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Making Sense of Current and Emerging Therapies in Pancreatic Cancer: Balancing Benefit and Value

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OVERVIEW

Pancreatic cancer remains the fourth leading cause of cancer deaths in the United States with a dismal prognosis and a 5-year survival of less than 5% across all stages.¹ In 2014, there were approximately 46,420 new cases of pancreatic cancer with only 9% of patients having localized disease.² Given that the vast majority of patients present with advanced disease, much of the focus for drug development has been in the metastatic setting, which is evident with the advent of two combination chemotherapy regimens for this indication. Although conventional cytotoxic chemotherapy remains the standard of care, an ongoing search for novel therapeutic approaches continues. We will highlight several new approaches here, with a particular emphasis on immunotherapeutic strategies. We will also introduce concepts regarding the potential economic effects associated with the development and implementation of new treatments in pancreatic cancer.

Conventional cytotoxic chemotherapy remains the standard of care for pancreatic cancer. Table 1 highlights major findings from key clinical trials in advanced pancreatic cancer. Before recent advances, the last significant therapy approved for pancreatic cancer was erlotinib in 2007, based on a phase III randomized control trial showing that this agent when added to gemcitabine improved survival.³ However, because the degree of survival improvement was of questionable clinical significance and at the expense of significant toxicities (62% grade 3 to 4 adverse events), the combination has never found significant traction in the treatment of pancreatic cancer. During the past several years, two

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chemotherapy regimens, FOLFIRINOX and gemcitabine/nabpaclitaxel, have emerged as new standards of care for the first-line treatment of metastatic pancreatic cancer, both based on randomized phase III trials that show more clinically meaningful benefits when compared with gemcitabine.

Despite these recent advances, the median survival for patients with metastatic disease remains less than a year, highlighting a desperate need to continue the developmental therapeutic path in pancreatic cancer.

RECENT DEVELOPMENTS WITH TARGETED THERAPEUTIC AGENTS

Beyond conventional cytotoxic chemotherapy, the modern trend in developing novel therapeutic approaches offers promise for improving the outlook of patients with advanced pancreatic cancer.

TARGETING TUMOR MICROENVIRONMENT

The stromal compartment in pancreatic cancer is dense and contributes to the aggressive nature of this tumor by fostering tumor growth and enhancing drug resistance by inhibiting effective penetration of chemotherapy. With an increased understanding of the importance of the role of the tumor microenvironment and its role in tumor proliferation, agents aimed at targeting the tumor microenvironment is an area of increased interest in pancreatic cancer.⁴⁻⁹ However, previous attempts to target the tumor microenvironment, in particular with Hedgehog signaling inhibitors, have proved unsuccessful.^{10,11}

Recent early phase studies have shown promising results in targeting tumor stroma in pancreatic cancer with PEGPH20. PEGPH20, a pegylated form of recombinant hyaluronidase, has been shown to successfully degraded hyaluronic acid (HA), a primary component of tumor peristroma, leading to the re-expansion of tumor microvasculature and improving the delivery of gemcitabine.¹² Early studies of PEGPH20 in combination with gemcitabine have demonstrated provocative progression-free survival and overall survival (OS) in patients with elevated levels of hyaluronic acid,¹³ which has resulted in two ongoing randomized phase II trials in metastatic pancreatic cancer ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01959139) NCT01959139 and NCT01839487).

TARGETING THE RAS PATHWAY

Targeting signaling pathways in cancer remains an attractive therapy in pancreatic cancer. Given the nearly universal presence of activating *KRAS* mutations in pancreatic cancer and its key function in cell survival and proliferation, *KRAS* represents an ideal target; although, its relevance as a therapeutic target is not fully established.¹⁴⁻¹⁶ Targeting *RAS* directly is a challenge; one approach using oncolytic viruses is described below. Attempts have been made to inhibit downstream effector molecules to *RAS*, although cross-talk between parallel downstream signaling pathways and negative loop feedback inhibition have been indicated as potential mechanisms for resistance and highlight the need to inhibit multiple pathways simultaneously.¹⁷

TAKING ADVANTAGE OF SYNTHETIC LETHALITY

For a distinct group of patients with pancreatic cancer, the concept of synthetic lethality may afford a specific treatment strategy. Synthetic lethality occurs when a combination of mutations in two or more genes leads to cell death, whereas, a single mutation does not and by itself remains viable. Tumors harboring defective DNA repair mechanisms render them vulnerable to synthetic-lethality approaches, leading to the use of targeted agents that induced the death of tumor cells while sparing normal cells. Mutations in genes, including tumor suppressor genes (*BRCA 1/2*, *ATM*), may confer an increased sensitivity to DNA-damaging cytotoxic chemotherapy including platinum analogs and PARP inhibitors because of the associated defective homologous recombination and an inability to mount efficient DNA repair.^{18,19} In specific subgroups of patients, including those of Ashkenazi Jewish descent and individuals with a family history of pancreatic cancer, the prevalence of germ-line mutations of *BRCA1* and *BRCA2* has been reported in as many as 19%.^{20,21} For patients with germ-line *BRCA1/BRCA2* mutations, a phase III randomized, double-blind study, the POLO trial, is investigating the use of the PARP inhibitor olaparib in patients with metastatic pancreatic cancer whose disease has not progressed on first-line platinum-based chemotherapy ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02184195) NCT02184195).

IMMUNOTHERAPEUTIC APPROACHES IN PANCREAS CANCER

Targeting PD-1/PD-L1

Except for melanoma, renal cell carcinoma, and prostate cancer, immunotherapy for solid tumors remains experimental. Tumors resist an immune response by inducing tolerance in tumor-specific T cells and by expressing ligands that bind to inhibitory receptors, or immune checkpoints on T cells, which dampen their immune response against tumors. Immunotherapeutic approaches, notably agents targeting negative regulatory molecules on activated T cells, such as cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death-1 (PD-1), and its binding ligand, programmed death ligand 1 (PD-L1), are showing promise in a number of malignancies. Antagonism of these immune checkpoints can augment the nascent antitumor response from the immune system.

Pancreatic cancer has been mostly considered an immunosuppressive malignancy, with pancreatic cancer cells producing cytokines (transforming growth factor-beta) and surface molecules that mediate immunosuppression (FAsL, PDL-1). Moreover, it has been mostly considered a nonimmunogenic malignancy, since tumor-infiltrating effector T lymphocytes do not represent a histopathologic hallmark for this disease. Therapeutic approaches focusing on overcoming T-cell immunologic checkpoints with anti-CTLA-4 and anti-PD1 monoclonal antibodies alone have failed to demonstrate any meaningful activity in pancreatic cancer to date.^{22,23} However, studies investigating the combination of checkpoint inhibitors with “immune resensitizing” agents are currently in development in this disease, as described below.

VACCINE THERAPIES

With molecular identification of human tumor antigens, antitumor vaccine therapies specifically sensitize immune cells against tumor antigens. Several types of vaccinations are under investigation against pancreatic cancer, including whole-cell, peptide, DNA, and vaccines with microorganisms.

GVAX

GVAX is an irradiated whole-cell modified vaccine composed of two irradiated pancreatic cancer cell lines (PANC 6.03 and PANC 10.05) engineered to express granulocyte-macrophage colony-stimulating factor (GM-CSF), a growth factor that plays a key role in stimulating the immune system response by inducing dendritic cell differentiation. Administration of GVAX in addition to standard 5-FU-based chemoradiation as part of adjuvant therapy after pancreatic cancer resection demonstrated promising results in a single-institution phase II trial.²⁴ Moreover, several studies investigating the immunologic effects of GVAX have demonstrated its ability to create an inflammatory reaction causing an upregulation of PD-L1, suggesting the potential utility of combining this vaccine with immune checkpoint inhibitors.^{25,26}

CRS-207

An alternative immune-based strategy undergoing clinical investigation in pancreatic cancer is CRS-207, a live-attenuated *Listeria monocytogenes* (LM) vaccine (CRS-207, Aduro Biosciences, Berkeley, CA) genetically modified to express mesothelin, which is often overexpressed in pancreatic cancer. A recent randomized phase II trial in patients with chemotherapy-refractory metastatic pancreatic cancer suggested a significant improvement in overall survival when sequential treatment with GVAX/CRS-207 was administered, as compared with GVAX alone (median OS, 6.1 vs. 3.9 months; hazard ratio [HR] 0.59, $p = 0.02$).²⁷ These findings have led to an ongoing phase IIB randomized control trial comparing CRS-207 alone to CRS-207 in combination with GVAX or to chemotherapy in previously treated metastatic pancreatic cancer ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02004262) NCT02004262). Another phase II study is investigating the use of GVAX in combination with CRS-207 with or without nivolumab, an anti-PD-1 monoclonal antibody, in previously treated metastatic pancreatic cancer ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02243371) NCT02243371).

ALGENPANTUCEL-L

Algenpantucel-L (NewLink Genetics Corporation, Ames, Iowa) is a whole-cell vaccine made of two human pancreatic cancer cell lines (HAPa-1 and HAPa-2) that are genetically modified to express alpha^{1,3}-galactosyl epitopes (alphaGAL), a carbohydrate present in the cells of most mammals except humans, which have developed pre-existing immunity. On injection, algenpantucel-L induces an immune response that parallels the hyperacute rejection that can occur postorgan transplant. An open-label phase II trial of this vaccine in combination with adjuvant chemotherapy and chemoradiation in resected pancreatic cancer demonstrated promising 1-year disease-free survival and OS rates (62% and 86%,

respectively).²⁸ On this basis, a large phase III trial was recently completed in the United States, evaluating standard adjuvant chemotherapy or chemoradiation with or without algenpantucel-L in resected pancreatic cancer ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01072981) NCT01072981).

ONCOLYTIC VIROTHERAPY

Because of their tumor selectivity and ability to cause cancer cell lysis, oncolytic viruses continue to represent an area of considerable interest in cancer treatment. These viruses selectively target tumor cells through engineered mutations that prevent the binding and replication of the virus in normal, healthy cells and attack specific tumor epitopes that lead to cancer cell death.

Reovirus is a family of naturally occurring, ubiquitous nonenveloped human virus whose replication is dependent on cellular activity of *RAS*; specifically, it is cytopathic in transformed cells possessing an activated *RAS* signaling pathway.^{29–32} Given the prevalence of *KRAS* mutations in pancreatic cancer, reovirus has represented a promising and attractive candidate as an oncolytic virus in this disease. Bekaii-Saab et al reported the results of a phase II randomized trial in which 73 patients with metastatic pancreatic adenocarcinoma were randomly assigned to receive carboplatin/paclitaxel alone or in combination with Reolysin.³³ Although this agent was well tolerated overall, it failed to show an improvement in outcomes, including in those patients with *KRAS* mutations. Investigation into other oncolytic viruses (adenovirus, parvovirus, pox virus, measles virus) continues in patients with pancreatic cancer.

THE JAK/STAT PATHWAY

Recent studies have indicated that *JAK2*/signal transducers and activators of transcription 3 (STAT3) signaling pathways are important for the initiation and progression of pancreatic cancer.³⁴ In addition to its contribution to tumorigenesis, the clinical symptoms associated with pancreatic cancer, including cachexia and weight loss, reflect a chronic inflammatory state likely related in part to the *JAK/STAT* pathway.³⁵ Based on these findings, ruxolitinib, a *JAK1/JAK2* inhibitor, is currently under investigation in metastatic pancreatic cancer. A randomized phase II study (RECAP trial) compared the addition of ruxolitinib to capecitabine with capecitabine alone in patients after progression on gemcitabine-based therapy.³⁶ Although no survival difference was observed in the overall study population, a preplanned analysis in the subgroup of patients with elevated levels of C-reactive protein (CRP) revealed a significant survival benefit in favor of the ruxolitinib-containing arm (HR 0.47, $p = 0.01$). Based on these findings, two phase III trials, JANUS-1 and JANUS-2, investigating the use of capecitabine with or without ruxolitinib in the first and second-line of therapy, respectively, are ongoing for patients with metastatic pancreatic cancer with elevated CRP, a biomarker of an inflammatory state ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02117479) NCT02117479 and NCT02119663).

CHIMERIC ANTIGEN RECEPTOR T CELLS

Last, albeit in its early stages, the role of autologous T cells manufactured to express chimeric antigen receptors, known as CAR T cells, is under active investigation in a variety of tumor types, including pancreatic cancer. These CARs can recognize specific membrane proteins expressed on tumor cells, such as mesothelin in pancreatic cancer.³⁷ This adoptive cell transfer approach has produced sustained remissions in hematologic malignancies,³⁸ but its safety and efficacy in solid tumors requires further study.

THE VALUE OF CURRENT AND EMERGING THERAPIES

Concern has been raised regarding the high costs of new innovations in oncology from a variety of perspectives, including society, payer, and patient.³⁹ From the patient perspective, high out-of-pocket expenses can affect personal finances and treatment adherence (Table 2). Given the increasing number of treatment options available for patients with advanced pancreatic cancer, coupled with the fact that the benefits of each recent advance have been incrementally modest, it is important to systematically compare the benefits and costs (i.e., the value) of each option. This will allow oncologists to help patients optimize treatment decisions, and payers and policymakers to rationally address resource allocations. The American Society of Clinical Oncology has stressed the importance of recognizing financial implications for patients,⁴⁰ and is developing a user-friendly framework for the assessment of value.

Pancreatic cancer treatments highlight the importance of not only considering anticancer drug costs in such analyses, but also supportive care and management of complications that may differ substantially between regimens. For example, recent economic analyses have indicated that although the drug costs associated with gemcitabine/nabpaclitaxel are much higher than those with FOLFIRINOX, the costs associated with supportive measures (including hematopoietic growth factors and hospitalization) are greater with FOLFIRINOX.^{41,42} Despite the higher costs associated with administration and toxicities with FOLFIRINOX, the monthly cost of gemcitabine/nab-paclitaxel remains higher. Although cost is one important factor in determining treatment, other factors not limited to quality of life and survival benefit should be considered in any treatment decision. As new treatments are developed, including a number of the newer (and likely very costly) agents discussed above, the inclusion of economic analyses in phase III clinical trials, supplemented by analyses of administrative data, will be essential for prioritizing and applying these various treatment approaches in a thoughtful way. This information will be useful both for our individual patients and for society at large.

CONCLUSION AND FUTURE DIRECTIONS

Despite advances in cancer care and research, pancreatic cancer remains very challenging, with standard treatment regimens providing modest gains at a significant cost. A variety of novel therapeutic approaches, including several targeting the immune system in different ways, have produced promising results and spurred further investigation in both early- and

later-phase studies. As these innovations continue to be developed, it is important that we set a high bar to ensure that we bring the greatest value to our patients.⁴³

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KEY POINTS

- Pancreatic cancer remains a devastating disease with an increasing prevalence and the highest mortality rate of any malignancy.
- Cytotoxic chemotherapy remains the primary treatment for advanced pancreatic cancer, with several new combination regimens emerging as first-line standards.
- New agents targeting the tumor microenvironment and cancer-signaling pathways are being investigated in pancreatic cancer.
- Although pancreatic cancer has been mostly considered an immunosuppressive malignancy, developments have renewed interest in immunotherapy as a treatment option in this disease.
- Attention to the value of new therapeutics is critical to prioritizing efforts and selecting treatment for individual patients.

TABLE 1

Standard Chemotherapy Regimens in Metastatic Adenocarcinoma of the Pancreas

Chemotherapy Regimen	Sample Size	Survival, Median (Months)	Hazard Ratio	Objective Response Rate	Toxicities (Grade 3 to 4)	Author
Gemcitabine vs. 5-FU	126	5.65 vs. 4.41	Not reported	5.4	Neutropenia 25.9%	Burris III et al 1997 ⁴⁴
Gemcitabine/erlotinib vs. gemcitabine	569	6.24 vs. 5.9	0.82	8.6	62% (fatigue 15%, infection 17%)	Moore et al 2007 ³
FOLFIRINOX vs. gemcitabine	342	11.1 vs. 6.8	0.57	31.6	Fatigue 23.6% neutropenia 45.7%	Conroy et al 2011 ⁴⁵
Gemcitabine/nab-paclitaxel vs. gemcitabine	861	8.5 vs. 6.7	0.72	23	Fatigue 17% neutropenia 38%	Von Hoff et al 2013 ⁴⁶
5-FU/leucovorin + MM-398 vs. 5-FU	417	6.1 vs. 4.2	0.57	16	Fatigue 14% neutropenia 20% diarrhea 13% vomiting 11%	Von Hoff et al 2014 ⁴⁷

TABLE 2Cost of First-Line Standard Chemotherapy Regimens in Metastatic Pancreatic Cancer^{*48}

Regimen	Monthly Costs of Drugs	Monthly Cost of Administration	Monthly Cost of Toxicities^{**}	Total Monthly Cost[†]
Gemcitabine	\$188	\$143	\$1,032 ²	\$1,363
Gemcitabine/ nab-paclitaxel	\$9,008	\$522	\$2,692	\$12,221
FOLFIRINOX	\$763	\$531	\$5,940	\$7,234
Gemcitabine/ erlotinib	\$6,831	\$143	\$1,032 ²	\$8,007

* All costs were calculated in U.S. dollars (\$). The unit price of each drug was determined from the 2013 average sales price from the Centers for Medicare & Medicaid Services. Fees for administration and toxicities were calculated according to the 2013 physician fee schedule.⁴⁹

** The cost of growth factor is included.

[†] The cost of growth factor is based on data extrapolated from the gemcitabine arm in the MPACT trial.⁴⁶