Review Article

Personalized medicine in sporadic pancreatic cancer without homologous recombination-deficiency: are we any closer?

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Abstract: Pancreatic adenocarcinoma is the fourth leading cause of cancer related death in the United States. Most patients are diagnosed at a late stage and despite recent advances in chemotherapeutic approaches, outcomes are poor. With the introduction of combination chemotherapy, novel biomarkers are clearly needed to identify subsets of patients likely to benefit from these therapies. Advances in our understanding of the molecular drivers of pancreatic cancer offer the hope of personalized therapy that may benefit our patients. In this review, we summarize the current knowledge about the biology of pancreatic cancer and its implication for treatment. We discuss recent advances in targeted therapies and the role of potential biomarkers in predicting response to established therapies. We also review novel therapeutic approaches that may be able to fulfill the promise of personalized therapy for pancreatic cancer.

Keywords: Non homologous recombinant deficiency; pancreatic cancer; personalized therapy

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In 2015, pancreatic cancer was the 10th most commonly diagnosed cancer and the fourth leading cause of cancer death in the United States. The incidence of pancreatic cancer has been slowly rising over the past 10 years. It is estimated that about 53,000 new cases were diagnosed and 42,000 people died from pancreatic cancer in 2015 (1). The small difference between the incidence and death rate of pancreatic cancer reflect the early distant spread and inadequacy of current therapies. The 5-year survival rates for localized and advanced pancreatic cancer are 27% and less than 5%, respectively, lower than all other common cancers (2). The majority of patients are diagnosed at an advanced stage and are not eligible for surgical resection (2). These patients are often symptomatic and quickly deteriorate in the absence of effective therapy and many are unable to receive second and third line therapies for the same reason. Hence, finding the optimal first line regimen may be the key to improving outcomes. Increases in our knowledge of human and cancer genomics provide opportunities to understand the impact of genetic alterations on pancreatic cancer outcomes and develop predictive biomarkers for newer targeted therapies (3,4). Unfortunately, the amount of tissue obtained by fine needle aspiration of the primary pancreatic tumor is usually insufficient to perform adequate molecular analysis. As we move into the era of personalized medicine, obtaining core biopsy samples from metastatic sites, like liver, may help eliminate this problem.

What do we know about pancreatic cancer genetically?

Pancreatic cancer is a disease of significant genetic variability. Recent whole exome and genome sequencing have identified a wide range of genetic alterations including mutations and copy number variations that characterize pancreatic cancer (4,5). Some of these are recurrent and

significantly mutated (*KRAS*, *TP53*, *CDKN2A*, *SMAD4*, *MLL3*, *TGFBR2*, *ARID1A*, *ROBO2*, *SF3B1*, *EPC1*, *ARID2*, *ATM*). There are also reported focal amplifications in druggable oncogenes (*ERBB2*, *MET*, *FGFR1*, *CDK6*, *PIK3R3* and *PIK3CA*), but at low individual patient prevalence (5).

Unfortunately, a large amount of infrequently mutated genes result in significant intertumoral heterogeneity which makes mutation-based therapeutic development challenging (5). The most commonly altered gene in pancreatic cancer is *KRAS*, which is mutated in more than 90% of pancreatic cancers (as compared to 20–30% in other human malignancies) (6). It serves as an initiating step in pancreatic oncogenesis by activation of downstream pathways, like the *PI3K-AKT* pathway (7,8). *KRAS* activates *MEK* and *ERK1/2*, which play important roles in angiogenesis, cell proliferation and apoptosis. The majority of pancreatic tumors also have inactivation of the tumor suppressor genes p16, p53 and *SMAD4*, leading to loss of function (9). Inherited *p16* mutations, associated with the familial atypical multiple mole melanoma (FAMMM) syndrome, have an increased risk of developing pancreatic cancer. *p53* alterations occur in greater than 50% of pancreatic adenocarcinomas and disrupt regulation of cellular proliferation and apoptosis in response to DNA damage (9).

Despite knowledge of these gene alterations and identification of involved pathways, translation into therapeutic decision making remains limited.

Predictive markers for established therapies

Gemcitabine

Until a few years ago, the standard therapy for metastatic pancreatic cancer was single agent gemcitabine, based on a randomized trial that compared gemcitabine to bolus 5-fluorouracil (5-FU) as first line therapy. The gemcitabine treated group had a significantly better clinical response, defined as improvement in pain, performance status or weight (24% *vs.* 5%). Median overall survival (OS) (5.6 *vs.* 4.4 months) was also significantly but quite modestly improved (10).

A nucleoside transporter protein, human equilibrative nucleoside transporter 1 (hENT1), promotes transport of gemcitabine into malignant cells and has been widely studied as a potential biomarker predictive of gemcitabine response (11-13). In RTOG 9704, an adjuvant trial that randomized patients after pancreatic resection to gemcitabine or 5-FU, high levels of hENT1 expression in resected pancreatic tumor samples were associated with increased overall and disease-free survival in patients treated with gemcitabine but not in those treated with 5-FU (14). A retrospective analysis of the ESPAC-3 trial, a randomized trial that also compared gemcitabine to 5-FU as adjuvant therapy for pancreatic cancer, further suggested a survival advantage for patients treated with gemcitabine whose tumors had high hENT1 expression (OS 26.2 months for high hENT1 group *vs.* 17.1 months for low hENT1 group). These results were unfortunately not confirmed prospectively. The Low hENT1 and Adenocarcinoma of the Pancreas (LEAP) trial investigated hENT1 expression and outcomes in metastatic pancreatic cancer patients receiving either gemcitabine or a novel gemcitabine analog CO-101, which is not dependent on the nucleoside transport mechanism. hENT1 status was not an eligibility criteria but the cohort was divided into high and low hENT1 expression groups and the primary end point was OS in the low hENT1 tumor expression sub-group (CO-101 *vs.* gemcitabine). There was no difference in survival between treatments in the low hENT1 subgroup or overall population (HR of 0.994 and 1.072, respectively). Also, low versus high hENT1 expression level did not affect survival in patients treated with gemcitabine (15).

Ribonucleotide reductase-1 (RRM1) is a subunit of ribonucleotide reductase, a key enzyme in gemcitabine metabolism. In pancreatic cancer, a retrospective study demonstrated that RRM1 expression was inversely related to response rate and survival in gemcitabine treated patients (P=0.018) (16). Unfortunately these results were not reproduced in a subsequent analysis (13). A meta-analysis of eight clinical studies, with a total of 665 pancreatic cancer patients treated with adjuvant gemcitabine-based chemotherapy (373 patients with high RRM1 expression and 292 with low RRM1 expression), showed that high RRM1 expression was associated with improved OS (HR =1.56, P<0.001). This suggested a prognostic effect of RRM-1 in pancreatic cancer patients but lacked the ability to evaluate its predictive role (since all patients received gemcitabine) (17). To our knowledge, no prospective studies have evaluated RRM1's predictive value in pancreatic cancer to date. However, a prospective study in lung cancer failed to demonstrate the benefit of gemcitabine therapy compared to an alternative treatment based on RRM1 expression (18).

Another potential predictive marker investigated for gemcitabine is the mRNA binding protein, Hu antigen R (HuR). Activated HuR, apart from regulating cancer cell viability genes (19), also binds and stabilizes the deoxycytidine kinase (dCK) mRNA transcript, which in turn activates

gemcitabine (20). *In vitro* analysis suggests that pancreatic cell lines overexpressing HuR are more sensitive to gemcitabine than control lines (20). Pancreatic adenocarcinomas with increased cytoplasmic HuR were found to have better outcome after gemcitabine therapy, in part related to increased dCK levels (20). In a follow-up study, HuR status was again found to be a positive predictive marker for survival in patients treated with adjuvant gemcitabine (median OS 45 *vs.* 23 months in high versus low cytoplasmic HuR expression groups, P=0.033) and its predictive value was found to be independent of tumor stage (20,21). Unfortunately, this has not been validated prospectively.

Targeting epidermal growth factor receptor (EGFR)

The EGFR inhibitor erlotinib is the only "targeted" agent found to have clinical efficacy in pancreatic cancer. This was confirmed through a phase III study with gemcitabine (NCIC CTG PA.3) (22), where the gemcitabine/erlotinib combination produced a small but statistically significant benefit in survival compared to gemcitabine plus placebo (6.2 *vs.* 5.9 months). However, given the cost, modest benefit, and side effect profile, erlotinib is not widely used in clinical practice (23). Further efforts to identify a subset of patients who may benefit from this combination were subsequently undertaken. The mutational status of *KRAS* and *EGFR* gene copy numbers, evaluated in 117 and 107 patients enrolled on the NCIC CTG PA.3, were not predictive of a survival benefit in patients receiving the combination of gemcitabine/erlotinib (24). Contrary to this, in the AIO-PK0104 study, a multicenter trial comparing gemcitabine/erlotinib followed by capecitabine with capecitabine/erlotinib followed by gemcitabine in advanced pancreatic cancer, *KRAS* wild-type status was associated with improved survival (HR =1.68, P=0.005) in patients treated with erlotinib (25). Another post hoc analysis of the AIO-PK0104 study correlated the biomarker data on *KRAS* exon 2 mutation status with objective response to 1st-line therapy and with OS after start of 2nd-line chemotherapy. *KRAS* codon 12 mutation was found in 70% of the patients, but showed no association with objective response (P=0.40). *KRAS* wild type patients had an improved survival (HR =1.68, P=0.005) and this trend was also observed during non-erlotinib containing 2nd-line chemotherapy. The authors concluded that *KRAS* is more likely a prognostic rather than predictive biomarker in pancreatic cancer (26). In contrast to erlotinib, the anti-*EGFR* antibody cetuximab did not improve outcomes when combined with gemcitabine in a phase III randomized study. *EGFR* expression was tested at baseline using immunohistochemistry on all available samples. Of the 595 patients evaluated, 547 (92%) stained positive. Even in the *EGFR*-positive group, cetuximab did not provide a survival advantage (HR =0.98) (27).

Nab-paclitaxel

Until recently, combination chemotherapy had failed to show a benefit over single agent gemcitabine (28-33). One approach to this problem is to develop more potent chemotherapeutic drugs by incorporating nanotechnology.

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) was approved for first-line treatment of metastatic pancreatic cancer in combination with gemcitabine based on the results of the phase III MPACT study, where 861 untreated patients with metastatic pancreatic cancer were randomized to receive gemcitabine plus nab-paclitaxel or gemcitabine alone (34). Overall and progression free survival and tumor response rates were significantly improved in the gemcitabine plus nab-paclitaxel group compared with gemcitabine alone (8.5 *vs.* 6.7 months, P<0.001; 5.5 *vs.* 3.7 months, P<0.001; 23% *vs.* 7%, P<0.001, respectively). Nab-paclitaxel increases the intra-cellular availability of paclitaxel by allowing its delivery in the form of nanoparticles to the tumor. For its uptake, specific proteins like the Secreted Protein Acidic and Rich in Cysteine (SPARC) are required (35). Stromal fibroblasts in pancreatic adenocarcinoma overexpress SPARC and its overexpression in the stroma was previously found to be a marker of poor prognosis (35). In the phase I/II trial of gemcitabine plus nab-paclitaxel (36), SPARC status was evaluated in 36 patients. A significant increase in OS was seen in patients in the high-SPARC expression group compared with patients in the low-SPARC expression group (17.8 *vs.* 8.1 months; P=0.431). In contrast, a phase II trial of nab-paclitaxel in the second line setting did not show this relationship between SPARC expression and patient outcomes (37). Further, an analysis of SPARC expression and OS in the MPACT study was recently reported. Stromal SPARC was evaluable in 30% of patients and its expression [high (n=71) *vs.* low (n=185)] was not associated with survival (HR =1.019; P=0.903). Similarly, tumor epithelial SPARC was low or negative in the majority of samples and was not associated with survival (38).

5-FU-based therapy

Several older combination regimens containing 5-FU were

studied in randomized trials in the 1980's and 1990's (39,40). None showed a survival benefit over single agent 5-FU. In contrast and guided by impressive phase II data (41), the phase III ACCORD 11 trial compared a combination of leucovorin modulated 5-FU, irinotecan, and oxaliplatin (FOLFIRINOX) with gemcitabine (42) and demonstrated an objective response rate of 31.6% *vs.* 9.4% (P<0.001), median PFS 6.4 *vs.* 3.3 months (P<0.001) and median OS 11.1 *vs.* 6.8 months (P<0.001) favoring the FOLFIRINOX arm. Given the excessive toxicity of this regimen and lingering questions about whether all three agents are required in all patients, there is interest in exploring the role of biomarkers like thymidylate synthase [(TS), for 5-FU], excision repair cross-complementation group 1 (ERCC1) (for oxaliplatin) and topoisomerase 1 (TOPO1) (for irinotecan) in this setting.

TS is a critical enzyme in the synthesis of dTMP, the cellular target for 5-FU, making it a potential predictive biomarker for response (43). A significant association has been reported between low TS expression and longer disease free survival (median DFS 15.9 *vs.* 7 months; P=0.03) in patients receiving 5-FU based adjuvant therapy for pancreatic cancer (44). In another study, a marked trend to a longer survival was seen pancreatic cancer patients with low-TS-expressing tumors compared with the high-TS expressing tumors when treated with adjuvant 5-FU based therapy (45). Two other studies found no association between survival and TS expression levels in the neoadjuvant and palliative settings (46,47). The marker has not been prospectively studied in pancreatic cancer to our knowledge.

Irinotecan is an inhibitor of TOPO1, a nuclear protein that can relax supercoiled double-stranded DNA during mitosis. TOPO1 is expressed in 64% of metastatic pancreatic adenocarcinomas. In colorectal cancer, TOPO1 immunohistochemistry identified subpopulations that did or did not benefit from irinotecan, and possibly also from oxaliplatin (48), and a prospective trial is currently underway analyzing this biomarker in the same disease site (NCT00975897). There is limited data on its predictive value in pancreatic cancer. ERCC1 is an excision nuclease within the nucleotide excision repair pathway. ERCC1 nuclear protein expression, evaluated by immunohistochemistry, is a promising predictive marker of platinum-based chemotherapy as shown in non-small cell lung cancer, gastric cancer and colorectal cancer among others (49-51). Kamikozuru *et al.* reported a relationship between ERCC1 codon 118 polymorphism and survival in pancreatic cancer patients treated with a platinum compound (52). Clinical trial designs where baseline tumor expression of markers such as ERCC1, TOPO1 among others, will be used to guide choice of initial treatment compared to standard therapy are being developed/underway in advanced pancreatic cancer (53). Unfortunately a similar prospective, randomized phase II study in colon cancer (MAVERICC) comparing mFOLFOX or FOLFIRI with bevacizumab failed to establish the predictive value of intratumoral ERCC1 for oxaliplatin based therapy (54).

Nano-liposomal irinotecan

Another example of modification in chemotherapeutic drugs using nano-technology is irinotecan encapsulated into liposomal-based nanoparticles, or MM-398 (also known as nal-IRI, Onivyde^{TM}). This modification alters the delivery of irinotecan and prolongs the time the drug remains in circulation, potentially increasing its efficacy without increasing toxicity. In the phase III NAPOLI-1 study, comparing MM-398, infusional 5-FU and leucovorin, or a combination of both in the second line setting after progression on gemcitabine based therapy, OS was significantly improved with the combination compared to 5-FU alone (6.1 *vs.* 4.2 months; HR =0.67; P=0.012). MM-398 alone did not improve outcome compared to 5-FU (55). Ferumoxytol is an iron-oxide superparamagnetic nanoparticle that has been used off-label for its MRI contrast properties. It is taken up by tumor associated macrophages in a pattern similar to MM-398 in preclinical models. If tumor deposition of MM-398 and formation of its active metabolite, SN-38, in tumor cells and associated macrophages correlates with response, ferumoxytol levels in tumor lesions (evaluated using functional MRIs) may serve as a potential biomarker for MM-398 deposition and response in solid tumors (56,57). In an early phase study comparing ferumoxytol uptake and response to MM-398 in advanced solid tumors, lesions that shrank after MM-398 showed higher early levels of ferumoxytol compared to the study median in metastatic breast cancer patients (57). Further study of MM-398 in pancreatic cancer will evaluate this potential biomarker.

Investigational targets and biomarkers

PEGPH20

Pancreatic cancer is associated with a dense tumor stroma which may promote tumor growth and limit chemotherapy perfusion. A major component of the stroma which is

present in high levels is hyaluronic acid (HA), which leads to elevated interstitial fluid pressures and also regulates cell adhesion, migration, and proliferation by interacting with specific cell surface receptors (58). In preclinical models of pancreatic cancer, administration of hyaluronidase depletes HA and improves response rates when administered with gemcitabine (59). PEGylated recombinant human hyaluronidase, PEGPH20, depletes HA in tumors and is being investigated in patients with pancreatic cancer in combination with chemotherapy. In a recently reported randomized phase II study of nab-paclitaxel + gemcitabine with or without PEGPH20 in treatment naïve metastatic pancreatic cancer patients, progression free survival favored the combination in tumors with high HA levels (median PFS was 9.2 and 4.8 months, for high and low HA levels respectively, P=0.03) (60). A follow-up phase 3 study in the high HA population is ongoing (NCT02715804).

Janus kinase (JAK) 1/2

The JAK activated signal transducer and activator of transcription (STAT) pathway is responsible for cellular growth, survival and differentiation (61) and it plays a major role in many conditions such as inflammatory diseases and cancer. Multiple studies have demonstrated a negative prognostic value for elevated markers of systemic inflammation in patients with pancreatic cancer (62,63). CRP and hypoalbuminemia are markers of inflammation and incorporated into the modified Glasgow prognostic score (64). In preclinical pancreatic cancer models, the *JAK/STAT* and related inflammatory pathways were found to drive cancer progression. Ruxolitinib is a *JAK 1/2* inhibitor which has been evaluated in refractory pancreatic cancer with or without capecitabine in a randomized phase II study (65). In a pre-specified subgroup of patients with systemic inflammation as measured by elevated serum C-reactive protein (CRP >13 mg/L), survival significantly favored the ruxolitinib arm (3 and 6 months survivals of 48% and 42% *vs.* 29% and 11%, respectively). These encouraging results led to the phase III JANUS 1 and JANUS 2 studies with a similar study design but restricted to patients with elevated CRP (NCT02117479). Unfortunately, both studies were closed after a planned interim analysis demonstrated no added benefit of ruxolitinib to capecitabine (66).

Several other agents are in phase 3 evaluation, building upon promising phase 1/2 data. Human Mucin-1 (MUC-1) is a protein biomarker secreted by over 85% of pancreatic adenocarcinomas and absent in normal pancreas (67). We found that patients with metastatic pancreatic cancer and MUC-1 expressing circulating tumor cells (CTCs) demonstrated a trend toward inferior survival (68). Clivatuzumab tetraxetan (PAM4) is a monoclonal antibody that specifically targets pancreatic mucins like MUC-1 and with [90]Y {[90]Y-labeled hPAM4} and low-dose gemcitabine had shown promise in early phase studies in pancreatic cancer. A phase I study of single dose [90]Y-labeled hPAM4 demonstrated its safety and also potential efficacy with 3 out of 21 patients achieving partial response (69). A second phase I study of repeated cycles of the same drug in combination with low dose gemcitabine demonstrated an encouraging response rate of 16% and a disease control rate of 42%, translating into a median survival of 7.7 months (including 11.8 months for those who received repeated cycles) (70). Guided by these results, a phase 3 study in the third line setting of low-dose gemcitabine with [90]Y-hPAM4 or placebo with a 2:1 randomization was undertaken (NCT01956812). The study was recently terminated after an interim analysis for futility (71).

Candidate biomarkers and molecular targets

KRAS and associated targets

Mutations in the *KRAS* gene are seen in over 90% of pancreatic cancers, making oncogenic *KRAS* an important therapeutic target in this disease. However, the unique conformation of *KRAS*, its position in the cell membrane, and its extremely high affinity for GTP make it a challenge to inhibit in clinical practice (72,73). Many proteins including *KRAS* require posttranslational farnesylation to reach their membrane positions and function properly in cell signaling (74). Selective inhibitors of farnesyl transferases (e.g., tipifarnib) have been used to manipulate *KRAS* processing successfully in preclinical setting. Phase I studies of farnesyl transferase inhibitors as a single agent and in combination with other chemotherapeutic agents were promising (75-77). Unfortunately, a phase III study comparing gemcitabine with or without tipifarnib showed no added benefit for the combination (78). Salirasib is a novel agent that inhibits *RAS*-dependent cell growth by dislodging all *RAS* isoforms from the plasma membrane with activity demonstrated in pancreatic cell lines and xenograft models (79). A phase I study combining Salirasib with gemcitabine in advanced pancreatic cancer demonstrated a median OS of 6.2 months and a 1 year survival of 37%. The authors also noted biomarker

modulation with decreased level of *RAS* and *KRAS* protein in tumor samples, as early as day 9 of cycle 1 (80).

The *MEK/MAPK* and *PI3K/AKT/mTOR* pathways are the principal downstream pathways of *KRAS*. Efforts to target the *KRAS* pathway by focusing on these downstream effectors of *KRAS* activation are being undertaken (81), although results have been discouraging thus far. A randomized, double-blind trial of gemcitabine with or without trametinib (*MEK* inhibitor) did not show any improvement in overall or progression free survival for the combination in the first line setting of metastatic pancreatic cancer (82). Similar results were seen with another *MEK* inhibitor, pimasertib, when given in combination with gemcitabine (83).

Unfortunately, the inhibition of *MEK* leads to enhanced signaling through *EGFR* with hyperactivation of the *PI3K-AKT* pathway, supporting the strategy of multiple pathway inhibition. Selumetinib, a mitogen-activated protein kinase inhibitor, demonstrated similar efficacy as capecitabine in a phase II study (84), and was further tested in combination with erlotinib in the second line setting (85). There were no responders but median OS was about 7.5 months with 51% disease control rate. In contrast, a combination of selumetinib and MK-2206 (*AKT* inhibitor) did not improve OS in patients progressing after gemcitabine-based chemotherapy when compared to mFOLFOX in a randomized phase II study (86). Also, *mTOR* inhibitors (block the *PI3K-AKT* pathway downstream), have failed to show activity in previously treated metastatic pancreatic cancer (87,88). Interestingly, Peutz-Jeghers syndrome patients harbor an alternation in the *STK11* tumor suppressor gene that encodes an *mTOR1* inhibitor and may be exceptionally susceptible to these drugs, as shown by a case report of response to everolimus in a patient with pancreatic cancer related to this syndrome (89).

Novel strategies to inhibit *KRAS* are also being developed. RNA interference involves post-transcriptional inhibition of a gene by a double-stranded RNA homologous to the target gene. This is accomplished by generation of small interfering RNA (siRNA). Targeting mutant *KRAS* using specific siRNA was effective in *KRAS* oncogene silencing and tumor growth inhibition in pancreatic tumor xenografts (90). A biodegradable polymeric matrix encompassing siRNA such as anti-$KRAS^{G12D}$ siRNA (known as Local Drug Eluter; siG12D LODER) is designed to provide slow and stable local drug release within a tumor over a period of a few months. This method of drug delivery can suppress *KRAS* expression, *in vitro* and *in vivo*, resulting in anti-tumor activity and improved survival in mouse models (91).

Other possible pathways

Inhibition of the hedgehog pathway decreases the growth of various types of tumors, including pancreatic cancer (92,93). Also, cancer-associated stromal fibroblasts overexpress the hedgehog receptor smoothened (*SMO*), leading to inappropriate activation and deregulation of the sonic hedgehog pathway (94). In preclinical study, the *SMO* receptor inhibitor saridegib with gemcitabine in gemcitabine-resistant mice resulted in increased tumor vasculature and extended survival (95). However, a phase IB/II study in pancreatic cancer comparing gemcitabine with or without the hedgehog inhibitor vismodegib did not show any benefit for the combination (96). *HER2* overexpression, by immunohistochemistry, is infrequently reported in pancreatic cancer, but clinical trials of *HER2* inhibitors in patients with *HER2*-overexpresing tumors have reported disappointing results (97).

Conclusions

We have made significant progress in the treatment of advanced pancreatic cancer, with survival approaching 1 year. However, there is a clear unmet need to improve outcomes for this deadly disease. A better understanding of pancreatic cancer genomics has provided new opportunities to personalize therapy and identify novel targets and drugs. Instead of targeting a specific gene or pathway, therapies with a multi-faceted approach targeting the primary tumor, microenvironment, stroma and host factors (immune response) at the same time are the likely next steps to yield benefit. In this manner, we can improve clinical response and outcomes with a multi-pronged approach and ultimately realize the dream of personalized therapy in sporadic or non-homologous recombination deficient pancreatic cancer.

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Footnote

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