Title

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Clinical Trial Results

A Randomized, Double-Blinded, Phase II Trial of Gemcitabine and Nab-Paclitaxel Plus Apatorsen or Placebo in Patients with Metastatic Pancreatic Cancer: The RAINIER Trial

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01844817
- **Sponsor**: Sarah Cannon Research Institute
- **Principal Investigators**: Andrew H. Ko, Johanna C. Bendell
- **IRB Approved**: Yes

Lessons Learned

- The addition of the heat shock protein 27 (Hsp27)-targeting antisense oligonucleotide, apatorsen, to a standard first-line chemotherapy regimen did not result in improved survival in unselected patients with metastatic pancreatic cancer.
- Findings from this trial hint at the possible prognostic and predictive value of serum Hsp27 that may warrant further investigation.

Abstract

Background. This randomized, double-blinded, phase II trial evaluated the efficacy of gemcitabine/nab-paclitaxel plus either apatorsen, an antisense oligonucleotide targeting heat shock protein 27 (Hsp27) mRNA, or placebo in patients with metastatic pancreatic cancer.

Methods. Patients were randomized 1:1 to Arm A (gemcitabine/nab-paclitaxel plus apatorsen) or Arm B (gemcitabine/nab-paclitaxel plus placebo). Treatment was administered in 28-day cycles, with restaging every 2 cycles, until progression or intolerable toxicity. Serum Hsp27 levels were analyzed at baseline and on treatment. The primary endpoint was overall survival (OS).

Results. One hundred thirty-two patients were enrolled, 66 per arm. Cytopenias and fatigue were the most frequent grade 3/4 treatment-related adverse events for both arms. Median progression-free survival (PFS) and OS were 2.7 and 5.3 months, respectively, for arm A, and 3.8 and 6.9 months, respectively, for arm B. Objective response rate was 18% for both arms. Patients with high serum level of Hsp27 represented a poor-prognosis subgroup who may have derived modest benefit from addition of apatorsen.

Conclusion. Addition of apatorsen to chemotherapy does not improve outcomes in unselected patients with metastatic pancreatic cancer in the first-line setting, although a trend toward prolonged PFS and OS in patients with high baseline serum Hsp27 suggests this therapy may warrant further evaluation in this subgroup. ***The Oncologist*** 2017;22:1427–e129

Discussion

Heat shock protein 27 (Hsp27) is a protein chaperone whose expression is induced by cytotoxic chemotherapy, as well as other cell stressors such as hyperthermia, oxidative stress, and radiation, resulting in cytoprotection against these insults [1, 2]. Various malignancies, including pancreatic adenocarcinoma, overexpress Hsp27 [3]; furthermore, preclinical studies show that Hsp27 expression may play a role in the resistance of pancreatic cancer cell lines to gemcitabine [4–6]. Thus, inhibiting Hsp27 activity represents a viable therapeutic strategy in this disease. Apatorsen, an antisense oligonucleotide designed to bind to Hsp27 mRNA and block its translation into functional protein, offers one such approach [7].

On these bases, we performed a randomized phase II trial to compare the safety and efficacy of gemcitabine and nab-paclitaxel in combination with either apatorsen or

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Table 1. Median PFS and OS stratified by heat shock protein 27 levels

		Median PFS, months (95% CI)			Median OS, months (95% CI)		
	N	Nab-paclitaxel/ gemcitabine + apatorsen	Nab-paclitaxel/ gemcitabine + placebo	PFS hazard ratio	Nab-paclitaxel/ gemcitabine + apatorsen	Nab-paclitaxel/ gemcitabine + placebo	OS hazard ratio
Low/ normal Hsp27	102	2.9 (2.2, 4.0)	4.1 (3.1, 5.7)	1.178 (0.902, 1.539)	6.0 (3.2, 7.2)	9.0 (6.3, 11.2)	1.243 (0.813, 1.901)
High Hsp27	18	3.3 (0.3, 11.8)	0.9 (0.4, 1.4)	0.381 (0.120, 1.208)	3.3 (0.3, 11.8)	1.0 (0.6, 14.0)	0.587 (0.195, 1.770)

Abbreviations: CI, confidence interval; Hsp27, heat shock protein 27; OS, overall survival; PFS, progression-free survival.

placebo in the first-line setting for patients with metastatic pancreatic cancer. The planned sample size of 130 provided 80% power to detect a difference in median survival of 8.5 versus 13.4 months (hazard ratio [HR] for death, 0.634; 1-sided a = 0.1).

Although the incidence of toxicities did not differ significantly between the two treatment arms (most common treatment-related toxicities of all grades on both arms included fatigue, cytopenias, and gastrointestinal symptoms), the addition of apatorsen to chemotherapy did not produce any improvement in clinical outcomes in the intent-to-treat population. The objective response rate (ORR) was identical (18%) on both treatment arms, whereas patients on the apatorsen arm fared numerically worse in terms of both progression-free survival (PFS) and overall survival (OS) when compared with patients on the placebo arm, although these differences were not statistically significant (median PFS, 2.7 vs. 3.8 months, respectively [$p = .92$; HR 1.0]; median OS, 5.3 vs. 6.9 months, respectively [$p = .62$; HR 1.1]). Notably, the survival outcomes for patients on both arms of this study were considerably inferior to those observed on the gemcitabine/nab-paclitaxel arm from the phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial (MPACT) study [8], for unclear reasons.

The only subgroup for whom a potential benefit of apatorsen could be identified was those patients with high serum levels of Hsp27, a marker associated with a very poor prognosis overall (median PFS for patients with high baseline serum Hsp27 levels, 3.3 vs. 0.9 months for apatorsen vs. placebo, respectively [HR 0.38], median OS 3.3 vs. 1.0 months [HR 0.59]). However, the number of subjects who fit into this category was too small, representing only 14% of the entire study population, to draw any definitive conclusions.

In summary, the addition of apatorsen to a standard combination chemotherapy regimen in the first-line setting did not result in improvement in survival or other clinically relevant endpoints in patients with metastatic pancreatic cancer. Although further studies of this agent in unselected patients do not appear to be indicated, the findings from this trial do hint at the possible prognostic and predictive value of serum Hsp27 that may warrant further investigation.

Trial Information	
Disease	Metastatic pancreatic adenocarcinoma
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	None
Type of Study – 1	Phase II
Type of Study – 2	Randomized
PFS	$p = 0.92$, HR: 1.0
OS	$p = 0.62$, HR: 1.1
Primary Endpoint	Overall survival
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Toxicity
Investigator's Analysis	Feasible, possibly effective in patients with high Hsp27 serum levels

Drug Information for Phase II Control	
Drug 1	
Generic/Working name	Nab-paclitaxel
Trade name	Abraxane
Company name	Celgene
Drug type	Other

Drug class	Microtubule-targeting agent
Dose	125 milligrams (mg) per square meter (m^2)
Route	IV
Schedule of administration	Placebo days 1, 8, 15, and 22 of a 28-day cycle Nab-paclitaxel and gemcitabine days 1, 8, and 15 of a 28-day cycle
Drug 2	
Generic/Working name	Gemcitabine
Trade name	Gemzar
Company name	Eli Lilly
Drug type	Other
Drug class	Antimetabolite
Dose	1,000 mg/m^2
Route	IV
Schedule of administration	Placebo days 1, 8, 15, and 22 of a 28-day cycle Nab-paclitaxel and gemcitabine days 1, 8, and 15 of a 28-day cycle

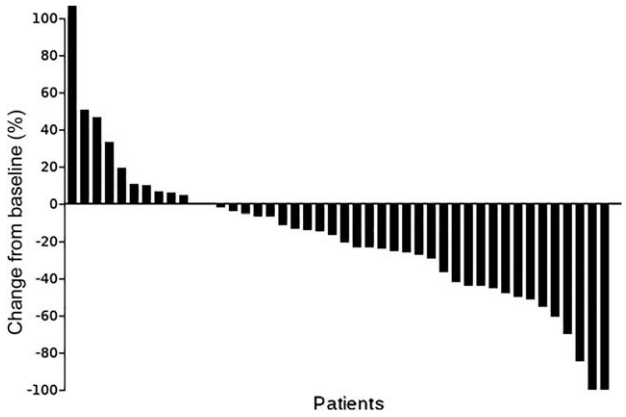
Drug Information for Phase II Experimental

Drug 1	
Generic/Working name	Apatorsen
Trade name	Not applicable
Company name	OncoGenex
Drug type	Other
Drug class	Antisense oligonucleotide
Dose	600 mg per flat dose
Route	IV
Schedule of administration	Apatorsen days 1, 8, 15, and 22 of a 28-day cycle Nab-paclitaxel and gemcitabine days 1, 8, and 15 of a 28-day cycle
Drug 2	
Generic/Working name	Nab-paclitaxel
Trade name	Abraxane
Company name	Celgene
Drug type	Other
Drug class	Microtubule-targeting agent
Dose	125 mg/m^2
Schedule of administration	Apatorsen days 1, 8, 15, and 22 of a 28-day cycle Nab-paclitaxel and gemcitabine days 1, 8, and 15 of a 28-day cycle pfof
Drug 3	
Generic/Working name	Gemcitabine
Trade name	Gemzar
Company name	Eli Lilly
Drug type	Other
Drug class	Antimetabolite
Dose	1,000 mg/m^2
Route	IV
Schedule of administration	Apatorsen 1, 8, 15, and 22 of a 28-day cycle Nab-paclitaxel and gemcitabine days 1, 8, and 15 of a 28-day cycle

Patient Characteristics for Phase II Control	
Number of Patients, Male	38
Number of Patients, Female	28
Stage	IV
Age	Median (range): 65.5 (47–83)
Number of Prior Systemic Therapies	Median (range): None
Performance Status ECOG	0 — 32 1 — 32 2 — 3 — Unknown — 2
Cancer Types or Histologic Subtypes	CA19-9 levels ≤90 U/mL 11 CA19-9 levels >90 U/mL 54 CA19-9 levels Unknown 1 Hsp27 expression high 11 Hsp27 expression low 47 Hsp27 expression Unknown 8

Patient Characteristics for Phase II Experimental	
Number of Patients, Male	37
Number of Patients, Female	29
Stage	IV
Age	Median (range): 66.5 (39–82)
Number of Prior Systemic Therapies	Median (range): None
Performance Status: ECOG	0 — 30 1 — 36 2 — 3 — Unknown —
Cancer Types or Histologic Subtypes	CA19-9 levels ≤90 U/mL 18 CA19-9 levels >90 U/mL 47 CA19-9 levels unknown 1 Hsp27 expression high 7 Hsp27 expression low 55 Hsp27 expression unknown 4

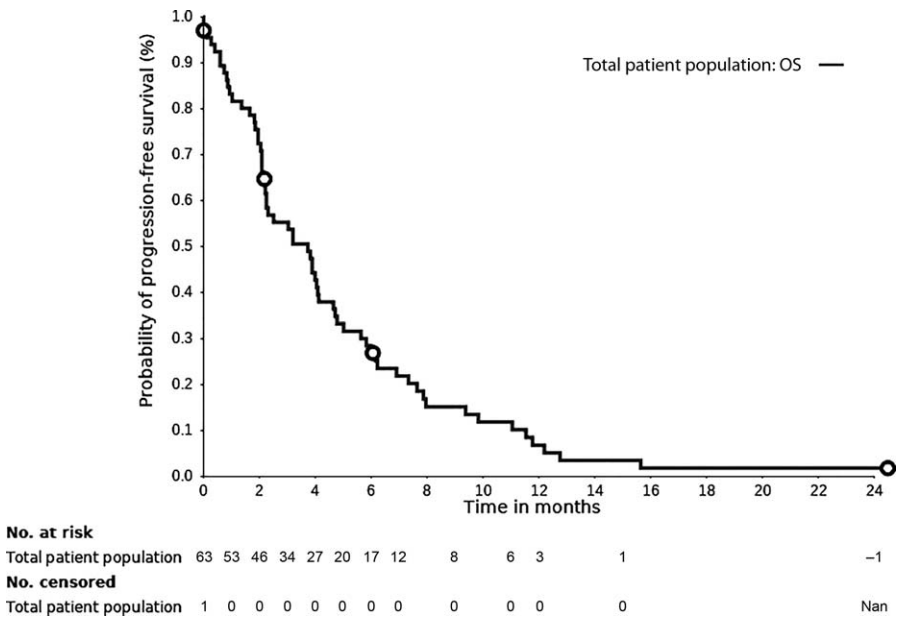
Primary Assessment Method for Phase II Control	
Assessment: Total Patient Population: Overall Survival	
Number of patients screened	66
Number of patients enrolled	66
Number of patients evaluable for toxicity	63
Number of patients evaluated for efficacy	66
Evaluation method	RECIST 1.1
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 12$ (18%)
Response assessment SD	$n = 21$ (32%)
Response assessment PD	$n = 18$ (28%)
Response assessment OTHER	$n = 15$ (22%)
(Median) duration assessments PFS	3.8 months
(Median) duration assessments OS	6.9 months
Kaplan-Meier time units	months



Waterfall plot demonstrating best objective response in response-evaluable subjects on control arm.

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
0.03	0	1	100.00	100.00	65
0.13	1	0	100.00	98.46	64
0.30	1	0	98.46	96.92	63
0.43	1	0	96.92	95.38	62
0.62	1	0	95.38	93.85	61
0.76	1	0	93.85	92.31	60
0.85	1	0	92.31	90.77	59
0.89	1	0	90.77	89.23	58
0.95	1	0	89.23	87.69	57
1.05	1	0	87.69	86.15	56
1.12	1	0	86.15	84.62	55
1.35	0	1	84.62	84.62	54
1.38	1	0	84.62	83.05	53
1.84	1	0	83.05	81.48	52
1.97	1	0	81.48	79.91	51
2.23	0	1	79.91	79.91	50
2.53	1	0	79.91	78.32	49
2.92	1	0	78.32	76.72	48
3.06	1	0	76.72	75.12	47
3.22	1	0	75.12	73.52	46
3.45	1	0	73.52	71.92	45
3.52	1	0	71.92	70.32	44
3.75	1	0	70.32	68.73	43
4.11	1	0	68.73	67.13	42
4.37	0	1	67.13	67.13	41
4.47	1	0	67.13	65.49	40
4.73	1	0	65.49	63.85	39
5.85	1	0	63.85	62.22	38
6.14	1	0	62.22	60.58	37
6.24	1	0	60.58	58.94	36
6.34	1	0	58.94	57.30	35
6.37	1	0	57.30	55.67	34

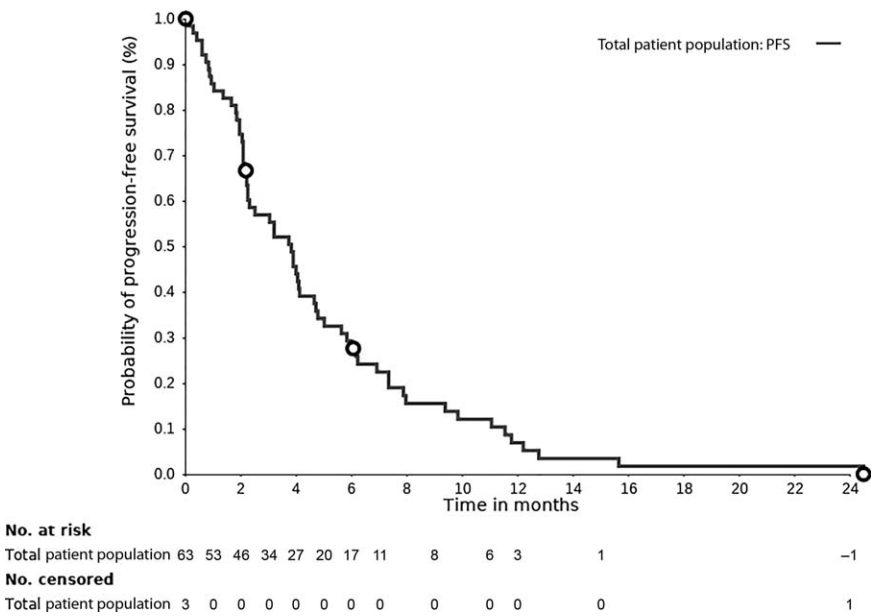
6.60	1	0	55.67	54.03	33
6.83	1	0	54.03	52.39	32
6.93	2	0	52.39	49.12	30
7.52	2	0	49.12	45.84	28
7.98	1	0	45.84	44.21	27
8.11	1	0	44.21	42.57	26
8.21	1	0	42.57	40.93	25
9.00	1	0	40.93	39.29	24
9.26	1	0	39.29	37.66	23
9.30	1	0	37.66	36.02	22
9.33	1	0	36.02	34.38	21
9.66	0	1	34.38	34.38	20
10.02	1	0	34.38	32.66	19
10.12	0	1	32.66	32.66	18
10.91	1	0	32.66	30.85	17
11.07	1	0	30.85	29.03	16
11.24	1	0	29.03	27.22	15
11.53	1	0	27.22	25.41	14
11.93	1	0	25.41	23.59	13
12.22	1	0	23.59	21.78	12
12.94	1	0	21.78	19.96	11
14.00	1	0	19.96	18.15	10
14.75	1	0	18.15	16.33	9
14.95	0	1	16.33	16.33	8
15.70	0	1	16.33	16.33	7
18.17	1	0	16.33	14.00	6
18.53	1	0	14.00	11.67	5
18.99	1	0	11.67	9.33	4
21.32	0	1	9.33	9.33	3
22.14	1	0	9.33	6.22	2
22.87	1	0	6.22	3.11	1
25.76	0	1	3.11	0.00	0



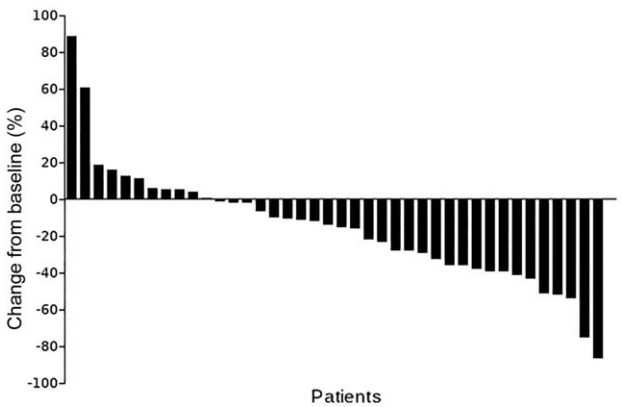
Assessment: Total Patient Population: Progression-Free Survival	
Number of patients screened	66
Number of patients enrolled	66
Number of patients evaluable for toxicity	63
Number of patients evaluated for efficacy	66
Evaluation method	RECIST 1.1
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 12$ (18%)
Response assessment SD	$n = 21$ (32%)
Response assessment PD	$n = 18$ (28%)
Response assessment OTHER	$n = 15$ (22%)
(Median) duration assessments PFS	3.8 months
(Median) duration assessments OS	6.9 months
Kaplan-Meier time units	months

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
0.03	0	3	100.00	100.00	63
0.13	1	0	100.00	98.41	62
0.30	1	0	98.41	96.83	61
0.43	1	0	96.83	95.24	60
0.62	2	0	95.24	92.06	58
0.76	1	0	92.06	90.48	57
0.85	1	0	90.48	88.89	56
0.89	1	0	88.89	87.30	55
0.95	1	0	87.30	85.71	54
1.05	1	0	85.71	84.13	53
1.38	1	0	84.13	82.54	52
1.68	1	0	82.54	80.95	51
1.84	1	0	80.95	79.37	50
1.87	1	0	79.37	77.78	49
1.97	2	0	77.78	74.60	47
2.07	1	0	74.60	73.02	46
2.10	3	0	73.02	68.25	43
2.14	1	0	68.25	66.67	42
2.20	0	1	66.67	66.67	41
2.23	2	0	66.67	63.41	39
2.27	2	0	63.41	60.16	37
2.33	1	0	60.16	58.54	36
2.53	1	0	58.54	56.91	35
3.06	1	0	56.91	55.28	34
3.22	2	0	55.28	52.03	32
3.75	1	0	52.03	50.41	31
3.84	1	0	50.41	48.78	30
3.91	2	0	48.78	45.53	28

4.01	1	0	45.53	43.90	27
4.07	1	0	43.90	42.28	26
4.11	1	0	42.28	40.65	25
4.14	1	0	40.65	39.02	24
4.67	1	0	39.02	37.40	23
4.73	1	0	37.40	35.77	22
4.80	1	0	35.77	34.15	21
5.03	1	0	34.15	32.52	20
5.65	1	0	32.52	30.89	19
5.85	1	0	30.89	29.27	18
6.01	1	0	29.27	27.64	17
6.08	0	1	27.64	27.64	16
6.18	1	0	27.64	25.91	15
6.24	1	0	25.91	24.19	14
6.93	1	0	24.19	22.46	13
7.36	2	0	22.46	19.00	11
7.89	1	0	19.00	17.28	10
7.98	1	0	17.28	15.55	9
9.40	1	0	15.55	13.82	8
9.86	1	0	13.82	12.09	7
11.07	1	0	12.09	10.37	6
11.56	1	0	10.37	8.64	5
11.79	1	0	8.64	6.91	4
12.22	1	0	6.91	5.18	3
12.78	1	0	5.18	3.46	2
15.67	1	0	3.46	1.73	1
24.51	0	1	1.73	0.00	0



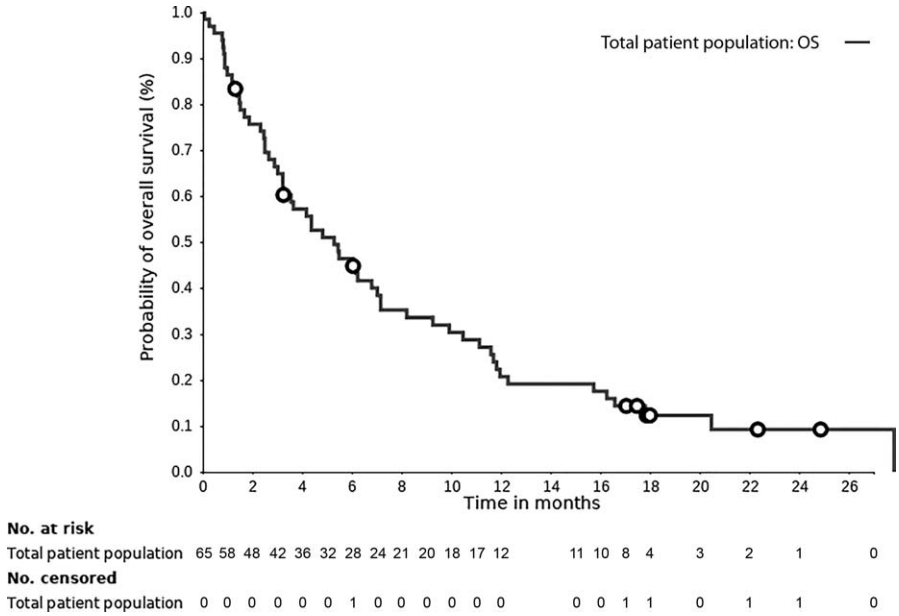
Primary Assessment Method for Phase II Experimental	
Assessment: Total Patient Population: Overall Survival	
Number of patients screened	66
Number of patients enrolled	66
Number of patients evaluable for toxicity	64
Number of patients evaluated for efficacy	66
Evaluation method	RECIST 1.1
Response assessment CR	$n = 0$ (0%)
Response assessment PR	$n = 12$ (18%)
Response assessment SD	$n = 16$ (24%)
Response assessment PD	$n = 21$ (32%)
Response assessment OTHER	$n = 17$ (26%)
(Median) duration assessments PFS	2.7 months
(Median) duration assessments OS	5.3
Kaplan-Meier time units	months



Waterfall plot demonstrating best objective response in response-evaluable subjects on experimental arm.

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
0.07	1	0	100.00	98.48	65
0.26	1	0	98.48	96.97	64
0.46	1	0	96.97	95.45	63
0.79	1	0	95.45	93.94	62
0.82	1	0	93.94	92.42	61
0.85	1	0	92.42	90.91	60
0.89	2	0	90.91	87.88	58
0.99	1	0	87.88	86.36	57
1.18	1	0	86.36	84.85	56
1.22	1	0	84.85	83.33	55
1.31	0	1	83.33	83.33	54
1.38	1	0	83.33	81.79	53
1.48	1	0	81.79	80.25	52

1.51	1	0	80.25	78.70	51
1.68	1	0	78.70	77.16	50
1.87	1	0	77.16	75.62	49
2.33	1	0	75.62	74.07	48
2.46	1	0	74.07	72.53	47
2.50	2	0	72.53	69.44	45
2.66	1	0	69.44	67.90	44
2.89	1	0	67.90	66.36	43
3.02	1	0	66.36	64.81	42
3.22	2	0	64.81	61.73	40
3.25	1	0	61.73	60.19	39
3.55	1	0	60.19	58.64	38
3.65	1	0	58.64	57.10	37
4.17	1	0	57.10	55.56	36
4.37	2	0	55.56	52.47	34
4.83	1	0	52.47	50.93	33
5.29	1	0	50.93	49.38	32
5.45	1	0	49.38	47.84	31
5.49	1	0	47.84	46.30	30
6.05	1	1	46.30	44.70	28
6.18	1	0	44.70	43.10	27
6.24	1	0	43.10	41.51	26
6.80	1	0	41.51	39.91	25
7.03	1	0	39.91	38.31	24
7.16	2	0	38.31	35.12	22
8.21	1	0	35.12	33.52	21
9.26	1	0	33.52	31.93	20
9.92	1	0	31.93	30.33	19
10.48	1	0	30.33	28.74	18
11.14	1	0	28.74	27.14	17
11.60	1	0	27.14	25.54	16
11.70	1	0	25.54	23.95	15
11.83	1	0	23.95	22.35	14
11.96	1	0	22.35	20.75	13
12.29	1	0	20.75	19.16	12
15.74	1	0	19.16	17.56	11
16.26	1	0	17.56	15.96	10
16.59	1	0	15.96	14.37	9
17.05	0	1	14.37	14.37	8
17.48	0	1	14.37	14.37	7
17.81	1	0	14.37	12.32	6
17.87	0	1	12.32	12.32	5
18.00	0	1	12.32	12.32	4
20.47	1	0	12.32	9.24	3
22.34	0	1	9.24	9.24	2
24.87	0	1	9.24	9.24	1
27.83	1	0	9.24	0.00	0



Assessment: Total Patient Population: Progression-Free Survival	
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Number of patients evaluated for efficacy	66
Evaluation method	RECIST 1.1
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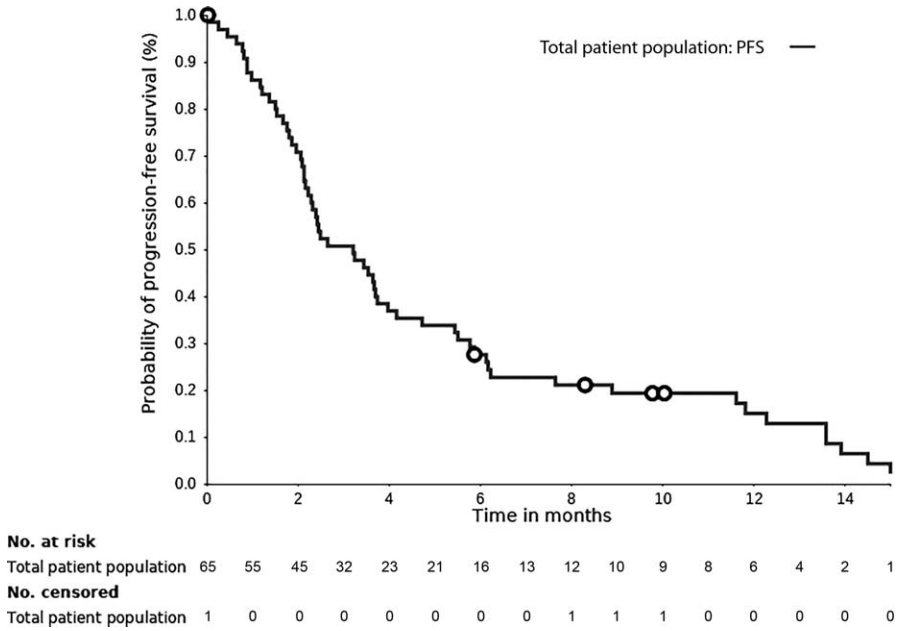
Response assessment SD	$n = 16$ (24%)
Response assessment PD	$n = 21$ (32%)
Response assessment OTHER	$n = 17$ (26%)
Kaplan-Meier time units	months

Time of scheduled assessment and/or time of event	No. progressed (or deaths)	No. censored	Percent at start of evaluation period	Kaplan-Meier %	No. at next evaluation/No. at risk
0.03	0	1	100.00	100.00	65
0.07	1	0	100.00	98.46	64
0.26	1	0	98.46	96.92	63
0.46	1	0	96.92	95.38	62
0.66	1	0	95.38	93.85	61
0.79	1	0	93.85	92.31	60
0.82	1	0	92.31	90.77	59
0.85	1	0	90.77	89.23	58
0.89	2	0	89.23	86.15	56
0.99	1	0	86.15	84.62	55
1.18	1	0	84.62	83.08	54
1.22	1	0	83.08	81.54	53
1.38	1	0	81.54	80.00	52
1.51	1	0	80.00	78.46	51
1.54	1	0	78.46	76.92	50

1.68	1	0	76.92	75.38	49
1.77	1	0	75.38	73.85	48
1.81	1	0	73.85	72.31	47
1.87	1	0	72.31	70.77	46
1.97	1	0	70.77	69.23	45
2.07	1	0	69.23	67.69	44
2.10	1	0	67.69	66.15	43
2.14	2	0	66.15	63.08	41
2.17	1	0	63.08	61.54	40
2.23	1	0	61.54	60.00	39
2.30	1	0	60.00	58.46	38
2.33	1	0	58.46	56.92	37
2.40	1	0	56.92	55.38	36
2.43	1	0	55.38	53.85	35
2.46	1	0	53.85	52.31	34
2.50	1	0	52.31	50.77	33
2.66	1	0	50.77	49.23	32
3.22	1	0	49.23	47.69	31
3.25	1	0	47.69	46.15	30
3.45	1	0	46.15	44.62	29
3.55	1	0	44.62	43.08	28
3.65	1	0	43.08	41.54	27
3.68	1	0	41.54	40.00	26
3.71	1	0	40.00	38.46	25
3.75	1	0	38.46	36.92	24
3.98	1	0	36.92	35.38	23
4.17	1	0	35.38	33.85	22
4.73	1	0	33.85	32.31	21
5.45	1	0	32.31	30.77	20
5.52	1	0	30.77	29.23	19
5.78	1	0	29.23	27.69	18
5.88	1	1	27.69	26.06	16
6.14	1	0	26.06	24.43	15
6.18	1	0	24.43	22.81	14
6.24	1	0	22.81	21.18	13
7.66	1	0	21.18	19.55	12
8.31	0	1	19.55	19.55	11
8.90	1	0	19.55	17.77	10
9.79	0	1	17.77	17.77	9
10.05	0	1	17.77	17.77	8
11.63	1	0	17.77	15.55	7
11.83	1	0	15.55	13.33	6
12.29	1	0	13.33	11.11	5
13.60	2	0	11.11	6.66	3
13.93	1	0	6.66	4.44	2
14.52	1	0	4.44	2.22	1
15.01	1	0	2.22	0.00	0



Adverse Events

	Patients, *n* (%)				
Adverse event	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Total**
Hematologic					
Anemia	1 (8%)	1 (8%)	0	0	2 (17%)
Thrombocytopenia	1 (8%)	1 (8%)	0	0	2 (17%)
Leukopenia	1 (8%)	0	0	0	1 (8%)
Nonhematologic					
Nausea	3 (25%)	5 (42%)	0	0	8 (67%)
Diarrhea	3 (25%)	4 (33%)	0	0	7 (58%)
Fatigue	3 (25%)	2 (17%)	0	0	5 (42%)
Vomiting	3 (25%)	2 (17%)	0	0	5 (42%)
Mucosal inflammation	1 (8%)	2 (17%)	1 (8%)	0	3 (25%)
Stomatitis	2 (17%)	0	0	0	3 (25%)
Decreased appetite	2 (17%)	0	0	0	2 (17%)
Hypokalemia	0	0	2 (17%)	0	2 (17%)
Constipation	1 (8%)	0	0	0	1 (8%)
Dehydration	0	1 (8%)	0	0	1 (8%)
Dysgeusia	0	1 (8%)	0	0	1 (8%)
Dysphagia	1 (8%)	0	0	0	1 (8%)
Fall	0	1 (8%)	0	0	1 (8%)
Hyperglycemia	0	0	1 (8%)	0	1 (8%)
Hypersensitivity	0	0	1 (8%)	0	1 (8%)
Hypomagnesemia	1 (8%)	0	0	0	1 (8%)
Insomnia	1 (8%)	0	0	0	1 (8%)
Myalgia	1 (8%)	0	0	0	1 (8%)
Peripheral neuropathy	1 (8%)	0	0	0	1 (8%)
Peripheral edema	0	1 (8%)	0	0	1 (8%)
Peripheral embolism	0	1 (8%)	0	0	1 (8%)
Pruritus	1 (8%)	0	0	0	1 (8%)

Rash	0	1 (8%)	0	0	1 (8%)
Generalized rash	0	0	1 (8%)	0	1 (8%)
Maculo-papular rash	0	0	1 (8%)	0	1 (8%)
Sinus tachycardia	1 (8%)	0	0	0	1 (8%)
Temperature intolerance	1 (8%)	0	0	0	1 (8%)
Weight decreased	0	1 (8%)	0	0	1 (8%)

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics/Pharmacodynamics	Correlative endpoints not met
Investigator's Assessment	Feasible, possibly effective in patients with high Hsp27 serum levels

Pancreatic adenocarcinoma is expected to rise to the second leading cause of cancer-related mortality in the U.S. by the end of this decade [9]. Systemic therapy represents the mainstay of treatment for patients with advanced or metastatic disease, for whom two combination chemotherapy regimens have emerged as front-line standards of care: gemcitabine plus nab-paclitaxel [8], and FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan, and oxaliplatin) [10]. However, despite these recent improvements in available cytotoxic therapies, overall prognosis in this disease remains very poor; for example, in the phase III MPACT trial leading to the approval of nab-paclitaxel for metastatic pancreatic cancer, the median survival for patients receiving the combination of gemcitabine plus nab-paclitaxel was only 8.5 months, representing a statistically significant but relatively modest absolute improvement of 1.8 months when compared with single-agent gemcitabine [8]. Clearly, novel drugs with unique mechanisms of action warrant further exploration.

Molecularly targeted therapies that have been approved for use in clinical oncology include monoclonal antibodies and small molecule inhibitors, particularly tyrosine kinase inhibitors. Unfortunately, many potential therapeutic targets are not amenable to these specific pharmacologic approaches, highlighting the importance of developing alternative strategies, including agents that can disrupt these targets at the gene expression level. Antisense oligonucleotides (ASOs), which are chemically modified stretches of single-strand DNA complementary to the mRNA regions of a target gene that inhibit translation by forming RNA/DNA duplexes, represent one such approach to specifically prevent translation of functionally relevant genes.

Apatorsen, a 2'-methoxyethyl oligonucleotide with phosphorothiolated internucleotide linkages, is designed to bind to heat shock protein 27 (Hsp27) mRNA and prevent translation into a functional protein. Targeting this specific heat shock protein represents an attractive therapeutic option, because Hsp27 can potentially affect multiple pathways implicated in cancer progression and resistance, as opposed to targeting a single pathway, a strategy that might have limited benefits in the face of the redundant signaling pathways and significant tumor heterogeneity. For example, overexpression of Hsp27 in cancer cells is induced by cytotoxic chemotherapy, as well as other cell stressors including hyperthermia, oxidative stress, and radiation, resulting in cytoprotection against these insults [1, 2]. Furthermore, Hsp27 serves to stabilize mutated or inappropriately activated oncoproteins that contribute to the initiation, growth, and metastasis of human cancers [2, 11].

The phase I dose-escalation study of apatorsen in patients with castration-resistant prostate cancer and other advanced cancers showed evidence of monotherapy activity as demonstrated by decline in tumor markers and circulating tumor cells, as well as stable measurable disease in 12 of 42 patients [12]. Further evaluation of apatorsen has been pursued in combination with chemotherapeutic agents in clinical trials specific to non-small cell lung and bladder cancer [13, 14].

Pancreatic adenocarcinomas show higher levels of Hsp27 expression when compared with healthy pancreatic tissue, and the protein can also be detected with high sensitivity in the serum of patients with pancreatic cancer [3]. Preclinical studies additionally show that Hsp27 expression may play a role in the resistance of pancreatic cancer cell lines to gemcitabine [4–6]. On these bases, the current study was designed to compare the safety and efficacy of gemcitabine and nab-paclitaxel in combination with either apatorsen or placebo in the first-line setting for patients with metastatic pancreatic cancer. However, we did not observe any improvement in clinical outcomes in the intent-to-treat population in this trial; indeed, patients on the apatorsen arm fared numerically worse in terms of both PFS and OS when compared with patients on the placebo control arm, although these differences were not statistically significant. The only subgroup for whom a potential benefit of apatorsen could be identified was those patients with high serum levels of Hsp27, a marker that portended a very poor prognosis overall. However, the number of subjects who fit into this category was too small, representing only 14% of the entire study population, to draw any definitive conclusions. Further studies, either prospectively designed trials or retrospective analyses of available clinically annotated samples, will be required to assess whether Hsp27 truly represents an adverse prognostic marker in this disease.

Several additional points are worth noting. First, the clinical outcomes for patients on both arms of this study were considerably inferior to those observed on the gemcitabine plus nab-

paclitaxel arm from the phase III MPACT trial [8], in which patients achieved a median OS and PFS of 8.5 and 5.5 months, respectively. It is unclear why subjects on the current study fared so poorly, given similar demographics to the MPACT study; nevertheless, it seems fairly unlikely that a benefit from apatorsen would somehow be unmasked even if patients had achieved outcomes that more similarly matched those of the MPACT trial. Furthermore, because this study did not mandate pretreatment collection of tumor specimens, putative tissue-based predictive markers of apatorsen sensitivity could not be assessed, nor could the pharmacodynamic effects of this agent given the absence of requiring on-treatment tumor biopsies. No consistent trend was identified on serial serum Hsp27 measurements in responders versus nonresponders (data not shown). This lack of robust correlative data represents a major limitation of our study and highlights one of the major ongoing challenges in pancreatic cancer trial design in general, especially when trying to confirm the putative mechanism of action of novel targeted agents.

In conclusion, the addition of apatorsen to a standard combination chemotherapy regimen in the first-line setting did not result in improved survival or other clinically relevant endpoints in patients with metastatic pancreatic cancer. Further studies of this agent in unselected patients do not appear to be indicated, although the findings from this trial do hint at the possible prognostic and predictive value of serum Hsp27 that may warrant further investigation. If ASO technologies targeting this and other cancer-related genes continue to be pursued in pancreatic cancer, they should ideally be evaluated in the context of trials that mandate serial collection of both tumor and blood samples to look for predictive markers and pharmacodynamic markers of response, notwithstanding the clinical and logistic hurdles these may present in this patient population.

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