Targeted therapies for pancreatic adenocarcinoma: Where do we stand, how far can we go?

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Pancreatic adenocarcinoma (usually referred to as pancreatic cancer) is a highly lethal and aggressive malignancy with a disease-related mortality almost equaling its incidence, and one of the most challenging cancers to treat. The notorious resistance of pancreatic cancer not only to conventional cytotoxic therapies but also to almost all targeted agents developed to date, continues to puzzle the oncological community and represents one of the biggest hurdles to reducing the death toll from this ominous disease. This editorial highlights the most important recent advances in preclinical a

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Core tip: Expansion of our knowledge regarding the molecular basis of pancreatic cancer has facilitated the development of a significant number of innovative targeted therapies for this lethal disease. Almost all these agents have, nevertheless, failed to produce statistically significant survival benefits when tested in clinical trial settings; therefore, successful clinical translation of preclinical advancements in pancreatic cancer research has yet to be materialized. Future treatment options might include multi-targeted and individualized molecular therapies, ideally guided by patient-specific genomic data, in combination with conventional cytotoxic or other regimens.

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INTRODUCTION

Despite recent advances in our understanding of the molecular mechanisms involved in the development and progression of pancreatic adenocarcinoma and an abundance of preclinical data suggesting the potential value of several targeted agents in treatment of this lethal disease, pancreatic cancer statistics remain grim and nearly the same as they were almost 30 years ago\(^1\text{-}^3\). Pancreatic adenocarcinoma - usually referred to as “pancreatic cancer” - currently ranks as the fourth most frequent cause of cancer-related death among males and the fifth among females in the Western world, and is sadly expected to rise to the second leading position within the next decade\(^4\text{-}^6\). Median survival is 4 to 6 mo following diagnosis while long term (5-year) survival rates do not exceed 4%-5%, for all stages combined\(^7\). The only treatment option with a curative potential is surgery, but less than 20% of patients are eligible for this approach, while the survival rates are poor (25%-30%) even among those with localized node-negative disease undergoing complete surgical resection and adjuvant chemotherapy\(^8\).

This dismal clinical record inevitably leads to the following questions: Why have we failed thus far to reduce the death toll from this lethal disease? And, most importantly, what can we do to widen the range of available treatment options and improve their clinical effectiveness?

PRECLINICAL AND CLINICAL DATA: DISCREPANCY PREVAILS

In the preclinical arena of pancreatic cancer research the picture is much rosier; a significant and rather rapidly expanding number of different targeted agents have shown considerable efficacy in controlling growth of human pancreatic cancer cells, both in vitro and in vivo, and prolonging survival of pancreatic cancer models, as summarized in recent reviews on this topic\(^9\text{-}^{11}\). This rather extensive armamentarium includes, among others, inhibitors of epidermal growth factor receptor (EGFR)\(^12\text{-}^{13}\), human epidermal growth factor receptor 2 (HER2)\(^14\text{-}^{15}\), vascular endothelial growth factor (VEGF) and VEGF receptors\(^16\), insulin-like growth factor receptor\(^17\text{-}^{19}\), KRAS and its downstream effectors (mainly mitogen-activated protein kinase)\(^20\text{-}^{21}\), the developmental Wnt, Hedgehog and Notch signaling pathways\(^22\text{-}^{24}\), as well as reagents targeting the tumor extracellular matrix/stromal microenvironment or molecules overexpressed in the surface of pancreatic cancer cells (i.e., mesothelin, carcinoembryonic antigen, epithelial cell adhesion molecule, MUC1)\(^25\text{-}^{29}\). Dual-agent and multi-kinase molecular targeting represent additional exciting therapeutic possibilities and are gaining increasing research attention and popularity\(^30\text{-}^{34}\). Alternative approaches, such as targeting the cellular process of autophagy - which plays a key role in the development and progression of malignancy or combined targeting of oncogene-driven signaling pathways and critical energy sources (such as mitochondrial respiration) of the subpopulation of dormant tumor cells surviving oncogene ablation, have also been studied as potential treatment options in pancreatic cancer, but are still in their infancy\(^35\text{-}^{36}\).

Interestingly, in accordance with increasing data suggesting potential preventive and therapeutic effects of aspirin and non-steroidal inflammatory drugs in gastrointestinal cancers, particularly colorectal cancer\(^37\text{-}^{38}\), aspirin is being explored as a targeted therapeutic agent for pancreatic cancer as well\(^39\text{-}^{40}\). As shown in recent preclinical studies, aspirin, either alone or in combination with the antidiabetic drug metformin, may inhibit pancreatic cancer cell growth, counteract desmoplasia and cancer stem cell features and enhance the therapeutic efficacy of cytotoxic agents-such as gemcitabine- in pancreatic cancer by sensitizing pancreatic cancer cells to chemotherapy-mediated cytotoxicity\(^41\text{-}^{43}\).

Modified cytotoxic agents, mainly including nab-paclitaxel (paclitaxel conjugated with albumin nanoparticles) or other nanovector-based anticancer drugs, such as cationic liposome encapsulated paclitaxel (EndoTAGTM-1) or liposomal doxorubicin, cisplatin and irinotecan, have been recently developed using sophisticated nanotechnology and tested in preclinical studies of pancreatic cancer, with some encouraging results\(^44\text{-}^{49}\). These selective drug formulations offer the advantage of improved drug delivery to the tumor tissue and selective targeting via binding to tumor-associated receptors or macromolecules, thus positively modulating the pharmacokinetics and therapeutic index of cytotoxic chemotherapy\(^44\). Nab-paclitaxel, in particular, can bind to SPARC (secreted protein acid and rich in cysteine), an extracellular matrix protein which is frequently overexpressed in pancreatic adenocarcinomas\(^10\text{-}^{50}\), and, presumably, result in depletion of desmoplastic tumor stroma and an increase in vascularization, thus enhancing transvascular transport and delivery of cytotoxic agents to tumor cells\(^52\).

The overwhelming majority of the abovementioned targeted therapies have, nevertheless, failed to demonstrate any statistically significant efficacy in clinical trials of pancreatic cancer patients; the EGFR and VEGF monoclonal antibodies cetuximab and bevacizumab, respectively, and the multikinase inhibitor sorafenib are representative examples of once-promising targeted agents who failed to produce a statistically significant improvement of survival when used in combination with gemcitabine or gemcitabine alone in phase III randomized trials\(^53\text{-}^{55}\). Hence, successful translation of our otherwise encouraging preclinical achievements into tangible clinical benefit remains an elusive goal. Two notable exceptions, though, leave some room for optimism. Erlotinib, an EGFR tyrosine kinase inhibitor which was United States Food and Drug Administration (FDA)-approved in 2007 for the treatment of advanced pancreatic cancer, is the first targeted agent which
succeeded in producing a significant—albeit modest-survival benefit when administered as an adjunct to gemcitabine, especially among patients experiencing erlotinib-induced skin rash[7,56] ; still, given the marginal effect of erlotinib on survival and its unclear therapeutic value in localized, resectable disease this drug has yet to be widely adopted as standard of care in routine clinical practice[8,10]. Based on the results of the recent phase III Metastatic Pancreatic Adenocarcinoma Clinical Trial[57] of nab-paclitaxel and gemcitabine combination vs gemcitabine alone in 861 patients with metastatic pancreatic cancer, showing a statistically significant survival benefit (as regards overall, progression-free and 1-year survival) in the combinatorial arm, nab-paclitaxel was also approved by the FDA in 2013 to be administered in combination with gemcitabine as first-line therapy for metastatic pancreatic cancer.

CONCLUSION

Considering all available evidence, as summarized above, we should first acknowledge that, although some revolutionary progress has indeed been achieved on the theoretical front, preclinical enthusiasm has been severely tempered by clinical disappointment. The reasons behind this discrepancy remain largely unknown and can only be speculated upon at this point. Resistance of pancreatic cancer to anticancer drugs, including both standard cytotoxic and novel targeted agents, is often attributed to the abundant, dense, fibroinflammatory stroma surrounding pancreatic tumor tissue, which is believed to function as a barrier to efficient delivery of drug formulations to their target tumor cells by restricting blood supply and limiting diffusion of large molecules[10,58,59]. The high genetic heterogeneity and complexity of pancreatic cancer may also explain why targeting a specific mutation in a tumor containing 63 genetic alterations on average - as shown by previous genomic studies[22,60] - or “randomly combining drugs in the hope of achieving a better outcome in an unselected patient population”[10], may be doomed to fail.

Hopefully, the results of ongoing clinical trials on current and emerging targeted therapeutics, including, among others, the anti-EGFR and anti-HER2/neu monoclonal antibodies nimotuzumab (NCT02395016) and trastuzumab (NCT01204372), respectively, the hedgehog inhibitors vismodegib (NCT01195415) and LDE225 (NCT01485744) and agents targeting the Notch pathway, such as the gamma-secretase inhibitor MK-0752 (NCT01098344), may help bridge the gap between preclinical and clinical outcomes. The increasing advances in structural and functional genomics are also expected to further elucidate the key molecular events underlying pancreatic tumorigenesis and identify additional targets for novel agents. Based on data derived from global genomic analyses of pancreatic tumors, previous authors have suggested that agents broadly targeting downstream mediators of critical physiologic functions (such as neo-angiogenesis or cell cycle alterations) may be preferable to agents targeting specific mutated genes[60]. Most importantly, personalized genomic medicine, utilizing patient-specific genomic data for guidance of treatment selection in each individual patient, may not only significantly enhance the clinical efficacy of molecular targeted therapy but also reduce the burden of unnecessary - and potentially harmful-drugs.

As previously commented by Kleger et al[7], in a recent review article critically discussing current and future targeted therapies for pancreatic cancer, “smart drugs need smart applications”. Indeed, most experts concur that the latter applications should include multi-targeted and, ideally, individualized molecular therapies, in combination with conventional cytotoxic agents or other regimens (such as immunotherapy)[61], guided by reliable biomarkers of treatment response. Increased toxicity resulting from these combinatorial approaches as well as their cost-effectiveness and socioeconomic implications should, nevertheless, be carefully considered and may represent major limiting factors for their widespread use. In a disease as aggressive and lethal as pancreatic cancer, maintaining the highest possible quality of life for as long as possible is the most important target, and expectations should always be based on realistic goals.

REFERENCES

1 Tanaka S. Molecular Pathogenesis and Targeted Therapy of Pancreatic Cancer. Ann Surg Oncol 2015 Mar 7; Epub ahead of print [PMID: 25749932 DOI: 10.1245/s10434-015-4463-x]
2 Vincent A, Herman J, Schulick R, Hruban RH, Goggins M. Pancreatic cancer. Lancet 2011; 378: 607-620 [PMID: 21620466 DOI: 10.1016/S0140-6736(10)62307-0]
3 Krejs GJ. Pancreatic cancer: epidemiology and risk factors. Dig Dis 2010; 28: 355-358 [PMID: 20814212 DOI: 10.1159/000319414]
4 Carlin DB, Berlin JD. Pancreas cancer on the rise: are we up to the challenge? J Natl Cancer Inst 2013; 105: 1675-1676 [PMID: 24203986 DOI: 10.1093/jnci/djt316]
5 Saff MW. Pancreatic neoplasm in 2011: an update. JOP 2011; 12: 316-321 [PMID: 21737886]
6 Teague A, Lim KH, Wang-Gillam A. Advanced pancreatic adenocarcinoma: a review of current treatment strategies and developing therapies. Ther Adv Med Oncol 2015; 7: 68-84 [PMID: 25755680 DOI: 10.1177/1758834014568775]
7 Kleger A, Perkhofer L, Seufferlein T. Smarter drugs emerging in pancreatic cancer therapy. Ann Oncol 2014; 25: 1260-1270 [PMID: 24631947 DOI: 10.1093/annonc/mdu103]
8 Antoniou G, Kountourakis P, Papadimitriou K, Vassiliou V, Papamichaud D. Adjuvant therapy for resectable pancreatic adenocarcinoma: a review of the current treatment approaches and future directions. Cancer Treat Rev 2014; 40: 78-85 [PMID: 23810287 DOI: 10.1016/j.ctrv.2013.05.008]
9 Haung ZQ, Buchsbaum DJ. Monoclonal antibodies in the treatment of pancreatic cancer. Immunotherapy 2009; 1: 223-229 [PMID: 20046965 DOI: 10.2217/1757043X.1.2.223]
10 Oettle H. Progress in the knowledge and treatment of advanced pancreatic cancer: from benchside to bedside. Cancer Treat Rev 2014; 40: 1039-1047 [PMID: 25087471 DOI: 10.1016/j.ctrv.2014.07.003]
11 Ozmen F, Sahin TT, Ozmen MM. Current adjuvant therapeutic
 approaches for pancreatic cancer. Adv Ther 2015; 32: 42-56 [PMID: 25595483 DOI: 10.1007/s12325-015-0177-5]

12 **Huang QZ**, Buchsbaum DJ, Raisch KP, Bonner JA, Bland KI, Vickers SM. Differential responses by pancreatic carcinoma cell lines to prolonged exposure to Erlotinib (IMC-C225) anti-EGFR antibody. J Surg Res 2003; 111: 274-283 [PMID: 12850474 DOI: 10.1016/s0022-4804(03)00763-5]

13 **Morgan MA**, Parsels LA, Kollar LE, Nomolle DP, Maybaum J, Lawrence TS. The combination of epidermal growth factor receptor inhibitors with gemcitabine and radiation in pancreatic cancer. Clin Cancer Res 2009; 15: 5412-5419 [PMID: 18693032 DOI: 10.1158/1078-0432.CCR-07-4072]

14 **Sasaki H**, Yamana S, Takemoto S, Sugimura Y, Akaike M, Yawaka N, Rino Y, Imada T. Antitumor activity of a combination of trastuzumab (Herceptin) and oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2-overexpressing pancreatic cancer. Oncol Rep 2007; 18: 433-439 [PMID: 17611667]

15 **Kimura K**, Sawada T, Komatsu S, Inoue M, Muguruma K, Nishihara T, Yamashita Y, Yamada N, Ohira M, Hirakawa K. Antitumor effect of trastuzumab for pancreatic cancer with high HER-2 expression and enhancement of effect by combined therapy with gemcitabine. Clin Cancer Res 2006; 12: 4925-4932 [PMID: 16914581 DOI: 10.1158/1078-0432.CCR-05-0544]

16 **Wilhelm SM**, Carter C, Tang L, Wilkie D, McNabola A, Rong H, Chen C, Zhang X, Vincent P, McHugh M, Cao Y, Shujath J, Gawlak S, Eveleigh D, Rowley B, Liu L, Adnane L, Lynch M, Auclair D, Taylor I, Gedingh R, Voznessensky A, Riedl B, Post LE, Bollag G, Trail PA. BAY 43-9006 exhibits broad spectrum oral antitumor activity and targets the Raf/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis. Cancer Res 2004; 64: 7099-7109 [PMID: 15466206 DOI: 10.1158/0008-5472.CAN-04-1443]

17 **Neid M**, Datta K, Stephan S, Khanna I, Pal S, Shaw L, White M, Mukhopadhyay D. Role of insulin receptor substrates and protein kinase C-zeta in vascular permeability factor/vascular endothelial growth factor expression in pancreatic cancer cells. J Biol Chem 2004; 279: 3941-3948 [PMID: 14660946 DOI: 10.1074/jbc.M303752000]

18 **Liu W**, Bloom DA, Cance WG, Kureeva EV, Golubovskaya VM,эт al. Near infra-red photoimmunotherapy with anti-CEA-IR700 results in extensive tumor lysis and a significant decrease in tumor burden in orthotopic mouse models of pancreatic cancer. PLoS One 2015; 10: e0121989 [PMID: 25799218 DOI: 10.1371/journal.pone.0121989]

19 **Lund K**, Bostad M, Skarpén E, Braugamel M, Kirpijanov S, Krauss S, Duncan A, Hogsted A, Selbo PK. The novel EpCAM-targeting monoclonal antibody C-1-17 linked to sorafenib is highly cytotoxic after photochemical internalization in breast, pancreas and colon cancer cell lines. Mol Cancer 2014; 6: 1038-1050 [PMID: 24525727 DOI: 10.4161/mabs.28207]

20 **Tholey RM**, Lal S, Jinmo B, Burkhart RA, Blanco FP, Cozzitorto JA, Eisenberg JD, Jiang W, Iacobuzio-Donahue CA, Witkiewicz A, Amadori D, Leonetti C. In vitro and in vivo antitumor efficacy of the farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res 2001; 61: 131-137 [PMID: 11196150]

21 **Zimmermann G**, Papke B, Ismael S, Vartak N, Chandra A, Hoffmann M, Hahn SA, Troila G, Wittighofner A, Bastiaens PI, Waldmann H. Small molecule inhibition of the KRAS-PDE5 interaction impairs oncogenic KRAS signalling. Nature 2013; 497: 638-642 [PMID: 23669381 DOI: 10.1038/nature12205]

22 **Witkiewicz AK**, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, Mollaei M, Wagner KU, Koduru P, Yopp A, Choti MA, Yeo CJ, McCue P, White MA, Knudsen ES. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. Nat Commun 2015; 6: 6744 [PMID: 25855538 DOI: 10.1038/ncomms7744]

23 **Olive KP**, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KD, Denicola G, Feig C, Combs C, Winter SP, Ireland-D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KD, Denicola G, Feig C, Combs C, Winter SP, Ireland-D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, Frese KD, Denicola G, Feig C, Combs C, Winter SP, Ireland-D. Inhibitory effects of the farnesyl protein transferase inhibitor R115777 on gemcitabine-resistant orthotopic mouse models of pancreatic cancer. Clin Cancer Res 2006; 12: 7099-7107 [PMID: 17145384 DOI: 10.1158/1078-0432.CCR-05-0833]

24 **Pan Y**, Zheng M, Zhong L, Yang J, Zhou S, Qin Y, Xiang R, Chen Y, Yang SY. A preclinical evaluation of SKLB261, a multikinase inhibitor of EGFR/Src/VEGFR2, as a therapeutic agent against pancreatic cancer. Mol Cancer Ther 2015; 14: 407-418 [PMID: 25519702 DOI: 10.1158/1535-7163.MCT-14-0485]

25 **Ulivi P**, Arienti C, Zoli W, Scarsella M, Carloni S, Fabbrini F, Tesei A, Chiadini E, Orlandi A, Passeri D, Zupi G, Milandri C, Silvestrini R, Amadori D, Leonetti C. In vitro and in vivo antitumor efficacy of the therapeutic targets. Nat Commun 2015; 6: 6744 [PMID: 25855538 DOI: 10.1038/ncomms7744]
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docetaxel and sorafenib combination in human pancreatic cancer. Curr Cancer Drug Targets 2010; 10: 600-610 [PMID: 20491617 DOI: 10.2174/1568060910791893498]

Donadelli M, Dando I, Zaniboni T, Costanza C, Dalla Pozza E, Scapuoli MT, Scurra A, Zapponigria Mura M, Abbруззезе A, Bifulco M, Caraglia M, Palmieri M. Gemicitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism. Cell Death Dis 2011; 2: e152 [PMID: 21525393 DOI: 10.1038/cddis.2011.36]

Viale A, Pettazzoni P, Lysiytsiat CA, Ying H, Sánchez N, Marchesini M, Carago A, Green T, Seth S, Giuliani V, Kost-Alimova M, Muller F, Colla S, Nezi L, Genovess E, Deem AK, Kapoor A, Yao W, Brunetto E, Kang Y, Yuan M, Asara J, Wang Y, Heffernan TP, Kimmelman AC, Wang H, Fleming JB, Cantley LC, DePinho RA, Draetta GF. Oncogene ablation-resistant breast cancer cells depend on mitochondrial function. Nature 2014; 514: 628-632 [PMID: 25159024 DOI: 10.1038/nature13611]

Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Cheng Y, Grapsa D, Zheng X, Lin Y, Yang CS, Xu Q, Carpizo D, Huang WJGO | www.wjgnet.com 176 October 15, 2015 | Volume 7 | Issue 10 |

Efficacy and toxicity of different pegylated liposomal doxorubicin formulations in preclinical models: is a conventional bioequivalence approach sufficient to ensure therapeutic equivalence of pegylated liposomal doxorubicin products? Cancer Chemother Pharmacol 2010; 66: 1173-1184 [PMID: 20661737 DOI: 10.1007/s00280-009-0106-x]

Yoshida M, Takimoto R, Murase K, Sato Y, Hirakawa M, Tamura F, Sato T, Iyama S, Osuga T, Miyahsni K, Takada K, Hayashi T, Kobune M, Kato J. Targeting anticancer drug delivery to pancreatic cancer cells using a fucos-bound nanoparticle approach. PLoS One 2012; 7: e39545 [PMID: 22808043 DOI: 10.1371/journal.pone.0039545]

Pat A, Khan S, Wang YF, Kamath N, Sarker AK, Ahmad A, Sheikh S, Ali S, Carbonaro D, Zhang A, Ahmad I. Preclinical safety, pharmacokinetics and antitumor efficacy profile of liposome-entrapped SN-38 formulation. Anticancer Res 2005; 25: 331-341 [PMID: 15816556]

Neuzillet C, Tijeras-Raballand A, Coss J, Faivre S, Himmel P, Raymond E. Stromal expression of SPARC in pancreatic adenocarcinoma. Cancer Metastasis Rev 2013; 32: 585-602 [PMID: 23690170 DOI: 10.1007/s10637-013-9439-3]

Sinn M, Sinn BV, Striefer JK, Lindner JL, Stieler JM, Lohneis P, Bischoff S, Blaker H, Pelzer U, Bahrea M, Dietel M, Dörken B, Oettle H, Riess H, Denkert C. SPARC expression in resected pancreatic cancer patients treated with gemcitabine: results from the CONKO-001 study. Ann Oncol 2014; 25: 1025-1032 [PMID: 25624499 DOI: 10.1016/j.annonc.2014.04.025]

At-Batran SE, Geissler M, Seufferlein T, Oettle H. Nab-paclitaxel for metastatic pancreatic cancer: clinical outcomes and potential mechanisms of action. Oncol Res Treat 2013; 37: 128-134 [PMID: 24685917 DOI: 10.1159/000355890]

Philip PA, Benedetti J, Corless CL, Wong R, O’Reilly EM, Flynn PJ, Rowland KM, Atkins JN, Mirtsching BC, Rivkin SE, Khorana AA, Goldman B, Fengielio-Preiser CM, Abbруззезе J, Blanke CD. Phase III study comparing gemcitabine plus cetuximab versus gemcitabine plus panitumumab in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. J Clin Oncol 2010; 28: 3605-3610 [PMID: 20660693 DOI: 10.1200/JCO.2010.30.0322]

Van Cutsem E, Vennou W, Benhouma Y, Gill S, Van Laethem JL, Verslype C, Scheithauer W, Shang A, Cosaert J, Moore MJ. Phase III trial of bevacizumab in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. J Clin Oncol 2009; 27: 2231-2237 [PMID: 19307500 DOI: 10.1200/JCO.2008.20.0238]

Kindler HL, Wrablewski K, Wallace JA, Hall MJ, Locker G, Nattam S, Agamaah E, Stadler WM, Vokes EE. Gemcitabine plus sorafenib in patients with advanced pancreatic cancer: a phase II trial of the University of Chicago Phase II Consortium. Invest New Drugs 2012; 30: 382-386 [PMID: 20803052 DOI: 10.1007/s10637-010-9526-z]

Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lin R, Ding K, Clark G, Voskoglou-Nomikos T, Tsatsakis M, Parulekar W. 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 [PMID: 17452677]

Tabernero J, Chiorone EG, Infante JR, Hingorani SR, Ganju V, Weekes C, Scheithauer W, Ramanathan RK, Goldstein D, Penenberg DN, Romano A, Ferrara S, von Hoff DD. Prognostic factors of survival in a randomized phase III trial (IMPACT) of weekly nab-paclitaxel plus gemcitabine versus gemcitabine alone in patients with metastatic pancreatic cancer. Oncologist 2015; 20: 143-150 [PMID: 25582141 DOI: 10.1634/theoncologist.2014-0394]

Hidalgo M. Pancreatic cancer. N Engl J Med 2010; 362: 1605-1617 [PMID: 20427809 DOI: 10.1056/NEJMra0901557]

Trédan O, Galmiriani CM, Patel K, Tannock IF. Drug resistance and the solid tumor microenvironment. J Natl Cancer Inst 2007; 99: 1441-1454 [PMID: 17895480]

Jones S, Zhang X, Parsons DW, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Kamiyama H, Jimeno A, Hong SM, Fu B, Lin
MT, Callhoun ES, Kamiyama M, Walter K, Nikolskaya T, Nikolsky Y, Hartigan J, Smith DR, Hidalgo M, Leach SD, Klein AP, Jaffee EM, Goggins M, Mantra A, Iacobuzio-Donahue C, Eshleman JR, Kern SE, Hruban RH, Karchin R, Papadopoulos N, Parmigiani G, Vogelstein B, Velculescu VE, Kinzler KW. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. *Science* 2008; **321**: 1801-1806 [PMID: 18772397 DOI: 10.1126/science.1164368]

61 Springett GM. Novel pancreatic cancer vaccines could unleash the army within. *Cancer Control* 2014; **21**: 242-246 [PMID: 24955709]

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