Pharmacogenomic Modeling of Circulating Tumor and Invasive Cells for Prediction of Chemotherapy Response and Resistance in Pancreatic Cancer

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Abstract

Purpose: Despite a challenging prognosis, modern cytotoxic therapy can induce tumor responses and extend life in pancreatic adenocarcinoma (PDAC). Pharmacogenomic (PGx) modeling of tumor tissue can predict the efficacy of chemotherapeutic agents in preclinical cancer models. We hypothesized that PGx profiling of circulating tumor and invasive cells (CTIC) isolated from peripheral blood could predict tumor response, progression, and resistance.

Experimental Design: A PGx model was created and validated in preclinical models. A prospective clinical trial was conducted. Fifty patients with advanced PDAC were enrolled. Before treatment, 10 mL of peripherally drawn blood was collected. CTICs isolated from this blood sample were expression profiled and the PGx model was used to predict effective and ineffective chemotherapeutic agents. The treating physicians were blinded to PGx prediction.

Results: We found that CTICs could be reliably isolated, total RNA extracted and profiled from 10 mL of peripheral blood from patients with unresectable PDAC before chemotherapy treatment and at disease progression. Using previously created PGx models to predict chemotherapy sensitivity, we found that clinical benefit was seen for study participants treated with chemotherapy regimens predicted to be effective versus chemotherapy regimens predicted to be ineffective with regard to progression-free (10.4 mo vs. 3.6 mo; \( P < 0.0001; \) HR, 0.14) and overall survival (17.2 mo vs. 8.3 mo; \( P < 0.0249; \) HR, 0.29).

Conclusions: These findings suggest that PGx profiling of CTICs can predict treatment response.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) currently represents the fourth leading cause of cancer mortality in the United States. Of the five most lethal cancers, incidence and death rates are only increasing for PDAC. Therefore, it is estimated that by 2015, PDAC is likely to rise to the second leading cause of cancer death in the United States (1). Despite this, the emergence of active combination chemotherapy regimens during the past 3 years has led to incremental improvements in overall survival. FOLFIRINOX (2) and gemcitabine with nab-paclitaxel (3) represent clinically meaningful improvements over the prior standard of care, single-agent gemcitabine. As with most cancers, however, clinicians are without tools to help choose the most effective therapeutic agents for individual patients with PDAC. Biomarkers for choosing second-line therapy are similarly unavailable. Therefore, a biomarker capable of identifying upfront the most effective treatment regimen for each individual patient is greatly needed. Inevitably, PDAC develops resistance to treatment. A greater understanding of treatment resistance and development of a biomarker allowing physicians to anticipate and change treatment accordingly are both greatly needed.

Over the years, there have been multiple approaches to developing biomarkers for predicting drug effect. In general, the most actively sought strategy is to determine in the host tumor, biologic traits that are linked to drug response. Although this strategy has been useful in several settings, particularly when the biomarker is linked to the mechanism of action of the agent, i.e., Her2 expression and trastuzumab treatment, it has not been useful in PDAC. A recent example is human equilibrative nucleoside transporter-1 (hENT1), a...
Translational Relevance

We present results of a validation study of an innovative pharmacogenomic tool to predict effective chemotherapeutic treatments for patients based on profiling of circulating tumor and invasive cells isolated from peripheral blood. This study provides proof of principle that an individualized approach to treating pancreatic cancer is feasible.

In vitro drug sensitivity testing of the NCI-60 tumor cell line collection against each chemotherapeutic in the panel was performed, with two biologic replicates, by the National Cancer Institute’s Developmental Therapeutics Program as previously described (10). The NCI-60 cell lines have been authenticated previously by DNA fingerprinting (11). Following standardization of the IC_{50} values, we consider cell lines with a standardized GI_{50} score (z-score) > 0.75 as sensitive to the chemotherapeutic in question. Normalized log_{2} mRNA expression data for the non–drug-treated NCI-60 tumor cell line was obtained and filtered for 416 genes that comprise the ABC, SLC, and CYP family of genes. Supplementary Table S1 lists a series of genes that were used to create the pharmacogenomic models of 12 commonly used chemotherapy treatment regimens for the subsequent enrichment analysis based on GI_{50} values for each chemotherapeutic and corresponding expression profiles of the filtered gene sets.

Materials and Methods

PGx model

In vitro drug sensitivity testing of the NCI-60 tumor cell line collection against each chemotherapeutic in the panel was performed, with two biologic replicates, by the National Cancer Institute’s Developmental Therapeutics Program as previously described (10). The NCI-60 cell lines have been authenticated previously by DNA fingerprinting (11). Following standardization of the IC_{50} values, we consider cell lines with a standardized GI_{50} score (z-score) > 0.75 as sensitive to the chemotherapeutic in question. Normalized log_{2} mRNA expression data for the non–drug-treated NCI-60 tumor cell line was obtained and filtered for 416 genes that comprise the ABC, SLC, and CYP family of genes. Supplementary Table S1 lists a series of genes that were used to create the pharmacogenomic models of 12 commonly used chemotherapy treatment regimens for the subsequent enrichment analysis based on GI_{50} values for each chemotherapeutic and corresponding expression profiles of the filtered gene sets.

Study design

An Institutional Review Board (IRB)–approved observational study was conducted at Memorial Sloan Kettering Cancer Center (registered at Clinicaltrials.gov, identifier NCT01474564). Enrollment occurred from November 2011 to October 2012. The primary objective of the study was to assess the feasibility of (1) obtaining and characterizing CTICs, and (2) using the resulting microarray analysis to generate a treatment profile for patients with PDAC. Target accrual for the study was between 30 and 60 patients, and a total of 50 study participants were ultimately enrolled (see Fig. 3). At the time of the current analysis, 35 study participants were evaluable for treatment response, as they have met criteria for progression of disease or death. Key eligibility criteria included histologic or cytologic confirmation of pancreatic adenocarcinoma, the patient was deemed eligible for chemotherapy treatment and an ECOG performance status of 0, 1, or 2.

Following written informed consent and before the initiation of chemotherapy treatment, a 10 mL blood sample was obtained in a heparinized Vacutainer (Becton Dickinson) tube from each study participant using standard clinical procedures. Blood samples were collected by venipuncture or by accessing an indwelling catheter normally used for phlebotomy.

Cell enrichment

Coded and deidentified samples were shipped at 4°C overnight to CellPath Therapeutics, Inc. for CTIC isolation and enrichment. A collagen-adhesion matrix (CAM) in a modified cell invasion assay was used to capture invasive cells. Three-milliliter aliquots of whole blood were subjected to enrichment in a CAM-coated modified cell invasion assay (Vita-Cap; Vitatex) and cultured for 2 hours in the Cancer Cell Culture (CCC) media (1:1 mixture of Dulbecco’s modified Eagle medium and RPMI-1640 medium.
supplemented with 10% calf serum, 10% Nu-serum, 2 mmol/L L-glutamine, 1 U/mL penicillin and 10 μg/mL streptomycin). Captured cells were then washed and lysed in situ.

Microarray data analysis

Lyzed CAM-adherent cells that were directly isolated from the invasion assay were used in mRNA microarray analyses. Specifically, total RNA from lyzed CAM-bound cells was purified by the RNeasy Mini Kit (Qiagen) and then subjected to DNA microarray analysis. Generation of ssDNA labeling were performed (NuGen Pico; NuGen, Inc.) with subsequent hybridization and scanning of the Affymetrix high-density 3’ IVT oligonucleotide microarray HG_U133_Plus_2 chip (containing 54,675 gene probes) according to the manufacturer’s specifications (Affymetrix).

Enrichment analysis and determination of sensitivity score

The CEL file from the Affymetrix scanner was used to determine the intensity value of each probe, and then collapsed to a single maximum value resulting in an array of 20,606 genes (Expression Console; Affymetrix). Gene expression of study participant CTICs was then assessed for differentially expressed pharmacogenomic models using gene-set enrichment analysis (GSEA v2.0.12; Broad Institute, Cambridge MA) based on a panel of chemotherapeutic regimens commonly used in PDAC. The following chemotherapeutic regimens were modeled: FOLFIRINOX (5-FU, irinotecan, and oxaliplatin), FOLFOX (5-FU and oxaliplatin), Gem-Ox (gemcitabine and the agent with the highest NES and, therefore, likely to be effective. The results fully supported our hypothesis. Panc19 with a high NES for gemcitabine was susceptible to this drug (Fig. 2A). Likewise, Panc20, predicted to be resistant to gemcitabine and susceptible to irinotecan, showed concordant responses when treated with these two agents (Fig. 2B). Finally, Panc10, which showed intermediate response to gemcitabine and susceptibility to paclitaxel responded as expected (Fig. 2C).

PGx profiling, a prospective study

To further test our hypothesis in the clinical setting, a PGx model was developed for a number of chemotherapy regimens commonly used in PDAC. The following chemotherapy regimens were modeled: FOLFIRINOX (5-FU, irinotecan, and oxaliplatin), FOLFOX (5-FU and oxaliplatin), Gem-nab (gemcitabine + nab-paclitaxel), Gem-Ox (gemcitabine + oxaliplatin), Gem-Cap (gemcitabine + capecitabine), and GTX (gemcitabine, docetaxel, and capecitabine) from single-agent response data obtained from the NCI 60 cell line dataset. In addition, instead of using tumor biopsies to determine the patient gene expression profile, we decided to study CTICs. The rationale for this is provided above and was supported by preliminary work showing overall survival were gathered and collated. Follow-up blood samples were drawn and analysis was performed in study participants at the time of disease progression.

Results

PGx model development and validation

To test our central hypothesis, we took advantage of the PDX models that had been treated with gemcitabine was selected for this work. As shown in Fig. 1A, these models display a range of response to gemcitabine. By comparing the gene expression profile of the highly sensitive PANC253 model with the resistant JH033 model using a predefined set of 450 genes involved in drug transport, distribution, and metabolism, we established a set of genes overexpressed in the sensitive model (Fig. 1B). We next tested if this PGx model of gemcitabine susceptibility predicted the response of this drug in the remaining 30 models using gene GSEA. The PGx model of gemcitabine performed well for predicting treatment response (Fig. 1C). For tumors predicted to be sensitive to gemcitabine, the positive predictive value (PPV) for tumor growth inhibition was 0.72, with a negative predictive value (NPV) of 0.79.

Intrigued by these results, we created similar PGx models for paclitaxel, oxaliplatin, irinotecan, 5-fluorouracil (5-FU), and erlotinib using the NCI60 cell line publicly available data and the principle defined above. We next tested the central hypothesis of this work by prospectively establishing three PDAC PDX models, determining the gene expression profiles of these models and the relative enrichment, as determined by NES, of the drugs PGx models (Supplementary Table S3). We next treated these models with gemcitabine and the agent with the highest NES and, therefore, likely to be effective. The result fully supported our hypothesis. Panc19 with a high NES for gemcitabine was susceptible to this drug (Fig. 2A). Likewise, Panc20, predicted to be resistant to gemcitabine and susceptible to irinotecan, showed concordant responses when treated with these two agents (Fig. 2B). Finally, Panc10, which showed intermediate response to gemcitabine and susceptibility to paclitaxel responded as expected (Fig. 2C).

The chemotherapeutic regimens are then assigned to a predicted response category as SENSITIVE, INTERMEDIATE, or RESISTANT based upon the Sensitivity Scores.

Laboratory investigators were blinded to the treatments received and clinical outcomes of study participants. Treating physicians were blinded to study participants’ PGx prediction profiles. Information about treatment regimens administered, treatment responses, progression-free and...
strong correlation between tumor tissue and CTIC profiles (Supplementary Table S2 and Supplementary Fig. S1).

A total of 50 patients with advanced or locally advanced PDAC, whose pertinent demographic characteristics are listed in Table 1, were treated in a prospective clinical trial. The study was IRB-approved and registered at clinicaltrials.gov (identifier #NCT01474564). As shown in Fig. 3 and described in Materials and Methods, blood samples for CTIC were collected at baseline and at the time of progression. Patients were, for the most part, treated with one of the above-mentioned regimens as per physician discretion.

Table 2 shows representative profiles for three study participants. As detailed in Materials and Methods, a score is calculated for each one of the regimens based on the NES of each one of the individual agents.

All 3 patients in this example received FOLFIRINOX chemotherapy. In Patient A in whom the PGx profiling predicted sensitivity to FOLFIRINOX, the PFS with this regimen was 7.3 months. This is in contrast with patients B and C, in whom the profile predicted intermediate and low sensitivity to FOLFIRINOX; PFS was 2.1 and 1.7 months, respectively.

Adequate numbers of CTICs were captured and sufficient RNA was subsequently isolated for successful gene expression analysis and PGx profiling from all the 50 study participants. At the time of the current analysis, 35 study participants were evaluable for disease progression to first-line chemotherapy. Fifteen study participants were deemed not evaluable for response for a variety of reasons. Seven study participants with locally advanced PDAC were treated with concurrent chemoradiotherapy following their initial line of chemotherapy, before disease progression. Radiotherapy is a treatment modality not accounted for by the PGx model. Two study participants received investigational agents that were also not present in the PGx model. Two patients died of cancer-related causes, and another 2 patients died of cancer-unrelated causes, all before receiving any treatment. One patient went on to have the tumor resected. One patient had yet to progress on first-line treatment at the time of the analysis.

On the basis of the CTIC PGx profiling, the 35 evaluable study participants were classified into three groups: those whose chemotherapy regimen was predicted to be effective (“sensitive”), ineffective (“resistant”), or of intermediate effectiveness (“intermediate”). Sixteen (45.7%) of the evaluable study participants fell into the sensitive group and 12 (34.3%) into the resistant group. All evaluable study participants received combination chemotherapy in the first-line
setting. The majority of study participants, 22 (62.9%), received FOLFIRINOX chemotherapy and 10 (28.6%) received gemcitabine-based combination chemotherapy.

PGx profiling predicts treatment response
There was a statistically significant difference in median progression-free survival (PFS) among the three groups as predicted by PGx profiling, with those in the sensitive group responding the longest (10.4 months), those in the resistant group responding the shortest (3.6 months), and those in the intermediate group responding in between (7.8 months, Fig. 4A). These differences were statistically significant ($P = 0.0001$, log-rank test; $P < 0.0001$, log-rank test for trend). The HR for PFS comparing sensitive with resistant groups was 0.14. The PFS of 10.4 months seen in the sensitive group was numerically greater than the median PFS of 7.5 months seen in all evaluable patients; however, this did not reach statistical significance. Patients in the resistant group experienced significantly worse PFS when compared with all evaluable patients (3.6 vs. 7.5 months, $P = 0.0084$, Log-rank test).

An overall survival (OS) difference was seen among the three groups, median OS for the sensitive group was 17.2 months, compared with 13.8 months in the intermediate group and 8.3 months in the resistant group ($P = 0.083$, log-rank test; $P < 0.0304$, log-rank test for trend; Fig. 4B). Comparing OS between only the sensitive and resistant groups, a statistically significant difference was seen ($P = 0.0249$, log-rank test).

Although gender and treatment regimens were not significantly different among the three groups, the age of study participants in the resistant group was significantly older than those in the sensitive group ($P = 0.006$, Table 1). The age of study participants in the intermediate group was in between the sensitive and resistant groups. Despite this, there was not a statistically significant correlation between age and either PFS or OS. Baseline ECOG performance status, location and number of disease sites, presence of ascites, albumin level, CA 19-9, CEA, and total bilirubin

Figure 2. Prospective validation of PGx model of a range of cytotoxic and targeted chemotherapeutic agents in three PDAC PDX models. For the Panc19 PDX (A), the PGx model predicted sensitivity to gemcitabine (GEM), with a NES of 0.90. In Panc20 (B), highest sensitivity was predicted for Irinotecan (NES of 1.14), whereas resistance was predicted for GEM (NES of –0.06). In Panc10 (C), highest sensitivity was predicted for paclitaxel (NES of 1.32), whereas intermediate sensitivity was predicted for GEM (NES of 0.75). Tumor response in all three PDX closely mirrored the PGx model prediction. See Supplementary Table S3 for model prediction of a number of chemotherapeutic agents.
were compared and not found to be significantly different among the three groups.

An overall analysis of the treatment score assigned to the treatment regimen patients received and the magnitude of response was performed. The treatment score assigned by PGx profiling demonstrated a statistically significant positively correlated with both PFS ($r = 0.4583; P = 0.0056$) and OS ($r = 0.5152; P = 0.015$; See Supplementary Fig. S2).

The PPV of PGx profiling was determined for predicting PFS of 6 months or better. For study participants with PFS > 6 months, the PPV was 0.81. For study participants with PFS < 6 months, the NPV was 0.75 (Fig. 4C).

Interestingly, PGx profiles performed longitudinally in individual study participants showed changes following treatment (Table 2). In patient D, the initial PGx profile demonstrated treatment sensitivity to FOLFOX. The patient received this treatment and ultimately progressed and PGx profiling was repeated. At this point, the CTIC PGx profile has changed dramatically, predicting resistance to FOLFOX chemotherapy and increased sensitivity to a regimen such as gemcitabine and nab-paclitaxel. Analysis to determine the predictive ability of the PGx model for second-line treatment is under way.

**Discussion**

PDAC remains among the most challenging malignancies to diagnose and treat. The development of more effective therapies has, nevertheless, made it possible to improve the treatment and prolong the life of affected patients. As more effective cytotoxic and targeted agents become available, there is a growing need to develop cost-effective and efficient therapeutic strategies.
available, development of a clinical assay capable of predicting optimal therapy becomes increasingly important. In a more indolent disease, there may be time to try a number of different regimens to find an effective approach. In PDAC, upfront treatment with a regimen effective for the individual patient is critical as opportunities for second and subsequent lines of therapy are often limited. Developing such an assay that is not contingent on tissue acquisition is particularly attractive in PDAC, as the primary tumor is not convenient for biopsy, and serial biopsies pose both risk along with inconvenience and expense. Furthermore, tumor cells in active vascular transit represent a population of tumor cells of particular interest.

The current approach offers advantages to prior PGx approaches to guide cancer therapy. For example, a recently developed approach termed COXEN (CO-eXpression ExtrapolatioN; ref. 12) similarly uses \textit{in vitro} gene expression profiles to model drug responses. The \textit{in vitro} model is then used to predict treatment responses \textit{in vivo} by profiling tumor tissue. One advantage of our approach is the ability to profile CTICs, easily obtained in a peripheral blood sample, as opposed to tumor tissue. The COXEN approach was originally designed to model one drug at a time, and was shown to predict response to docetaxel and tamoxifen in two breast cancer cohorts. An overall survival difference, however, was not seen between responders and nonresponders, as seen in our study. When the COXEN approach was tested against a multidrug regimen in breast cancer (13), it was found not to be a good predictor of response, whereas our model is capable of predicting response to standard multidrug combinations. Comparing the genes used in the two models, there is limited overlap. The COXEN approach models expression across a wide variety of biologic pathways, whereas our approach focuses on three major gene families: ATP binding cassette (ABC) transporters, solute (SLC) transporters, and cytochrome p450 (CYP) enzymes. Genes composing the PGx assay were derived empirically from the \textit{in vitro} modeling studies. Biologically, there is no surprise that changes in expression of genes in these three families predict treatment resistance. The ABC and SLC families of genes are two of the best-studied pathways by which cells develop chemotherapy resistance. Both families consist of a wide variety of transmembrane proteins that can actively remove chemotherapeutic agents and their active metabolites (14, 15). A recent example of cell line work to study drug resistance also identified changes in expression of genes in the ABC and SLC families associated with resistance to cytotoxic chemotherapeutic agents (16). CYP enzymes are also classically associated with drug resistance. CYP enzymes are often upregulated in cancer cells, and may act by increased breakdown of the active chemotherapeutic metabolites. (17) The key breakthrough of our study is the ability to model these changes in a circulating population of cells and correlating this to clinical response.

The current study provides proof of principle that PGx profiling of CTICs can effectively predict treatment response in patients with advanced PDAC. A number of questions are raised, which will require further study. Because of the

Table 2. PGx profiles of three study participants (patients A–C) before treatment, and comparison of PGx profiles in 1 study participant (patient D) before and after treatment

<table>
<thead>
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<th>Patient</th>
<th>A</th>
<th>B</th>
<th>C</th>
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<tbody>
<tr>
<td>PFS (mo)</td>
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<tr>
<td>Regimen</td>
<td>Score</td>
<td>Regimen</td>
<td>Score</td>
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<tr>
<td>FOLFOX</td>
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<td>FOLFOX</td>
<td>0.65</td>
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<td>Gem-Cap</td>
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<td>GemOX</td>
<td>0.53</td>
</tr>
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<td>FOLFIRINOX</td>
<td>0.15</td>
</tr>
<tr>
<td>Gem-nab</td>
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<td>Gem-nab</td>
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<table>
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<tr>
<th>Patient</th>
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<th>D (posttreatment)</th>
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<td>FOLFOX</td>
</tr>
</tbody>
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NOTE: Shaded values highlight drug regimens of interest discussed in the article.
timing of this study, the majority of patients received 5-FU–based chemotherapy; in particular, FOLFIRINOX was most commonly used. Although there is no reason to believe that PGx profiling is more effective at predicting response to 5-FU–based regimens compared with other regimens, such as gemcitabine, a prospective study is in progress to specifically study the patients receiving gemcitabine and nab-paclitaxel to validate the utility of PGx profiling in this particular regimen. Although our matrix invasion approach has been shown in numerous studies to isolate classically defined circulating tumor cells, we are likely capturing a heterogeneous population of cells. Current work is under way to define the cell types composing this population of invasive cells and to characterize their contributions to the overall PGx profile. It is certainly possible that some of the profiled cells are malignant cells undergoing epithelial–mesenchymal transition (EMT) or nonmalignant cells that contribute to the treatment response and resistance in other ways. For example, a robust stromal response is a hallmark feature of PDAC (18), a response in which PBMCs play a crucial role (19). A recent global gene expression profiling study demonstrated a rich set of differentially expressed genes in PBMCs from patients with PDAC compared with healthy controls (20). Another study previously demonstrated that mononuclear cells protect PDAC cells from chemotherapy induced apoptosis (21) Therefore, profiling a diverse variety of circulating cells may be more informative than restricting the analysis to circulating cells expressing a classic CTC phenotype.

The current study provides the first evidence that PGx profiling of a specific invasive subset of cells found in peripheral blood, CTICs, can be used to predict treatment response in PDAC. The test is convenient, requiring a single tube of blood drawn peripherally, and reliable; adequate profiles were generated for all 50 study participants before treatment and in 22 study participants at progression. Importantly, PGx profiling of CTICs accurately stratified treatment response of study participants based on the treatment regimen they received. Study participants treated with chemotherapeutic agents predicted to be effective by PGx profiling experienced significantly longer PFS and OS.
compared with the study participants treated with chemotherapeutic agents predicted to be ineffective. This study is the first of its kind to predict treatment response in PDAC. Such an approach would be highly valuable in guiding front-line therapy in PDAC. As data mature, we may be able determine utility in predicting response in the second-line setting. Digging deeper into the gene expression data has yielded insights into pathways that may predict prognosis and drug resistance. A detailed discussion of these findings will be presented separately. Two active regimens, FOLFIRINOX and gemcitabine with nab-paclitaxel, are currently offered to patients with advanced PDAC; a prospective study using our PCx assay to guide front-line therapy is warranted. Further studies are warranted to expand applicability to other malignancies or as a tool to choose effective targeted agents and clinical trials for patients.

Disclosure of Potential Conflicts of Interest

K.H. Yu is an uncompensated consultant/advisory board member for CellPath Therapeutics. M.J. Ricigliano is an employee of and has ownership interest (including patents) in CellPath Therapeutics. M. Hidalgo has ownership interest (including patents) in CellPath Therapeutics. No potential conflicts of interest were disclosed by the other authors.

References


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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): K.H. Yu, M. Ricigliano, M. Hidalgo, G.K. Abou-Alfa, E.M. O’Reilly

Writing, review, and/or revision of the manuscript: K.H. Yu, M. Ricigliano, M. Hidalgo, G.K. Abou-Alfa, M.A. Lowery, L.B. Saltz, K. Gary, E.M. O’Reilly

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K.H. Yu, J.F. Croty, K. Gary

Study supervision: K.H. Yu, E.M. O’Reilly

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