

## Literatur

- 1 Kleeff J, Korc M, Apte M, La Vecchia C, Johnson CD, Biankin AV, Neale RE, Tempero M, Tuveson DA, Hruban RH, et al. Pancreatic cancer. *Nat Rev Dis Primers.* 2016;2:16022.
- 2 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7–30.
- 3 Quante AS, Ming C, Rottmann M, Engel J, Boeck S, Heinemann V, Westphalen CB, Strauch K. Projections of cancer incidence and cancer-related deaths in Germany by 2020 and 2030. *Cancer Med.* 2016;5(9):2649–56.
- 4 Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res.* 2014; 74(11):2913–21.
- 5 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med.* 2003; 348(17):1625–38.
- 6 Font-Burgada J, Sun B, Karin M. Obesity and Cancer: The Oil that Feeds the Flame. *Cell Metab.* 2016;23(1):48–62.
- 7 Rahn S, Zimmermann V, Viol F, Knaack H, Stemmer K, Peters L, Lenk L, Ungefroren H, Saur D, Schafer H, et al. Diabetes as risk factor for pancreatic cancer: Hyperglycemia promotes epithelial-mesenchymal transition and stem cell properties in pancreatic ductal epithelial cells. *Cancer Lett.* 2018;415:129–50.
- 8 Hecht SS. Tobacco smoke carcinogens and lung cancer. *J Natl Cancer Inst.* 1999; 91(14):1194–210.
- 9 Blot WJ, McLaughlin JK, Winn DM, Austin DF, Greenberg RS, Preston-Martin S, Bernstein L, Schoenberg JB, Stemhagen A, Fraumeni JF Jr. Smoking and drinking in relation to oral and pharyngeal cancer. *Cancer Res.* 1988; 48(11):3282–7.
- 10 Blot WJ. Alcohol and cancer. *Cancer Res.* 1992;52(7 Suppl):2119s–23s.
- 11 Gapstur SM, Jacobs EJ, Deka A, McCullough ML, Patel AV, Thun MJ. Association of alcohol intake with pancreatic cancer mortality in never smokers. *Arch Intern Med.* 2011; 171(5):444–51.
- 12 Pelucchi C, Galeone C, Polesel J, Manzari M, Zucchetto A, Talamini R, Franceschi S, Negri E, La Vecchia C. Smoking and body mass index and survival in pancreatic cancer patients. *Pancreas.* 2014;43(1):47–52.
- 13 Olson SH, Chou JF, Ludwig E, O'Reilly E, Allen PJ, Jarnagin WR, Bayuga S, Simon J, Gonen M, Reisacher WR, et al. Allergies, obesity, other risk factors and survival from pancreatic cancer. *Int J Cancer.* 2010; 127(10):2412–9.
- 14 Delitto D, Zhang D, Han S, Black BS, Knowlton AE, Vlada AC, Sarosi GA, Behrns KE, Thomas RM, Lu X, et al. Nicotine Reduces Survival via Augmentation of Paracrine HGF-MET Signaling in the Pancreatic Cancer Microenvironment. *Clin Cancer Res.* 2016; 22(7):1787–99.
- 15 Zhang S, Wang C, Huang H, Jiang Q, Zhao D, Tian Y, Ma J, Yuan W, Sun Y, Che X, et al. Effects of alcohol drinking and smoking on pancreatic ductal adenocarcinoma mortality: A retrospective cohort study consisting of 1783 patients. *Sci Rep.* 2017;7(1):9572.
- 16 Petersen GM, Amundadottir L, Fuchs CS, Kraft P, Stolzenberg-Solomon RZ, Jacobs KB, Arslan AA, Bueno-de-Mesquita HB, Gallinger S, Gross M, et al. A genome-wide association study identifies pancreatic cancer susceptibility loci on chromosomes 13q22.1, 1q32.1 and 5p15.33. *Nat Genet.* 2010;42(3):224–8.
- 17 Pihlak R, Valle JW, McNamara MG. Germline mutations in pancreatic cancer and potential new therapeutic options. *Oncotarget.* 2017; 8(42):73240–57.
- 18 Hu C, Hart SN, Polley EC, Gnanaolivu R, Shimelis H, Lee KY, Lilyquist J, Na J, Moore R, Antwi SO, et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. *JAMA.* 2018;319(23):2401–9.
- 19 Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med.* 2010; 7(4):e1000267.
- 20 Werner J, Combs SE, Springfield C, Hartwig W, Hackert T, Buchler MW. Advanced-stage pancreatic cancer: therapy options. *Nat Rev Clin Oncol.* 2013;10(6):323–33.
- 21 Manji GA, Olive KP, Saenger YM, Oberstein P. Current and Emerging Therapies in Metastatic Pancreatic Cancer. *Clin Cancer Res.* 2017; 23(7):1670–8.
- 22 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(2):68–84.
- 23 Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Foucardiere C, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011; 364(19):1817–25.
- 24 Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, Seay T, Tjuland SA, Ma WW, Saleh MN, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013; 369(18):1691–703.
- 25 Gourgou-Bourgade S, Bascoul-Mollevi C, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, Adenis A, Raoul JL, Boige V, et al. Impact of FOLFIRINOX compared with gemcitabine on quality of life in patients with metastatic pancreatic cancer: results from the PRODIGE 4/ACCORD 11 randomized trial. *J Clin Oncol.* 2013;31(1):23–9.
- 26 Hall WA, Goodman KA. Radiation therapy for pancreatic adenocarcinoma, a treatment option that must be considered in the management of a devastating malignancy. *Radiat Oncol.* 2019;14(1):114.
- 27 Roeder F. Neoadjuvant radiotherapeutic strategies in pancreatic cancer. *World J Gastrointest Oncol.* 2016;8(2):186–97.
- 28 Brunner TB, Scott-Brown M. The role of radiotherapy in multimodal treatment of pancreatic carcinoma. *Radiat Oncol.* 2010;5:64.
- 29 Mukherjee S, Hurt CN, Bridgewater J, Falk S, Cummins S, Wasan H, Crosby T, Jephcott C, Roy R, Radhakrishna G, et al. Gemcitabine-based or capecitabine-based chemoradiotherapy for locally advanced pancreatic cancer (SCALOP): a multicentre, randomised, phase 2 trial. *Lancet Oncol.* 2013;14(4):317–26.
- 30 Murphy JE, Wo JY, Ryan DP, Jiang W, Yeap BY, Drapek LC, Blaszkowsky LS, Kwak EL, Allen JN, Clark JW, et al. Total Neoadjuvant Therapy With FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma: A Phase 2 Clinical Trial. *JAMA Oncol.* 2018; 4(7):963–9.
- 31 Reygold M, Parikh P, Crane CH. Ablative radiation therapy for locally advanced pancreatic cancer: techniques and results. *Radiat Oncol.* 2019;14(1):95.
- 32 Boldrini L, Cusumano D, Cellini F, Azario L, Mattiucci GC, Valentini V. Online adaptive magnetic resonance guided radiotherapy for pancreatic cancer: state of the art, pearls and pitfalls. *Radiat Oncol.* 2019;14(1):71.
- 33 Nanda RH, El-Rayes B, Maithel SK, Landry J. Neoadjuvant modified FOLFIRINOX and chemoradiation therapy for locally advanced pancreatic cancer improves resectability. *J Surg Oncol.* 2015;111(8):1028–34.
- 34 Buwenge M, Macchia G, Arcelli A, Frakulli R, Fuccio L, Guerri S, Grassi E, Cammelli S, Cellini F, Morganti AG. Stereotactic radiotherapy of pancreatic cancer: a systematic review on pain relief. *J Pain Res.* 2018;11:2169–78.
- 35 Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, et al. Safety and activity of anti-PD1 antibody in patients with advanced cancer. *N Engl J Med.* 2012; 366(26):2455–65.
- 36 Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Filip E, Holgado E, et al. Nivolumab versus Docetaxel in Advanced Non-squamous Non-Small-Cell Lung Cancer. *N Engl J Med.* 2015; 373(17):1627–39.
- 37 Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol.* 2014; 32(10):1020–30.
- 38 Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med.* 2015; 373(13):1270–1.
- 39 Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother.* 2010;33(8):828–33.

- 40 Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017; 357(6349):409–13.
- 41 Lemery S, Keegan P, Pazdur R. First FDA Approval Agnostic of Cancer Site - When a Biomarker Defines the Indication. *N Engl J Med*. 2017; 377(15):1409–12.
- 42 Dougan SK. The Pancreatic Cancer Microenvironment. *Cancer J*. 2017;23(6):321–5.
- 43 Puri S, Folias AE, Hebrok M. Plasticity and dedifferentiation within the pancreas: development, homeostasis, and disease. *Cell Stem Cell*. 2015;16(1):18–31.
- 44 Kopp JL, von Figura G, Mayes E, Liu FF, Dubois CL, Morris JP, Pan FC, Akiyama H, Wright CV, Jensen K, et al. Identification of Sox9-dependent acinar-to-ductal reprogramming as the principal mechanism for initiation of pancreatic ductal adenocarcinoma. *Cancer Cell*. 2012;22(6):737–50.
- 45 Gidekel Friedlander SY, Chu GC, Snyder EL, Girnius N, Dibelius G, Crowley D, Vasile E, DePinho RA, Jacks T. Context-dependent transformation of adult pancreatic cells by oncogenic K-Ras. *Cancer Cell*. 2009; 16(5):379–89.
- 46 Kanda M, Matthaei H, Wu J, Hong SM, Yu J, Borges M, Hruban RH, Maitra A, Kinzler K, Vogelstein B, et al. Presence of somatic mutations in most early-stage pancreatic intraepithelial neoplasia. *Gastroenterology*. 2012; 142(4):730–3 e739.
- 47 Morris JP, Wang SC, Hebrok M. KRAS, Hedgehog, Wnt and the twisted developmental biology of pancreatic ductal adenocarcinoma. *Nat Rev Cancer*. 2010;10(10):683–95.
- 48 Witkiewicz AK, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, Mollaee M, Wagner KU, Koduru P, Yopp A, et al. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. *Nat Commun*. 2015;6:6744.
- 49 Waddell N, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, Johns AL, Miller D, Nones K, Quek K, et al. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature*. 2015;518(7540):495–501.
- 50 Bailey P, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, Miller DK, Christ AN, Bruxner TJ, Quinn MC, et al. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature*. 2016;531(7592):47–52.
- 51 Cancer Genome Research Network. Electronic address aadhe, Cancer Genome Atlas Research N. Integrated Genomic Characterization of Pancreatic Ductal Adenocarcinoma. *Cancer Cell*. 2017;32(2):185–203 e113.
- 52 Mueller S, Engleitner T, Maresch R, Zukowska M, Lange S, Kaltenbacher T, Konukiewitz B, Ollinger R, Zwiebel M, Strong A, et al. Evolutionary routes and KRAS dosage define pancreatic cancer phenotypes. *Nature*. 2018; 554(7690):62–8.
- 53 Altomare DA, Tanno S, De Rienzo A, Klein-Szanto AJ, Tanno S, Skele KL, Hoffman JP, Testa JR. Frequent activation of AKT2 kinase in human pancreatic carcinomas. *J Cell Biochem*. 2002;87(4):470–6.
- 54 Ying H, Dey P, Yao W, Kimmelman AC, Draetta GF, Maitra A, DePinho RA. Genetics and biology of pancreatic ductal adenocarcinoma. *Genes Dev*. 2016;30(4):355–85.
- 55 Hu ZI, Shia J, Stadler ZK, Varghese AM, Capanu M, Salo-Mullen E, Lowry MA, Diaz LA Jr, Mandelker D, Yu KH, et al. Evaluating Mismatch Repair Deficiency in Pancreatic Adenocarcinoma: Challenges and Recommendations. *Clin Cancer Res*. 2018;24(6):1326–36.
- 56 Iguchi E, Safgren SL, Marks DL, Olson RL, Fernandez-Zapico ME. Pancreatic Cancer, A Mis-interpreter of the Epigenetic Language. *Yale J Biol Med*. 2016;89(4):575–90.
- 57 Roe JS, Hwang CI, Somerville TDD, Milazzo JP, Lee EJ, Da Silva B, Maiorino L, Tiriac H, Young CM, Miyabayashi K, et al. Enhancer Reprogramming Promotes Pancreatic Cancer Metastasis. *Cell*. 2017; 170(5):875–88 e820.
- 58 McDonald OG, Li X, Saunders T, Tryggvadottir R, Mentch SJ, Warmoes MO, Word AE, Carrer A, Salz TH, Natsume S, et al. Epigenomic reprogramming during pancreatic cancer progression links anabolic glucose metabolism to distant metastasis. *Nat Genet*. 2017;49(3):367–76.
- 59 Lomberk G, Blum Y, Nicolle R, Nair A, Gandonkar KS, Marisa L, Mathison A, Sun Z, Yan H, Elarouci N, et al. Distinct epigenetic landscapes underlie the pathobiology of pancreatic cancer subtypes. *Nat Commun*. 2018; 9(1):1978.
- 60 Connor AA, Denroche RE, Jang GH, Timms L, Kalimuthu SN, Selander I, McPherson T, Wilson GW, Chan-Seng-Yue MA, Borozan I, et al. Association of Distinct Mutational Signatures With Correlates of Increased Immune Activity in Pancreatic Ductal Adenocarcinoma. *JAMA Oncol*. 2017;3(6):774–83.
- 61 Moffitt RA, Marayati R, Flate EL, Volmar KE, Loeza SG, Hoadley KA, Rashid NU, Williams LA, Eaton SC, Chung AH, et al. Virtual microdissection identifies distinct tumor- and stroma-specific subtypes of pancreatic ductal adenocarcinoma. *Nat Genet*. 2015; 47(10):1168–78.
- 62 Collisson EA, Sadanandam A, Olson P, Gibb WJ, Truitt M, Gu S, Cooc J, Weinkle J, Kim GE, Jakkula L, et al. Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy. *Nat Med*. 2011;17(4):500–3.
- 63 Veenstra VL, Garcia-Garijo A, van Laarhoven HW, Bijlsma MF. Extracellular Influences: Molecular Subclasses and the Microenvironment in Pancreatic Cancer. *Cancers (Basel)*. 2018; 10(2). <https://doi.org/10.3390/cancers10020034>.
- 64 Muckenthaler A, Berger AK, Schlitter AM, Steiger K, Konukiewitz B, Trumpp A, Eils R, Werner J, Friess H, Esposito I, et al. Pancreatic Ductal Adenocarcinoma Subtyping Using the Biomarkers Hepatocyte Nuclear Factor-1A and Cytokeratin-81 Correlates with Outcome and Treatment Response. *Clin Cancer Res*. 2018; 24(2):351–9.
- 65 Aung KL, Fischer SE, Denroche RE, Jang GH, Dodd A, Creighton S, Southwood B, Liang SB, Chadwick D, Zhang A, et al. Genomics-Driven Precision Medicine for Advanced Pancreatic Cancer: Early Results from the COMPASS Trial. *Clin Cancer Res*. 2018;24(6):1344–54.
- 66 Nielsen MF, Mortensen MB, Detlefsen S. Key players in pancreatic cancerstroma interaction: Cancer-associated fibroblasts, endothelial and inflammatory cells. *World J Gastroenterol*. 2016;22(9):2678–700.
- 67 Biffi G, Oni TE, Spielman B, Hao Y, Elyada E, Park Y, Preall J, Tuveson DA. IL1-Induced JAK/STAT Signaling Is Antagonized by TGF-beta to Shape CAF Heterogeneity in Pancreatic Ductal Adenocarcinoma. *Cancer Discov*. 2019; 9(2):282–301.
- 68 Ohlund D, Handly-Santana A, Biffi G, Elyada E, Almeida AS, Ponz-Sarvise M, Corbo V, Oni TE, Hearn SA, Lee EJ, et al. Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. *J Exp Med*. 2017;214(3):579–96.
- 69 Melstrom LG, Salazar MD, Diamond DJ. The pancreatic cancer microenvironment: A true double agent. *J Surg Oncol*. 2017;116(1):7–15.
- 70 Masamune A, Watanabe T, Kikuta K, Shimogawa T. Roles of pancreatic stellate cells in pancreatic inflammation and fibrosis. *Clin Gastroenterol Hepatol*. 2009;7(11 Suppl):S48–54.
- 71 Apte MV, Haber PS, Darby SJ, Rodgers SC, McCaughey GW, Korsten MA, Pirola RC, Wilson JS. Pancreatic stellate cells are activated by pro-inflammatory cytokines: implications for pancreatic fibrogenesis. *Gut*. 1999;44(4):534–41.
- 72 Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, Feig C, Nakagawa T, Caldwell ME, Zecchini HI, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut*. 2013;62(1):112–20.
- 73 Jiang H, Hegde S, Knolhoff BL, Zhu Y, Hernondon JM, Meyer MA, Nywening TM, Hawkins WG, Shapiro IM, Weaver DT, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. *Nat Med*. 2016;22(8):851–60.
- 74 Erkan M, Kurtoglu M, Kleeff J. The role of hypoxia in pancreatic cancer: a potential therapeutic target? *Expert Rev Gastroenterol Hepatol*. 2016; 10(3):301–16.
- 75 Heinemann V, Reni M, Ychou M, Richel DJ, Macarulla T, Ducreux M. Tumour-stroma interactions in pancreatic ductal adenocarcinoma: rationale and current evidence for new therapeutic strategies. *Cancer Treat Rev*. 2014; 40(1):118–28.
- 76 Li N, Li Y, Li Z, Huang C, Yang Y, Lang M, Cao J, Jiang W, Xu Y, Dong J, et al. Hypoxia Inducible Factor 1 (HIF-1) Recruits Macrophage to Activate Pancreatic Stellate Cells in Pancreatic Ductal Adenocarcinoma. *Int J Mol Sci*. 40 2016; 17(6). <https://doi.org/10.3390/ijms17060799>.
- 77 Ene-Obong A, Clear AJ, Watt J, Wang J, Fatah R, Riches JC, Marshall JF, Chin-Aleong J, Chehla C, Gribben JG, et al. Activated pancreatic stellate cells sequester CD8+ T cells to reduce their infiltration of the juxtatumoral compartment of pancreatic ductal adenocarcinoma. *Gastroenterology*. 2013;145(5):1121–32.
- 78 Ozdemir BC, Pentcheva-Hoang T, Carstens JL, Zheng X, Wu CC, Simpson TR, Laklai H, Sugimoto H, Kahlert C, Novitskiy SV, et al. Depletion of carcinomaassociated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. *Cancer Cell*. 2014;25(6):719–34.

- 79 Daniel SK, Sullivan KM, Labadie KP, Pillai-Setty VG. Hypoxia as a barrier to immunotherapy in pancreatic adenocarcinoma. *Clin Transl Med*. 2019;8(1):10.
- 80 Clark CE, Hingorani SR, Mick R, Combs C, Tuveson DA, Vonderheide RH. Dynamics of the immune reaction to pancreatic cancer from inception to invasion. *Cancer Res*. 2007; 67(19):9518–27.
- 81 Mahajan UM, Langhoff E, Goni E, Costello E, Greenhalf W, Halloran C, Ormanns S, Kruger S, Boeck S, Ribback S, et al. Immune Cell and Stromal Signature Associated With Progression-Free Survival of Patients With Resected Pancreatic Ductal Adenocarcinoma. *Gastroenterology*. 2018;155(5):1625–39 e1622.
- 82 Mitchem JB, Brennan DJ, Knolhoff BL, Belt BA, Zhu Y, Sanford DE, Belaygorod L, Carpenter D, Collins L, Piwnica-Worms D, et al. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. *Cancer Res*. 2013; 73(3):1128–41.
- 83 Hu H, Hang JJ, Han T, Zhuo M, Jiao F, Wang LW. The M2 phenotype of tumor-associated macrophages in the stroma confers a poor prognosis in pancreatic cancer. *Tumour Biol*. 2016;37(7):8657–64.
- 84 Bronte V, Brandau S, Chen SH, Colombo MP, Frey AB, Greten TF, Mandruzzato S, Murray PJ, Ochoa A, Ostrand-Rosenberg S, et al. Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat Commun*. 2016;7:12150.
- 85 Nywening TM, Wang-Gillam A, Sanford DE, Belt BA, Panni RZ, Cusworth BM, Toriola AT, Nieman RK, Worley LA, Yano M, et al. Targeting tumourassociated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. *Lancet Oncol*. 2016;17(5):651–62.
- 86 Li J, Byrne KT, Yan F, Yamazoe T, Chen Z, Baslan T, Richman LP, Lin JH, Sun YH, Rech AJ, et al. Tumor Cell-Intrinsic Factors Underlie Heterogeneity of Immune Cell Infiltration and Response to Immunotherapy. *Immunity*. 2018; 49(1):178–193.e177.
- 87 Daley D, Zambirinis CP, Seifert L, Akkad N, Mohan N, Werba G, Barilla R, Torres-Hernandez A, Hundeyin M, VRK M, et al. gammadelta T Cells Support Pancreatic Oncogenesis by Restraining alphabeta T Cell Activation. *Cell*. 2016;166(6):1485–99 e1415.
- 88 Gunderson AJ, Kaneda MM, Tsujikawa T, Nguyen AV, Affara NI, Ruffell B, Gorjestani S, Liudahl SM, Truit M, Olson P, et al. Bruton Tyrosine Kinase-Dependent Immune Cell Cross-talk Drives Pancreas Cancer. *Cancer Discov*. 2016;6(3):270–85.
- 89 Pylayeva-Gupta Y, Das S, Handler JS, Hajdu CH, Coffre M, Koralov SB, Bar-Sagi D. IL35Producing B Cells Promote the Development of Pancreatic Neoplasia. *Cancer Discov*. 2016; 6(3):247–55.
- 90 Stromnes IM, Hulbert A, Pierce RH, Greenberg PD, Hingorani SR. T-cell Localization, Activation, and Clonal Expansion in Human Pancreatic Ductal Adenocarcinoma. *Cancer Immunol Res*. 2017;5(11):978–91.
- 91 Poschke I, Faryna M, Bergmann F, Flossdorf M, Lauenstein C, Hermes J, Hinz U, Hank T, Ehrenberg R, Volkmar M, et al. Identification of a tumor-reactive T-cell repertoire in the immune infiltrate of patients with resectable pancreatic ductal adenocarcinoma. *Oncoimmunology*. 2016;5(12):e1240859.
- 92 Johnson BA 3rd, Yarchoan M, Lee V, Laheru DA, Jaffee EM. Strategies for Increasing Pancreatic Tumor Immunogenicity. *Clin Cancer Res*. 2017;23(7):1656–69.
- 93 Yako YY, Kruger D, Smith M, Brand M. Cytokines as Biomarkers of Pancreatic Ductal Adenocarcinoma: A Systematic Review. *PLoS One*. 2016;11(5):e0154016.
- 94 Roshani R, McCarthy F, Hagemann T. Inflammatory cytokines in human pancreatic cancer. *Cancer Lett*. 2014;345(2):157–63.
- 95 Poruk KE, Firpo MA, Adler DG, Mulvihill SJ. Screening for pancreatic cancer: why, how, and who? *Ann Surg*. 2013;257(1):17–26.
- 96 Yachida S, Jones S, Bozic I, Antal T, Leary R, Fu B, Kamiyama M, Hruban RH, Eshleman JR, Nowak MA, et al. Distant metastasis occurs late during the genetic evolution of pancreatic cancer. *Nature*. 2010; 467(7319):1114–7.
- 97 Makohon-Moore AP, Zhang M, Reiter JG, Bozic I, Allen B, Kundu D, Chatterjee K, Wong F, Jiao Y, Kohutek ZA, et al. Limited heterogeneity of known driver gene mutations among the metastases of individual patients with pancreatic cancer. *Nat Genet*. 2017;49(3):358–66.
- 98 Campbell PJ, Yachida S, Mudie LJ, Stephens PJ, Pleasance ED, Stebbings LA, Morsberger LA, Latimer C, McLaren S, Lin ML, et al. The patterns and dynamics of genomic instability in metastatic pancreatic cancer. *Nature*. 2010; 467(7319):1109–13.
- 99 Rhim AD, Mirek ET, Aiello NM, Maitra A, Bailey JM, McAllister F, Reichert M, Beatty GL, Rustgi AK, Vonderheide RH, et al. EMT and dissemination precede pancreatic tumor formation. *Cell*. 2012;148(1-2):349–61.
- 100 Wang S, Huang S, Sun YL. Epithelial-Mesenchymal Transition in Pancreatic Cancer: A Review. *Biomed Res Int*. 2017;2017:2646148.
- 101 Takano S, Reichert M, Bakir B, Das KK, Nishida T, Miyazaki M, Heeg S, Collins MA, Marchand B, Hicks PD, et al. Prrx1 isoform switching regulates pancreatic cancer invasion and metastatic colonization. *Genes Dev*. 2016;30(2):233–47.
- 102 Krebs AM, Mitschke J, Lasierra Losada M, Schmalhofer O, Boerries M, Busch H, Boettcher M, Mougiakakos D, Reichardt W, Bronsert P, et al. The EMTActivator Zeb1 is a key factor for cell plasticity and promotes metastasis in pancreatic cancer. *Nat Cell Biol*. 2017;19(5):518–29.
- 103 Giovannetti E, van der Borden CL, Frampton AE, Ali A, Firuzi O, Peters GJ. Never let it go: Stopping key mechanisms underlying metastasis to fight pancreatic cancer. *Semin Cancer Biol*. 2017;44:43–59.
- 104 Mees ST, Mardin WA, Wendel C, Baeumer N, Willscher E, Senniger N, Schleicher C, Colombo-Benkmann M, Haier J. EP300—a miRNA-regulated metastasis suppressor gene in ductal adenocarcinomas of the pancreas. *Int J Cancer*. 2010;126(1):114–24.
- 105 Aiello NM, Maddipati R, Norgard RJ, Balli D, Li J, Yuan S, Yamazoe T, Black T, Sahmoud A, Furth EE, et al. EMT Subtype Influences Epithelial Plasticity and Mode of Cell Migration. *Dev Cell*. 2018;45(6):681–95 e684.
- 106 Yao D, Dai C, Peng S. Mechanism of the mesenchymal–epithelial transition and its relationship with metastatic tumor formation. *Mol Cancer Res*. 2011;9(12):1608–20.
- 107 Reichert M, Bakir B, Moreira L, Pitarresi JR, Feldmann K, Simon L, Suzuki K, Maddipati R, Rhim AD, Schlitter AM, et al. Regulation of Epithelial Plasticity Determines Metastatic Organotropism in Pancreatic Cancer. *Dev Cell*. 2018;45(6):696–711.e698.
- 108 Stratford JK, Bentrem DJ, Anderson JM, Fan C, Volmar KA, Marron JS, Routh ED, Caskey LS, Samuel JC, Der CJ, et al. A six-gene signature predicts survival of patients with localized pancreatic ductal adenocarcinoma. *PLoS Med*. 2010;7(7):e1000307.
- 109 Chaika NV, Yu F, Purohit V, Mehla K, Lazembaj AJ, DiMaio D, Anderson JM, Yeh JJ, Johnson KR, Hollingsworth MA, et al. Differential expression of metabolic genes in tumor and stromal components of primary and metastatic loci in pancreatic adenocarcinoma. *PLoS One*. 2012;7(3):e32996.
- 110 Abel EV, Simeone DM. Biology and clinical applications of pancreatic cancer stem cells. *Gastroenterology*. 2013;144(6):1241–8.
- 111 Kruger A. Premetastatic niche formation in the liver: emerging mechanisms and mouse models. *J Mol Med (Berl)*. 2015; 93(11):1193–201.
- 112 Costa-Silva B, Aiello NM, Ocean AJ, Singh S, Zhang H, Thakur BK, Becker A, Hoshino A, Mark MT, Molina H, et al. Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver. *Nat Cell Biol*. 2015; 17(6):816–26.
- 113 Grunwald B, Harant V, Schaten S, Fruhschutz M, Spallek R, Hochst B, Stutzer K, Berchtold S, Erkan M, Prokophuk O, et al. Pancreatic Premalignant Lesions Secrete Tissue Inhibitor of Metalloproteinases-1, Which Activates Hepatic Stellate Cells Via CD63 Signaling to Create a Premetastatic Niche in the Liver. *Gastroenterology*. 2016; 151(5):1011–24 e1017.
- 114 Amrutkar M, Gladhaug IP. Pancreatic Cancer Chemoresistance to Gemcitabine. *Cancers (Basel)*. 2017;9(11). <https://doi.org/10.3390/cancers9110157>.
- 115 Grasso C, Jansen G, Giovannetti E. Drug resistance in pancreatic cancer: Impact of altered energy metabolism. *Crit Rev Oncol Hematol*. 2017;114:139–52.
- 116 Morrison AH, Byrne KT, Vonderheide RH. Immunotherapy and Prevention of Pancreatic Cancer. *Trends Cancer*. 2018;4(6):418–28.

- 117 Nakano Y, Tanno S, Koizumi K, Nishikawa T, Nakamura K, Minoguchi M, Izawa T, Mizukami Y, Okumura T, Kohgo Y. Gemcitabine chemoresistance and molecular markers associated with gemcitabine transport and metabolism in human pancreatic cancer cells. *Br J Cancer*. 2007;96(3):457–63.
- 118 Nakahira S, Nakamori S, Tsujie M, Takahashi Y, Okami J, Yoshioka S, Yamasaki M, Marubashi S, Takemasa I, Miyamoto A, et al. Involvement of ribonucleotide reductase M1 subunit overexpression in gemcitabine resistance of human pancreatic cancer. *Int J Cancer*. 2007;120(6):1355–63.
- 119 Kurata N, Fujita H, Ohuchida K, Mizumoto K, Mahawithitwong P, Sakai H, Onimaru M, Manabe T, Ohtsuka T, Tanaka M. Predicting the chemosensitivity of pancreatic cancer cells by quantifying the expression levels of genes associated with the metabolism of gemcitabine and 5-fluorouracil. *Int J Oncol*. 2011;39(2):473–82.
- 120 Valsecchi ME, Holdbrook T, Leiby BE, Pequignot E, Littman SJ, Yeo CJ, Brody JR, Witkiewicz AK. Is there a role for the quantification of RRM1 and ERCC1 expression in pancreatic ductal adenocarcinoma? *BMC Cancer*. 2012;12:104.
- 121 Duxbury MS, Ito H, Benoit E, Waseem T, Ashley SW, Whang EE. RNA interference demonstrates a novel role for integrin-linked kinase as a determinant of pancreatic adenocarcinoma cell gemcitabine chemoresistance. *Clin Cancer Res*. 2005;11(9):3433–8.
- 122 Erkan M, Kleeff J, Esposito I, Giese T, Ketterer K, Buchler MW, Giese NA, Friess H. Loss of BNIP3 expression is a late event in pancreatic cancer contributing to chemoresistance and worsened prognosis. *Oncogene*. 2005;24(27):4421–32.
- 123 Hessmann E, Patzak MS, Klein L, Chen N, Kari V, Ramu I, Bapiro TE, Frese KK, Gopinathan A, Richards FM, et al. Fibroblast drug scavenging increases intratumoural gemcitabine accumulation in murine pancreas cancer. *Gut*. 2018;67(3):497–507.
- 124 Caparello C, Meijer LL, Garajova I, Falcone A, Le Large TY, Funel N, Kazemier G, Peters GJ, Vasile E, Giovannetti E. FOLFIRINOX and translational studies: Towards personalized therapy in pancreatic cancer. *World J Gastroenterol*. 2016;22(31):6987–7005.
- 125 Huguet F, Mukherjee S, Jayle M. Locally advanced pancreatic cancer: the role of definitive chemoradiotherapy. *Clin Oncol (R Coll Radiol)*. 2014;26(9):560–8.
- 126 Quintiliani M. Modification of radiation sensitivity: the oxygen effect. *Int J Radiat Oncol Biol Phys*. 1979;5(7):1069–76.
- 127 Matsumoto S, Kishimoto S, Saito K, Takakusagi Y, Munasinghe JP, Devasahayam N, Hart CP, Gillies RJ, Mitchell JB, Krishna MC. Metabolic and Physiologic Imaging Biomarkers of the Tumor Microenvironment Predict Treatment Outcome with Radiation or a Hypoxia-Activated Prodrug in Mice. *Cancer Res*. 2018;78(14):3783–92.
- 128 Maacke H, Jost K, Opitz S, Miska S, Yuan Y, Hasselbach L, Luttges J, Kalthoff H, Sturzbecher HW. DNA repair and recombination factor Rad51 is over-expressed in human pancreatic adenocarcinoma. *Oncogene*. 2000;19(23):2791–5.
- 129 Mathews LA, Cabarcas SM, Hurt EM, Zhang X, Jaffee EM, Farrar WL. Increased expression of DNA repair genes in invasive human pancreatic cancer cells. *Pancreas*. 2011;40(5):730–9.
- 130 Wang F, Xia X, Yang C, Shen J, Mai J, Kim HC, Kirui D, Kang Y, Fleming JB, Koay EJ, et al. SMAD4 Gene Mutation Renders Pancreatic Cancer Resistance to Radiotherapy through Promotion of Autophagy. *Clin Cancer Res*. 2018;24(13):3176–85.
- 131 Cordes N, Frick S, Brunner TB, Pilarsky C, Grutzmann R, Sipos B, Kloppel G, McKenna WG, Bernhard EJ. Human pancreatic tumor cells are sensitized to ionizing radiation by knockdown of caveolin-1. *Oncogene*. 2007;26(48):6851–62.
- 132 Hehlgans S, Eke I, Storch K, Haase M, Baretton GB, Cordes N. Caveolin-1 mediated radioresistance of 3D grown pancreatic cancer cells. *Radiother Oncol*. 2009;92(3):362–70.
- 133 Kalbasi A, Komar C, Tooker GM, Liu M, Lee JW, Gladney WL, Ben-Josef E, Beatty GL. Tumor-Derived CCL2 Mediates Resistance to Radiotherapy in Pancreatic Ductal Adenocarcinoma. *Clin Cancer Res*. 2017;23(1):137–48.
- 134 Murphy JD, Adusumilli S, Griffith KA, Ray ME, Zalupski MM, Lawrence TS, Ben-Josef E. Full-dose gemcitabine and concurrent radiotherapy for unresectable pancreatic cancer. *Int J Radiat Oncol Biol Phys*. 2007;68(3):801–8.
- 135 Loehrer PJ Sr, Feng Y, Cardenes H, Wagner L, Brell JM, Celli D, Flynn P, Ramanathan RK, Crane CH, Alberts SR, et al. Gemcitabine alone versus gemcitabine plus radiotherapy in patients with locally advanced pancreatic cancer: an Eastern Cooperative Oncology Group trial. *J Clin Oncol*. 2011;29(31):4105–12.
- 136 Chang DT, Schellenberg D, Shen J, Kim J, Goodman KA, Fisher GA, Ford JM, Desser T, Quon A, Koong AC. Stereotactic radiotherapy for unresectable adenocarcinoma of the pancreas. *Cancer*. 2009;115(3):665–72.
- 137 Kastenhuber ER, Lowe SW. Putting p53 in Context. *Cell*. 2017;170(6):1062–78.
- 138 Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable RAS: Mission possible? *Nat Rev Drug Discov*. 2014;13(11):828–51.
- 139 Agbunag C, Bar-Sagi D. Oncogenic K-ras drives cell cycle progression and phenotypic conversion of primary pancreatic duct epithelial cells. *Cancer Res*. 2004;64(16):5659–63.
- 140 Eser S, Schnieke A, Schneider G, Saur D. Oncogenic KRAS signalling in pancreatic cancer. *Br J Cancer*. 2014;111(5):817–22.
- 141 Philip PA, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, Rowland KM, Atkins JN, Mirtsching BC, Rivkin SE, 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(22):3605–10.
- 142 Kim YJ, Jung K, Baek DS, Hong SS, Kim YS. Co-targeting of EGF receptor and neuropilin-1 overcomes cetuximab resistance in pancreatic ductal adenocarcinoma with integrin beta1-driven Src-Akt bypass signaling. *Oncogene*. 2017;36(18):2543–52.
- 143 Fleming JB, Shen GL, Holloway SE, Davis M, Brekken RA. Molecular consequences of silencing mutant K-ras in pancreatic cancer cells: justification for K-ras-directed therapy. *Mol Cancer Res*. 2005;3(7):413–23.
- 144 Baines AT, Xu D, Der CJ. Inhibition of Ras for cancer treatment: the search continues. *Future Med Chem*. 2011;3(14):1787–808.
- 145 Zimmermann G, Papke B, Ismail S, Vartak N, Chandra A, Hoffmann M, Hahn SA, Triola G, Wittinghofer A, Bastiaens PI, et al. Small molecule inhibition of the KRAS-PDEdelta interaction impairs oncogenic KRAS signalling. *Nature*. 2013;497(7451):638–42.
- 146 Moore MJ, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, 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(15):1960–6.
- 147 Boeck S, Jung A, Laubender RP, Neumann J, Egg R, Goritschan C, Ormanns S, Haas M, Modest DP, Kirchner T, et al. KRAS mutation status is not predictive for objective response to anti-EGFR treatment with erlotinib in patients with advanced pancreatic cancer. *J Gastroenterol*. 2013;48(4):544–8.
- 148 Conradt L, Godl K, Schaaf C, Tebbe A, Eser S, Diersch S, Michalski CW, Kleeff J, Schnieke A, Schmid RM, et al. Disclosure of erlotinib as a multikinase inhibitor in pancreatic ductal adenocarcinoma. *Neoplasia*. 2011;13(11):1026–34.
- 149 Ardito CM, Gruner BM, Takeuchi KK, Lubedseder-Martellato C, Teichmann N, Mazur PK, Delgироно KE, Carpenter ES, Halbrook CJ, Hall JC, et al. EGF receptor is required for KRAS-induced pancreatic tumorigenesis. *Cancer Cell*. 2012;22(3):304–17.
- 150 Schneeweis C, Wirth M, Saur D, Reichert M, Schneider G. Oncogenic KRAS and the EGFR loop in pancreatic carcinogenesis—A connection to licensing nodes. *Small GTPases*. 2018;9(6):457–64.
- 151 Diersch S, Wirth M, Schneeweis C, Jors S, Geisler F, Siveke JT, Rad R, Schmid RM, Saur D, Rustgi AK, et al. Kras(G12D) induces EGFR-MYC cross signaling in murine primary pancreatic ductal epithelial cells. *Oncogene*. 2016;35(29):3880–6.
- 152 Bergmann L, Maute L, Heil G, Russel J, Weidmann E, Koberle D, Fuxius S, Weigang-Kohler K, Aulitzky WE, Wormann B, et al. A prospective randomised phase-II trial with gemcitabine versus gemcitabine plus sunitinib in advanced pancreatic cancer: a study of the CESAR Central European Society for Anticancer Drug Research-EWIV. *Eur J Cancer*. 2015;51(1):27–36.

- 153 Miyabayashi K, Ijichi H, Mohri D, Tada M, Yamamoto K, Asaoka Y, Ikenoue T, Tateishi K, Nakai Y, Isayama H, et al. Erlotinib prolongs survival in pancreatic cancer by blocking gemcitabine-induced MAPK signals. *Cancer Res.* 2013; 73(7):2221–34.
- 154 Vaseva AV, Blake DR, Gilbert TSK, Ng S, Hostetter G, Azam SH, Ozkan-Dagliyan I, Gautam P, Bryant KL, Pearce KH, et al. KRAS Suppression-Induced Degradation of MYC Is Antagonized by a MEK5-ERK5 Compensatory Mechanism. *Cancer Cell.* 2018; 34(5):807–22 e807.
- 155 Hayes TK, Neel NF, Hu C, Gautam P, Chennard M, Long B, Aziz M, Kassner M, Bryant KL, Pierobon M, et al. Long-Term ERK Inhibition in KRAS-Mutant Pancreatic Cancer Is Associated with MYC Degradation and Senescence-like Growth Suppression. *Cancer Cell.* 2016;29(1):75–89.
- 156 Ruess DA, Heynen GJ, Ciecielski KJ, Ai J, Berninger A, Kabacaoglu D, Gorgulu K, Dantes Z, Wormann SM, Diakopoulos KN, et al. Mutant KRAS-driven cancers depend on PTPN11/SHP2 phosphatase. *Nat Med.* 2018; 24(7):954–60.
- 157 Zeitouni D, Pylayeva-Gupta Y, Der CJ, Bryant KL. KRAS Mutant Pancreatic Cancer: No Lone Path to an Effective Treatment. *Cancers (Basel).* 2016;8(4). <https://doi.org/10.3390/cancers8040045>.
- 158 Collisson EA, Trejo CL, Silva JM, Gu S, Korkola JE, Heiser LM, Charles RP, Rabinovich BA, Hann B, Dankort D, et al. A central role for RAF->MEK->ERK signaling in the genesis of pancreatic ductal adenocarcinoma. *Cancer Discov.* 2012;2(8):685–93.
- 159 Eser S, Reiff N, Messer M, Seidler B, Gottschalk K, Dobler M, Hieber M, Arbeiter A, Klein S, Kong B, et al. Selective requirement of PI3K/PDK1 signaling for Kras oncogene-driven pancreatic cell plasticity and cancer. *Cancer Cell.* 2013;23(3):406–20.
- 160 Alagesan B, Contino G, Guimaraes AR, Corcoran RB, Deshpande V, Wojtkiewicz GR, Hezel AF, Wong KK, Loda M, Weissleder R, et al. Combined MEK and PI3K inhibition in a mouse model of pancreatic cancer. *Clin Cancer Res.* 2015;21(2):396–404.
- 161 Ischenko I, Petrenko O, Hayman MJ. A MEK/PI3K/HDAC inhibitor combination therapy for KRAS mutant pancreatic cancer cells. *Oncotarget.* 2015;6(18):15814–27.
- 162 Junnila MR, Devasthali V, Cheng JH, Castillo J, Metcalfe C, Clermont AC, Otter DD, Chan E, Bou-Reslan H, Cao T, et al. Modeling targeted inhibition of MEK and PI3 kinase in human pancreatic cancer. *Mol Cancer Ther.* 2015;14(1):40–7.
- 163 Ciuffreda L, Del Curatolo A, Falcone I, Conciatori F, Bazzichetto C, Cognetti F, Corbo V, Scarpa A, Milella M. Lack of growth inhibitory synergism with combined MAPK/PI3K inhibition in preclinical models of pancreatic cancer. *Ann Oncol.* 2017;28(11):2896–8.
- 164 Chung V, McDonough S, Philip PA, Cardin D, Wang-Gillam A, Hui L, Tejani MA, Seery TE, Dy IA, 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(4):516–22.
- 165 Stoy C, Sundaram A, Rios Garcia M, Wang X, Seibert O, Zota A, Wendler S, Mannle D, Hinz U, Sticht C, et al. Transcriptional co-factor Transducin betalike (TBL) 1 acts as a checkpoint in pancreatic cancer malignancy. *EMBO Mol Med.* 2015;7(8):1048–62.
- 166 Fiskus W, Sharma S, Saha S, Shah B, Devaraj SG, Sun B, Horrigan S, Leveque C, Zu Y, Iyer S, et al. Pre-clinical efficacy of combined therapy with novel beta-catenin antagonist BC2059 and histone deacetylase inhibitor against AML cells. *Leukemia.* 2015; 29(6):1267–78.
- 167 Populo H, Lopes JM, Soares P. The mTOR signalling pathway in human cancer. *Int J Mol Sci.* 2012;13(2):1886–918.
- 168 Wei F, Zhang Y, Geng L, Zhang P, Wang G, Liu Y. mTOR inhibition induces EGFR feedback activation in association with its resistance to human pancreatic cancer. *Int J Mol Sci.* 2015;16(2):3267–82.
- 169 Utomo WK, Narayanan V, Biemann K, van Eijck CH, Bruno MJ, Peppelenbosch MP, Braat H. mTOR is a promising therapeutic target in a subpopulation of pancreatic adenocarcinoma. *Cancer Lett.* 2014; 346(2):309–17.
- 170 Lou HZ, Weng XC, Pan HM, Pan Q, Sun P, Liu LL, Chen B. The novel mTORC1/2 dual inhibitor INK-128 suppresses survival and proliferation of primary and transformed human pancreatic cancer cells. *Biochem Biophys Res Commun.* 2014;450(2):973–8.
- 171 Morran DC, Wu J, Jamieson NB, Mrowinska A, Kalna G, Karim SA, Au AY, Scarlett CJ, Chang DK, Pajak MZ, et al. Targeting mTOR dependency in pancreatic cancer. *Gut.* 2014; 63(9):1481–9.
- 172 Soares HP, Ni Y, Kisfalvi K, Sinnott-Smith J, Rozengurt E. Different patterns of Akt and ERK feedback activation in response to rapamycin, active-site mTOR inhibitors and metformin in pancreatic cancer cells. *PLoS One.* 2013;8(2):e57289.
- 173 Soares HP, Ming M, Mellon M, Young SH, Han L, Sinnott-Smith J, Rozengurt E. Dual PI3K/mTOR Inhibitors Induce Rapid Overactivation of the MEK/ERK Pathway in Human Pancreatic Cancer Cells through Suppression of mTORC2. *Mol Cancer Ther.* 2015;14(4):1014–23.
- 174 O'Reilly KE, Rojo F, She QB, Solit D, Mills GB, Smith D, Lane H, Hofmann F, Hicklin DJ, Ludwig DL, et al. mTOR inhibition induces upstream receptor tyrosine kinase signaling and activates Akt. *Cancer Res.* 2006; 66(3):1500–8.
- 175 Hassan Z, Schneeweis C, Wirth M, Veltkamp C, Dantes Z, Feuerecker B, Ceyhan GO, Knauer SK, Weichert W, Schmid RM, et al. MTOR inhibitor-based combination therapies for pancreatic cancer. *Br J Cancer.* 2018; 118(3):366–77.
- 176 Driscoll DR, Karim SA, Sano M, Gay DM, Jacob W, Yu J, Mizukami Y, Gopinathan A, Jodrell DI, Evans TR, et al. mTORC2 Signaling Drives the Development and Progression of Pancreatic Cancer. *Cancer Res.* 2016; 76(23):6911–23.
- 177 Shimizu T, Tolcher AW, Papadopoulos KP, Beoram M, Rasco DW, Smith LS, Gunn S, Smetzer L, Mays TA, Kaiser B, et al. The clinical effect of the dualtargeting strategy involving PI3K/AKT/mTOR and RAS/MEK/ERK pathways in patients with advanced cancer. *Clin Cancer Res.* 2012;18(8):2316–25.
- 178 Wolpin BM, Hezel AF, Abrams T, Blaszczakowsky LS, Meyerhardt JA, Chan JA, Enzinger PC, Allen B, Clark JW, Ryan DP, et al. Oral mTOR inhibitor everolimus in patients with gemcitabine-refractory metastatic pancreatic cancer. *J Clin Oncol.* 2009;27(2):193–8.
- 179 Javle MM, Shroff RT, Xiong H, Varadhachary GA, Fogelman D, Reddy SA, Davis D, Zhang Y, Wolff RA, Abbruzzese JL. Inhibition of the mammalian target of rapamycin (mTOR) in advanced pancreatic cancer: results of two phase II studies. *BMC Cancer.* 2010;10:368.
- 180 Iriana S, Ahmed S, Gong J, Annamalai AA, Tuli R, Hendifar AE. Targeting mTOR in Pancreatic Ductal Adenocarcinoma. *Front Oncol.* 2016;6:99.
- 181 Kordes S, Klumpen HJ, Weterman MJ, Schellens JH, Richel DJ, Wilmink JW. Phase II study of capecitabine and the oral mTOR inhibitor everolimus in patients with advanced pancreatic cancer. *Cancer Chemother Pharmacol.* 2015;75(6):1135–41.
- 182 Chan J, Kulke M. Targeting the mTOR signaling pathway in neuroendocrine tumors. *Curr Treat Options Oncol.* 2014;15(3):365–79.
- 183 Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, Madhu B, Goldgraben MA, Caldwell ME, Allard D, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. *Science.* 2009; 324(5933):1457–61.
- 184 Itakura J, Ishiwata T, Friess H, Fujii H, Matsumoto Y, Buchler MW, Korc M. Enhanced expression of vascular endothelial growth factor in human pancreatic cancer correlates with local disease progression. *Clin Cancer Res.* 1997;3(8):1309–16.
- 185 Kindler HL, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, 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(22):3617–22.
- 186 Kindler HL, Ioka T, Richel DJ, Bennouna J, Letourneau R, Okusaka T, Funakoshi A, Furuse J, Park YS, Ohkawa S, 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(3):256–62.

- 187 Van Cutsem E, Vervenne WL, Bennouna J, Humbert Y, Gill S, Van Laethem JL, Verslype C, Scheithauer W, Shang A, Cosaert 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(13):2231–7.
- 188 Craven KE, Gore J, Korc M. Overview of pre-clinical and clinical studies targeting angiogenesis in pancreatic ductal adenocarcinoma. *Cancer Lett.* 2016;381(1):201–10.
- 189 Powell SN, Kachnic LA. Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation. *Oncogene.* 2003; 22(37):5784–91.
- 190 Golan T, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, Aderka D, Paluch-Shimon S, Kaufman B, Gershoni-Baruch R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. *Br J Cancer.* 2014;111(6):1132–8.
- 191 Blair AB, Groot VP, Gemenetzis G, Wei J, Cameron JL, Weiss MJ, Goggins M, Wolfgang CL, Yu J, He J. BRCA1/BRCA2 Germline Mutation Carriers and Sporadic Pancreatic Ductal Adenocarcinoma. *J Am Coll Surg.* 2018; 226(4):630–7 e631.
- 192 Helleday T. The underlying mechanism for the PARP and BRCA synthetic lethality: clearing up the misunderstandings. *Mol Oncol.* 2011;5(4):387–93.
- 193 Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmana J, Mitchell G, Fried G, Stemmer SM, Hubert A, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol.* 2015;33(3):244–50.
- 194 Bendell J, O'Reilly EM, Middleton MR, Chau I, Hochster H, Fielding A, Burke W, Burris H 3rd. Phase I study of olaparib plus gemcitabine in patients with advanced solid tumours and comparison with gemcitabine alone in patients with locally advanced/metastatic pancreatic cancer. *Ann Oncol.* 2015; 26(4):804–11.
- 195 Lowery MA, Kelsen DP, Capanu M, Smith SC, Lee JW, Stadler ZK, Moore MJ, Kindler HL, Golan T, Segal A, et al. Phase II trial of veliparib in patients with previously treated BRCA-mutated pancreas ductal adenocarcinoma. *Eur J Cancer.* 2018;89:19–26.
- 196 O'Reilly EM, Lee JW, Lowery MA, Capanu M, Stadler ZK, Moore MJ, Dhani N, Kindler HL, Estrella H, Maynard H, et al. Phase 1 trial evaluating cisplatin, gemcitabine, and veliparib in 2 patient cohorts: Germline BRCA mutation carriers and wild-type BRCA pancreatic ductal adenocarcinoma. *Cancer.* 2018; 124(7):1374–82.
- 197 Perkhofer L, Schmitt A, Romero Carrasco MC, Ihle M, Hampp S, Ruess DA, Hessmann E, Russell R, Lechel A, Azoitei N, et al. ATM Deficiency Generating Genomic Instability Sensitizes Pancreatic Ductal Adenocarcinoma Cells to Therapy-Induced DNA Damage. *Cancer Res.* 2017;77(20):5576–90.
- 198 Hessmann E, Johnsen SA, Siveke JT, Ellenrieder V. Epigenetic treatment of pancreatic cancer: is there a therapeutic perspective on the horizon? *Gut.* 2017;66(1):168–79.
- 199 Mazur PK, Herner A, Mello SS, Wirth M, Hausmann S, Sanchez-Rivera FJ, Lofgren SM, Kuschma T, Hahn SA, Vangala D, et al. Combined inhibition of BET family proteins and histone deacetylases as a potential epigenetics-based therapy for pancreatic ductal adenocarcinoma. *Nat Med.* 2015;21(10):1163–71.
- 200 Krantz BA, O'Reilly EM. Biomarker-Based Therapy in Pancreatic Ductal Adenocarcinoma: An Emerging Reality? *Clin Cancer Res.* 2018;24(10): 2241–50.
- 201 McDonald PC, Chafe SC, Brown WS, Saberi S, Swayampakula M, Venkateswaran G, Nemirovsky O, Gillespie JA, Karasinska JM, Kaloger SE, et al. Regulation of pH by Carbonic Anhydrase 9 Mediates Survival of Pancreatic Cancer Cells With Activated KRAS in Response to Hypoxia. *Gastroenterology.* 2019. <https://doi.org/10.1053/j.gastro.2019.05.004>.
- 202 Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12(4):252–64.
- 203 Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, Gonzalez R, Robert C, Schadendorf D, Hassel JC, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010; 363(8):711–23.
- 204 Sahin IH, Askan G, Hu ZI, O'Reilly EM. Immunotherapy in pancreatic ductal adenocarcinoma: an emerging entity? *Ann Oncol.* 2017;28(12):2950–61.
- 205 Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science.* 2015;348(6230):124–8.
- 206 Balachandran VP, Lukszta M, Zhao JN, Makarov V, Moral JA, Remark R, Herbst B, Askan G, Bhanot U, Senbabaooglu Y, et al. Identification of unique neoantigen qualities in long-term survivors of pancreatic cancer. *Nature.* 2017;551(7681):512–6.
- 207 Bauer C, Kuhnemuth B, Duewell P, Ormanns S, Gress T, Schnurr M. Prevailing over T cell exhaustion: New developments in the immunotherapy of pancreatic cancer. *Cancer Lett.* 2016;381(1):259–68.
- 208 Gjertsen MK, Buanes T, Rosseland AR, Balka A, Gladhaug I, Soreide O, Eriksen JA, Moller M, Baksaas I, Lothe RA, et al. Intra-dermal ras peptide vaccination with granulocyte-macrophage colony-stimulating factor as adjuvant: Clinical and immunological responses in patients with pancreatic adenocarcinoma. *Int J Cancer.* 2001;92(3):441–50.
- 209 Hardacre JM, Mulcahy M, Small W, Talamonti M, Obel J, Krishnamurthi S, Rocha-Lima CS, Safran H, Lenz HJ, Chiorean EG. Addition of algenpantucel-L immunotherapy to standard adjuvant therapy for pancreatic cancer: a phase 2 study. *J Gastrointest Surg.* 2013;17(1):94–100 discussion p. 100–101.
- 210 Yan J, Pankhong P, Shin TH, Obeng-Adjei N, Morrow MP, Walters JN, Khan AS, Sardesai NY, Weiner DB. Highly optimized DNA vaccine targeting human telomerase reverse transcriptase stimulates potent antitumor immunity. *Cancer Immunol Res.* 2013; 1(3):179–89.
- 211 NewLink Genetics Announces Results from Phase 3 IMPRESS Trial of Algenpantucel-L for Patients with Resected Pancreatic Cancer [https://globenewswire.com/news-release/2016/05/09/837878/0/en/NewLink-Genetics-Announces-Results-from-Phase-3-IMPRESS-Trial-of-Algenpantucel-L-for-Patients-with-Resected-Pancreatic-Cancer.html]. Accessed 30 July.
- 212 Middleton G, Silcocks P, Cox T, Valle J, Wadsley J, Propper D, Coxon F, Ross P, Madhusudan S, Roques 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(8):829–40.
- 213 Le DT, Wang-Gillam A, Picozzi V, Greten TF, Crocenzi T, Springett G, Morse M, Zeh H, Cohen D, Fine RL, et al. Safety and survival with GVAX pancreas prime and Listeria Monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *J Clin Oncol.* 2015; 33(12):1325–33.
- 214 Tran E, Ahmadzadeh M, Lu YC, Gros A, Turcotte S, Robbins PF, Gartner JJ, Zheng Z, Li YF, Ray S, et al. Immunogenicity of somatic mutations in human gastrointestinal cancers. *Science.* 2015;350(6266):1387–90.
- 215 Tran E, Robbins PF, Lu YC, Prickett TD, Gartner JJ, Jia L, Pasetto A, Zheng Z, Ray S, Groh EM, et al. T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer. *N Engl J Med.* 2016;375(23):2255–62.
- 216 Bauer C, Dauer M, Saraj S, Schnurr M, Bauernfeind F, Sterzik A, Junkmann J, Jakl V, Kiefl R, Oduncu F, et al. Dendritic cell-based vaccination of patients with advanced pancreatic carcinoma: results of a pilot study. *Cancer Immunol Immunother.* 2011; 60(8):1097–107.
- 217 Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest.* 2012;122(3):787–95.
- 218 Elgueta R, Benson MJ, de Vries VC, Wasiuk A, Guo Y, Noelle RJ. Molecular mechanism and function of CD40/CD40L engagement in the immune system. *Immunol Rev.* 2009; 229(1):152–72.
- 219 Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, Huhn RD, Song W, Li D, Sharp LL, et al. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Science.* 2011;331(6024):1612–6.
- 220 Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell.* 2010; 140(6):805–20.
- 221 Jacobs C, Duewell P, Heckelsmiller K, Wei J, Bauernfeind F, Ellermeier J, Kissel U, Bauer CA, Dauer M, Eigler A, et al. An ISCOM vaccine combined with a TLR9 agonist breaks immune evasion mediated by regulatory T cells in an orthotopic model of pancreatic carcinoma. *Int J Cancer.* 2011; 128(4):897–907.

- 222 Duewell P, Steger A, Lohr H, Bourhis H, Hoelz H, Kirchleitner SV, Stieg MR, Grassmann S, Kobold S, Siveke JT, et al. RIG-I-like helicases induce immunogenic cell death of pancreatic cancer cells and sensitize tumors toward killing by CD8(+) T cells. *Cell Death Differ.* 2014;21(12):1825–37.
- 223 Corrales L, Glickman LH, McWhirter SM, Kanne DB, Sivick KE, Katibah GE, Woo SR, Lemmens E, Banda T, Leong JJ, et al. Direct Activation of STING in the Tumor Microenvironment Leads to Potent and Systemic Tumor Regression and Immunity. *Cell Rep.* 2015;11(7):1018–30.
- 224 Maude SL, Laetsch TW, Buechner J, Rives S, Boyer M, Bittencourt H, Bader P, Verneris MR, Stefanski HE, Myers GD, et al. Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med.* 2018; 378(5):439–48.
- 225 Benmebarek MR, Karches CH, Cadilha BL, Lesch S, Endres S, Kobold S. Killing Mechanisms of Chimeric Antigen Receptor (CAR) T Cells. *Int J Mol Sci.* 2019; 20(6). <https://doi.org/10.3390/ijms20061283>.
- 226 Posey AD Jr, Schwab RD, Boesteanu AC, Steentoft C, Mandel U, Engels B, Stone JD, Madsen TD, Schreiber K, Haines KM, et al. Engineered CAR T Cells Targeting the Cancer-Associated Tn-Glycoform of the Membrane Mucin MUC1 Control Adenocarcinoma. *Immunity.* 2016;44(6):1444–54.
- 227 Akce M, Zaidi MY, Waller EK, El-Rayes BF, Lesinski GB. The Potential of CAR T Cell Therapy in Pancreatic Cancer. *Front Immunol.* 2018;9:2166.
- 228 Hingorani SR, Zheng L, Bullock AJ, Seery TE, Harris WP, Sigal DS, Braiteh F, Ritch PS, Zalupska MM, Bahary N, 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.* 2018;36(4):359–66.
- 229 Doherty GJ, Temporo M, Corrie PG. HALO-109-301: a Phase III trial of PEGPH20 (with gemcitabine and nab-paclitaxel) in hyaluronic acid-high stage IV pancreatic cancer. *Futura Oncol.* 2018;14(1):13–22.
- 230 Kanteti R, Mirzapozazova T, Riehm JJ, Dhannasingh I, Mambetsariev B, Wang J, Kulkarni P, Kaushik G, Seshacharyulu P, Ponnusamy MP, et al. Focal adhesion kinase a potential therapeutic target for pancreatic cancer and malignant pleural mesothelioma. *Cancer Biol Ther.* 2018;19(4):316–27.
- 231 Begum A, Ewachiw T, Jung C, Huang A, Norberg KJ, Marchionni L, McMillan R, Penchev V, Rajeshkumar NV, Maitra A, et al. The extracellular matrix and focal adhesion kinase signaling regulate cancer stem cell function in pancreatic ductal adenocarcinoma. *PLoS One.* 2017;12(7):e0180181.
- 232 Joyce JA, Fearon DT. T cell exclusion, immune privilege, and the tumor microenvironment. *Science.* 2015;348(6230):74–80.
- 233 Albeituni SH, Ding C, Yan J. Hampering immune suppressors: therapeutic targeting of myeloid-derived suppressor cells in cancer. *Cancer J.* 2013;19(6):490–501.
- 234 Stromnes IM, Brockenbrough JS, Izeradjene K, Carlson MA, Cuevas C, Simmons RM, Greenberg PD, Hingorani SR. Targeted depletion of an MDSC subset unmasks pancreatic ductal adenocarcinoma to adaptive immunity. *Gut.* 2014;63(11):1769–81.
- 235 Sanford DE, Belt BA, Panni RZ, Mayer A, Deshpande AD, Carpenter D, Mitchem JB, Plambeck-Suess SM, Worley LA, Goetz BD, et al. Inflammatory monocyte mobilization decreases patient survival in pancreatic cancer: a role for targeting the CCL2/CCR2 axis. *Clin Cancer Res.* 2013;19(13):3404–15.
- 236 Linehan D, Noel MS, Hezel AF, Wang-Gillam A, Eskens F, Sleijfer S, Desar IIME, Erdkamp F, Wilmink J, Diehl J, et al. Overall survival in a trial of orally administered CCR2 inhibitor CCX872 in locally advanced/ metastatic pancreatic cancer: Correlation with blood monocyte counts. *J Clin Oncol.* 2018; 36(5\_suppl):92.
- 237 Zhu Y, Knolhoff BL, Meyer MA, Nywening TM, West BL, Luo J, Wang-Gillam A, Goedebuure SP, Linehan DC, DeNardo DG. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. *Cancer Res.* 2014; 74(18):5057–69.
- 238 Schnurr M, Duewell P, Bauer C, Rothenfusser S, Lauber K, Endres S, Kobold S. Strategies to relieve immunosuppression in pancreatic cancer. *Immunotherapy.* 2015;7(4):363–76.
- 239 Vokes EE. Combined modality therapy of solid tumours. *Lancet.* 1997; 349(Suppl 2):SII4–6.
- 240 Niyazi M, Maihoefer C, Krause M, Rodel C, Budach W, Belka C. Radiotherapy and “new” drugs-new side effects? *Radiat Oncol.* 2011;6: 177.
- 241 Buchsbaum DJ, Bonner JA, Grizzle WE, Stackhouse MA, Carpenter M, Hicklin DJ, Bohlen P, Raisch KP. Treatment of pancreatic cancer xenografts with Erbitux (IMC-C225) anti-EGFR antibody, gemcitabine, and radiation. *Int J Radiat Oncol Biol Phys.* 2002; 54(4):1180–93.
- 242 Morgan MA, Parsels LA, Kollar LE, Normolle DP, Maybaum J, Lawrence TS. The combination of epidermal growth factor receptor inhibitors with gemcitabine and radiation in pancreatic cancer. *Clin Cancer Res.* 2008; 14(16):5142–9.
- 243 Demols A, Mahin C, Maréchal R, Delaunoit T, Borbath I, Hendilisz A, Jacqy C, Mitine C, Laethem JV. Cetuximab plus chemoradiation combined therapy for locally advanced inoperable pancreatic adenocarcinoma: A phase I study. *J Clin Oncol.* 2008;26(15\_suppl):4629.
- 244 Munter M, Timke C, Abdollahi A, Friess H, Jaeger D, Heeger S, Buchler M, Debus J, Huber P, Krempien R. Final results of a phase II trial [PARC-Study ISRCTN56652283] for patients with primary inoperable locally advanced pancreatic cancer combining intensity modulated radiotherapy (IMRT) with cetuximab and gemcitabine. *J Clin Oncol.* 2008; 26(15\_suppl):4613.
- 245 Arnoletti JP, Frolov A, Eloubeidi M, Keene K, Posey J, Wood T, Greeno E, Jhala N, Varadarajulu S, Russo S, et al. A phase I study evaluating the role of the anti-epidermal growth factor receptor (EGFR) antibody cetuximab as a radiosensitizer with chemoradiation for locally advanced pancreatic cancer. *Cancer Chemother Pharmacol.* 2011;67(4):891–7.
- 246 Rembielak AI, Jain P, Jackson AS, Green MM, Santorelli GR, Whitfield GA, Crellin A, Garcia-Alonso A, Radhakrishna G, Cullen J, et al. Phase II Trial of Cetuximab and Conformal Radiotherapy Only in Locally Advanced Pancreatic Cancer with Concurrent Tissue Sampling Feasibility Study. *Transl Oncol.* 2014; 7(1):55–64.
- 247 Hayman TJ, Wahba A, Rath BH, Bae H, Kramp T, Shankavaram UT, Camphausen K, Tofilon PJ. The ATP-competitive mTOR inhibitor INK128 enhances in vitro and in vivo radiosensitivity of pancreatic carcinoma cells. *Clin Cancer Res.* 2014;20(1):110–9.
- 248 Dai ZJ, Gao J, Kang HF, Ma YG, Ma XB, Lu WF, Lin S, Ma HB, Wang XJ, Wu WY. Targeted inhibition of mammalian target of rapamycin (mTOR) enhances radiosensitivity in pancreatic carcinoma cells. *Drug Des Dev Ther.* 2013;7:149–59.
- 249 Williams TM, Flecha AR, Keller P, Ram A, Karnak D, Galban S, Galban CJ, Ross BD, Lawrence TS, Rehemtulla A, et al. Cotargeting MAPK and PI3K signaling with concurrent radiotherapy as a strategy for the treatment of pancreatic cancer. *Mol Cancer Ther.* 2012;11(5):1193–202.
- 250 Park JH, Jung KH, Kim SJ, Fang Z, Yan HH, Son MK, Kim J, Kang YW, Lee JE, Han B, et al. Radiosensitization of the PI3K inhibitor HS-173 through reduction of DNA damage repair in pancreatic cancer. *Oncotarget.* 2017; 8(68):112893–906.
- 251 Yang L, Yang G, Ding Y, Dai Y, Xu S, Guo Q, Xie A, Hu G. Inhibition of PI3K/ AKT Signaling Pathway Radiosensitizes Pancreatic Cancer Cells with ARID1A Deficiency in Vitro. *J Cancer.* 2018;9(5):890–900.
- 252 Chang L, Graham PH, Hao J, Ni J, Bucci J, Cozzi PJ, Kearsley JH, Li Y. PI3K/ Akt/mTOR pathway inhibitors enhance radiosensitivity in radioresistant prostate cancer cells through inducing apoptosis, reducing autophagy, suppressing NHEJ and HR repair pathways. *Cell Death Dis.* 2014;5:e1437.
- 253 Durrant DE, Das A, Dyer S, Tavallai S, Dent P, Kukreja RC. Targeted Inhibition of Phosphoinositide 3-Kinase/Mammalian Target of Rapamycin Sensitizes Pancreatic Cancer Cells to Doxorubicin without Exacerbating Cardiac Toxicity. *Mol Pharmacol.* 2015; 88(3):512–23.
- 254 Lomax ME, Folkes LK, O'Neill P. Biological consequences of radiationinduced DNA damage: relevance to radiotherapy. *Clin Oncol (R Coll Radiol).* 2013;25(10):578–85.
- 255 O'Connor MJ. Targeting the DNA Damage Response in Cancer. *Mol Cell.* 2015; 60(4):547–60.
- 256 Lord CJ, Ashworth A. The DNA damage response and cancer therapy. *Nature.* 2012; 481(7381):287–94.

- 257 Prevo R, Fokas E, Reaper PM, Charlton PA, Pollard JR, McKenna WG, Muschel RJ, Brunner TB. The novel ATR inhibitor VE-821 increases sensitivity of pancreatic cancer cells to radiation and chemotherapy. *Cancer Biol Ther.* 2012;13(11):1072–81.
- 258 Fokas E, Prevo R, Pollard JR, Reaper PM, Charlton PA, Cornelissen B, Vallis KA, Hammond EM, Olcina MM, Gillies McKenna W, et al. Targeting ATR in vivo using the novel inhibitor VE-822 results in selective sensitization of pancreatic tumors to radiation. *Cell Death Dis.* 2012;3:e441.
- 259 Walcz Y, Dunlop CR, Johnson TI, Koh SB, Fornari C, Yates JWT, Bernaldo de Quiros Fernandez S, Lau A, Richards FM, Jodrell DI. The ATR Inhibitor AZD6738 Synergizes with Gemcitabine In Vitro and In Vivo to Induce Pancreatic Ductal Adenocarcinoma Regression. *Mol Cancer Ther.* 2018;17(8):1670–82.
- 260 Morgan MA, Parsels LA, Zhao L, Parsels JD, Davis MA, Hassan MC, Arumugarajah S, Hylander-Gans L, Morosini D, Simeone DM, et al. Mechanism of radiosensitization by the Chk1/2 inhibitor AZD7762 involves abrogation of the G2 checkpoint and inhibition of homologous recombinational DNA repair. *Cancer Res.* 2010;70(12):4972–81.
- 261 Venkatesha VA, Parsels LA, Parsels JD, Zhao L, Zabludoff SD, Simeone DM, Maybaum J, Lawrence TS, Morgan MA. Sensitization of pancreatic cancer stem cells to gemcitabine by Chk1 inhibition. *Neoplasia.* 2012; 14(6):519–25.
- 262 Engelke CG, Parsels LA, Qian Y, Zhang Q, Karnak D, Robertson JR, Tanska DM, Wei D, Davis MA, Parsels JD, et al. Sensitization of pancreatic cancer to chemoradiation by the Chk1 inhibitor MK8776. *Clin Cancer Res.* 2013;19(16):4412–21.
- 263 Al-Ejeh F, Pajic M, Shi W, Kalimutho M, Miranda M, Nagrial AM, Chou A, Biankin AV, Grimmond SM, Australian Pancreatic Cancer Genome I, et al. Gemcitabine and CHK1 inhibition potentiate EGFR-directed radioimmunotherapy against pancreatic ductal adenocarcinoma. *Clin Cancer Res.* 2014; 20(12):3187–97.
- 264 Tuli R, Surmak AJ, Reyes J, Armour M, Hacker-Prietz A, Wong J, DeWeese TL, Herman JM. Radiosensitization of Pancreatic Cancer Cells In Vitro and In Vivo through Poly (ADP-ribose) Polymerase Inhibition with ABT-888. *Transl Oncol.* 2014. <https://doi.org/10.1016/j.tranon.2014.04.003>.
- 265 Rajan A, Carter CA, Kelly RJ, Gutierrez M, Kummar S, Szabo E, Yancey MA, Ji J, Mannargudi B, Woo S, et al. A phase I combination study of olaparib with cisplatin and gemcitabine in adults with solid tumors. *Clin Cancer Res.* 2012; 18(8):2344–51.
- 266 Brix N, Tiefenthaler A, Anders H, Belka C, Lauber K. Abscopal, immunological effects of radiotherapy: Narrowing the gap between clinical and preclinical experiences. *Immunol Rev.* 2017;280(1):249–79.
- 267 Filatenkov A, Baker J, Mueller AM, Kenkel J, Ahn GO, Dutt S, Zhang N, Kohrt H, Jensen K, Dejbakhsh-Jones S, et al. Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions. *Clin Cancer Res.* 2015; 21(16):3727–39.
- 268 Lennon S, Oweida A, Milner D, Phan AV, Bhatia S, Van Court B, Darragh L, Mueller AC, Raben D, Martinez-Torrecuadrada JL, et al. Pancreatic Tumor Microenvironment Modulation by EphB4-ephrinB2 Inhibition and Radiation Combination. *Clin Cancer Res.* 2019;25(11):3352–65.
- 269 Golden EB, Chhabra A, Chachoua A, Adams S, Donach M, Fenton-Kerimian M, Friedman K, Ponzo F, Babb JS, Goldberg J, et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. *Lancet Oncol.* 2015;16(7):795–803.
- 270 Shi F, Wang X, Teng F, Kong L, Yu J. Abscopal effect of metastatic pancreatic cancer after local radiotherapy and granulocyte-macrophage colony-stimulating factor therapy. *Cancer Biol Ther.* 2017;18(3):137–41.
- 271 Azad A, Yin Lim S, D'Costa Z, Jones K, Diana A, Sansom OJ, Kruger P, Liu S, McKenna WG, Dushek O, et al. PD-L1 blockade enhances response of pancreatic ductal adenocarcinoma to radiotherapy. *EMBO Mol Med.* 2017;9(2):167–80.
- 272 Klug F, Prakash H, Huber PE, Seibel T, Bender N, Halama N, Pfirschke C, Voss RH, Timke C, Umansky L, et al. Low-dose irradiation programs macrophage differentiation to an iNOS(+)/M1 phenotype that orchestrates effective T cell immunotherapy. *Cancer Cell.* 2013;24(5):589–602.
- 273 Timke C, Winnenthal HS, Klug F, Roeder FF, Bonertz A, Reissfelder C, Rochet N, Koch M, Tjaden C, Buechler MW, et al. Randomized controlled phase I/II study to investigate immune stimulatory effects by low dose radiotherapy in primarily operable pancreatic cancer. *BMC Cancer.* 2011;11:134.
- 274 Deng L, Liang H, Xu M, Yang X, Burnette B, Arina A, Li XD, Mauceri H, Beckett M, Darga T, et al. STING-Dependent Cytosolic DNA Sensing Promotes Radiation-Induced Type I Interferon-Dependent Antitumor Immunity in Immunogenic Tumors. *Immunity.* 2014; 41(5):843–52.
- 275 Vanpouille-Box C, Alard A, Aryankalayil MJ, Sarfraz Y, Diamond JM, Schneider RJ, Inghirami G, Coleman CN, Formenti SC, Demaria S. DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. *Nat Commun.* 2017;8:15618.
- 276 Baird JR, Friedman D, Cottam B, Dubensky TW Jr, Kanne DB, Bambina S, Bahjat K, Crittenden MR, Gough MJ. Radiotherapy Combined with Novel STING-Targeting Oligonucleotides Results in Regression of Established Tumors. *Cancer Res.* 2016;76(1):50–61.
- 277 Rech AJ, Dada H, Kotzin JJ, Henao-Mejia J, Minn AJ, Twyman-Saint Victor C, Vonderheide RH. Radiotherapy and CD40 Activation Separately Augment Immunity to Checkpoint Blockade in Cancer. *Cancer Res.* 2018; 78(15):4282–91.
- 278 Lee V, Rodriguez C, Shupe E-M, Chen L, Parkinson R, Durham JN, Sugar E, Wilt C, McIntyre KR, Hacker-Prietz A, et al. Phase II study of GM-CSF secreting allogeneic pancreatic cancer vaccine (GVAX) with PD-1 blockade antibody and stereotactic body radiation therapy (SBRT) for locally advanced pancreas cancer (LAPC). *J Clin Oncol.* 2017; 35(15\_suppl):TPS4154.