

Past Pitfalls and Potential Promise for Pancreatic Cancer

By Michael Becker

November marks Pancreatic Cancer Awareness Month. Visibility for the disease is already on the rise due to the recent news of Steve Jobs of Apple Inc., and the death of actor Patrick Swayze. According to the American Cancer Society's most recent estimates for pancreatic cancer, roughly 43,000 men and women in the United States will be diagnosed with the disease in 2010; and about 36,800 people will die of pancreatic cancer. Although accounting for only 3% of all cancers, this disease is the fourth leading cause of death among adults, and represents 6% of all cancer related deaths.¹

The disease remains one of the most difficult to treat due to its extreme resistance to treatment and its usually late initial diagnosis. For example, at the time of initial diagnosis, 50% of patients have distant metastases to the liver or peritoneal surface, and more than 80% of the remaining patients have locally advanced tumors.² The majority of pancreatic tumors (95%) are adenocarcinomas

that mainly develop from exocrine cells in the tissues of the pancreas.³ The tumors are characterized by an aggressive behavior with a fast progression rate that makes them highly metastatic. Neuroendocrine tumors (NET) of the pancreas (islet cell tumors) are much less common (1%–2%)⁴ than exocrine pancreatic tumors and are considered less deadly.⁵

In terms of treatment, surgical removal of the tumor represents the best option for patients with pancreatic cancer without invasion into surrounding organs or distant metastasis. Unfortunately, only 15%–20% of all patients are candidates for potentially curative surgery.⁶ Depending on the tumor localization, pancreaticoduodenectomy, distal or total pancreatectomy may be performed. However, even with an optimal curative surgery, metastases often occur. Median survival time without evidence of recurrent disease is 21.2 months after resection.⁷

For locally advanced or metastatic disease, treatment is still palliative rather than curative, and chemotherapy remains the only option for patients. Since its approval in 1997, Gemzar [gemcitabine; Eli Lilly & Company] is the current standard first-line treatment in the United States for locally advanced or metastatic pancreatic cancer. Studies have shown that gemcitabine may improve the median time to disease progression and overall survival (OS) in patients. However, similar to lupus and sepsis, this author believes that pancreatic cancer is referenced as one of those challenging diseases where good drugs (and companies) go to die.

I don't say this lightly, but since 2005, nine late-stage clinical trials have been conducted to improve the efficacy of gemcitabine in patients with pancreatic cancer with little success in terms of improving survival outcomes (Table 1). Such failures resulted in at least two companies filing for bankruptcy in 2006 (Aphton Corporation and Therion Biologics).

Table 1. Prominent Late-stage Pancreatic Cancer Product Failures

Company	Product	Class	Phase	Year
GenVec, Inc.	TNFerade	Gene therapy	3	2010
Pfizer, Inc.	Axitinib	Kinase inhibitor	3	2009
SciClone Pharmaceuticals, Inc.	RP101	Chemotherapy	2	2009
Regeneron Pharmaceuticals, Inc. / Sanofi-Aventis	Aflibercept	Fusion protein	3	2009
ImClone / Eli Lilly & Co.	Erbix (cetuximab)	Monoclonal antibody	3	2007
Roche Holding AG	Avastin (bevacizumab)	Monoclonal antibody	3	2007
Therion Biologics	PANVAC-VF	Immunotherapy	3	2006
Aphton Corp	Insergia	Immunotherapy	3	2005
Supergen, Inc.	Orathecin	Chemotherapy	3	2005

In fact, the only combination of drugs approved by the U.S. Food and Drug Administration (FDA) for pancreatic cancer is gemcitabine plus Tarceva [erlotinib; Genentech, OSI] which increases the median OS from 6.0 to 6.4 months.

Despite these past failures, drug developers continue to explore new options for treating pancreatic cancer and more than a dozen new molecular entities are currently being evaluated in clinical trials (Table 2). Several programs have recently demonstrated impressive results in Phase 2 studies and are now enrolling patients in pivotal trials. While a comprehensive review of investigational pancreatic cancer therapies is beyond the scope of this article, here are some of the more promising pancreatic treatments currently in clinical development by manufacturers.

» CELGENE CORPORATION

Historically known more for its franchise in treating blood cancers, Celgene moved into the realm of solid tumors through its recent acquisition of Abraxis BioScience, Inc. As a result, Celgene is now developing Abraxane [paclitaxel protein-bound particles for injectable suspension] for the treatment of pancreatic cancer. Updated overall survival (OS) findings from a Phase 1/2 study of Abraxane given in combination with gemcitabine demonstrated increased survival of the first-line treatment of patients with advanced pancreatic cancer. In 44 patients treated at the recommended dose of 125 mg/m² Abraxane plus gemcitabine (1000 mg/m²), the median OS time was 12.2 months, an impressive doubling of survival compared with historical control of gemcitabine administered alone. The findings were presented at the 2010 annual meeting of the American Association for Cancer Research (AACR). The

combination of Abraxane and gemcitabine is now the treatment arm of a randomized Phase 3 clinical trial that is currently enrolling patients with metastatic adenocarcinoma of the pancreas (ClinicalTrials.gov identifier NCT00844649).



» NOVARTIS AG

In June 2010, at the World Congress on Gastrointestinal Cancer, Novartis reported that its RADIANT-3 Phase 3 study of Afinitor [everolimus] in combination with best supportive care met its primary endpoint, showing that the drug more than doubled median progression-free survival (PFS), or time without tumor growth, from 4.6 to 11.0 months when compared with placebo in patients with advanced pancreatic NET. More recently, Novartis presented data from a second Phase 3 study called RADIANT-2 at the recently held European Society for Medical Oncology (ESMO) Congress. The study, which evaluated Afinitor in combination with Sandostat LAR Depot [octreotide acetate for injectable suspension], demonstrated that everolimus plus octreotide LAR pro-

vided a clinically meaningful extension in the median time without tumor growth from 11.3 months to 16.4 months when compared with placebo plus octreotide LAR. However, the study did not meet its primary endpoint of PFS based on central radiologic review of the data ($P = .026$ vs $P = .024$ predefined). According to Novartis, results from the two RADIANT trials will form the basis for regulatory filings later in 2010.

» AMGEN, INC.

Amgen is developing AMG 479, an investigational fully human monoclonal antibody that targets type 1 insulin-like growth factor receptor (IGF-1R), which plays an important role in the regulation of cell growth and survival. At the 2010 American Society of Clinical Oncology (ASCO), Amgen announced results from a Phase 2 study demonstrating that the addition of AMG 479 to gemcitabine in patients with pancreatic cancer resulted in an overall survival rate of 57% vs 50% with gemcitabine alone at 6 months; and 39% vs 23%, respectively, at 12 months. Median OS was 8.7 months vs 5.9 months in the gemcitabine arm. AMG 479 is moving into a Phase 3 study for metastatic pancreatic cancer.

» THRESHOLD PHARMACEUTICALS, INC.

Also, at the 2010 ASCO meeting, Threshold Pharmaceuticals presented results with its hypoxia-activated prodrug, TH-302, in combination with gemcitabine in 34 patients with advanced or metastatic pancreatic cancer that had at least one evaluable post-treatment tumor assessment. One patient (3%) demonstrated a complete response as measured by RECIST (Response Evaluation Criteria In Solid Tumors) and 8 patients (24%) had a partial response. Of the 34 assessed patients, [cont. on pg 20](#) »

28 had elevated carbohydrate antigen CA19-9 levels at baseline, and 17 of 28 patients (61%) had a CA19-9 reduction of greater than 50%. This is important, as a greater than 20% decrease in levels of this tumor-associated antigen has been shown to correlate with improved OS. The biomarker CA19-9 has been shown to be highly specific and sensitive for pancreatic cancer and approximately three-quarters of all pancreatic cancer patients have elevated baseline serum CA19-9 level at baseline.

» NEOGENIX ONCOLOGY, INC.

Neogenix Oncology is developing a novel, chimeric monoclonal antibody, ensituximab, intended for the treatment of advanced pancreatic and colorectal cancer. Pre-clinical studies have demonstrated that ensituximab specifically targets pancreatic and colorectal cancer sparing healthy tissue. In 2010, the company initiated a multi-center Phase 1 trial in patients with late-stage pancreatic or colorectal cancer. Neogenix is also exploring the diagnostic and prognostic utility

of ensituximab using a new serum ELISA test in a prospective study. Preliminary results demonstrate that the biomarker test can differentiate between blood serum of healthy donors and that of patients with colorectal or pancreatic cancer. In addition, the results of the biomarker test indicate superior sensitivity as compared to commercially available carcinoembryonic antigen and CA19-9 assays.

Conclusion

In contrast to the prominent late-stage failures over the past 5 years, several drugs have recently shown promise for the treatment of pancreatic cancer. Going forward, early detection of pancreatic cancer using biomarkers, more effective treatments, and novel drug targets may provide new hope for the treatment of this deadly disease. **MB**

Table 2. Select Pancreatic Cancer Products in Active Clinical Development*

Company	Product	Class	Phase
Celgene / Abraxis	Abraxane	Chemotherapy	3
Novartis AG	Afinitor	Signal transduction inhibitor	3
Amgen	AMG 479	Monoclonal antibody	2
Threshold Pharmaceuticals	TH-302	Chemotherapy	2
Oncolytics Biotech	Reolysin	Reovirus	2
Celgene / GlobelImmune	GI-4000	Targeted molecular immunotherapy	2
Pharmacyclics	PCI-27483	Signal transduction inhibitor	2
BioSante Pharmaceuticals	GVAX Pancreas Vaccine	Immunotherapy	2
Novartis AG and Bayer Schering Pharma AG	Vatalanib (PTK787/ZK-222584)	Kinase inhibitor	1/2
Infinity Pharma	IPI-926	Signal transduction inhibitor	1b/2
Immunomedics	Clivatuzumab tetraxetan, 90Y-hPAM4	Monoclonal antibody – radiolabeled	1b
Neogenix Oncology	Ensituximab, NPC-1C	Monoclonal antibody	1
Seattle Genetics / Astellas Pharma	ASG-5ME	Monoclonal antibody – drug conjugate	1
Celldex Therapeutics	CDX-1307	Monoclonal antibody	1

*Based on ClinicalTrials.gov

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The screenshot shows the OBR dashboard interface with the following sections:

- OBR Finance:** A user-specific, streaming stock ticker at the top right showing OBR Index, ACCPOB, DCTH, and KERK with their respective price changes.
- Featured News Headlines:** A section for streaming feature oncology news headlines, such as "Experts Wristle with Vaccinating Boys for HPV".
- Oncology Publications Summary by Interest Area:** A table listing interest areas and the number of articles.

INTEREST AREAS	# OF ARTICLES	MUST READ
Acute Myelogenous Leukemia (AML) (Includes APL)	273	
Basal Cell Carcinoma (BCC)	2	
Breast	485	
CMS, Policy, Cost, Quality and Reimbursement	16	
FDA/Regulatory (Includes biologics and generics)	1	
Health, Diet/Exercise, and Lifestyle	20	
Legal	1	
Ovarian	56	
Patient care (Includes Quality of life)	114	
Prostate	132	
Rare Cancers and Disorders	96	
- OBR Radar:** A section for upcoming pivotal events, listing dates, companies, and products.
- Oncology Events Calendar:** A calendar for planning meeting attendance with upcoming and past events.
- OBR Finance Winners/Losers:** A table showing stock performance.

SYMBOL	LAST	Δ	% Δ
SCLN	\$3.37	\$0.14	+4.2%
AVEO	\$15.19	\$0.63	+4.1%
ONTY	\$3.44	\$0.13	+3.8%
ANDS	\$1.45	\$-0.06	-4.1%
VICL	\$2.16	\$-0.08	-3.7%
CYTR	\$0.86	\$-0.03	-3.5%
- OBR Pipeline Online:** A table for tracking drug development by phase.

INTEREST AREAS	PRE	PH	P2	P3
Acute Myelogenous Leukemia (AML)	3	8	9	8
Basal Cell Carcinoma (BCC)	0	4	2	0
Breast	13	17	61	28
Non-Hodgkin's Lymphoma (NHL)	0	2	0	0
Ovarian	6	8	25	13
Prostate	9	12	17	15
- OBR Finance Bulls/Bears:** A table showing stock performance.

SYMBOL	LAST	PRE-DAY	% Δ
AVEO	\$15.19	\$8.96	+69%
YMI	\$2.03	\$1.47	+38%
ONCY	\$4.53	\$3.32	+36%
AFFY	\$5.07	\$12.06	-58%
SNSS	\$0.33	\$0.57	-42%
PPHM	\$1.52	\$2.32	-34%
- OBR Green:** A section for the online journal, providing insightful and original content.

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