Pancreatic cancer: a split type therapy idea

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Despite decades of research, non- resectable pancreatic cancer remain uncurable with 5 year survival rate not more than 8% of patients. Factors behind that unsatisfactory statistics could be split to: 1) genetical, 2) physiological, 3) metastatic, 4) unreachable place and 5) dangerous environment within pancreas. Tumors in pancreas are poorly accessible to chemotherapy, their hypoxia and low blood supply adds to chemical resistance. Metastasis are growing fast, giving unbelievably low blood pH and high levels of tumor growth driving lactic acid. Pancreas is hard to access from skin for methods of complementary medicine. Injections in pancreas could trigger dangerous pancreatitis.

Mainstream is clearly lacking adequate ideas here, help could probably come from holistic approach (cf. Wang et al, 2015 „*Therefore, rather than investigating methods of eliminating cancer cells, we should be looking into methods for inhibiting cancer growth and metastasis. Instead of starving cancer cells by inhibiting angiogenesis, it may be preferable to 'feed' cancer cells by promoting blood circulation; and instead of inducing apoptosis of cancer cells by targeting the anti-apoptotic proteins, it may be preferable to prolong the lifespan of cancer cells through overexpression of these proteins, as living with cancer may be preferable to dying from cancer*".)

Limited experience of myself and others had shown, that even after radical pancreatic tumor reduction with combination therapy it comes back, because some questions of holistic biology are not answered.

Analysis of available literature let us propose a split type therapy idea:

1) for metastasis- killing with low-dose chemotherapy or metabolic therapy,
2) for patient- to rise blood pH and lower concentration of lactic acid. Detox the body and look tightly to hepatobiliary system. Locally boost blood supply and blood oxygenation. Reduce inflammation,
3) for tumor in pancreas- act trough the artery, which feeds pancreas. Controlled drug release 24/7. Reduce effects from hypoxia and reduce tumor smartly with metabolic therapy/phytotherapy,

After getting out of initial crisis appropriate questions of holistic biology should be formulated and answered.

References.

Abou-Alfa G. et al. (2006) Randomized phase III study of exatecan and gemcitabine compared with gemcitabine alone in untreated advanced pancreatic cancer. J Clin Oncol 24: 4441–4447

Aglietta M. et al. (2010) A phase I dose escalation trial of CP-675206 (tremelimumab) in combination with gemcitabine in patients with chemotherapy-naive metastatic pancreatic cancer. *Journal of Clinical Oncology*. 2010;28(15_suppl):4134–4134.

Aprile G. et al. (2017) Second-line chemotherapy for advanced pancreatic cancer: Which is the best option? Crit. Rev. Oncol. Hematol. 2017;115:1–12.

Assenat E., et al. Dual targeting of HER1/EGFR and HER2 with cetuximab and trastuzumab in patients with metastatic pancreatic cancer after gemcitabine failure: Results of the "THERAPY" phase 1-2 trial. Oncotarget. 2015;6:12796–12808.
Bailey P. et al. (2016) Genomic analyses identify molecular subtypes of pancreatic cancer. Nature. 531:47–52.
Bali M. et al. (2011) Tumoral and nontumoral pancreas: correlation between quantitative dynamic contrast-enhanced MR imaging and histopathologic parameters. Radiology 261: 456–466
Bekaii-Saab T. et al A phase Ib/II study of cancer stemness inhibitor napabucasin (BBI-608) in combination with gemcitabine (gem) and nab-paclitaxel (nabPTX) in metastatic pancreatic adenocarcinoma (mPDAC) patients (pts) Am. Soc. Clin. Oncol. 2017
Belli C. et al. Phase II trial of salvage therapy with trabectedin in metastatic pancreatic adenocarcinoma. Cancer Chemother. Pharmacol. 2016;77:477–484.
Bergmann L., et al. A prospective randomised phase-II trial with gemcitabine versus gemcitabine plus sunitinib in advancedpancreatic cancer: A study of the CESAR Central European Society for Anticancer Drug Research-EWIV. Eur J. Cancer. 2015;51:27–36.
Berlin J. et al (2002) 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 20: 3270–3275
Berman D. et al. (2003) Widespread requirement for hedgehog ligand stimulation in growth of digestive tract tumours. Nature 425: 846–851.
Bodoky G., Timcheva C., Spigel D.R., La Stella P., Ciuleanu T.E., Pover G., Tebbutt N.C. A phase II open-label randomized study to assess the efficacy and safety of selumetinib (AZD6244 [ARRY-142886]) versus capecitabine in patients with advanced or metastatic pancreatic cancer who have failed first-line gemcitabine therapy. Invest. New Drugs. 2012;30:1216–1223.
Bramhall S. et al (2001) Marimastat as first-line therapy for patients with unresectable pancreatic cancer: a randomized trial. J Clin Oncol 19: 3447–3455.
Burris H., 3rd, 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.
Bustinza-Linares E., Kurzrock R., Tsimberidou A.M. Salirasib in the treatment of pancreatic cancer. Future Oncol. 2010;6:885–891.
Catenacci D. et al. Randomized Phase Ib/II Study of Gemcitabine Plus Placebo or Vismodegib, a Hedgehog Pathway Inhibitor, in Patients With Metastatic Pancreatic Cancer. J. Clin. Oncol. 2015;33:4284–4292.
Chan K., et al A Bayesian meta-analysis of multiple treatment comparisons of systemic regimens for advanced pancreatic cancer. PLoS ONE. 2014;9
Chantrill L. et al. Precision medicine for advanced pancreas cancer: The individualized molecular pancreatic cancer therapy (IMPaCT) trial. Clin. Cancer Res. 2015;21:2029–2037.
Chiorean E. Et al Randomized phase II study of 2nd-line FOLFIRI versus modified FOLFIRI with PARP inhibitor ABT-888 (veliparib) (NSC-737664) in metastatic pancreatic cancer (mPC): SWOG S1513. J. Clin. Oncol. 2017;35
Cho M. et al. (2015) A phase II study of adjuvant gemcitabine plus docetaxel followed by concurrent chemoradation in resected pancreaticobiliary carcinoma. HPB. 2015;17:587–593.
Choi M. et al Challenges in Ras therapeutics in pancreatic cancer. Semin. Cancer Biol. 2017
Cutsem E.V., van de Velde H., Karasek P., Oettle H., Vervenne W.L., Szawlowski A., Schoffski P., Post S., Verslype C., Neumann H., 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.
Chung V., McDonough S., Philip P.A., Cardin D., Wang-Gillam A., Hui L., Tejani M.A., Seery T.E., Dy I.A., al Baghdadi T., et al. Effect of Selumetinib and MK-2206 vs. Oxaliplatin and Fluorouracil in patients with metastatic pancreatic cancer after prior therapy: SWOG S1115 study randomized clinical trial. JAMA Oncol. 2017;3:516–522.
Collins M. et al. (2012) Oncogenic Kras is required for both the initiation and maintenance of pancreatic cancer in mice. J Clin Invest 122: 639–653
Colucci G. et al. (2010) 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 28: 1645–1651
Conroy T. et al. (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 364:1817–1825.
Cook N. et al. (2012) Gamma secretase inhibition promotes hypoxic necrosis in mouse pancreatic ductal adenocarcinoma. J Exp Med 209: 437–444
Crippa S. et al. (2008) Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. Ann Surg. 247:571–579.
Cunningham D. et al. (2009) Phase III randomized comparison of gemcitabine *versus* gemcitabine plus capecitabine in patients with advanced pancreatic cancer. J Clin Oncol 27: 5513–5518
Douillard J. et al. (2006) Adjuvant vinorelbine plus cisplatin *versus* observation in patients with completely resected stage Ib–IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [Anita]): a randomised controlled trial. Lancet Oncol 7: 719–727
Eliopoulos N. et al(1998) Drug resistance to 5-aza-2′-deoxycytidine, 2′,2′-difluorodeoxycytidine, and cytosine arabinoside conferred by retroviral-mediated transfer of human cytidine deaminase cDNA into murine cells. Cancer Chemother Pharmacol 42: 373–378
Erez N., et al Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-κB-dependent manner. Cancer Cell. 2010;17:135–147.
Erkan M. et al. (2012) The Role of stroma in pancreatic cancer: diagnostic and therapeutic implications. Nat Rev Gastroenterol Hepatol 9: 454–467.
Esposito I. Et al (2014) Pathology of pancreatic ductal adenocarcinoma: facts, challenges and future developments. World J Gastroenterol. 20:13833–13841.
Estrella V. et al. (2013) Acidity generated by the tumor microenvironment drives local invasion. Cancer Res. 73:1524–1535.
Ettrich T. et al. DocOx (AIO-PK0106): A phase II trial of docetaxel and oxaliplatin as a second line systemic therapy in patients with advanced pancreatic ductal adenocarcinoma. BMC Cancer. 2016;16 4.
Farrell J. et al (2012) Cytidine deaminase single-nucleotide polymorphism is predictive of toxicity from gemcitabine in patients with pancreatic cancer: RTOG 9704. Pharmacogenomics J 12: 395–403
Feldmann G., et al (2007) Molecular genetics of pancreatic intraepithelial neoplasia. J Hepatobiliary Pancreat Surg. 2007;14:224–232.
Ferrone C. et al. (2012) Pancreatic ductal adenocarcinoma: long-term survival does not equal cure. Surgery 152(Suppl.): S43–S49
Garrido-Laguna I, Hidalgo M. (2015) Pancreatic cancer: from state-of-the-art treatments to promising novel therapies. Nat Rev Clin Oncol. 12:319–334.
Ghosn M., et al Dilemma of first line regimens in metastatic pancreatic adenocarcinoma. World J. Gastroenterol. 2016;22:10124–10130.

Ghosn M., et al Dilemma of first line regimens in metastatic pancreatic adenocarcinoma. World J. Gastroenterol. 2016;22:10124–10130.
Goji T., al. (2015)vA phase I/II study of fixed-dose-rate gemcitabine and S-1 with concurrent radiotherapy for locally advanced pancreatic cancer. Cancer Chemother. Pharmacol. 2015;76:615–620.
Goldstein D., et al. nab-Paclitaxel plus gemcitabine for metastatic pancreatic cancer: Long-term survival from a phase III trial. J. Natl. Cancer Inst. 2015;107
Goncalves A. et al. (2012) 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 23: 2799–2805
Guo Y. Et al. (2016) Helicobacter pylori infection and pancreatic cancer risk: A meta-analysis. J Cancer Res Ther. 12:C229–C232.
Haarberg H.E., Smalley K.S. Resistance to Raf inhibition in cancer. Drug Discov. Today Technol. 2014;11:27–32.]
Haeno H. et al (2012) Computational modeling of pancreatic cancer reveals kinetics of metastasis suggesting optimum treatment strategies. Cell 148: 362–375
Hagen T. (2019) SM-88 Shows Efficacy in Pancreatic, Prostate Cancers. *Oncology Live*.
Hajatdoost :L. (2018) Chemotherapy in Pancreatic Cancer: A Systematic Review. Medicina (Kaunas). 54: 48.
Hammel P. et al. (2016) Effect of Chemoradiotherapy vs Chemotherapy on Survival in Patients With Locally Advanced Pancreatic Cancer Controlled After 4 Months of Gemcitabine With or Without Erlotinib: The LAP07 Randomized Clinical Trial. JAMA. 2016;315:1844–1853.
Hansel D. et al (2003) Molecular Pathogenesis of pancreatic cancer. Annu Rev Genomics Hum Genet 4: 237–256
Heinemann V. et al. (2012) Gemcitabine plus erlotinib followed by capecitabine *versus* capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase III trial of the ‘Arbeitsgemeinschaft Internistische Onkologie’ (AIO-PK0104). Gut, in press.
Herman J. et al. Phase 2 multi-institutional trial evaluating gemcitabine and stereotactic body radiotherapy for patients with locally advanced unresectable pancreatic adenocarcinoma. Cancer. 2015;121:1128–1137.
Herrmann R. et al. (2007) 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 25: 2212–2217
Hezel A. et al. (2006) Genetics and Biology of pancreatic ductal adenocarcinoma. Genes Dev 20: 1218–1249
Hingorani S. et al. HALO 202: Randomized phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus NAB-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J. Clin. Oncol. 2017
Hobday T. et al. Multicenter Phase II Trial of Temsirolimus and Bevacizumab in Pancreatic Neuroendocrine Tumors. J. Clin. Oncol. 2015;33:1551–1556. Lombard-Bohas C., Yao J.C.,
Hong S. et al (2011) Molecular signatures of pancreatic cancer. Arch Pathol Lab Med. 135:716–727.
Hruban RH, Maitra A, Goggins M. Update on pancreatic intraepithelial neoplasia. Int J Clin Exp Pathol. 2008;1:306–316.
Hurwitz H. et al Two randomized, placebo-controlled phase 3 studies of ruxolitinib (Rux)+ capecitabine (C) in patients (pts) with advanced/metastatic pancreatic cancer (mPC) after

failure/intolerance of first-line chemotherapy: JANUS 1 (J1) and JANUS 2 (J2) Am. Soc. Clin. Oncol. 2017
Hurwitz H. et al. Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed. J. Clin. Oncol. 2015;33:4039–4047.
Infante J. et al. A randomised, double-blind, placebo-controlled trial of trametinib, an oral MEK inhibitor, in combination with gemcitabine for patients with untreated metastatic adenocarcinoma of the pancreas. Eur. J. Cancer. 2014;50:2072–2081.
Ioka T., et al. Randomised phase II trial of irinotecan plus S-1 in patients with gemcitabine-refractory pancreatic cancer. Br. J. Cancer. 2017;116:464–471.
Jones S. et al. Core signaling pathways in human pancreatic cancers revealed by global genomic analyses. Science. 2008;321:1801–1806.
Jun S., Hong S. (2016) Nonductal Pancreatic Cancers. Surg Pathol Clin. 9:581–593.
Kamisawa T. (2016) Pancreatic cancer. *Lancet (London, England)* 388(10039):73–85.
Kanda T. et al (2014) Androgen receptor signaling in hepatocellular carcinoma and pancreatic cancers. World J Gastroenterol. 20:9229–9236.
Kindler H. et al. (2010) 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 28: 3617–3622
Kindler H. et al. (2011) Axitinib plus gemcitabine *versus* placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase III study. Lancet Oncol 12: 256–262
Kindler H. 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.
Klinkenbijl J. et al. (1999) Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III TRIAL of the EORTC Gastrointestinal Tract Cancer Cooperative Group. Ann Surg 230: 776–782; discussion 782–774.
Ko A. et al A phase Ib trial of FOLFIRINOX plus saridegib, an oral hedgehog (Hh) inhibitor, in pts with advanced pancreatic cancer (PDAC) J. Clin. Oncol. 2012;30:3105.
Ko A. et al. A multicenter, open-label phase II clinical trial of combined MEK plus EGFR inhibition for chemotherapy-refractory advanced pancreatic adenocarcinoma. Clin. Cancer Res. 2016;22:61–68.
Komar G. et al. (2009) Decreased blood flow with increased metabolic activity: a novel sign of pancreatic tumor aggressiveness. Clin Cancer Res 15: 5511–5517
Konduri S. et al (2007) Androgen receptor blockade in experimental combination therapy of pancreatic cancer. J Surg Res. 142:378–386.
Koong A. et al. (2000) Pancreatic tumors show high levels of hypoxia. Int J Radiat Oncol Biol Phys 48: 919–922
Kordes S., et al Phase II study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced pancreatic cancer. Cancer Chemother. Pharmacol. 2015;75:1135–1141.
Kota J., et al Pancreatic cancer: Stroma and its current and emerging targeted therapies. Cancer Lett. 2017;391:38–49.
Kumar J., et al Radiofrequency assisted pancreaticoduodenectomy for palliative surgical resection of locally advanced pancreatic adenocarcinoma. Oncotarget. 2018;9:15732–15739.
Laheru D., Shah P., Rajeshkumar N.V., McAllister F., Taylor G., Goldsweig H., Le D.T., Donehower R., Jimeno A., Linden S., et al. Integrated preclinical and clinical development of

S-trans, trans-Farnesylthiosalicylic Acid (FTS, Salirasib) in pancreatic cancer. Investig. New Drugs. 2012;30:2391–2399.
Le D. et al. (2013) Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. *Journal of Immunotherapy*. 36(7):382–389.
Le D. et al. (2015) Safety and survival with GVAX pancreas prime and listeria monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. J. Clin. Oncol. 33:1325–1333.
Lee H. et al. A randomized, multicenter, phase III study of gemcitabine combined with capecitabine versus gemcitabine alone as first-line chemotherapy for advanced pancreatic cancer in South Korea. Medicine. 2017;96
Lombard-Bohas C., et al Impact of prior chemotherapy use on the efficacy of everolimus in patients with advanced pancreaticneuroendocrine tumors: A subgroup analysis of the phase III RADIANT-3 trial. Pancreas. 2015;44:181–189.
Louvet C. et al. (2005) 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 23: 3509–3516
Luchini C. et al (2016) Pancreatic Ductal Adenocarcinoma and Its Variants. Surg Pathol Clin. 9:547–560.
Lugovskoy A. et al. Abstract CT237: Preclinical characterization and first-in-human study of MM-141, a dual antibody inhibitor of IGF-1R and ErbB3. Cancer Res. 2015;75
Madden J. Infinity Reports Update from Phase 2 Study of Saridegib plus Gemcitabine in Patients with Metastatic Pancreatic Cancer. Infinity Pharmaceuticals; Cambridge, MA, USA: 2012.
Madden R., et al Lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer: A systematic review. Int. J. Clin. Pharmacol. Ther. 2018;56:72–80.
Mahaseth H. et al (2013) Modified FOLFIRINOX regimen with improved safety and maintained efficacy in pancreatic adenocarcinoma. Pancreas. 42:1311–1315.
Maitra A., Hruban R. (2008) Pancreatic cancer. Annu Rev Pathol 3: 157–188
Makielski R.et al A phase II study of sorafenib, oxaliplatin, and 2 days of high-dose capecitabine in advanced pancreas cancer. Cancer Chemother. Pharmacol. 2015;76:317–323.
Mangray S., King T.C. Molecular pathobiology of pancreatic adenocarcinoma. Front. Biosci. 1998;3:D1148–D1160.
Midha S. et al (2016) Modifiable and non-modifiable risk factors for pancreatic cancer: A review. Cancer Lett. 381:269–277.
Mohammed S. et al (2014) Pancreatic cancer: advances in treatment. World J Gastroenterol. 20:9354–9360.
Moore M. et al. (2003) 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 21: 3296–3302
Moore M. et al. (2007) 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 25: 1960–1966
Morton J. et al. (2010) Mutant P53 drives metastasis and overcomes growth arrest/senescence in pancreatic cancer. Proc Natl Acad Sci U S A 107: 246–251
Mullendore M. et al Ligand-dependent Notch signaling is involved in tumor initiation and tumor maintenance in pancreatic cancer. Clin. Cancer Res. 2009;15:2291–2301.
Neesse A. et al. (2011) Stromal biology and therapy in pancreatic cancer. Gut 60: 861–868

Neoptolemos J et al. (2010) Chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 304:1073–1081.
Neoptolemos J. et al. (2010) Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA 304: 1073–108
Nolan-Stevaux O. et al. (2009) Gli1 is regulated through smoothened-independent mechanisms in neoplastic pancreatic ducts and mediates pdac cell survival and transformation. Genes Dev 23: 24–36
O'Reilly E. et al. Phase IB trial of cisplatin (C), gemcitabine (G), and veliparib (V) in patients with known or potential BRCA or PALB2-mutated pancreas adenocarcinoma (PC) J. Clin. Oncol. 2014;32:4023.
Oettle H. et al. (2005) A phase III trial of pemetrexed plus gemcitabine *versus* gemcitabine in patients with unresectable or metastatic pancreatic cancer. Ann Oncol 16: 1639–1645
Oettle H. et al. (2013) Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA. 310:1473–1481.
Of U. et al, (2013). Pancreas Cancer.
Ohkawa S., et al. Randomised phase II trial of S-1 plus oxaliplatin vs S-1 in patients with gemcitabine-refractory pancreatic cancer. Br. J. Cancer. 2015;112:1428–1434.
Olive K. et al. (2009) Inhibition of hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science 324: 1457–1461
Palagani V. et al. Epithelial mesenchymal transition and pancreatic tumor initiating CD44+/EpCAM+ cells are inhibited by gamma-secretase inhibitor IX. PLoS ONE. 2012;7:e46514.
Pausch T. et al. (2012) Cachexia but not obesity worsens the postoperative outcome after pancreatoduodenectomy in pancreatic cancer. Surgery 152: S81–88
Pellegata N. et al. (1994) K-ras and p53 gene mutations in pancreatic cancer: ductal and nonductal tumors progress through different genetic lesions. Cancer Res 54: 1556–1560
Perez-Mancera P. et al. (2012) The deubiquitinase USP9X suppresses pancreatic ductal adenocarcinoma. Nature 486: 266–270
Petrioli R., et al Gemcitabine, oxaliplatin, and capecitabine (GEMOXEL) compared with gemcitabine alone in metastaticpancreatic cancer: A randomized phase II study. Cancer Chemother. Pharmacol. 2015;75:683–690.
Petrioli R., et al Gemcitabine, oxaliplatin, and capecitabine (GEMOXEL) compared with gemcitabine alone in metastaticpancreatic cancer: A randomized phase II study. Cancer Chemother. Pharmacol. 2015;75:683–690.
Philip P. et al. (2010) 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 28: 3605–3610
Poplin E. et al. (2009) 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 27: 3778–3785
Porta M. et al. (2005) Exocrine pancreatic cancer: symptoms at presentation and their relation to tumour site and stage. Clin Transl Oncol 7: 189–197
Postlewait L.et al Combination gemcitabine/cisplatin therapy and ERCC1 expression for resected pancreatic adenocarcinoma: Results of a Phase II prospective trial. J. Surg. Oncol. 2016;114:336–341.
Provenzano P. Et al.(2012) Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell 21: 418–429

Pylayeva-Gupta Y., et al (2012) Oncogenic Kras-induced GM-CSF production promotes the development of pancreatic neoplasia. Cancer Cell 21: 836–847
Rahib L., et al Evaluation of Pancreatic Cancer Clinical Trials and Benchmarks for Clinically Meaningful Future Trials: A Systematic Review. JAMA Oncol. 2016;2:1209–1216.
Raimondi S. et al. (2010). Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 24:349–358.
Regine W., et al. (2008) Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. JAMA 299: 1019–1026
Reni M., et al. Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: A phase II randomised trial. Eur. J. Cancer. 2013;49:3609–3615.
Rhim A. et al. (2012) EMT and dissemination precede pancreatic tumor formation. Cell 148: 349–361
Riva F. et al. (2016) Clinical applications of circulating tumor DNA and circulating tumor cells in pancreatic cancer. Mol Oncol. 10:481–493.
Rocha Lima C. et al. (2004) 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 22: 3776–3783
Royal R. et al. (2010) Phase 2 trial of single agent ipilimumab (Anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *Journal of Immunotherapy*. 33(8):828–833.
Satoi S., et al. Multicenter Phase II Study of Intravenous and Intraperitoneal Paclitaxel With S-1 for Pancreatic Ductal Adenocarcinoma Patients With Peritoneal Metastasis. Ann. Surg. 2017;265:397–401..
Schultheis B. et al. Gemcitabine combined with the monoclonal antibody nimotuzumab is an active first-line regimen in KRAS wildtype patients with locally advanced or metastatic pancreatic cancer: A multicenter, randomized phase IIb study. Ann. Oncol. 2017;28:2429–2435.
Seyfried T., Huysentruyt L.(2013) On the origin of cancer metastasis. Crit Rev Oncog. 18(1-2): 43–73.
Sherman W. et al. Neoadjuvant gemcitabine, docetaxel, and capecitabine followed by gemcitabine and capecitabine/radiationtherapy and surgery in locally advanced, unresectable pancreatic adenocarcinoma. Cancer. 2015;121:673–680.
Shimoda M. et al (2015) Randomized clinical trial of adjuvant chemotherapy with S-1 versus gemcitabine after pancreatic cancer resection. Br. J. Surg.;102:746–754.
Soto A., Sonnenschein C. (2011) The tissue organization field theory of cancer: a testable replacement for the somatic mutation theory. Bioessays. 33:332–340.
Stathis A., Moore M. (2010) Advanced pancreatic carcinoma: current treatment and future challenges. Nat Rev Clin Oncol 7: 163–172
Stein S. et al. Final analysis of a phase II study of modified FOLFIRINOX in locally advanced and metastatic pancreatic cancer. Br. J. Cancer. 2016;114:737–743.
Suhail Y. (2019) Systems biology of cancer metastasis.
Tabernero J., Macarulla T. (2009) Changing the paradigm in conducting randomized clinical studies in advanced pancreatic cancer: an opportunity for better clinical development. J Clin Oncol 27: 5487–5491
Tai C. et al. Combination of Two Targeted Medications (Bevacizumab Plus Cetuximab) Improve the Therapeutic Response of Pancreatic Carcinoma. Medicine. 2016;95 doi:
Takebe N. Et alTargeting cancer stem cells by inhibiting Wnt, Notch, and Hedgehog pathways. Nat. Rev. Clin. Oncol. 2010;8:97.

Tanaka M. et al (2006) International Association of Pancreatology. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology. 6:17–32.
Tanaka M. et al (2017) Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. Pancreatology. 17:738–753.
Tanaka M. et al, (2010) Gemcitabine metabolic and transporter gene polymorphisms are associated with drug toxicity and efficacy in patients with locally advanced pancreatic cancer. Cancer 116: 5325–5335
Tarin D. et al (2005) The fallacy of epithelial mesenchymal transition in neoplasia. Cancer Res. 65:5996.
Thiebaut A. et al. (2009) Dietary fatty acids and pancreatic cancer in the NIH-AARP Diet and Health Study. J Natl Cancer Inst 101: 1001–1011
Tian H. et al. (2009) Hedgehog signaling is restricted to the stromal compartment during pancreatic carcinogenesis. Proc Natl Acad Sci U S A 106: 4254–4259
Topalian S. (2015) Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell*. 27(4):450–461.
Trajkovic-Arsic M. et al. The role of insulin and IGF system in pancreatic cancer. J. Mol. Endocrinol. 2013;50:R67–R74.
Tremblay I. Et al The MEK/ERK pathway promotes NOTCH signalling in pancreatic cancer cells. PLoS ONE. 2013;8:e85502.
Tyagi N., Bhardwaj A., Singh A.P., McClellan S., Carter J.E., Singh S. p-21 activated kinase 4 promotes proliferation and survival of pancreatic cancer cells through AKT- and ERK-dependent activation of NF-κB pathway. Oncotarget. 2014;5:8778–8789.
Ueno H. (2016) Phase I/II study of nab-paclitaxel plus gemcitabine for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. Cancer Chemother. Pharmacol. 77:595–603.
Ueno M., et al. A randomized phase II study of S-1 plus oral leucovorin versus S-1 monotherapy in patients with gemcitabine-refractory advanced pancreatic cancer. Ann. Oncol. 2016;27:502–508.
Uesaka K., et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: A phase 3, open-label, randomised, non-inferiority trial (JASPAC 01) Lancet. 2016;388:248–257.
Vaccaro V. Et al (2011) FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *The New England Journal of Medicine*. 365(8):768–769.
Van Cutsem E. et al. (2004) Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer. J Clin Oncol 22: 1430–1438
Verbeke C. (2016) Morphological heterogeneity in ductal adenocarcinoma of the pancreas - Does it matter? Pancreatology. 16:295–301.
Viaud J., et al Gemcitabine as second-line chemotherapy after Folfirinox failure in advanced pancreatic adenocarcinoma: A retrospective study. Dig. Liver Dis. 2017;49:692–696.
Von Hoff D. et al. (2011) Gemcitabine plus *nab*-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. J Clin Oncol 29: 4548–4554
Von Hoff D. et al. Increased survival in pancreatic cancer with nab-Paclitaxel plus Gemcitabine. N. Engl. J. Med. 2013;369:1691–1703.
Wang J. et al. Erlotinib is effective in pancreatic cancer with epidermal growth factor receptor mutations: A randomized, open-label, prospective trial.
Wang R. et al (2015) Reasons for cancer metastasis: A holistic perspective.

Wang-Gillam A., et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): A global, randomised, open-label, phase 3 trial. Lancet. 2016;387:545–557.
Weekes C., Winn R. The many faces of Wnt and pancreatic ductal adenocarcinoma oncogenesis. Cancers. 2011;3:3676–3786.
Wiggermann P. Et al (2012) Apparent diffusion coefficient measurements of the pancreas, pancreas carcinoma, and mass-forming focal pancreatitis. Acta Radiol 53: 135–139
Wu Z. Et al Phase II study of lapatinib and capecitabine in second-line treatment for metastatic pancreatic cancer. Cancer Chemother. Pharmacol. 2015;76:1309–1314.
Yachida S., Jones S., Bozic I., Antal T., Leary R., Fu B., et al. (2010) Distant metastasis occurs late during the genetic evolution of pancreatic cancer. Nature 467: 1114–1117
Yamamoto Y. Et al (2014) targeting ligand enhances infectivity and cytotoxicity of an oncolytic adenovirus in human pancreatic cancer tissues. J Control Release. 192:284–293.
Yao X. Et al (2012) Evaluation of pancreatic cancer by multiple breath-hold dynamic contrast-enhanced magnetic resonance imaging at 3.0T. Eur J Radiol 81: e917–922
Ying H. et al. (2012) Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell 149: 656–670
Zhan H. et al (2017) Neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of prospective studies. Cancer Med. 6:1201–1219.