2)	36 (21.8)
Gemcitabine	52 (15.9)	25 (15.2)
Paclitaxel albumin	38 (11.6)	16 (9.7)
Capecitabine	20 (6.1)	7 (4.2)
Calcium folinate	11 (3.4)	6 (3.6)
Gemcitabine hydrochloride	7 (2.1)	5 (3.0)
Irinotecan monohydrochloride trihydrate	9 (2.8)	3 (1.8)
Paclitaxel	5 (1.5)	5 (3.0)
Calcium folinate/ fluorouracil/ IRI/08193001	4 (1.2)	5 (3.0)
Investigational antineoplastic	5 (1.5)	4 (2.4)
Calcium levofolinate	4 (1.2)	4 (2.4)
Gimeracil/oteracil potassium/tegafur	5 (1.5)	3 (1.8)
Levofolinic acid	6 (1.8)	2 (1.2)
Cisplatin	2 (0.6)	5 (3.0)
Irinotecan hydrochloride	1 (0.3)	5 (3.0)
Interleukins	4 (1.2)	1 (0.6)
Erlotinib hydrochloride	2 (0.6)	2 (1.2)
FOLFOX	3 (0.9)	1 (0.6)
Nivolumab	2 (0.6	2 (1.2)

AG, nab-paclitaxel/gemcitabine; PEGPH20, pegvorhyaluronidase alfa.

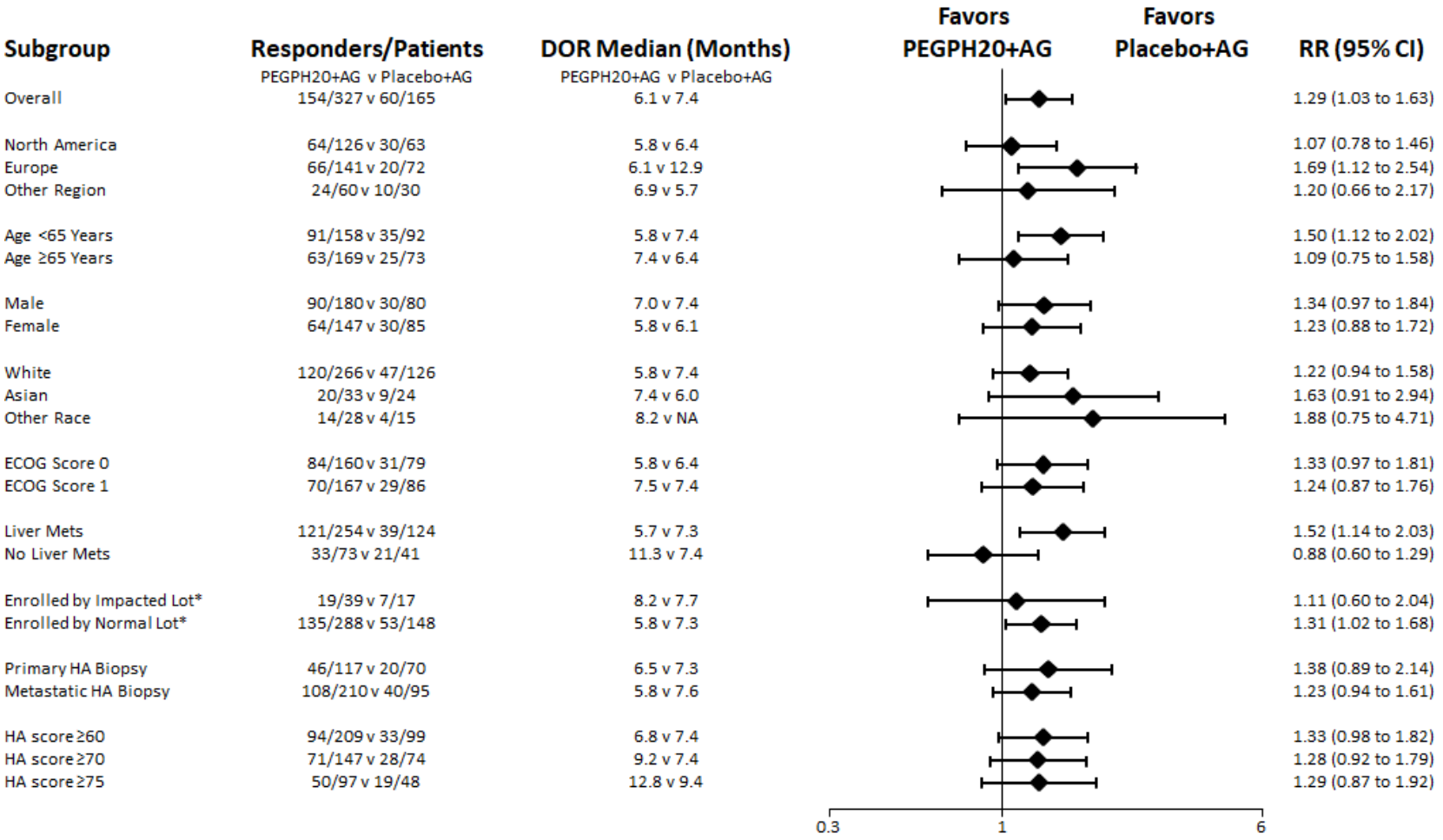
Supplemental Figure S1. Supportive overall survival analysis. Data cut-off September 10, 2019, after 363 deaths. AG, nab-paclitaxel/gemcitabine; CI, confidence interval; OS, overall survival; PEGPH20, pegvorhyaluronidase alfa.



Supplemental Figure S2. Progression-free survival in prespecified and exploratory subgroups. *Refers to manufacturing batch. AG, nab-paclitaxel/gemcitabine; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HA, hyaluronan; HR, hazard ratio; NE, not estimable; PEGPH20, pegvorhyaluronidase alfa.



Supplemental Figure S3. Objective response rate in prespecified and exploratory subgroups. *Refers to manufacturing batch. AG, nab-paclitaxel/gemcitabine; CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HA, hyaluronan; RR, response ratio; NE, not estimable; PEGPH20, pegvorhyaluronidase alfa.



Supplemental Table S2. Tumor Response

	PEGPH20 + AG (N = 327)	Placebo + AG (N = 165)
Objective response rate, %*	47	36
Response ratio (95% CI)	1.29 (1.03 to 1.63)	
Best response, n (%)		
Complete response	2 (0.6)	1 (0.6)
Partial response	152 (46.5)	59 (35.8)
Stable disease	71 (21.7)	54 (32.7)
Non-CR/non-PD	9 (2.8)	2 (1.2)
Progressive disease	47 (14.4)	22 (13.3)
Not evaluable/unknown	46 (14.1)	27 (16.4)
Duration of response, median, months[†]	6.1	7.4
Confirmed objective response rate, %	34	27
Confirmed response ratio (95% CI)	1.22 (0.91 to 1.62)	

*Complete and partial responses assessed by blinded independent centralized review based on RECIST version 1.1.

[†]Estimated by the Kaplan-Meier method.

AG, nab-paclitaxel/gemcitabine; CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PEGPH20, pegvorhyaluronidase alfa.

Supplemental Table S3. Study Treatment Exposure

	PEGPH20 + AG (N = 325)			Placebo + AG (N = 156)		
No. of cycles initiated, median (range)	5.0 (1–36)			5.0 (1–21)		
Duration of treatment, median (range), months	4.4 (0.1–35)			4.2 (0.1–19)		
	PEGPH20	**Gemcitabine**	**Nab-paclitaxel**	**Placebo**	**Gemcitabine**	**Nab-paclitaxel**
Relative dose intensity, median (range), %	83 (31–107)	80 (37–110)	79 (38–110)	89 (39–109)	77 (37–109)	78 (37–106)

AG, nab-paclitaxel/gemcitabine; PEGPH20, pegvorhyaluronidase alfa.

Supplemental Table S4. Dose Modification

	PEGPH20 + AG (N = 325)	Placebo + AG (N = 156)
AE leading to dose interruption of any drug, n (%)	251 (77.2)	116 (74.4)
AE leading to dose reduction of any drug, n (%)	140 (43.1)	73 (46.8)
AE leading to treatment discontinuation, n (%)	94 (28.9)	45 (28.8)

AE, adverse event; AG, nab-paclitaxel/gemcitabine; PEGPH20, pegvorhyaluronidase alfa.

Supplemental Table S5. All-Cause Grade 5 Adverse Events

	PEGPH20 + AG (N = 325)	**Placebo + AG (N = 156)**
Any event, n (%)	19 (5.8)	7 (4.5)
Infections and infestations	6 (1.8)	5 (3.2)
Gastrointestinal disorders	5 (1.5)	0
Respiratory/thoracic/mediastinal disorders	3 (0.9)	1 (0.6)
Blood/lymphatic system disorders	1 (0.3)	0
Cardiac disorders	1 (0.3)	0
General disorders/administration site conditions	1 (0.3)	0
Nervous system disorders	1 (0.3)	0
Psychiatric disorders	1 (0.3)	0
Metabolism/nutrition disorders	0	1 (0.6)

AG, nab-paclitaxel/gemcitabine; PEGPH20, pegvorhyaluronidase alfa.