SPARC Expression Did Not Predict Efficacy of nab-Paclitaxel plus Gemcitabine or Gemcitabine Alone for Metastatic Pancreatic Cancer in an Exploratory Analysis of the Phase III MPACT Trial

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Abstract

Purpose: nab-Paclitaxel plus gemcitabine was superior to gemcitabine alone for patients with metastatic pancreatic cancer (MPC) in the phase III MPACT trial. This study evaluated the association of secreted protein acidic and rich in cysteine (SPARC) levels with efficacy as an exploratory endpoint.

Experimental Design: Patients with previously untreated MPC (N = 861) received nab-paclitaxel plus gemcitabine or gemcitabine alone. Baseline SPARC level was measured in the tumor stroma and epithelia (archival biopsies) and plasma. Experiments were performed in pancreatic cancer mouse models in which SPARC was intact or deleted.

Results: SPARC was measured in the tumor stroma of 256 patients (30%), the tumor epithelia of 301 patients (35%), and plasma of 343 patients (40%). Stroma-evaluable samples were from metastases (71%), from the pancreas (11%), or of unidentifiable origin (insufficient tissue to determine; 17%). For all patients, stromal SPARC level [high (n = 71) vs. low (n = 185)] was not associated with overall survival (OS; HR, 1.019; P = 0.903); multivariate analysis confirmed this lack of association. There was no association between stromal SPARC level and OS in either treatment arm. Neither tumor epithelial SPARC nor plasma SPARC was associated with OS. Results from a SPARC knockout mouse model treated with nab-paclitaxel plus gemcitabine revealed no correlation between SPARC expression and tumor progression or treatment efficacy.

Conclusions: SPARC levels were not associated with efficacy in patients with MPC. This exploratory analysis does not support making treatment decisions regarding nab-paclitaxel plus gemcitabine or gemcitabine alone in MPC based on SPARC expression.

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Introduction

The field of pancreatic cancer treatment would greatly benefit from the identification of biomarkers to guide therapy selection. Unfortunately, current treatment guidelines do not indicate which of the few recommended treatments for metastatic pancreatic cancer (MPC) is most likely to benefit a given patient based on tumor biology (1).

Secreted protein acidic and rich in cysteine (SPARC), also known as BM-40 or osteonectin, was first reported by Sage and colleagues in 1984 (2–4). Originally purified as an albumin-binding protein, SPARC was found to localize to the extracellular matrix and play roles in tissue remodeling, embryonic development, cell migration, and angiogenesis (2, 4–10). The role of SPARC in cancer is unclear, with most studies suggesting a protumorigenic role, but some suggesting an antitumorigenic role (11).

In pancreatic cancer, SPARC has been found to localize to tumor stroma, particularly fibroblasts and tumor epithelial cells (12). In a seminal retrospective analysis of patients with resectable pancreatic cancer (N = 299), Infante and colleagues found that SPARC positivity in stromal fibroblasts was associated with worse overall survival (OS) compared with SPARC negativity (HR, 1.89; 95% CI, 1.31–2.74; P = 0.001; ref. 12). The presence of SPARC in tumor epithelial cells did not significantly associate with OS in that study.

A prospective phase III trial of patients with resectable pancreatic cancer (CONKO-001) demonstrated that those who received adjuvant gemcitabine experienced a longer disease-free survival (DFS; median 13.4 vs. 6.7 months; HR, 0.55; P < 0.001) and OS (median 22.8 vs. 20.2 months; HR, 0.76; P = 0.01) than those who received no adjuvant therapy (13, 14). In accord with the Infante study, a recent subanalysis from CONKO-001 revealed that high stromal SPARC expression was associated with worse DFS (median 9.0 vs. 12.6 months, P = 0.005) and OS (median 19.8 vs. 26.6 months, P = 0.033).
Translational Relevance

Results from a previous study suggested that SPARC might be a predictive efficacy biomarker for nab-paclitaxel + gemcitabine in metastatic pancreatic cancer (MPC). These results led to secreted protein acidic and rich in cysteine (SPARC) being included as an exploratory endpoint in the phase III MPACT trial, which compared nab-paclitaxel + gemcitabine with gemcitabine alone for MPC. A SPARC assay was developed and used to examine samples, largely from metastatic lesions, from MPACT. In contrast to previous adjuvant pancreatic cancer studies, no significant association was observed between stromal SPARC level and efficacy in either treatment arm. No correlations were observed between plasma SPARC and efficacy in this study. Moreover, a preclinical experiment performed in mouse models of pancreatic cancer in which SPARC was intact or deleted demonstrated the lack of association. The results of this exploratory analysis do not support the use of SPARC expression to guide treatment with nab-paclitaxel + gemcitabine or gemcitabine alone in MPC.

Patients and Methods

The patients and methods of the MPACT trial have been described previously (18). Key parameters and methods specific to this subanalysis are presented below.

Patients

Eligible patients were ≥18 years of age, had confirmed measurable metastatic adenocarcinoma of the pancreas, had a Karnofsky performance status (KPS) of ≥70, and had not received prior chemotherapy for metastatic disease. SPARC biomarker collection was optional. Written consent was required for collection of samples and biomarker analysis. As a consequence, not all patients permitted examination of tumor samples.

Study design

Patients were randomized 1:1 (stratified by KPS, presence of liver metastases, and region) to receive nab-P 125 mg/m² plus gemcitabine 1,000 mg/m² on days 1, 8, and 15 every 28 days or gemcitabine alone 1,000 mg/m² on days 1, 8, 15, 22, 29, 36, and 43 every 56 days (cycle 1) and then on days 1, 8, and 15 every 28 days (cycle ≥2). Treatment continued until disease progression or unacceptable toxicity.

Statistical analysis

The primary endpoint of the MPACT trial was OS. Secondary endpoints included PFS and ORR by independent evaluation. Correlation between SPARC findings and efficacy endpoints was an exploratory analysis of the MPACT trial intended to provide a better understanding of the utility of SPARC as a biomarker in MPC. The study was not powered to test the hypothesis of an association between SPARC and efficacy. Cox regression models were used to investigate the correlation of OS with different SPARC variables. Multivariate analyses were performed to assess the influence of the following on OS (conducted using a Cox proportional hazards model with stepwise procedure): treatment group, age, sex, KPS, geographic region, primary tumor location, presence of biliary stent, previous Whipple procedure, presence of liver metastases, presence of pulmonary metastases, peritoneal carcinomatosis, stage of diagnosis, number of metastatic sites, CA 19-9 level at baseline, and SPARC score. Correlations between percentage changes in plasma SPARC from baseline and OS were examined by landmark analysis with the Cox regression model.

SPARC IHC assay development

IHC methods for three commercially available antibodies were optimized and tested to select the most appropriate one for assay development [ON1-1 (Invitrogen), 15G12 (Novocasta), and a polyclonal rabbit antibody (Sigma-Aldrich)]. The ON1-1 monoclonal antibody used in the study by Infante and colleagues (12)
was chosen because it provided the most intense staining in tumor epithelial and stromal cells (19).

SPARC staining was based on a modification of the accepted scoring methodology for HER2 in gastric cancer (20) and scored in two separate compartments: peritumoral stromal SPARC in fibroblasts and tumor epithelial SPARC. Stromal staining was very high and homogeneous in positive fibroblasts; therefore, the score was based solely on the percentage of fibroblasts stained. An IHC score of 0–3 was defined as high expression (90% or more positive cells). A score of 4 was defined as very high expression (90% or more positive cells). Scores of 0, 1, and 2 were defined as low expression (0%, 10%, or 20% of positive cells, respectively).

The same doses and schedules. To protect animals from lethal administration, tumors were harvested and homogenized in 4 volumes of Milli-Q water (EMD Millipore). Homogenates were centrifuged for 30 minutes at 12,000 rpm. Supernatants were treated to precipitate proteins and extract phospholipids in order to reduce potential matrix effects. Paclitaxel was then quantified by liquid chromatography (Agilent 1200; Agilent Technologies) coupled with a triple quadrupole mass spectrometer (API2000; Applied Biosystems), interpolating the peak area in a calibration curve made using tissue homogenates from untreated mice.

SPARC Results for nab-Paclitaxel + Gemcitabine in the MPACT Study

Masson trichrome staining and IHC were carried out on formalin fixed paraffin-embedded tumor samples from 115 patients (21%) were classiﬁed as high SPARC and samples from 88 (70%) were classiﬁed as low SPARC. In the gemcitabine arm with evaluable stromal SPARC, samples from 34 patients (25%) were classiﬁed as high SPARC and samples from 125 patients with stroma-evaluable samples and were consistent with those of the intent-to-treat (ITT) population (Supplementary Table S1). Of the 131 patients in the nab-P + gemcitabine arm with evaluable stromal SPARC, samples from 34 patients (26%) were classiﬁed as high SPARC and samples from 97 patients (74%) were classiﬁed as low SPARC. In the gemcitabine-alone arm (n = 125 patients with stroma-evaluable samples), samples from 37 patients (30%) were classiﬁed as high SPARC and those from 88 (70%) were classiﬁed as low SPARC. In a pooled-treatment-arm analysis, stromal SPARC score did not correlate with OS (Fig. 2). The median OS for patients with high versus low stromal SPARC scores was 8.0 versus 7.6 months (HR, 1.019; 95% CI, 0.750–1.386; P = 0.903). Furthermore, a
multivariate analysis revealed that stromal SPARC score did not appear to be an independent predictor of OS. Consistent with the primary report of the ITT analysis (18), treatment, KPS, and the presence of liver metastases were significant independent predictors of OS (Table 1) in this exploratory analysis. In agreement with the OS analyses, stromal SPARC score did not correlate with PFS or ORR.

In addition, the exploratory analysis revealed a lack of significant association between stromal SPARC score and OS within either treatment arm (Fig. 3). In the nab-P + gemcitabine arm, the HR for OS in patients with high versus low SPARC was 1.505 (95% CI, 0.978–2.315). In the gemcitabine-alone arm, the HR for OS in patients with high versus low SPARC was 0.658 (95% CI, 0.423–1.023). Among patients with high stromal SPARC, the nab-P + gemcitabine group had more patients than the gemcitabine group with a KPS of 70 to 80 (50% vs. 32%) and liver metastases (94% vs. 81%), both of which appeared to be significant predictors of shorter OS in this analysis (Fig. 3; Table 1). A multivariate analysis within the nab-P + gemcitabine arm, which included SPARC level, KPS, and the presence of liver metastases, did not identify SPARC level as a significant independent predictor of OS (HR, 1.395; 95% CI, 0.904–2.153; P = 0.133).

Stromal SPARC IHC score

<table>
<thead>
<tr>
<th>SPARC level</th>
<th>High</th>
<th>Low</th>
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<tr>
<td>n (%)</td>
<td>71 (28)</td>
<td>185 (72)</td>
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<tr>
<td>HR high vs. low (95% CI)</td>
<td>1.019 (0.750–1.386)</td>
<td></td>
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<tr>
<td>P (log rank)</td>
<td>0.903</td>
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Figure 2.
Relationship of stromal SPARC with OS. Kaplan–Meier analysis of OS in a pooled-treatment-arm analysis based on SPARC level.
SPARC Results for nab-Paclitaxel + Gemcitabine in the MPACT Study

Tumor SPARC
Baseline characteristics between treatment arms in the tumor epithelial SPARC-evaluable population were well balanced (Supplementary Table S2). The majority of evaluable samples had low or negative SPARC staining in the tumor epithelia (97%); samples from only 10 of 301 patients had high SPARC (3%). There was no significant correlation between tumor epithelial SPARC score and OS. The HR for high versus low SPARC was 1.16 (95% CI, 0.52–2.62). Multivariate analysis revealed that tumor epithelial SPARC did not appear to be a significant independent predictor of OS.

Plasma SPARC
The baseline characteristics between treatment arms in the plasma SPARC-evaluable population were well balanced (Supplementary Table S3). There was no correlation between baseline plasma SPARC level and baseline SPARC level in the tumor or stroma. (Supplementary Fig. S2 and Supplementary Table S4). In addition, there were no significant changes in plasma SPARC from baseline to cycle 2 or cycle 4 of the treatment (Supplementary Table S5). Furthermore, neither baseline plasma SPARC nor change from baseline appeared to be a significant independent predictor of OS by multivariate analysis.

Preclinical experiments in SPARC knockout mice
To determine whether SPARC might play a role in tumor development or progression, we generated genetically engineered compound mice that ubiquitously lack SPARC and develop pancreatic cancer: Elas-tTA/tetO-Cre; K-Ras<sup>fl/fl</sup>; P53<sup>fl/fl</sup>/C0 (further referred to as SPARC<sup>-/-</sup>). There were no histologic differences observed between the tumors that developed in SPARC<sup>-/-</sup> mice compared with SPARC<sup>+/+</sup> littermate controls (Fig. 4A). OS was also examined in these animals. No difference in OS was observed between SPARC<sup>-/-</sup> and SPARC<sup>+/+</sup> or SPARC<sup>+/+</sup> control animals (Fig. 4B). To investigate whether SPARC expression could affect the intratumoral accumulation of nab-P, SPARC<sup>+/+</sup>, SPARC<sup>+/+</sup>, and SPARC<sup>-/-</sup> tumor-bearing animals were treated with a single dose of nab-P. Similar levels of paclitaxel were observed in the tumors of all three genotypes, suggesting that tumor penetration of nab-P is SPARC independent (Fig. 4C).

To determine whether, despite equal nab-P intratumoral accumulation, SPARC might be involved in tumor sensitivity upon long-term treatment with nab-P, we generated a second tumor-bearing animal model in which SPARC-null mice (Spars<sup>tm1Hwe</sup>) were orthotopically implanted with the pancreatic cancer cell line Panc02. Treatment with nab-P, gemcitabine, or the combination each led to similar OS in SPARC-null mice compared with the same treatment in SPARC wild-type littermate controls, although there were differences between treatments. These data suggest that the activity of nab-P is independent of SPARC expression (Fig. 4D).

Discussion
This exploratory analysis represents the largest work to date (n = 256 for stromal SPARC) on SPARC in a clinical trial of patients with MPC. The results of this exploratory analysis from MPACT suggest that there is no relationship between SPARC levels and OS in patients with MPC treated with either nab-P + gemcitabine or gemcitabine alone. Furthermore, a multivariate analysis within the nab-P + gemcitabine arm, which included SPARC level, KPS, and the presence of liver metastases (KPS and liver metastases were included because they were significant, independent predictors of OS in the primary efficacy analysis; ref. 18), did not identify SPARC as an independent predictor of survival. Two
Figure 4.
Characterization of tumors, paclitaxel accumulation, and OS in SPARC−/− and SPARC+/− mice. A, IHC in tumors from Elas-1TA/tetO-Cre; K-Ras+/−;LSLG12Vgeo, p53lox/lox, p5E39 treatment mice with wild-type (SPARC+/+) or null SPARC (SPARC−/−). Pixel positivity was quantified. Ck-19, cytokeratin 19; αSMA, α smooth muscle actin. B, Kaplan–Meier analysis of OS in Elas-1TA/tetO-Cre; K-Ras+/−;LSLG12Vgeo, p53lox/lox, p5E39 mice in which SPARC was wild-type (SPARC+/+), heterozygous (SPARC+/−), or knocked out (SPARC−/−). C, SPARC+/++, SPARC+/−, or SPARC−/− tumors from Elas-1TA/tetO-Cre; K-Ras+/−;LSLG12Vgeo, p53lox/lox mice that were treated with nab-P were harvested and tested by mass spectrometry to determine the concentration of paclitaxel. Differences between tumor concentrations were analyzed by the unpaired two-sided t test. D, Kaplan–Meier analysis of OS in SPARC−/−, SPARC+/−, and SPARC+/+ mice that had been implanted with Panc02 cells and treated with nab-P, gemcitabine, or the combination.

preclinical models of pancreatic cancer, one a genetically engineered mouse model and the other an orthotopic model, also revealed no significant difference in the efficacy of nab-P treatment based on the presence or absence of SPARC. These preclinical results were consistent with those of a previous study that was conducted by Neesse and colleagues in a different genetically engineered mouse model of pancreatic cancer (23). Agreement of the SPARC analysis in the MPACT trial with these independent mouse studies strengthens the conclusion that the activity of nab-P was not influenced by SPARC level.

The lack of association between SPARC expression and OS in this post hoc exploratory analysis of patients with metastatic disease stands in contrast with results reported from the CONKO-001 study and the Infante and colleagues study in resectable pancreatic cancer (12, 15). In fact, the CONKO-001 study demonstrated worse efficacy with gemcitabine treatment in patients with high versus low SPARC expression (15), whereas this finding was not observed in our analysis of patients being treated for metastatic disease. One of the differences among these studies was the assay used to evaluate SPARC. The Infante and colleagues study of resectable pancreatic cancer used the same antibody as the present study (ON1-1), but used a more lenient scoring system for positivity (12). The CONKO-001 trial used a different antibody (Novoceastra clone 15G12) and a more complex scoring system (15). Another difference of note was the source of the analyzed tissue. For both the Infante and CONKO-001 studies, pancreatic lesions were evaluated (12, 15), whereas only 11% of tissues from the MPACT trial were confirmed to be pancreatic lesions, with the remaining being either metastatic tissues or from regions that could not be identified.

It has been noted in other studies that SPARC expression can differ between primary and metastatic lesions (24, 25). In a study of pancreatic cancer, extensive SPARC immunostaining was present in the neoplastic epithelial cells of primary lesions, in contrast with weak or absent SPARC immunostaining in neoplastic cells of metastatic tissues (26). One possible mechanism for down-regulation of SPARC expression is DNA methylation: the SPARC gene has been shown to be epigenetically silenced in numerous pancreatic cancer cell lines and in most xenograft tumors established from human primary pancreatic carcinomas (27). Among
SPARC's many potential protumorigenic qualities is its ability to promote tumor cell migration and invasiveness, and suppression of SPARC expression has been found to reduce tumor cell adhesion and invasive capacities (26, 28). This potentiation of migration and invasiveness may come at the cost of reduced proliferation, as excess SPARC has been shown to inhibit cancer cell proliferation (26, 28). Enhanced SPARC expression may therefore be important for the metastatic process, but may be silenced in metastatic cells to allow for establishment of metastatic lesions.

The difference in SPARC results between this analysis of the MPACT phase III study and that of the phase I/II study which preceded it (17) prompts an evaluation of differences in trial design and methodology. One substantial difference between the two studies was the number of patients analyzed—specifically, stromal SPARC was evaluable in 256 patients in the MPACT trial versus 36 patients in the phase I/II trial. In addition, 7% to 8% of patients in the MPACT trial had a KPS of 70 compared with no patients in the phase I/II trial (17, 18). As noted previously, the origin of the evaluated tissue is also important to consider: 11% of samples in the MPACT trial versus 44% in the phase I/II trial were from primary pancreatic tumors. Finally, the differences in the IHC assays used in the phase I/II and MPACT studies are unlikely to have been a major contributor to the disparate SPARC results, as 86% concordance was observed between the two assays on a set of samples from 22 of the 36 patients in the phase I/II study.

As is the case with many biomarker-related evaluations, this study had some limitations. For example, SPARC biomarker collection was optional, and not all patients permitted examination of tumor samples. In addition, SPARC analysis was an exploratory endpoint of the trial; therefore, the study was not specifically designed to test the hypothesis of an association between SPARC level and treatment efficacy. A consequence of this is that the method of tissue collection for SPARC analysis was not specified in the protocol with respect to amount and location of tissue. Many of the samples that were analyzed were fine-needle aspirates that included lumen tumor stroma. Thus, although 861 patients were enrolled in the trial, SPARC analysis was only possible in a subset of patients; stromal SPARC was evaluated in 30% of patients. Furthermore, the scoring methodology was not predefined. Analyses based on a different scoring methodology, in which patient samples were analyzed in four independent groups (IHC 0, 1+, 2+, and 3+) and IHC 0 and 1+ compared with IHC 2+ and 3+, or IHC 0, 1+, and 2+ compared with IHC 3+ as opposed to the high versus low classification were also conducted. In multivariate analysis, this methodology resulted in a similar lack of association between SPARC level and OS, PFS, or ORR. The need remains for useful biomarkers to guide treatment in pancreatic cancer, and robust preclinical experiments will be necessary to identify other potential markers to be tested in prospective trials.

On the basis of the results of this exploratory analysis, SPARC is not confirmed as a useful biomarker in selecting patients with MPC to receive nab-P + gemcitabine or gemcitabine alone. Current treatment selection in MPC is not based on the status of any particular biomarker (1). CA 19-9 has been used as a diagnostic and prognostic marker, but no data exist to suggest that patients with a particular level of CA 19-9 would benefit from one treatment over another (1). Human equilibrative nucleoside transporter (hENT1) has demonstrated some promise in predicting response to gemcitabine in the adjuvant setting (29, 30); however, the only prospective study to date of hENT1 in patients with MPC revealed no association of hENT1 level with efficacy (31). A number of other biomarkers, such as carcinoembryonic antigen (CEA), pancreatic antioncofetal antigen, tissue polypeptide antigen, and cancer antigen 125 (CA 125), have been studied in pancreatic cancer (1), but more research is needed to validate their utility.

The SPARC assay that was developed for this study was simple and reproducible, and showed high concordance with the more complex assay that was used in the phase I/II trial (17). Unlike the phase I/II study, this SPARC analysis of primarily metastatic biopsies revealed no prognostic or predictive value of SPARC level in patients who were being treated for MPC. A preclinical study also suggested that the effect of nab-P–based treatment was not dependent on the presence of SPARC. The results of this exploratory analysis do not support the use of SPARC expression level for clinical decision-making regarding nab-P + gemcitabine or gemcitabine alone in MPC.

Disclosure of Potential Conflicts of Interest

M. Hidalgo reports receiving a commercial research grant and speakers bureau honoraria from Celgene. P. Illei and F. Lopez-Rios report receiving a commercial research grant from Celgene. D. Pierce, A. Romano, and X. Wei have ownership interest (including patents) in Celgene. J. Tabernero is a consultant/advisory board member for Celgene. D.D. Von Hoff reports receiving other commercial research support from and is a consultant/ advisory board member for Celgene. No potential conflicts of interest were disclosed by the other authors.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Hidalgo, M. Musteanu, P. Illei, C.B. Brachmann, D. Pierce, P.P. Lopez-Casas, C. Menendez, J. Tabernero, A. Romano, X. Wei, F. Lopez-Rios, D.D. Von Hoff

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References


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Reference


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