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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 was translated into phase III clinical trials in metastatic pancreatic cancer as described in the paper. A systematic literature review conducted through the MEDLINE, EMBASE, and Cochrane Centre 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 RCT's, 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 influences the development of clinical regimens but so far the studies developed based on more solid preclinical evidence have been successful.

Keywords

Preclinical evidence; metastatic pancreatic cancer; randomized phase III trials

Introduction

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 decade¹. The majority of the patients with pancreatic cancer have advanced disease at diagnosis with limited treatment options.

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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.

While 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 one 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 is utilized in the development of agents and regimens but it remains unclear how informative this data is 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 to 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 was 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 paper. This data may inform us in methods for improvement for future drug development in advanced pancreatic cancer.

Methods

We conducted a systematic literature review through the MEDLINE, EMBASE, and Cochrane Centre 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 non-metastatic pancreatic cancer, second-line metastatic pancreatic cancer or non-randomized 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 FDA approval of a combination liposomal irinotecan (Onivyde) regimen in pancreatic cancer patients that progressed on gemcitabine or gemcitabine-based therapies. Further, in order 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 RCT's that met inclusion criteria. Data collected from the papers included: first author, publication year, chemotherapy regimens, and information on

preclinical studies. The preclinical data from published phase III trials was collected in a systematic manner. First, each published phase III study was carefully reviewed to verify that preclinical rationale was reported. If preclinical data was available, information was collected on the number and type of preclinical models tested (*in vitro*, cell-line derived xenograft, patient-derived xenograft, or genetically engineered mouse model) based on the reports referenced in the paper. 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, since preclinical evidence was not always reported in the phase III publication, the paper 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 RCT's (17%). Patient derived xenograft (PDX) models and genetically engineered mouse models (GEMM's) were cited in 2 RCT's (7%) and 1 RCT (3%), respectively (Figure 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 to the negative RCT's, we noted the recent positive RCT's, such as gemcitabine and nab-paclitaxel had extensive preclinical testing done in multiple preclinical models including PDX and GEMM's.

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 pre-clinical 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, pre-clinical data that set the rationale for the drug used or drug combinations may not all be referenced in the manuscripts for many reasons. Manuscript page limit may reduce the amount of introduction in the paper where most of the rationale is outlined; for example, the steps between pre-clinical data and phase III analysis can be myriad and often include phase I and II trials. Therefore, some of the pre-clinical data may simply not have been included in the papers 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 pre-clinical data may have only been in abstract form at national or international meetings, limiting the likelihood it will be used as a reference.

Nonetheless, the reality exists that many of the publications relevant to pancreatic cancer RCTs did not reference pre-clinical 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 pre-clinical 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 is 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 pre-clinical 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 paper are unaware of a systematic analysis of how much preclinical evidence is needed to bring an agent into a clinical trial. However, in pancreas 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 one model should be employed⁴. 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 is 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 cancer⁴. Those guidelines are as yet untested, but this data suggests 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 prior to phase II leads to greater likelihood of moving to phase III, but this would be flawed as an accompanying paper 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 re-evaluate how we have been developing our trials and designing our regimens. This paper is not meant as any indictment of the past, but instead it is meant to start that discussion.

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References

1. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014; 74:2913–2921. [PubMed: 24840647]
2. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011; 364:1817–1825. [PubMed: 21561347]
3. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013; 369:1691–1703. [PubMed: 24131140]
4. Philip PA, Mooney M, Jaffe D, et al. Consensus report of the national cancer institute clinical trials planning meeting on pancreas cancer treatment. *J Clin Oncol.* 2009; 27:5660–5669. [PubMed: 19858397]
5. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol.* 2011; 29:4548–4554. [PubMed: 21969517]
6. Frese KK, Neesse A, Cook N, et al. nab-Paclitaxel potentiates gemcitabine activity by reducing cytidine deaminase levels in a mouse model of pancreatic cancer. *Cancer Discov.* 2012; 2:260–269. [PubMed: 22585996]
7. Conroy T, Paillot B, Francois E, et al. Irinotecan plus oxaliplatin and leucovorin-modulated fluorouracil in advanced pancreatic cancer--a Groupe Tumeurs Digestives of the Federation

- Nationale des Centres de Lutte Contre le Cancer study. *J Clin Oncol.* 2005; 23:1228–1236. [PubMed: 15718320]
8. Mans DR, Grivicich I, Peters GJ, et al. Sequence-dependent growth inhibition and DNA damage formation by the irinotecan-5-fluorouracil combination in human colon carcinoma cell lines. *Eur J Cancer.* 1999; 35:1851–1861. [PubMed: 10674003]
 9. Mullany S, Svingen PA, Kaufmann SH, et al. Effect of adding the topoisomerase I poison 7-ethyl-10-hydroxycamptothecin (SN-38) to 5-fluorouracil and folinic acid in HCT-8 cells: elevated dTTP pools and enhanced cytotoxicity. *Cancer Chemother Pharmacol.* 1998; 42:391–399. [PubMed: 9771954]
 10. Pavillard V, Formento P, Rostagno P, et al. Combination of irinotecan (CPT11) and 5-fluorouracil with an analysis of cellular determinants of drug activity. *Biochem Pharmacol.* 1998; 56:1315–1322. [PubMed: 9825730]
 11. Zeghari-Squalli N, Raymond E, Cvitkovic E, et al. Cellular pharmacology of the combination of the DNA topoisomerase I inhibitor SN-38 and the diaminocyclohexane platinum derivative oxaliplatin. *Clin Cancer Res.* 1999; 5:1189–1196. [PubMed: 10353756]
 12. Azrak RG, Cao S, Slocum HK, et al. Therapeutic synergy between irinotecan and 5-fluorouracil against human tumor xenografts. *Clin Cancer Res.* 2004; 10:1121–1129. [PubMed: 14871992]
 13. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2007; 25:1960–1966. [PubMed: 17452677]
 14. Bruns CJ, Solorzano CC, Harbison MT, et al. Blockade of the epidermal growth factor receptor signaling by a novel tyrosine kinase inhibitor leads to apoptosis of endothelial cells and therapy of human pancreatic carcinoma. *Cancer Res.* 2000; 60:2926–2935. [PubMed: 10850439]
 15. Ng SS, Tsao MS, Nicklee T, et al. Effects of the epidermal growth factor receptor inhibitor OSI-774, Tarceva, on downstream signaling pathways and apoptosis in human pancreatic adenocarcinoma. *Mol Cancer Ther.* 2002; 1:777–783. [PubMed: 12492110]
 16. Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol.* 1997; 15:2403–2413. [PubMed: 9196156]
 17. Casper ES, Green MR, Kelsen DP, et al. Phase II trial of gemcitabine (2,2'-difluorodeoxycytidine) in patients with adenocarcinoma of the pancreas. *Invest New Drugs.* 1994; 12:29–34. [PubMed: 7960602]
 18. Hertel LW, Boder GB, Kroin JS, et al. Evaluation of the antitumor activity of gemcitabine (2',2'-difluoro-2'-deoxycytidine). *Cancer Res.* 1990; 50:4417–4422. [PubMed: 2364394]
 19. Colucci G, Giuliani F, Gebbia V, et al. Gemcitabine alone or with cisplatin for the treatment of patients with locally advanced and/or metastatic pancreatic carcinoma: a prospective, randomized phase III study of the Gruppo Oncologia dell'Italia Meridionale. *Cancer.* 2002; 94:902–910. [PubMed: 11920457]
 20. Heinemann V, Wilke H, Mergenthaler HG, et al. Gemcitabine and cisplatin in the treatment of advanced or metastatic pancreatic cancer. *Ann Oncol.* 2000; 11:1399–1403. [PubMed: 11142479]
 21. Philip PA, Zalupski MM, Vaitkevicius VK, et al. Phase II study of gemcitabine and cisplatin in the treatment of patients with advanced pancreatic carcinoma. *Cancer.* 2001; 92:569–577. [PubMed: 11505401]
 22. Kanzawa F, Saijo N. In vitro interaction between gemcitabine and other anticancer drugs using a novel three-dimensional model. *Semin Oncol.* 1997; 24:S7-8–S7-16.
 23. Bergman AM, Ruiz van Haperen VW, Veerman G, et al. Synergistic interaction between cisplatin and gemcitabine in vitro. *Clin Cancer Res.* 1996; 2:521–530. [PubMed: 9816199]
 24. Moore MJ, Hamm J, Dancey J, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol.* 2003; 21:3296–3302. [PubMed: 12947065]
 25. Gatto C, Rieppi M, Borsotti P, et al. BAY 12-9566, a novel inhibitor of matrix metalloproteinases with antiangiogenic activity. *Clin Cancer Res.* 1999; 5:3603–3607. [PubMed: 10589777]

26. Colucci G, Labianca R, Di Costanzo F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with single-agent gemcitabine as first-line treatment of patients with advanced pancreatic cancer: the GIP-1 study. *J Clin Oncol*. 2010; 28:1645–1651. [PubMed: 20194854]
27. van Moorsel CJ, Pinedo HM, Veerman G, et al. Mechanisms of synergism between cisplatin and gemcitabine in ovarian and non-small-cell lung cancer cell lines. *Br J Cancer*. 1999; 80:981–990. [PubMed: 10362105]
28. Yang LY, Li L, Jiang H, et al. Expression of ERCC1 antisense RNA abrogates gemcitabine-mediated cytotoxic synergism with cisplatin in human colon tumor cells defective in mismatch repair but proficient in nucleotide excision repair. *Clin Cancer Res*. 2000; 6:773–781. [PubMed: 10741696]
29. Peters GJ, van der Wilt CL, van Moorsel CJ, et al. Basis for effective combination cancer chemotherapy with antimetabolites. *Pharmacol Ther*. 2000; 87:227–253. [PubMed: 11008002]
30. Berlin JD, Catalano P, Thomas JP, et al. Phase III study of gemcitabine in combination with fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern Cooperative Oncology Group Trial E2297. *J Clin Oncol*. 2002; 20:3270–3275. [PubMed: 12149301]
31. Berlin JD, Adak S, Vaughn DJ, et al. A phase II study of gemcitabine and 5-fluorouracil in metastatic pancreatic cancer: an Eastern Cooperative Oncology Group Study (E3296). *Oncology*. 2000; 58:215–218. [PubMed: 10765123]
32. Cascinu S, Silva RR, Barni S, et al. A combination of gemcitabine and 5-fluorouracil in advanced pancreatic cancer, a report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). *Br J Cancer*. 1999; 80:1595–1598. [PubMed: 10408405]
33. Marantz A, Jovtis S, Almira E, et al. Phase II study of gemcitabine, 5-fluorouracil, and leucovorin in patients with pancreatic cancer. *Semin Oncol*. 2001; 28:44–49. [PubMed: 11510033]
34. Pastorelli D, Sperti C, et al. Phase II trial with gemcitabine (GEM) + 5-fluorouracil (5-FU) in advanced pancreatic cancer (APC). *Proc Am Soc Clin Oncol*. 2000; 19:284a. PS. 2000 (abstr).
35. Schulz L, Wilmanns W, et al. Synergistic interaction of gemcitabine and 5-fluorouracil in colon cancer cells. *Proc Am Soc Clin Oncol*. 1998; 17:251a. SA. (abstr). 1998.
36. Ren Q, Kao V, Grem JL. Cytotoxicity and DNA fragmentation associated with sequential gemcitabine and 5-fluoro-2'-deoxyuridine in HT-29 colon cancer cells. *Clin Cancer Res*. 1998; 4:2811–2818. [PubMed: 9829747]
37. Bramhall SR, Schulz J, Nemunaitis J, et al. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. *Br J Cancer*. 2002; 87:161–167. [PubMed: 12107836]
38. Evans JD, Stark A, Johnson CD, et al. A phase II trial of marimastat in advanced pancreatic cancer. *Br J Cancer*. 2001; 85:1865–1870. [PubMed: 11747327]
39. Zervos EE, Norman JG, Gower WR, et al. Matrix metalloproteinase inhibition attenuates human pancreatic cancer growth in vitro and decreases mortality and tumorigenesis in vivo. *J Surg Res*. 1997; 69:367–371. [PubMed: 9224409]
40. Chirivi RG, Garofalo A, Crimmin MJ, et al. Inhibition of the metastatic spread and growth of B16-BL6 murine melanoma by a synthetic matrix metalloproteinase inhibitor. *Int J Cancer*. 1994; 58:460–464. [PubMed: 8050828]
41. Davies B, Brown PD, East N, et al. A synthetic matrix metalloproteinase inhibitor decreases tumor burden and prolongs survival of mice bearing human ovarian carcinoma xenografts. *Cancer Res*. 1993; 53:2087–2091. [PubMed: 8347186]
42. Watson SA, Morris TM, Robinson G, et al. Inhibition of organ invasion by the matrix metalloproteinase inhibitor batimastat (BB-94) in two human colon carcinoma metastasis models. *Cancer Res*. 1995; 55:3629–3633. [PubMed: 7627972]
43. Watson SA, Morris TM, Collins HM, et al. Inhibition of tumour growth by marimastat in a human xenograft model of gastric cancer: relationship with levels of circulating CEA. *Br J Cancer*. 1999; 81:19–23. [PubMed: 10487607]
44. Zervos EE, Shafii AE, Rosemurgy AS. Matrix metalloproteinase (MMP) inhibition selectively decreases type II MMP activity in a murine model of pancreatic cancer. *J Surg Res*. 1999; 81:65–68. [PubMed: 9889060]

45. Van Cutsem E, van de Velde H, Karasek P, et al. Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. *J Clin Oncol.* 2004; 22:1430–1438. [PubMed: 15084616]
46. End DW, Smets G, Todd AV, et al. Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. *Cancer Res.* 2001; 61:131–137. [PubMed: 11196150]
47. Rocha Lima CM, Green MR, Rotche R, et al. Irinotecan plus gemcitabine results in no survival advantage compared with gemcitabine monotherapy in patients with locally advanced or metastatic pancreatic cancer despite increased tumor response rate. *J Clin Oncol.* 2004; 22:3776–3783. [PubMed: 15365074]
48. Rocha Lima CM, Savarese D, Bruckner H, et al. Irinotecan plus gemcitabine induces both radiographic and CA 19-9 tumor marker responses in patients with previously untreated advanced pancreatic cancer. *J Clin Oncol.* 2002; 20:1182–1191. [PubMed: 11870159]
49. Bahadori HR, Rocha Lima CM, Green MR, et al. Synergistic effect of gemcitabine and irinotecan (CPT-11) on breast and small cell lung cancer cell lines. *Anticancer Res.* 1999; 19:5423–5428. [PubMed: 10697572]
50. Oettle H, Richards D, Ramanathan RK, et al. A phase III trial of pemetrexed plus gemcitabine versus gemcitabine in patients with unresectable or metastatic pancreatic cancer. *Ann Oncol.* 2005; 16:1639–1645. [PubMed: 16087696]
51. Kindler HL. The pemetrexed/gemcitabine combination in pancreatic cancer. *Cancer.* 2002; 95:928–932. [PubMed: 12209673]
52. Schultz R, Koury M, et al. Sequence dependence using combinations of ALIMTA (pemetrexed disodium, LY231514, MTA), gemcitabine and oxaliplatin in human colorectal carcinoma cell lines. *Clin Cancer Res.* 2000; 6:1078. RM. (Abstr 503). 2000.
53. Louvet C, Labianca R, Hammel P, et al. Gemcitabine in combination with oxaliplatin compared with gemcitabine alone in locally advanced or metastatic pancreatic cancer: results of a GERCOR and GISCAD phase III trial. *J Clin Oncol.* 2005; 23:3509–3516. [PubMed: 15908661]
54. Louvet C, Andre T, Lledo G, et al. Gemcitabine combined with oxaliplatin in advanced pancreatic adenocarcinoma: final results of a GERCOR multicenter phase II study. *J Clin Oncol.* 2002; 20:1512–1518. [PubMed: 11896099]
55. Faivre S, Raymond E, Woynarowski JM, et al. Supraadditive effect of 2',2'-difluorodeoxycytidine (gemcitabine) in combination with oxaliplatin in human cancer cell lines. *Cancer Chemother Pharmacol.* 1999; 44:117–123. [PubMed: 10412945]
56. Reni M, Cordio S, Milandri C, et al. Gemcitabine versus cisplatin, epirubicin, fluorouracil, and gemcitabine in advanced pancreatic cancer: a randomised controlled multicentre phase III trial. *Lancet Oncol.* 2005; 6:369–376. [PubMed: 15925814]
57. Reni M, Passoni P, Panucci MG, et al. Definitive results of a phase II trial of cisplatin, epirubicin, continuous-infusion fluorouracil, and gemcitabine in stage IV pancreatic adenocarcinoma. *J Clin Oncol.* 2001; 19:2679–2686. [PubMed: 11352960]
58. Heinemann V, Quietzsch D, Gieseler F, et al. Randomized phase III trial of gemcitabine plus cisplatin compared with gemcitabine alone in advanced pancreatic cancer. *J Clin Oncol.* 2006; 24:3946–3952. [PubMed: 16921047]
59. Cascinu S, Labianca R, Catalano V, et al. Weekly gemcitabine and cisplatin chemotherapy: a well-tolerated but ineffective chemotherapeutic regimen in advanced pancreatic cancer patients. A report from the Italian Group for the Study of Digestive Tract Cancer (GISCAD). *Ann Oncol.* 2003; 14:205–208. [PubMed: 12562645]
60. Peters GJ, Bergman AM, Ruiz van Haperen VW, et al. Interaction between cisplatin and gemcitabine in vitro and in vivo. *Semin Oncol.* 1995; 22:72–79.
61. van Moorsel CJ, Veerman G, Bergman AM, et al. Combination chemotherapy studies with gemcitabine. *Semin Oncol.* 1997; 24:S7-17–S17-23.
62. Abou-Alfa GK, Letourneau R, Harker G, et al. Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. *J Clin Oncol.* 2006; 24:4441–4447. [PubMed: 16983112]

63. D'Adamo DHL, Donehower R, et al. Final results of a phase II study of exatecan (exatecan mesylate, DX) in advanced pancreatic cancer. *Proc Am Soc Clin Oncol*. 2001; 21:134a. (abstr 532). 2001.
64. In vitro evaluation of DX-8951f ± standard chemotherapy agents against tumor cell lines: Study report 8951J-PHA 020. Tokyo, Japan, Daiichi Pharmaceutical Co Ltd. Feb 5.1999 S: W. 1999.
65. In vitro antitumor effects of DX-8951f in combination with gemcitabine against human pancreatic cancer cell lines: Study report 8951J-PHA 024. Tokyo, Japan, Daiichi Pharmaceutical Co Ltd. Sep 30.1999 A: T. 1999.
66. Stathopoulos GP, Syrigos K, Aravantinos G, et al. A multicenter phase III trial comparing irinotecan-gemcitabine (IG) with gemcitabine (G) monotherapy as first-line treatment in patients with locally advanced or metastatic pancreatic cancer. *Br J Cancer*. 2006; 95:587–592. [PubMed: 16909140]
67. Stathopoulos GP, Rigatos SK, Dimopoulos MA, et al. Treatment of pancreatic cancer with a combination of irinotecan (CPT-11) and gemcitabine: a multicenter phase II study by the Greek Cooperative Group for Pancreatic Cancer. *Ann Oncol*. 2003; 14:388–394. [PubMed: 12598343]
68. Schwartz CMZG, Szrajner L, et al. Evaluation of gemcitabine and irinotecan (CPT-11) as single agents and combination in solid tumors using an ex-vivo ATP assay. *Proc Am Soc Clin Oncol*. 2001; 20:98. (Abstr 2143). 2001.
69. Kanzawa F. In vitro interaction between gemcitabine and other anticancer drugs using a novel three-dimensional model. *Semin Oncol*. 1997; 24(suppl 7):7–16. SN. 1997.
70. Herrmann R, Bodoky G, Ruhstaller T, et al. Gemcitabine plus capecitabine compared with gemcitabine alone in advanced pancreatic cancer: a randomized, multicenter, phase III trial of the Swiss Group for Clinical Cancer Research and the Central European Cooperative Oncology Group. *J Clin Oncol*. 2007; 25:2212–2217. [PubMed: 17538165]
71. Hess V, Salzberg M, Borner M, et al. Combining capecitabine and gemcitabine in patients with advanced pancreatic carcinoma: a phase I/II trial. *J Clin Oncol*. 2003; 21:66–68. [PubMed: 12506172]
72. Scheithauer W, Schull B, Ulrich-Pur H, et al. Biweekly high-dose gemcitabine alone or in combination with capecitabine in patients with metastatic pancreatic adenocarcinoma: a randomized phase II trial. *Ann Oncol*. 2003; 14:97–104. [PubMed: 12488300]
73. Stathopoulos GP, Syrigos K, Polyzos A, et al. Front-line treatment of inoperable or metastatic pancreatic cancer with gemcitabine and capecitabine: an intergroup, multicenter, phase II study. *Ann Oncol*. 2004; 15:224–229. [PubMed: 14760113]
74. Sawada NF-OK, Ishikawa T, et al. Antitumour activity of combination therapy with capecitabine plus vinorelbine, and capecitabine plus gemcitabine in human tumor xenograft models. *Proc Am Assoc Cancer Res* 2002 (abstr 5388). 2002
75. Van Cutsem E, Vervenne WL, Bennouna J, et al. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2009; 27:2231–2237. [PubMed: 19307500]
76. Kindler HLBK, Hochster HS, et al. A randomized phase II study of bevacizumab (B) and gemcitabine (G) plus cetuximab (C) or erlotinib (E) in patients (pts) with advanced pancreatic cancer (PC): A preliminary analysis. *J Clin Oncol*. 2006; 24(suppl):18s. abstr 4060.
77. Cunningham D, Chau I, Stocken DD, et al. Phase III randomized comparison of gemcitabine versus gemcitabine plus capecitabine in patients with advanced pancreatic cancer. *J Clin Oncol*. 2009; 27:5513–5518. [PubMed: 19858379]
78. Boeck S, Hoehler T, Seipelt G, et al. Capecitabine plus oxaliplatin (CapOx) versus capecitabine plus gemcitabine (CapGem) versus gemcitabine plus oxaliplatin (mGemOx): final results of a multicenter randomized phase II trial in advanced pancreatic cancer. *Ann Oncol*. 2008; 19:340–347. [PubMed: 17962204]
79. Poplin E, Feng Y, Berlin J, et al. Phase III, randomized study of gemcitabine and oxaliplatin versus gemcitabine (fixed-dose rate infusion) compared with gemcitabine (30-minute infusion) in patients with pancreatic carcinoma E6201: a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol*. 2009; 27:3778–3785. [PubMed: 19581537]

80. Tempero M, Plunkett W, Ruiz Van Haperen V, et al. Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. *J Clin Oncol.* 2003; 21:3402–3408. [PubMed: 12885837]
81. Csoka K, Larsson R, et al. Evaluation of the cytotoxic activity of gemcitabine in primary cultures of tumor cells from patients with hematologic or solid tumors. *Semin Oncol.* 1995; 22(4 suppl 11): 47–53. *LJ.* 1995.
82. Philip PA, Benedetti J, Corless CL, et al. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol.* 2010; 28:3605–3610. [PubMed: 20606093]
83. Xiong HQ, Rosenberg A, LoBuglio A, et al. Cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor, in combination with gemcitabine for advanced pancreatic cancer: a multicenter phase II Trial. *J Clin Oncol.* 2004; 22:2610–2616. [PubMed: 15226328]
84. Overholser JP, Prewett MC, Hooper AT, et al. Epidermal growth factor receptor blockade by antibody IMC-C225 inhibits growth of a human pancreatic carcinoma xenograft in nude mice. *Cancer.* 2000; 89:74–82. [PubMed: 10897003]
85. Kindler HL, Niedzwiecki D, Hollis D, et al. Gemcitabine plus bevacizumab compared with gemcitabine plus placebo in patients with advanced pancreatic cancer: phase III trial of the Cancer and Leukemia Group B (CALGB 80303). *J Clin Oncol.* 2010; 28:3617–3622. [PubMed: 20606091]
86. Kindler HL, Friberg G, Singh DA, et al. Phase II trial of bevacizumab plus gemcitabine in patients with advanced pancreatic cancer. *J Clin Oncol.* 2005; 23:8033–8040. [PubMed: 16258101]
87. Tsuzuki Y, Mouta Carreira C, Bockhorn M, et al. Pancreas microenvironment promotes VEGF expression and tumor growth: novel window models for pancreatic tumor angiogenesis and microcirculation. *Lab Invest.* 2001; 81:1439–1451. [PubMed: 11598156]
88. Solorzano CC, Baker CH, Bruns CJ, et al. Inhibition of growth and metastasis of human pancreatic cancer growing in nude mice by PTK 787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinases. *Cancer Biother Radiopharm.* 2001; 16:359–370. [PubMed: 11776753]
89. Bruns CJ, Shrader M, Harbison MT, et al. Effect of the vascular endothelial growth factor receptor-2 antibody DC101 plus gemcitabine on growth, metastasis and angiogenesis of human pancreatic cancer growing orthotopically in nude mice. *Int J Cancer.* 2002; 102:101–108. [PubMed: 12385004]
90. Luo J, Guo P, Matsuda K, et al. Pancreatic cancer cell-derived vascular endothelial growth factor is biologically active in vitro and enhances tumorigenicity in vivo. *Int J Cancer.* 2001; 92:361–369. [PubMed: 11291072]
91. Bockhorn M, Tsuzuki Y, Xu L, et al. Differential vascular and transcriptional responses to anti-vascular endothelial growth factor antibody in orthotopic human pancreatic cancer xenografts. *Clin Cancer Res.* 2003; 9:4221–4226. [PubMed: 14519649]
92. Kindler HL, Ioka T, Richel DJ, et al. Axitinib plus gemcitabine versus placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol.* 2011; 12:256–262. [PubMed: 21306953]
93. Spano JP, Chodkiewicz C, Maurel J, et al. Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: an open-label randomised phase II study. *Lancet.* 2008; 371:2101–2108. [PubMed: 18514303]
94. Goncalves A, Gilbert M, Francois E, et al. BAYPAN study: a double-blind phase III randomized trial comparing gemcitabine plus sorafenib and gemcitabine plus placebo in patients with advanced pancreatic cancer. *Ann Oncol.* 2012; 23:2799–2805. [PubMed: 22771827]
95. El-Khoueiry AB, Ramanathan RK, Yang DY, et al. A randomized phase II of gemcitabine and sorafenib versus sorafenib alone in patients with metastatic pancreatic cancer. *Invest New Drugs.* 2012; 30:1175–1183. [PubMed: 21424698]
96. Ulivi P, Arienti C, Amadori D, et al. Role of RAF/MEK/ERK pathway, p-STAT-3 and Mcl-1 in sorafenib activity in human pancreatic cancer cell lines. *J Cell Physiol.* 2009; 220:214–221. [PubMed: 19288493]

97. Vincent PZX, Chen C, et al. Chemotherapy with the raf kinase inhibitor BAY 43–9006 in combination with irinotecan, vinorelbine, or gemcitabine is well tolerated and efficacious in preclinical xenograft models. *Proc Am Soc Clin Oncol*. 2002; 21:2002. 2002.
98. Rougier P, Riess H, Manges R, et al. Randomised, placebo-controlled, double-blind, parallel-group phase III study evaluating aflibercept in patients receiving first-line treatment with gemcitabine for metastatic pancreatic cancer. *Eur J Cancer*. 2013; 49:2633–2642. [PubMed: 23642329]
99. Fukasawa M, Korc M. Vascular endothelial growth factor-trap suppresses tumorigenicity of multiple pancreatic cancer cell lines. *Clin Cancer Res*. 2004; 10:3327–3332. [PubMed: 15161686]
100. Middleton G, Silcocks P, Cox T, et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2014; 15:829–840. [PubMed: 24954781]
101. Nowak AK, Robinson BW, Lake RA. Synergy between chemotherapy and immunotherapy in the treatment of established murine solid tumors. *Cancer Res*. 2003; 63:4490–4496. [PubMed: 12907622]
102. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol*. 2013; 31:1640–1648. [PubMed: 23547081]
103. Ueno H, Okusaka T, Furuse J, et al. Multicenter phase II study of gemcitabine and S-1 combination therapy (GS Therapy) in patients with metastatic pancreatic cancer. *Jpn J Clin Oncol*. 2011; 41:953–958. [PubMed: 21715364]
104. Nakamura K, Yamaguchi T, Ishihara T, et al. Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. *Br J Cancer*. 2006; 94:1575–1579. [PubMed: 16721372]
105. Bruckner H, Haenel P. Ex vivo ATP tumor testing of gemcitabine for combination chemotherapy and biochemical modulation. *Proc Am Assoc Cancer Res* 199889310(abstract 2116). 1998 ZG.
106. Deplanque G, Demarchi M, Hebbar M, et al. A randomized, placebo-controlled phase III trial of masitinib plus gemcitabine in the treatment of advanced pancreatic cancer. *Ann Oncol*. 2015
107. Mitry E, Hammel P, Deplanque G, et al. Safety and activity of masitinib in combination with gemcitabine in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol*. 2010; 66:395–403. [PubMed: 20364428]
108. Humbert M, Casteran N, Letard S, et al. Masitinib combined with standard gemcitabine chemotherapy: in vitro and in vivo studies in human pancreatic tumour cell lines and ectopic mouse model. *PLoS One*. 2010; 5:e9430. [PubMed: 20209107]
109. Fuchs CS, Azevedo S, Okusaka T, et al. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial dagger. *Ann Oncol*. 2015; 26:921–927. [PubMed: 25609246]
110. Kindler HL, Richards DA, Garbo LE, et al. A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. *Ann Oncol*. 2012; 23:2834–2842. [PubMed: 22700995]
111. Beltran PJ, Mitchell P, Chung YA, et al. AMG 479, a fully human anti-insulin-like growth factor receptor type I monoclonal antibody, inhibits the growth and survival of pancreatic carcinoma cells. *Mol Cancer Ther*. 2009; 8:1095–1105. [PubMed: 19366899]

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

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 ³	Gemcitabine+ Nab-Paclitaxel	Yes ³	Yes ⁵				Yes ⁶	Yes ⁵	
Conroy et.al ²	FOLFIRINOX	Yes ²	Yes ⁷	Yes ⁸⁻¹¹	Yes ^{11,12}				
Moore et.al ¹³	Gemcitabine+ Erlotinib	Yes ¹³	No	Yes ¹⁴		Yes ¹⁴			Yes ¹⁵
Burris et.al ¹⁶	Gemcitabine	Yes ¹⁶	Yes ¹⁷	Yes ¹⁸	Yes ¹⁸				
Negative Trials									
Colucci et.al ¹⁹ 2001 GOIM	Gemcitabine+ Cisplatin	Yes ¹⁹	Yes ^{20,21}	Yes ^{22,23}					
Moore et.al ²⁴ 2003	BAY 12-9566	Yes ²⁴	No		Yes ²⁵				
Colucci et.al ²⁶ 2010 GIP-1	Gemcitabine+ Cisplatin	Yes ²⁶	NA	Yes ^{22,23,27-29}					
Berlin et.al ³⁰ 2002	Gemcitabine+ 5-Flourouracil	Yes ³⁰	Yes ³¹⁻³⁴	Yes ^{35,36}					
Brahmall et.al ³⁷ 2001	Gemcitabine+ Marimastat	Yes ³⁷	Yes ³⁸	Yes ³⁹	Yes ⁴⁰⁻⁴³	Yes ^{39,44}			
Van Custem et.al ⁴⁵ 2004	Gemcitabine+ Tipifarnib	Yes ⁴⁵	No	Yes ⁴⁶	Yes ⁴⁶				
RochaLima et.al ⁴⁷ 2004	Gemcitabine+ Irinotecan	Yes ⁴⁷	Yes ⁴⁸	Yes ⁴⁹					
Oettle et.al ⁵⁰ 2005	Gemcitabine+ Pemetrexed	Yes ⁵⁰	Yes ⁵¹	Yes ⁵²					
Louvet et.al ⁵³ 2005	Gemcitabine+ Oxaliplatin	Yes ⁵³	Yes ⁵⁴	Yes ⁵⁵					
Reni et.al ⁵⁶ 2005	Gemcitabine+ Epirubicin Cisplatin 5-Flourouracil	No ⁵⁶	No ⁵⁷						
Hienemann et.al ⁵⁸ 2006	Gemcitabine+ Cisplatin	Yes ⁵⁸	Yes ^{20,21,59}	Yes ^{28,60,61}	Yes ^{60,61}				
Abou-Alfa et.al ⁶² 2006	Gemcitabine+ Exatecan	Yes ⁶²	Yes ⁶³	Yes ^{64,65}					
Stathopoulos et.al ⁶⁶ 2006	Gemcitabine+ Irinotecan	No ⁶⁶	Yes ^{48,67}	Yes ^{49,68,69}					
Hermann et.al ⁷⁰ 2007	Gemcitabine+ Capecitabine	Yes ⁷⁰	Yes ⁷¹⁻⁷³	Yes ³⁶	Yes ⁷⁴				
Vancustem et.al ⁷⁵ 2009	Gemcitabine+ Erlotinib+ Bevacizumab	No ⁷⁵	No ⁷⁶						
Cunnigham et.al ⁷⁷ 2009	Gemcitabine+ capecitabine	No ⁷⁷	Yes ^{71-73,78}	Yes ³⁶	Yes ⁷⁴				

Study	Drug	Phase III	Phase II	In vitro cell line	Cell line derived xenograft		GEMM model	Patient derived xenograft	
					Hetero	Ortho		Hetero	Ortho
Poplin et.al ⁷⁹ 2009	Gemcitabine+ Oxaliplatin	No ⁷⁹	Yes ⁸⁰	Yes ⁸¹					
Philip et.al ⁸² 2010	Gemcitabine+ Cetuximab	Yes ⁸²	Yes ⁸³		Yes ⁸⁴	Yes ¹⁴			
Kindler et.al ⁸⁵ 2010	Gemcitabine+ Bevacizumab	Yes ⁸⁵	Yes ⁸⁶		Yes ⁸⁷	Yes ⁸⁷⁻⁹¹			
Kindler et.al ⁹² 2011	Gemcitabine+ Axitinib	No ⁹²	No ⁹³						
Goncalves et.al ⁹⁴ 2012	Gemcitabine+ Sorafenib	Yes ⁹⁴	Yes ⁹⁵	Yes ⁹⁶	Yes ⁹⁷				
Rougier et.al ⁹⁸ 2013	Gemcitabine+ Aflibercept	Yes ⁹⁸	No	Yes ⁹⁹	Yes ⁹⁹	Yes ⁹⁹			
Middleton et.al ¹⁰⁰ 2014	Gemcitabine+ Capecitabine+ GV1001	Yes ¹⁰⁰		Yes ¹⁰¹	Yes ¹⁰¹				
Ueno et.al ¹⁰² 2013	Gemcitabine+ S-1	No ¹⁰²	Yes ^{103,104}	Yes ¹⁰⁵					
Deplanque et.al ¹⁰⁶ 2015	Gemcitabine+ Masatinib	Yes ¹⁰⁶	Yes ¹⁰⁷	Yes ¹⁰⁸	Yes ¹⁰⁸				
Fuchs et.al ¹⁰⁹ 2015	Gemcitabine+ Ganitumumab	Yes ¹⁰⁹	Yes ¹¹⁰	Yes ¹¹¹	Yes ¹¹¹				

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 drug hits the target	Evidence of activity pancreatic cancer	Synergy tested and proven	Sequence or dosing schedule tested	Is the science for combination set up in pancreatic Cancer
Conroy et.al ²	FOLFIRINOX		NA	No	Colon HNSCC Intestine	No	No	Yes	No	No
Moore et.al ¹³	Gemcitabine+ Erlotinib	EGFR	Yes	Yes		Yes	Yes	Yes	No	Yes
Von Hoff et.al ³	Gemcitabine+ Nab-Paclitaxel	SPARC	Yes	Yes		Yes	Yes	Yes	No	Yes
Colucci et.al ¹⁹ 2001 GOIM	Gemcitabine+ Cisplatin		NA	No	HNSCC Ovarian Colon NSCLC	NA	No	Yes	Yes	No
Moore et.al ²⁴ 2003	BAY 12-9566	MMP 2,3,9,13	Yes	No	S.C FGF in normal mice	No	No	NA	Yes	NA
Colucci et.al ²⁶ 2010 GIP-1	Gemcitabine+ Cisplatin		NA	No	Ovarian NSCLC	NA	No	Yes	Yes	No
Berlin et.al 30 2002	Gemcitabine+ 5-Flourouracil		NA	No	Colon	NA	No	Yes	Yes	No
Brahmall et.al ³⁷ 2001	Gemcitabine+ Marimastat	MMP (BB94)	Yes	Yes	Ovarian Melanoma Gastric Lung	No	Yes	No	No	No
Van Custem et.al ⁴⁵ 2004	Gemcitabine+ Tipifarnib	Farnesyl transferase	Yes	Yes	Colon Melanoma	Yes	Yes	No	No	No
RochaLima et.al ⁴⁷ 2004	Gemcitabine+ Irinotecan		NA	No	Breast SCLC NSCLC	No	No	Yes	No	No
Oettle et.al 50 2005	Gemcitabine+ Pemetrexed		NA	No	Colorectal	No	No	Yes	Yes	No

Study	Drug	Target	Target valid pancreatic cancer	Tested in Pancreatic models or others	Other models tested	Evidence drug hits the target	Evidence of activity pancreatic cancer	Synergy tested and proven	Sequence or dosing schedule tested	Is the science for combination set up in pancreatic Cancer
Louvet et.al ⁵³ 2005	Gencitabine+ Oxaliplatin		NA	No	Leukemia Colon	No	No	Yes	Yes	No
Reni et.al ⁵⁶ 2005	Gencitabine+ Epirubicin Cisplatin 5-Flourouracil		NA	No	No	No	No	No	No	No
Hienemann et.al ⁵⁸ 2006	Gencitabine+ Cisplatin		NA	No	HNSCC Ovarian Colon NSCLC	No	No	Yes	Yes	No
Abou-Alfa et.al ⁶² 2006	Gencitabine+ Exatecan		NA	Yes		No	Yes	Yes	Yes	Yes
Stathopoulos et.al ⁶⁶ 2006	Gencitabine+ Irinotecan		NA	No	Colorectal	No	No	Yes	No	No
Hermann et.al ⁷⁰ 2007	Gencitabine+ Capecitabine		NA	No	Colon	NA	No	No	No	No
Vancustem et.al ⁷⁵ 2009	Gencitabine+ Erlotinib+ Bevacizumab	EGFR VEGF	No	No	No	No	No	No	No	No
Cunningham et.al ⁷⁷ 2009	Gencitabine+ Capecitabine		NA	No	Colon	NA	No	No	No	No
Poplin et.al ⁷⁹ 2009	Gencitabine+ Oxaliplatin		NA	No	Leukemia Colon	No	No	Yes	Yes	No
Philip et.al ⁸² 2010	Gencitabine+ Cetuximab	EGFR	Yes	Yes		Yes	Yes	Yes	No	Yes
Kindler et.al ⁸⁵ 2010	Gencitabine+ Bevacizumab	VEGF	Yes	Yes		Yes	Yes	Yes	No	Yes
Kindler et.al ⁹² 2011	Gencitabine+ Axitinib	VEGF	No	No		No	No	No	No	No
Goncalves et.al ⁹⁴ 2012	Gencitabine+ Sorafenib	VEGF PDGF RAF	Yes	Yes		Yes	Yes	No	No	No

Study	Drug	Target	Target valid pancreatic cancer	Tested in Pancreatic models or others	Other models tested	Evidence drug hits the target	Evidence of activity pancreatic cancer	Synergy tested and proven	Sequence or dosing schedule tested	Is the science for combination set up in pancreatic Cancer
Rougier et.al ⁹⁸ 2013	Gencitabine+ Afibercept	VEGF Trap	Yes	Yes		Yes	Yes	No	No	No
Middleton et.al ¹⁰⁰ 2014	Gencitabine+ Capecitabine+ GV1001	Telomerase	Yes	No	Mesothelioma	No	No	No	No	No
Ueno et.al ¹⁰² 2013	Gencitabine+ S-1		No	Yes	Colon	No	Yes	Yes	No	Yes
Deplanque et.al ¹⁰⁶ 2015	Gencitabine+ Masatinib	TKI c-Kit, Lyn, Fyn, EGFR3, PDGFR, FAK	Yes	Yes		Yes	Yes	Yes	No	No
Fuchs et.al ¹⁰⁹ 2015	Gencitabine+ Ganitumumab	IGFR	Yes	Yes		Yes	Yes	Yes	No	No