

Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer

Is Wishful Thinking Clouding Successful Drug Development for Pancreatic Cancer?

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Abstract: Prior phase III trials in advanced pancreatic cancer have been predominantly unsuccessful. In this review, we attempt to understand how past preclinical data were translated into phase III clinical trials in metastatic pancreatic cancer as described in the article. A systematic literature review conducted through the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases, from January 1997 to June 2015 using key words—phase III clinical trials, metastatic/advanced pancreatic adenocarcinoma or pancreatic cancer identified 30 randomized controlled trials (RCTs) that met criteria. The trials were limited to RCTs in the first-line treatment of patients with metastatic pancreatic cancer. The success rate of first-line phase III studies in advanced pancreatic cancer was only 13%. In 60% of the RCTs, no preclinical experiments were referenced in biologically cognate pancreatic models. Nine (30%) of the RCTs were designed based on preclinical evidence from in vitro cell lines alone without additional in vivo validation in xenograft models. It remains uncertain how strongly the preclinical data influence the development of clinical regimens but so far the studies developed based on more solid preclinical evidence have been successful.

Key Words: preclinical evidence, metastatic pancreatic cancer, randomized phase III trials

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Pancreatic cancer is the fourth leading cause of cancer related mortality in the United States and is expected to rise to the second leading within a decade.¹ The majority of the patients with pancreatic cancer have advanced disease at diagnosis with limited treatment options. Despite intensive research efforts over past several decades, the prognosis of advanced pancreatic cancer remains dismal. Even with the newest regimens, median survivals for advanced disease remain less than a year.^{2,3} Therefore, there is an urgent need for the development of new effective drugs to improve the survival of patients with metastatic pancreatic cancer.

Although we have made remarkable progress in understanding the biology of pancreatic cancer, this has not translated into new drug discovery. In fact, the only positive trials in recent years have involved traditional chemotherapy.^{2,3} Drug development in pancreatic cancer has been challenging. At least 1 issue that needs to be better understood is how preclinical data supporting the use of new agents or new combinations failed to result in clinical benefit in randomized phase III clinical trials.

The failure of clinical trials at later stages of drug development results in exposure of already symptomatic patients to unwanted toxicities causing further impairment in quality of life, waste of health care dollars, resources, and delay in development of therapies that may have a better chance of success. Preclinical data are used in the development of agents and regimens, but it remains unclear how informative these data are and how well it truly informs by the time the phase III is developed.

A diverse group of preclinical murine models have been used in cancer research. However, due to complex genetic and molecular heterogeneity in human tumors compared with mice, few, if any, of these animal models can faithfully recapitulate the in vivo pancreatic tumor microenvironment. This analysis was undertaken to better understand how past preclinical data were translated into clinical trials in pancreatic cancer. In this review, we report the preclinical rationale for all the published first-line phase III trials in metastatic pancreatic cancer as described in the article. These data may inform us in methods for improvement for future drug development in advanced pancreatic cancer.

MATERIALS AND METHODS

We conducted a systematic literature review through the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases, from January 1997 to June 2015 using key words—phase III clinical trials, metastatic/advanced pancreatic adenocarcinoma or pancreatic cancer. The trials were limited to randomized controlled trials (RCTs) in the first-line treatment of patients with metastatic pancreatic cancer. RCTs in nonmetastatic pancreatic cancer, second-line metastatic pancreatic cancer or nonrandomized trials in metastatic pancreatic cancer were excluded. As a result, we did not include the recent successful phase III NAPOLI-1 trial in the second line setting, which has led to the US Food and Drug Administration approval of a combination liposomal irinotecan (Onivyde) regimen in pancreatic cancer patients that progressed on gemcitabine or gemcitabine-based therapies. Further, to be included, the trial had to be published. Abstract only reports were not included because background data could not be reviewed.

We identified 30 published RCTs that met inclusion criteria. Data collected from the articles included: first author, publication year, chemotherapy regimens, and information on preclinical studies. The preclinical data from published phase III trials were

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collected in a systematic manner. First, each published phase III study was carefully reviewed to verify that preclinical rationale was reported. If preclinical data were available, information was collected on the number and type of preclinical models tested (in vitro, cell line–derived xenograft, patient-derived xenograft [PDX], or genetically engineered mouse model [GEMM]) based on the reports referenced in the article. Then each study was

analyzed for evidence of preclinical activity in pancreatic models and if the science for the combination drug therapy and sequencing of the drugs is proven in pancreatic cancer or not was noted. The science for the combination drug therapy was considered fully supported in pancreatic cancer only if evidence for synergy of the drug combinations was tested in pancreatic models specifically. In addition, because preclinical evidence was not always

TABLE 1. Preclinical Evidence Reported in Published Phase III Trials in Metastatic Pancreatic Cancer

Study	Drug	Phase III	Phase II	In Vitro Cell Line	Cell Line–Derived Xenograft		GEMM Model	Patient-Derived Xenograft	
					Hetero	Ortho		Hetero	Ortho
Positive trials									
Von Hoff et al, 2013 ³	Gemcitabine + nab-Paclitaxel	Yes ³	Yes ⁴				Yes ⁵	Yes ⁴	
Conroy et al, 2011 ²	FOLFIRINOX	Yes ²	Yes ⁶	Yes ^{7–10}	Yes ^{10,11}				
Moore et al, 2007 ¹²	Gemcitabine + erlotinib	Yes ¹²	No	Yes ¹³		Yes ¹³			Yes ¹⁴
Burris et al, 1997 ¹⁵	Gemcitabine	Yes ¹⁵	Yes ¹⁶	Yes ¹⁷	Yes ¹⁷				
Negative trials									
Colucci et al, 2002 ¹⁸ GOIM	Gemcitabine + cisplatin	Yes ¹⁸	Yes ^{19,20}	Yes ^{21,22}					
Moore et al, 2003 ²³	BAY 12-9566	Yes ²³	No		Yes ²⁴				
Colucci et al, 2010 ²⁵ GIP-1	Gemcitabine + cisplatin	Yes ²⁵	NA	Yes ^{21,22,26–28}					
Berlin et al, 2002 ²⁹	Gemcitabine + 5-flourouracil	Yes ²⁹	Yes ^{30–33}	Yes ^{34,35}					
Brahmall et al, 2001 ³⁶	Gemcitabine + marimastat	Yes ³⁶	Yes ³⁷	Yes ³⁸	Yes ^{39–42}	Yes ^{38,43}			
Van Custem et al, 2004 ⁴⁴	Gemcitabine + tipifarnib	Yes ⁴⁴	No	Yes ⁴⁵	Yes ⁴⁵				
Rocha Lima et al, 2004 ⁴⁶	Gemcitabine + irinotecan	Yes ⁴⁶	Yes ⁴⁷	Yes ⁴⁸					
Oettle et al, 2005 ⁴⁹	Gemcitabine + pemetrexed	Yes ⁴⁹	Yes ⁵⁰	Yes ⁵¹					
Louvet et al, 2005 ⁵²	Gemcitabine + oxaliplatin	Yes ⁵²	Yes ⁵³	Yes ⁵⁴					
Reni et al, 2005 ⁵⁵	Gemcitabine + epirubicin cisplatin 5-flourouracil	No ⁵⁵	No ⁵⁶						
Hienemann et al, 2006 ⁵⁷	Gemcitabine + cisplatin	Yes ⁵⁷	Yes ^{19,20,58}	Yes ^{27,59,60}	Yes ^{59,60}				
Abou-Alfa et al, 2006 ⁶¹	Gemcitabine + exatecan	Yes ⁶¹	Yes ⁶²	Yes ^{63,64}					
Stathopoulos et al, 2006 ⁶⁵	Gemcitabine + irinotecan	No ⁶⁵	Yes ^{47,66}	Yes ^{21,48,67}					
Hermann et al, 2007 ⁶⁸	Gemcitabine + capecitabine	Yes ⁶⁸	Yes ^{69–71}	Yes ³⁵	Yes ⁷²				
Van Custem et al, 2009 ⁷³	Gemcitabine + erlotinib + bevacizumab	No ⁷³	No ⁷⁴						
Cunningham et al, 2009 ⁷⁵	Gemcitabine + capecitabine	No ⁷⁵	Yes ^{69–71,76}	Yes ³⁵	Yes ⁷²				
Poplin et al, 2009 ⁷⁷	Gemcitabine + oxaliplatin	No ⁷⁷	Yes ⁷⁸	Yes ⁷⁹					
Philip et al, 2010 ⁸⁰	Gemcitabine + cetuximab	Yes ⁸⁰	Yes ⁸¹		Yes ⁸²	Yes ¹³			
Kindler et al, 2010 ⁸³	Gemcitabine + bevacizumab	Yes ⁸³	Yes ⁸⁴		Yes ⁸⁵	Yes ^{85–89}			
Kindler et al, 2011 ⁹⁰	Gemcitabine + axitinib	No ⁹⁰	No ⁹¹						
Gonçalves et al, 2012 ⁹²	Gemcitabine + sorafenib	Yes ⁹²	Yes ⁹³	Yes ⁹⁴	Yes ⁹⁵				
Rougier et al, 2013 ⁹⁶	Gemcitabine + aflibercept	Yes ⁹⁶	No	Yes ⁹⁷	Yes ⁹⁷	Yes ⁹⁷			
Middleton et al, 2014 ⁹⁸	Gemcitabine + capecitabine + GV1001	Yes ⁹⁸		Yes ⁹⁹	Yes ⁹⁹				
Ueno et al, 2013 ¹⁰⁰	Gemcitabine + S-1	No ¹⁰⁰	Yes ^{101,102}	Yes ¹⁰³					
Deplanque et al, 2015 ¹⁰⁴	Gemcitabine + masatinib	Yes ¹⁰⁴	Yes ¹⁰⁵	Yes ¹⁰⁶	Yes ¹⁰⁶				
Fuchs et al, 2015 ¹⁰⁷	Gemcitabine + ganitumumab	Yes ¹⁰⁷	Yes ¹⁰⁸	Yes ¹⁰⁹	Yes ¹⁰⁹				
NA indicates not applicable									

TABLE 2. Detailed Evidence for Preclinical Activity in Various Animal Models

Study	Drug	Target	Target Valid Pancreatic Cancer	Tested in Pancreatic Models or Others	Other Models Tested	Evidence of Activity Drug Hits the Target	Evidence of Activity Pancreatic Cancer	Synergy Tested and Proven	Sequence or Dosing Schedule Tested	Is the Science for Combination Setup in Pancreatic Cancer	
Conroy et al, 2011 ²	FOLFIRINOX		NA	No	Colon, HNSCC, Intestine	No	No	Yes	No	No	No
Moore et al, 2007 ¹²	Gemcitabine + erlotinib	EGFR	Yes	Yes		Yes	Yes	Yes	No	Yes	Yes
Von Hoff et al, 2013 ³	Gemcitabine + nab-paclitaxel	SPARC	Yes	Yes		Yes	Yes	Yes	No	Yes	Yes
Colucci et al, 2001 ¹⁸ GOIM	Gemcitabine + cisplatin		NA	No	HNSCC, Ovarian, Colon, NSCLC	NA	No	Yes	Yes	No	No
Moore et al, 2003 ²³	BAY 12-9566	MMP-2,3,9,13	Yes	No	Colon, Mammary, Melanoma, Lung	No	No	NA	Yes	Yes	NA
Colucci et al, 2010 ²⁵ GIP-1	Gemcitabine + cisplatin		NA	No	Ovarian, NSCLC	NA	No	Yes	Yes	No	No
Berlin et al, 2002 ²⁹	Gemcitabine + 5-fluorouracil		NA	No	Colon	NA	No	Yes	Yes	No	No
Brahmal et al, 2001 ³⁶	Gemcitabine + marimastat	MMP (BB94)	Yes	Yes	Ovarian, Melanoma, Gastric, Lung	No	Yes	No	No	No	No
Van Custem et al, 2004 ⁴⁴	Gemcitabine + tipifamib	Farnesyl transferase	Yes	Yes	Colon, Melanoma	Yes	Yes	No	No	No	No
Rocha Lima et al, 2004 ⁴⁶	Gemcitabine + irinotecan		NA	No	Breast, SCLC, NSCLC	No	No	Yes	No	No	No
Oettle et al, 2005 ⁴⁹	Gemcitabine + pemetrexed		NA	No	Colorectal	No	No	Yes	Yes	No	No
Louvet et al, 2005 ⁵²	Gemcitabine + oxaliplatin		NA	No	Leukemia, Colon	No	No	Yes	Yes	No	No
Reni et al, 2005 ⁵⁵	Gemcitabine + epirubicin cisplatin 5-fluorouracil		NA	No	No	No	No	No	No	No	No
Hienemann et al, 2006 ⁵⁷	Gemcitabine + cisplatin		NA	No	HNSCC, Ovarian, Colon, NSCLC	No	No	Yes	Yes	No	No
Abou-Alfa et al, 2006 ⁶¹	Gemcitabine + exatecan		NA	Yes		No	Yes	Yes	Yes	Yes	Yes
Stathopoulos et al, 2006 ⁶⁵	Gemcitabine + irinotecan		NA	No	Colorectal	No	No	Yes	No	No	No
Hermann et al, 2007 ⁶⁸	Gemcitabine + capecitabine		NA	No	Colon	NA	No	No	No	No	No
Van Custem et al, 2009 ⁷³	Gemcitabine + erlotinib + bevacizumab	EGFR, VEGF	No	No	No	No	No	No	No	No	No
Cunnigham et al, 2009 ⁷⁵	Gemcitabine + capecitabine		NA	No	Colon	NA	No	No	No	No	No

(Continued on next page)

TABLE 2. (Continued)

Study	Drug	Target	Target Valid Pancreatic Cancer or Not	Tested in		Evidence Drug Hits the Target	Evidence of		Synergy Tested and Proven	Sequence or Dosing Schedule		Is the Science for the Combo Setup
				Pancreatic Models or Others	Other Models Tested		Activity in Pancreatic Cancer	Tested		Tested	Setup	
Poplin et al, 2009 ⁷⁷	Gemcitabine + oxaliplatin		NA	No	Leukemia, Colon	No	No	Yes	Yes	Yes	No	No
Philip et al, 2010 ⁸⁰	Gemcitabine + cetuximab	EGFR	Yes	Yes		Yes	Yes	Yes	Yes	No	Yes	Yes
Kindler et al, 2010 ⁸³	Gemcitabine + bevacizumab	VEGF	Yes	Yes		Yes	Yes	Yes	Yes	No	Yes	Yes
Kindler et al, 2011 ⁹⁰	Gemcitabine + axitinib	VEGF	No	No		No	No	No	No	No	No	No
Gonçalves et al, 2012 ⁹²	Gemcitabine + sorafenib	VEGFR, PDGF, RAF	Yes	Yes		Yes	Yes	No	No	No	No	No
Rougier et al, 2013 ⁹⁶	Gemcitabine + aflibercept	VEGF, Trap	Yes	Yes		Yes	Yes	No	No	No	No	No
Middleton et al, 2014 ⁹⁸	Gemcitabine + capecitabine + GV1001	Telomerase	Yes	No	Mesothelioma	No	No	No	No	No	No	No
Ueno et al, 2013 ¹⁰⁰	Gemcitabine + S-1		No	Yes	Colon	No	Yes	Yes	Yes	No	Yes	Yes
Deplanque et al, 2015 ¹⁰⁴	Gemcitabine + masatinib	TKI c-Kit, Lyn, Fyn, FGFR3, PDGFR, FAK	Yes	Yes		Yes	Yes	Yes	Yes	No	No	No
Fuchs et al, 2015 ¹⁰⁷	Gemcitabine + ganitumab	IGFR	Yes	Yes		Yes	Yes	Yes	Yes	No	No	No

EGFR indicates epidermal growth factor receptor; FGFR, fibroblast growth factor; HNSCC, head and neck squamous cell cancer; NSCLC, non small cell lung cancer; PDGFR, placenta derived growth factor; VEGF, vascular endothelial growth factor; NA, not applicable.

reported in the phase III publication, the article for the corresponding and referenced phase II study was reviewed systematically as well to note if any preclinical rationale was reported.

RESULTS

Among the 30 published randomized phase III clinical trials in the first-line in metastatic pancreatic cancer, only 3 studies had true clinical impact. The combination of gemcitabine and erlotinib had a positive trial but did not change practice in a substantive manner due to infrequent adoption by clinicians. The success rate of phase III studies in advanced pancreatic cancer was only 13% in terms of meeting primary endpoint but 10% for practice changing trials. The detailed information on preclinical evidence and models used in each RCT is listed in Tables 1 and 2.

In the studies that reported preclinical rationale, in vitro cell lines or cell line-derived subcutaneous xenograft models were the most commonly used preclinical models ($n = 27$, 90%). Orthotopic xenograft models were referenced for preclinical experiments in only 5 RCTs (17%). The PDX models and GEMMs were cited in 2 RCTs (7%) and 1 RCT (3%), respectively (Fig. 1).

In 60% of the RCT studies ($n = 18$), no preclinical experiments were referenced in biologically cognate pancreatic models. The sequence/schedule of the combination therapy was not tested in 22 (73%) studies. Synergy for the combination was reported for 18 (60%) of the phase III studies. Overall, references for the science for the combination drug regimen was referenced in pancreatic cancer models in only 6 (20%) of the studies.

Nine (30%) of the RCTs were designed based on preclinical evidence from in vitro cell lines alone without additional in vivo validation in xenograft models. Common examples of drugs tested in vitro alone were the combination of *gemcitabine with 5-fluorouracil, irinotecan, oxaliplatin, S-1, exatecan, and pemetrexed*. The cell line-derived subcutaneous xenograft models were reportedly used in 15 (50%) of the 30 phase III studies.

When compared with the negative RCTs, we noted the recent positive RCTs, such as gemcitabine and nab-paclitaxel had extensive preclinical testing done in multiple preclinical models including PDX and GEMMs.

DISCUSSION

The failure rate of phase III clinical trials in advanced pancreatic cancer is high (87%). This analysis was undertaken to see if there might be information gleaned from the use of preclinical models in developing regimens that make it to phase III. There are several difficulties inherent in evaluating the impact of preclinical study on subsequent phase III success rate. First, there are only 4 positive phase III trials in first-line metastatic pancreatic cancer during the 18 years covered in this analysis, of which only 3 (10%) could be considered practice changing.

Second, preclinical data that set the rationale for the drug used or drug combinations may not all be referenced in the articles for many reasons. Article page limit may reduce the amount of introduction in the article where most of the rationale is outlined; for example, the steps between preclinical data and phase III analysis can be myriad and often include phase I and II trials. Therefore, some of the preclinical data may simply not have been included in the articles for sake of brevity. Many of the regimens come from work done within the pharmaceutical industry, and some of the data may be unpublished, limiting the ability to reference the data. Other preclinical data may have only been in abstract form at national or international meetings, limiting the likelihood it will be used as a reference.

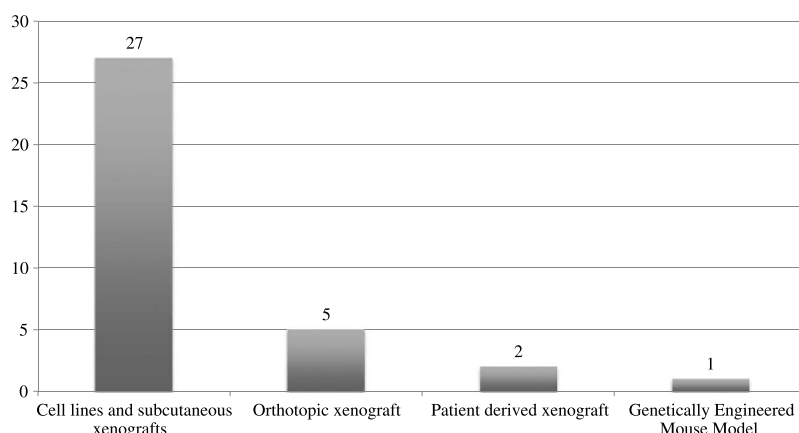


FIGURE 1. Preclinical models used for validation of phase III clinical trials in metastatic pancreatic cancer.

Nonetheless, the reality exists that many of the publications relevant to pancreatic cancer RCTs did not reference preclinical data in pancreatic models. We did not do an analysis of the novel agents to see where in the “life cycle” the pancreatic cancer trial occurred. In other words, when a company decides to bring an agent out of the preclinical realm into clinical development, there are primary targets that “lead off” the pipeline, and thereafter, secondary targets that are either planned later or come from outside leads. The vast majority of preclinical data are developed to establish or refute the rationale in the primary target diseases. The phase III trial may be then undertaken based on early phase clinical evidence, which would logically trump the need for preclinical evidence. In fact, in this analysis, very few, if any of the agents studied were primarily purposed for pancreatic cancer, including gemcitabine that was initially developed in lung cancer primarily, with hopes for effect in colorectal cancer as well.

The authors of this article are unaware of a systematic analysis of how much preclinical evidence is needed to bring an agent into a clinical trial. However, in pancreatic cancer, a State of the Science meeting attempted to define loose guidelines for preclinical evidence. Several conclusions about preclinical models were reached including: older models are flawed; newer models need to be interrogated and to fully test a hypothesis, more than 1 model should be used.¹¹⁰ It is noted that all of the trials that were positive had agents or combinations that were tested in multiple cell lines and/or models. Of the 3 combination trials, 2 of 3 were tested in pancreatic models and all 3 had synergy data presented in the references. This suggests at least that trials with more solid preclinical evidence have been successful even if some of the data are derived in models of other cancers.

The data presented here do show that there is no uniformity in developing the rationale for use of drugs or drug combinations in phase III trials. The clear, but broad recommendations from the 2007 State of the Science meeting were made with regard to developing clinical regimens in pancreatic cancer.¹¹⁰ Those guidelines are as yet untested, but these data suggest they may indicate a better way to move forward. An analysis of published phase II reports may be conducted to analyze if more robust preclinical data before phase II leads to greater likelihood of moving to phase III, but this would be flawed as an accompanying article demonstrates that robust phase II data has not been required to go to phase III trials in the past and, in fact, many studies went to phase III despite negative phase II data.

Finally, it remains uncertain how strongly the preclinical data influences the development of clinical regimens. Is compelling

science the rationale used to justify conducting a pivotal trial, or are many of these studies “trials of convenience”? Irrespective, with the exceptionally low success rate for clinical trials in pancreatic cancer (and, in fact, in most cancers), it is clear that we need to reevaluate how we have been developing our trials and designing our regimens. This article is not meant as any indictment of the past, but instead, it is meant to start that discussion.

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