original report

Phase IB/II Randomized Study of FOLFIRINOX Plus Pegylated Recombinant Human Hyaluronidase Versus FOLFIRINOX Alone in Patients With Metastatic Pancreatic Adenocarcinoma: SWOG S1313

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abstract

PURPOSE Pegylated recombinant human hyaluronidase (PEGPH20) degrades hyaluronan (HA) and, in combination with chemotherapy, prolongs survival in preclinical models. The activity of PEGPH20 with modified fluorouracil, leucovorin, irinotecan, and oxaliplatin (mFOLFIRINOX) was evaluated in patients with metastatic pancreatic cancer (mPC).

MATERIALS AND METHODS Patients had untreated mPC, a performance status of 0 to 1, and adequate organ function. Tumor HA status was not required for eligibility. After a phase Ib dose-finding study of mFOLFIRINOX plus PEGPH20, the phase II open-label study randomly assigned patients (1:1) to the combination arm or to mFOLFIRINOX alone (n = 138). The primary end point was overall survival (OS).

RESULTS PEGPH20 dosages of 3 μg/kg every 2 weeks were more tolerable than twice-weekly dosages used in the phase I study, so 3 μg/kg every 2 weeks was the phase II dosage. An amendment instituted enoxaparin prophylaxis in the PEGPH20 combination arm as a result of increased thromboembolic (TE) events. The planned interim futility analysis when 35 deaths (of 103 analyzable patients) occurred resulted in an OS hazard ratio (HR) of 2.07 that favored the control arm, and the study was closed to accrual. The treatment-related grade 3 to 4 toxicity was significantly increased in the PEGPH20 combination arm relative to control (odds ratio, 2.7; 95% CI, 1.1 to 7.1). The median OS in the mFOLFIRINOX arm was 14.4 months (95% CI, 10.1 to 15.7 months) versus 7.7 months (95% CI, 4.6 to 9.3 months) in the PEGPH20 combination arm.

CONCLUSION Addition of PEGPH20 to mFOLFIRINOX seems to be detrimental in patients unselected for tumor HA status. This combination caused increased toxicity (mostly GI and TE events) and resulted in decreased treatment duration compared with mFOLFIRINOX alone. The median OS in the mFOLFIRINOX control arm (14.4 months) is, to our knowledge, the longest yet reported and can be considered for patients with good PS.

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ASSOCIATED CONTENT
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Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The regimens of fluorouracil (FU), leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) and of gemcitabine plus nab-paclitaxel (GA) are the optimal choices for patients with metastatic pancreatic cancer (mPC) who have a good performance status (PS). FOLFIRINOX and GA have a median overall survival (OS) of 11.4 and 8.5 months, respectively, compared with 5.9 to 6.4 months with gemcitabine alone.[1-3] Despite these recent advances, the outcome remains poor, and fewer than 10% of patients survive 2 years.[2,3] A number of new agents are in active investigation, and the tumor stroma has emerged as a key focus of research in pancreatic cancer.[4-7] Primary and metastatic lesions are characterized by a dense desmoplastic stroma in which cancer cells are sparsely scattered.[8] Hyaluronic acid (hyaluronan, or HA) is a major component of this extracellular matrix. Preclinical studies have shown that high levels of HA in the extracellular matrix promote tumorigenesis.[7-9] Unmodified hyaluronidase has been used clinically, but a short half-life limits cancer applications. The pegylated form of human recombinant hyaluronidase (PEGPH20) has superior pharmacologic characteristics and, in preclinical models, depletes HA in the cancer extracellula matrix.[9,10] A phase I study of

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PEGPH20 in solid tumors established the tolerable dosage as 3 μg/kg given intravenously (IV) twice per week. In patients with pre- and post-dose tumor biopsies (n = 6), a decrease in tumor HA levels was observed, and Dynamic Contrast Enhanced magnetic resonance imaging (n = 11) showed changes in tumor perfusion consistent with the postulated mechanism of action.[11] Studies in genetically engineered mouse models of pancreatic cancer sparked interest in evaluation of PEGPH20 in clinical trials for mPC.[12,13] Rapid depletion of tumor HA after PEGPH20 administration was seen and resulted in significantly improved survival for the combination of gemcitabine and PEGPH20 compared with gemcitabine alone.[12,13] Subsequently, a phase Ib study evaluated gemcitabine and PEGPH20 in patients with mPC (n = 28). The phase II dosage was gemcitabine 1,000 mg/m^2 per week with the PEGPH20 dosage of 3.0 μg/kg twice per week for 4 weeks then once per week for 3 weeks. The median progression-free survival (PFS) was 5.0 months, and the median OS was 6.6 months. High HA levels were seen in 35% of 17 tumor samples analyzed using a validated immunohistochemical assay. The response rate (RR) of 67%, the PFS (7.2 months), and the OS (13.0 months) favored the subset of patients with high HA levels (n = 6).[14] Subsequently, a randomized phase II study of combined PEGPH20 and GA was initiated (ClinicalTrials.gov identifier: NCT01839487 [Halo-109-202]). In parallel, the Southwest Oncology Group initiated a randomized, phase Ib/II study of PEGPH20 and FOLFIRINOX (ClinicalTrials.gov identifier: NCT01959139 [S1313]). Neither study selected patients according to HA tumor status.

MATERIALS AND METHODS

Eligibility Criteria

Pertinent eligibility criteria are as follows: age 18 to 75 years, Zubrod PS of 0 to 1, and measurable mPC. Adequate organ function was required (normal serum creatinine and bilirubin level). A pretreatment tumor sample was required for registration. Exclusion criteria included the following: prior therapy for mPC, exposure to oxaliplatin or irinotecan at least 3 years before registration, prior abdominal radiation, receipt of warfarin or megestrol acetate, and history of pre-existing carotid artery disease or arterial thromboembolic (TE) events that required intervention or treatment.

Treatments

Each 2-week cycle of mFOLFIRINOX consisted of oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 180 mg/m^2, and FU 2,400 mg/m^2 (by 46-h IV infusion) given according to published guidelines.[3] The FU bolus was omitted (the FOLFIRINOX modification). All patients received pegfilgrastim or filgrastim after disconnection of the FU ambulatory pump. PEGPH20 was provided by Halozyme Pharmaceuticals (San Diego, CA). PEGPH20 was administered IV over 10 minutes, 24 hours before each dose of mFOLFIRINOX. The administration of PEGPH20 required corticosteroid premedication before and after dosing (ie, dexamethasone 8 mg twice per day by mouth or IV on day 1 of dosing, then 4 mg twice per day for the 3 subsequent days) to reduce the incidence of myalgias and arthralgias. The protocol was subsequently amended to require the use of prophylactic enoxaparin 1 mg/kg per day beginning 1 day before treatment with PEGPH20 because of an imbalance in TE events in this and the parallel Halo-109-202 study.

Phase Ib Study Design

The phase I part was a standard 3 plus 3, limited dose de-escalation study to evaluate safety and to determine a recommended phase II dose of PEGPH20. Potential PEGPH20 dose levels in a 2-week cycle included 3 μg/kg on day 1 and day 3 or 4; 3 μg/kg on day 1 only; and 1.6 μg/kg on day 1 only. The study schema and dose-limiting toxicity (DLT) definitions are listed in Appendix Table A1 (online only).

Phase II Study Design

The primary end point of the phase II study was OS in patients treated with PEGPH20 plus mFOLFIRINOX compared with those treated with mFOLFIRINOX alone. We hypothesized a hazard ratio (HR) of 0.67 in a comparison of the two arms, with the assumption that the investigational arm would improve median survival from 10 months with mFOLFIRINOX alone to 15 months in combination. With a one-sided type I error of 10% and 80% power, this design required 138 eligible patients. Secondary objectives were to assess the PFS, the RR, and the toxicity profile. Translational objectives were to correlate cancer antigen 19-9 (CA 19-9) levels, plasma HA levels, and tumor HA levels with clinical outcomes of treated patients. The study did not require stratification or selection on the basis of tumor HA status.

Patients were seen every 2 weeks for a history and physical examination with routine blood tests. The CA19-9 level was measured at baseline and every 4 weeks. Dose reductions for mFOLFIRINOX followed published guidelines.[3] The PEGPH20 dose could be reduced to 1.6 μg/kg on day 1 if specific drug-related grade 3 or 4 toxicity occurred (eg, musculoskeletal toxicity). Patients were removed from the study if an arterial TE event or a grade 4 venous TE event occurred during the study or if a patient was receiving enoxaparin at the start of study. Adverse events (AEs) were assessed for severity using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.[15] Patients were evaluated for tumor response every 8 weeks by RECIST, version 1.1, criteria.[16]

Tumoral and Serum HA Studies

A total of 10 mL of whole blood was collected at baseline, 48 hours after the first PEGPH20 dose, before cycle 2, and before cycle 3. Serum HA analysis was performed by Micro

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Constants (San Diego, CA). Paraffin-embedded tissue or five unstained slides from diagnosis of metastatic tumor were required for tumor HA assay. A Clinical Laboratory Improvement Amendments certified laboratory performed the assays (Ventana Medical Systems, Tucson, AZ), and high HA was defined as extracellular matrix HA tumor staining ≥ 50%).

Random Assignment

In the open-label, phase II study, patients were randomly assigned in a 1:1 manner into the two treatment groups. Assignment used a dynamic balancing algorithm[17] with stratification by Zubrod PS (0 *v* 1).

Statistical Analysis

The primary analysis of OS was conducted in all eligible patients according to a modified intent-to-treat principle. Probabilities of OS and PFS were estimated using the Kaplan-Meier method. Statistical differences in event rates between treatment arms were assessed via stratified Cox regression model. An interim futility analysis of OS was planned when one third of the expected events (approximately 37 deaths) was observed. Evidence to suggest early closure would consist of rejection of the alternative hypothesis (HR of 0.67 for OS) at a one-sided alpha level of .07. RR was compared by treatment arm via χ^2 test in patients with measurable disease. The mean number of treatment cycles per patient was compared across treatment arms using a Wilcoxon rank-sum test. Proportions of patients who experienced grades 3 to 5 toxicities were compared by treatment arm using an odds ratio estimated by simple logistic regression. Statistical tests were reported as two sided.

RESULTS

This was a study conducted by the Southwest Oncology Group (SWOG) and National Clinical Trials Network. Participating site institutional review board approval and patient written informed consent were obtained before trial enrollment.

Phase I

The study opened to accrual in January 2014 at limited SWOG institutions. At dose-level 1 (PEGPH20 3 μg/kg on day 1 and day 3 or 4 of each cycle), two DLTs (myalgia and fatigue/mucositis) were observed in the first five patients enrolled. This cohort was closed because of intolerability and dose-level 2 (PEGPH20 at 3 μg/kg on day 1 only, every 2 weeks) accrued six patients. One patient experienced DLTs (AST/ALT elevation, fatigue, dehydration, sepsis), and the phase II dosage was established as PEGPH20 at 3 μg/kg on day 1 with mFOLFIRINOX on days 2 to 4 every 2 weeks.

Study Amendments

The study temporarily closed to accrual in April 2014 after two patients were enrolled in the phase I part, when the parallel Halo-109-202 study was suspended because of the higher-than-expected TE rate in the PEGPH20-and-GA

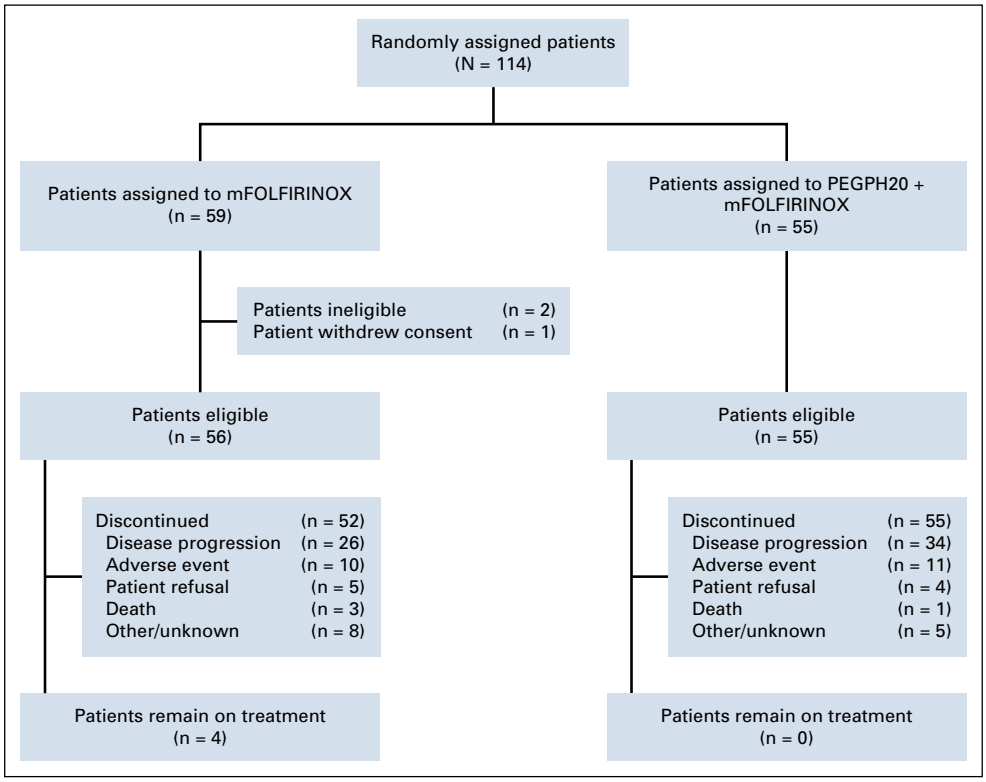

FIG 1. CONSORT flow diagram. mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

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arm. To reduce the risk of TE events, a study amendment (October 2014) required patients to receive aspirin 81 mg/d, and those with a history of TE events or who received warfarin were excluded. After the phase II study was activated in May 2015, a preplanned interim safety analysis after 40 patients were randomly assigned and completed two cycles was performed in March 2016. Imbalance in all-grade TE events was noted in the PEGPH20-plus-mFOLFIRINOX arm compared with the control arm (38% *v* 11%). There were no arterial TE events. Aspirin was replaced by enoxaparin prophylaxis (1mg/kg subcutaneously per day or equivalent) for the PEGPH20-plus-mFOLFIRINOX arm only. Ongoing toxicity analysis revealed higher-than-expected levels of nausea, vomiting, and diarrhea in the PEGPH20-plus-mFOLFIRINOX arm. An amendment (October 2016) recommended that patients on the mFOLFIRINOX-plus-PEGPH20 arm receive antiemetics suitable for a highly emetogenic regimen, prophylactic use of loperamide per guidelines for the first sign of diarrhea, and a lower threshold grade 2 or greater diarrhea) for dose reduction and delay of chemotherapy. On March 14, 2017, accrual was suspended on the basis of the results of a planned interim futility analysis; the study was permanently closed in July 2017.

Patient Characteristics

The randomized, phase II study accrued 114 patients from May 2015 to March 2017 at 30 SWOG member institutions. Three patients were excluded from the efficacy analysis: two patients were ineligible, and one withdrew consent (Fig 1). Patient characteristics (n = 111) are listed in Table 1.

Safety and Toxicity

The safety analysis included 105 patients, because six did not receive protocol therapy. In the mFOLFIRINOX arm (n = 54), there was one death as a result of sepsis. Four patients had grade 4 treatment-related AEs: neutropenia, hypokalemia, decreased platelets, and sepsis. An additional 26 patients had grade 3 toxicities (Table 2). Of the 51 patients assessed for AEs on the PEGPH20-plus-mFOLFIRINOX arm, seven patients had grade 4 treatment-related AEs, including hypokalemia, hyperglycemia, infusion-related reaction, decreased lymphocytes, sepsis, TE, and vomiting. Thirty-three additional patients experienced grade 3 AEs, including four TE events and one GI bleed (Table 2). The incidence of TE events in the PEGPH20 arm decreased from 33% to 9% after enoxaparin prophylaxis. The treatment exposure was higher in the mFOLFIRINOX arm compared with the combined arm (Appendix Table A2, online only). Dose delays and severe AEs were all increased in the PEGPH20-plus-mFOLFIRINOX arm compared with the mFOLFIRINOX arm (Table 2).

TABLE 1. Patient Characteristics

Characteristic	% of Patients	
	mFOLFIRINOX (n = 56)	mFOLFIRINOX Plus PEGPH20 (n = 55)
Age, years		
Median	61	64
Range	32-75	40-74
Sex		
Male	55	44
Female	45	56
Ethnicity		
White	82	78
Black	7	2
Asian	7	13
Other	4	7
Zubrod PS		
0	55	58
1	45	42
Primary site		
Head of pancreas	29	35
Body of pancreas	29	29
Tail of pancreas	27	20
Pancreas, NOS	16	17
Sites of involvement		
Primary tumor/ pancreas	91	89
Regional lymph nodes	39	29
Distant lymph nodes	11	9
Lung	32	25
Liver	80	76
Peritoneum	21	20
Other	21	16
Serum CA 19-9, U/mL		
< 37	18	13
≥ 37	82*	87†
Prior treatment (for PC)		
Chemotherapy	5	7
Surgery	4	13

Abbreviations: CA 19-9, cancer antigen 19-9; mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; NOS, not otherwise specified; PC, pancreatic cancer; PEGPH20, pegylated recombinant human hyaluronidase; PS, performance status.

*No. of patients = 46; median, 4,840; range, 91 to 232,548.

†No. of patients = 48; median, 3,465; range, 52 to 416,315.

Efficacy

OS was statistically significantly longer in the mFOLFIRINOX arm (n = 56, and 30 deaths) compared with the PEGPH20-plus-mFOLFIRINOX arm (n = 55, and 40 deaths). The median OS durations were 14.4 versus 7.7 months, respectively (HR, 2.07; 95% CI, 1.28 to 3.34; $P < .01$; Fig 2). Similarly, the median PFS was longer in the

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TABLE 2. Treatment-Related Toxicities That Occurred in More Than 10% of Patients and Those of Special Interest in the Phase II Study

	No. (%) of Patients			
	mFOLFIRINOX (n = 54)		mFOLFIRINOX Plus PEGPH20 (n = 51)	
Toxicity	**Grade 1 and 2**	**Grade 3 and 4**	**Grade 1 and 2**	**Grade 3 and 4**
Elevated ALT	15 (28)	0	9 (18)	3 (6)
Elevated AST	14 (26)	0	11 (22)	0
Abdominal pain	10 (19)	1 (2)	10 (20)	3 (6)
Elevated alkaline phosphatase	14 (26)	0	13 (25)	2 (4)
Alopecia	12 (22)	0	10 (20)	0
Anemia	31 (57)	4 (7)	30 (59)	2 (4)
Anorexia	19 (35)	2 (4)	21 (41)	3 (6)
Arthralgia	4 (7)	0	5 (10)	1 (2)
Constipation	11 (20)	0	11 (22)	0
Diarrhea	29 (54)	10 (19)	26 (51)	12 (24)
Dysgeusia	11 (20)	0	13 (25)	0
Edema in limbs	7 (13)	0	8 (16)	3 (6)
Fatigue	34 (63)	6 (11)	28 (55)	10 (20)
Febrile neutropenia/sepsis	0	2* (4)	0	1 (2)
Muscle weakness	1 (2)	0	1 (2)	0
Hypoalbuminemia	16 (30)	0	14 (27)	0
Hyponatremia	7 (13)	1 (2)	6 (12)	3 (6)
Infusion reaction	6 (11)	0 (6)	6 (12)	1 (2)
Mucositis	10 (19)	0	6 (12)	4 (8)
Myalgias	4 (7)	0	17 (33)	2 (4)
Nausea	24 (44)	8 (15)	27 (53)	13 (25)
Paresthesias	9 (17)	1(2)	7 (14)	0
Peripheral neuropathy (motor)	1 (2)	1 (2)	4 (8)	1 (2)
Peripheral neuropathy (sensory)	30 (56)	2 (4)	18 (35)	6 (12)
Platelets	25 (46)	2 (4)	15 (29)	3 (6)
Thromboembolic events	1 (2)	1 (2)	4 (8)	5 (10)
Vomiting	18 (33)	7 (13)	13 (25)	11 (22)
Weight loss	14 (26)	1 (2)	23 (45)	0
White count	7 (13)	2 (4)	7 (14)	1 (2)
Maximum grade, any event	20 (37)	31 (57)	8 (16)	40 (78)
SAE (all grades, regardless of treatment attribution)	8 (15)		36 (71)	
SAE grade ≥ 3 (regardless of treatment attribution)	6 (11)		34 (67)	
Treatment-related SAE (all grades)	5 (9)		23 (45)	

NOTE. All grades 3 to 5 toxicities were increased in the PEGPH20-plus-mFOLFIRINOX arm (odds ratio, 2.7; 95% CI, 1.1 to 7.1).

Abbreviations: mFOLFIRIFOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase; SAE, serious adverse event.

*There was one death as a result of sepsis that occurred during the study in the mFOLFIRINOX arm.

control (n = 41 events) versus experimental arm (n = 48 events): 6.2 versus 4.3 months, respectively (HR, 1.74; 95% CI, 1.14 to 2.66; $P = .01$; Fig 3). The control arm of mFOLFIRINOX had a higher RR of 45% (95% CI, 32% to 58%) than the PEGPH20-plus-mFOLFIRINOX arm RR of 33% (which included two complete responses; 95% CI, 20% to 45%), although this difference did not reach statistical significance ($P = .20$; Table 3). In the mFOLFIRINOX arm, 73% received second-line therapy: 62% received GA, and a smaller number (11%) continued with a modification

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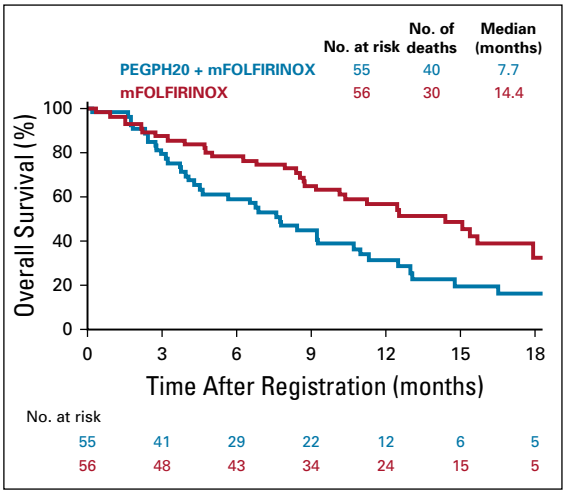

FIG 2. Overall survival. mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

of FOLFIRINOX. In the PEGPH20-plus-mFOLFIRINOX arm, 58% received second-line therapy: 47% received GA, and 11% continued with a modification of FOLFIRINOX.

CA 19-9 levels. The CA 19-9 levels were checked at baseline and every 4 weeks. The maximum percentage decrease in CA 19-9 from baseline was defined as high (≥ 50% decrease) versus low (< 50% decrease). Of the 20 patients on the PEGPH20-plus-mFOLFIRINOX arm with follow-up data, nine (45%) had a 50% or greater decrease in CA 19-9 that was associated with improved RR ($P = .04$) and PFS ($P = .04$) but not OS ($P = .27$). Of the 32 patients on the mFOLFIRINOX arm with follow-up data, 17 (53%) had a 50% or greater decrease in CA 19-9 that was associated with improved RR ($P = .04$), PFS ($P = .01$), and OS ($P = .07$).

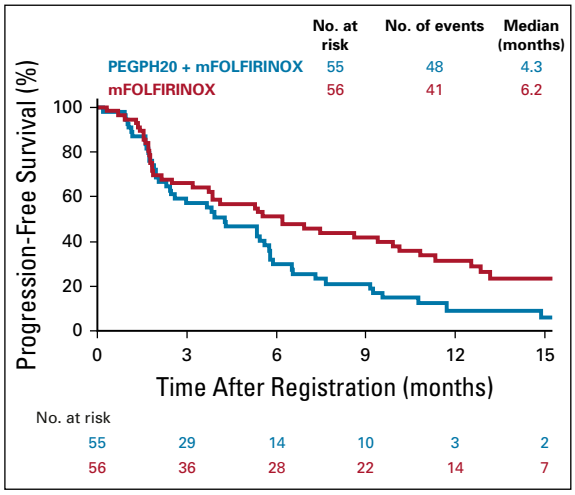

FIG 3. Progression-free survival. mFOLFIRINOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

Tumoral and Plasma HA

Plasma HA. Samples were assayed for total HA concentration using a validated method that measures pharmacodynamic response to PEGPH20 (MicroConstants, San Diego, CA) in the PEGPH20 + mFFOX arm only. Baseline circulating HA levels ranged from 29-838 ng/mL (n = 49, median 99). Consistent with previously published results (11), HA levels increased by a median of 33,708 ng/mL (n = 42, range 49-290,896 ng/mL), or over 300-fold at the 48-hour blood draw, demonstrating PEGPH20 activity.

Tumor HA. Tumor HA analysis and scoring was done with a validated immunohistochemistry test (Ventana Medical Systems, Tucson, AZ), as used in the Halo-109-202 study. This test was Clinical Laboratory Improvement Amendments certified for slides fewer than 90 days old; only 11 specimens in the SWOG biospecimen bank met these requirements, and eight were evaluable (results not shown).

DISCUSSION

The inferior outcomes in all efficacy measures (OS, PFS, and RR) with the addition of PEGPH20 to mFOLFIRINOX was unexpected, and the negative effect on survival (median OS of 7.7 months for the combination arm compared with 14.4 months for the mFOLFIRINOX-alone arm) is striking. The observed rate of expected AEs for the control arm of mFOLFIRINOX, such as nausea, diarrhea, neuropathy, fatigue, and neutropenic fever, was remarkably low compared with published data and was partly explained by the mFOLFIRINOX regimen and growth factor support.[3] In contrast, the addition of PEGPH20 to mFOLFIRINOX significantly increased GI toxicity and TE events. Enoxaparin prophylaxis was required to reduce TE events comparable to control arm occurrences. Because of toxicity, patients in the combination arm had increased dose delays, dose reductions, and reduced drug exposure of FOLFIRINOX. It is likely that lower overall drug exposure in patients who received the combination (median, four cycles *v* eight for mFOLFIRINOX alone) contributed to inferior survival. Another hypothesis is that PEGPH20 combined with the mFOLFIRINOX backbone had an unexpected negative effect on the tumor microenvironment or an adverse drug interaction with one or more of the FOLFIRINOX components, such as granulocyte colony-stimulating growth factor. Despite the incomplete tumor HA analysis because a majority of slides were more than 90 days old, it is unlikely, but not definitive that the median OS of patients with high-HA tumors (percentage not determined) treated in the combination arm would equal or exceed the 14.4 months seen in the mFOLFIRINOX-alone arm.

In contrast to this study (ie, S1313), the recently published, randomized Halo-109-202 study shows promise with the

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TABLE 3. Response Rate

Type	Response (%)	
	mFOLFIRINOX (n = 56)	mFOLFIRINOX Plus PEGPH20 (n = 55)
Complete response	0	4
Partial response	45	29
Stable disease	20	24
Response rate	45 (95% CI, 32 to 58)	33 (95% CI, 20 to 45)

Abbreviations: mFOLFIRIFOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

addition of PEGPH20 to GA.[18] Similar to the S1313 study, TE events increased with the addition of PEGPH20, and patients required enoxaparin. In our study, we also determined that enoxaparin was necessary, because low-dose aspirin (in the first 40 randomly assigned patients) did not completely eliminate TEs. The AE profile of the PEGPH20-plus-GA arm was acceptable. The tumor high-HA rate was 34%. In this subset of high-HA tumors, efficacy parameters favored the addition of PEGPH20; the RR was 45% versus 31%, the median PFS was 9.2 versus. 5.2 months (HR, 0.51; 95% CI, 0.26 to 1.00; $P = .048$), and the median OS was 11.5 versus 8.5 months (HR, 0.96; 95% CI, 0.57 to 1.61). There are several important differences between S1313 and Halo-109-202. PEGPH20 (3 ug/kg) could be administered on a twice-a-week schedule with weekly GA (days 1, 8, and 15); thus, patients received six doses in the first 4 weeks compared with only three doses of mFOLFIRINOX (days 1, 14 and 28). In the phase IB part of S1313, twice-a-week administration of PEGPH20 (six doses in the first 4 weeks) with mFOLFIRINOX was toxic and caused enhanced fatigue and general intolerance, so it required reduction in the frequency of dosing. Other differences between Halo-109-202 and S1313 are accrual (279 *v* 114), end points (PFS *v* OS), HA tumor analysis (246 *v* 11), and interim analysis (no *v* yes). Halo-109-301 is a multinational, double-blind, phase III, randomized study to evaluate PEGPH20 with GA in high-HA tumors only (ClinicalTrials.gov identifier: NCT02715804). The study is ongoing at this time and is without any safety issues reported by the sponsor.

The control arm of mFOLFIRINOX was remarkably well tolerated and resulted in a median OS of 14.4 months, which is—to our knowledge—the highest reported for this regimen. Because of concerns of toxicity, many oncologists reduce the dose of one or more of the components (FU, oxaliplatin, or irinotecan) by 15% to 25%.[19-22] We chose to modify the regimen by omitting bolus FU (which is a common modification of the FOLFOX regimen) without any other modifications, and we opted to give prophylactic growth factor support. On the basis of the results of S1313, mFOLFIRINOX can be considered for patients with good PS. The use of prophylactic granulocyte growth factor support with cycle 1 may not be needed in all cases and can be given per institutional guidelines.[23] TE events should be identified early and appropriately treated. There was one death as a result of sepsis in the mFOLFIRINOX arm, so oncologists are cautioned about the need for careful selection and monitoring of patients with mPC during therapy.

Stromal targeting agents should be evaluated cautiously given the negative results of Hedgehog inhibitors (vismodegib and saredigib) when combined with gemcitabine in phase II, randomized studies.[24,25] In summary, the results of S1313 highlight the importance of preclinical research when multiple agents are evaluated as well as the importance of robust clinical trial design and conduct with appropriate safety reviews. With close monitoring of toxicities as they emerged and appropriate study interim analyses, we stopped the study early for inferior survival in the investigational arm. We expect that other ongoing clinical and preclinical studies will give additional insights.

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APPENDIX

TABLE A1. Dose-Limiting Toxicity and Study Schema

Dose-limiting toxicity
Drug-related toxicities that occurred in the first cycle (2-week period) of treatment that were attributable to PEGPH20 and/or mFOLFIRINOX (possible, probable, or definite)
Any grade 3 or greater nonhematologic toxicity (except alopecia and grade 3 nausea, vomiting, and diarrhea that responded to medical treatment within 72 hours)
Hematologic toxicities, including grade 4 anemia or thrombocytopenia, grade 4 ANC decrease that lasted more than 7 days, or grade 3 or greater febrile neutropenia
Laboratory test results including grade 3 or greater elevation of AST/ALT, total bilirubin, or creatinine (if baseline values were elevated, then increase should be by two grades to be called a dose-limiting toxicity)
A delay in starting the second cycle of mFOLFIRINOX by more than 2 weeks because of drug-related toxicity.
Study schema
The schema included enrollment of a cohort of six patients treated with mFOLFIRINOX and PEGPH20 starting at dose-level 1 (3 μg/kg on day 1 and on day 3 or 4).
If two or more patients at dose level 1 experienced a dose-limiting toxicity, PEGPH20 was reduced for the next cohort (3 μg/kg on day 1 only).
If dose reduction to dose-level 3, then the study would be modified or closed (PEGPH20 at 1.6 μg/kg on day 1 only).
If none or one patient experienced a dose-limiting toxicity in a cohort of six patients, then that dose level was chosen as the phase II dose.

Abbreviations: ANC, absolute neutrophil count; mFOLFIRIFOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

TABLE A2. Treatment Exposure

	No. (%) of Patients	
Variable	**mFOLFIRINOX (n = 56)**	**mFOLFIRINOX Plus PEGPH20 (n = 55)**
Median (range) treatment, cycles	8 (0-37)	4 (0-43)*
Treatment administered, cycles		
≥ 2	47 (84)	45 (82)
≥ 4	42 (75)	34 (62)
≥ 6	33 (59)	23 (42)
≥ 8	29 (52)	21 (38)

Abbreviations: mFOLFIRIFOX, modified fluorouracil, leucovorin, irinotecan, and oxaliplatin; PEGPH20, pegylated recombinant human hyaluronidase.

*$P = .05$.