**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 65602

**Manuscript Type:** REVIEW

**Therapeutic resistance in pancreatic ductal adenocarcinoma: Current challenges and future opportunities**

Jain A *et al*. PDAC: Current therapies and future opportunities

Aditi Jain, Vikas Bhardwaj

**Aditi Jain,** The Jefferson Pancreas, Biliary and Related Cancer Center, Department of Surgery, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA 19107, United States

**Vikas Bhardwaj,** Department of Pharmaceutical Sciences, Jefferson College of Pharmacy, Thomas Jefferson University, Philadelphia, PA 19107, United States

**Author contributions:** Jain A and Bhardwaj V decided on topics, compiled information, wrote and reviewed the manuscript.

**Corresponding author: Vikas Bhardwaj, PhD, Assistant Professor,** Department of Pharmaceutical Sciences, Jefferson College of Pharmacy, Thomas Jefferson University, 130 South 9th Street, Philadelphia, PA 19107, United States. vikas.bhardwaj@jefferson.edu

**Received:** May 6, 2021

**Revised:** June 22, 2021

**Accepted:** August 30, 2021

**Published online:** October 21, 2021

**Abstract**

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer-related deaths in the United States. Although chemotherapeutic regimens such as gemcitabine+ nab-paclitaxel and FOLFIRINOX (FOLinic acid, 5-Fluroruracil, IRINotecan, and Oxaliplatin) significantly improve patient survival, the prevalence of therapy resistance remains a major roadblock in the success of these agents. This review discusses the molecular mechanisms that play a crucial role in PDAC therapy resistance and how a better understanding of these mechanisms has shaped clinical trials for pancreatic cancer chemotherapy. Specifically, we have discussed the metabolic alterations and DNA repair mechanisms observed in PDAC and current approaches in targeting these mechanisms. Our discussion also includes the lessons learned following the failure of immunotherapy in PDAC and current approaches underway to improve tumor’s immunological response.

**Key Words:** Pancreatic cancer; Metabolism; DNA repair; Therapy-resistance; Immunotherapy

**Citation:** Jain A, Bhardwaj V. Therapeutic resistance in pancreatic ductal adenocarcinoma: Current challenges and future opportunities. *World J Gastroenterol* 2021; 27(39): 6527-6550

URL: [https://www.wjgnet.com/1007-9327/full/v27/i39/6527.htm](https://www.wjgnet.com/1007-9327/full/v27/i39/0000.htm)

DOI: https://dx.doi.org/10.3748/wjg.v27.i39.6527

**Core Tip:** With a five-year survival rate of 10%, pancreatic adenocarcinomas are one of the most aggressive forms of cancer. Despite extensive efforts, only a few drug combinations have been found to be effective in improving patient outcomes. The drug-resistant mechanisms active in pancreatic ductal adenocarcinoma contribute to the ineffectiveness of therapies. Through this review, we discuss key mechanisms that contribute to the development of resistant phenotype in pancreatic tumors and how these mechanisms are being sought as a target to treat this cancer.

**INTRODUCTION**

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive tumor, with a 5-year overall survival of 10%. As the cause of approximately 47000 deaths annually, it is the third leading cause of cancer-related mortality in the United States and is expected to be the second primary cause of cancer-related deaths by 2030[1,2]. Surgical resection of the tumor remains the only curative option for patients with PDAC. However, due to late diagnosis, only a limited number of patients qualify for it. Relapse is common and often observed as early as two months post-surgery. Therefore, adjuvant chemotherapy is often prescribed to improve patient outcomes. For over a decade, gemcitabine was the mainstay for chemotherapy for resectable PDACs. The drug advanced the patient survival to 5.65 mo compared with 4.41 mo with 5-fluorouracil[3]. Recently, a combination therapy FOLFIRINOX (FOLinic acid, 5-Fluroruracil, IRINotecan, and Oxaliplatin) displayed better patient outcomes than gemcitabine[4]. The four-drug cocktail, although toxic, significantly improved survival in PDAC patients and is currently approved for both resectable and metastatic PDAC[5-9] (Table 1).

The complex pancreatic cancer biology is often attributed as the underlying cause of the poor chemotherapeutic response. This review will highlight the current knowledge of the therapeutic resistance mechanisms prevalent in PDAC and the opportunities PDAC tumor biology provides for its efficient targeting.

**CURRENT THERAPIES IN PDAC**

***Gemcitabine***

Gemcitabine has been a mainstay for PDAC treatment since 1997, when it was found to improve median and overall survival compared to 5-fluorouracil[3]. Gemcitabine (2’, 2’- difluorodeoxycytidine) is a difluoro analog of deoxycytidine which inhibits DNA synthesis through (1) inhibition of ribonucleotide reductase (RR), (2) inhibition of DNA polymerase (*via* diphosphate analog), or (3) mis-incorporation into the DNA, thus preventing chain elongation (*via* triphosphate analog)[10,11]. The inhibition of RR by the diphosphate analog depletes the deoxy-ribonucleotide pool essential for DNA synthesis.

Numerous mechanisms for gemcitabine inactivity have been demonstrated. Although resistance can be divided into innate and acquired forms, we will present evidence referring to both as “resistance” for this review.

The first interaction of gemcitabine with the cells occurs at the nucleotide transporter level. These transporters-concentrative nucleoside transporters (hCNTs) and equilibrative nucleoside transporters (hENTs) allow the transport of gemcitabine into the cells[12]. Evidence of the importance of nucleotide transporters for gemcitabine activity includes the observation that, in the absence of hENT1, PDAC patients treated with gemcitabine have reduced survival[13]. The enzyme deoxycytidine kinase (dCK) is the rate-limiting enzyme that converts gemcitabine into di-fluoro deoxycytidine mono-phosphate and is essential for gemcitabine-induced cytotoxicity[14]. Acquired resistant models demonstrate reduced expression of dCK in cells that do not respond to gemcitabine[14,15]. However, a recent analysis of the patient-derived xenograft PDAC model found no change in dCK levels in the gemcitabine-resistant tumors[16], indicating that mechanisms independent of dCK contribute to poor response to gemcitabine.

As mentioned earlier, when gemcitabine inhibits RR, the deoxy-ribonucleotide pool of the cells becomes depleted, leading to cell death. Overexpression of M1 and M2 isoforms, namely RRM1 and RRM2, is associated with reduced cellular response to gemcitabine[16-18]. Micro RNAs such as miR20a-5 and miR211 have been shown to downregulate RR, enhancing pancreatic cancer’s sensitivity to gemcitabine and inhibiting cellular invasion[19,20]. Similarly, natural product, small molecule, and miRNA-based inhibition of RR sensitizes PDAC cells to gemcitabine[19-21-24]. Although strong *in vitro* data indicate RRM1/RRM2 play a key role in gemcitabine sensitivity, conflicting clinical outcomes have limited the utility of these enzymes for PDAC prognosis[25-28].

Other cellular processes such as epithelial-mesenchymal transition (EMT), mitogenic signaling, and tumor-stroma interaction also contribute to gemcitabine resistance[29]. Analysis of PDAC lines revealed that the EMT gene expression profile differs considerably between drug-sensitive and -resistant cells[30]. The drug-resistant cells showed reduced response to gemcitabine, 5-fluorouracil, and cisplatin, and expressed elevated levels of EMT marker Zeb1[30]. In addition, suppression of EMT enhanced the sensitivity of PDAC to gemcitabine by regulating the expression of nucleoside transporters[31].

***5-Fluorouracil***

Similar to gemcitabine, 5-fluorouracil belongs to the antimetabolite class of anti-cancer agents. 5-Fluorouracil inhibits the enzyme thymidylate synthetase (TS), which is responsible for methylation of deoxyuridine mono-phosphate to deoxythymidine mono-phosphate, a precursor for DNA synthesis. 5-Fluorouracil was the first drug to be approved as PDAC adjuvant therapy[32,33]. Although no longer used as monotherapy, 5-fluorouracil forms a part of the PDAC chemotherapeutic regimen FOLFIRINOX. Compared to gemcitabine therapy, combination therapy with FOLFIRINOX improved the overall survival and median progression-free survival of patients with metastatic PDAC[4]. Although any improvement in PDAC patient outcomes should be observed as a positive sign, the high toxicity of the drug regimen, limited patient eligibility for FOLFIRINOX, and prevalence of 5-fluorouracil resistant mechanisms may further limit the use this combination therapy in PDAC[34-38]. Multiple mechanisms have demonstrated to contribute to 5-fluorouracil resistance, such as alteration in (1) 5-fluorouracil metabolizing enzymes, (2) membrane transporters, and (3) pro-survival/ pro-apoptotic pathways. High TS expression is associated with poor survival in PDAC patients, however, the difference in survival is more significant in patients that received 5-fluorouracil based therapy[39,40]. The enzyme dihydropyrimidine dehydrogenase (DPD) catabolizes the 5-fluorouracil in the liver. In colorectal cancer patients receiving 5-fluorouracil based therapy, high DPD levels was associated with significantly shorter disease-free survival and overall survival[41]. In vitro analysis of PDAC cells lines and 5-fluorouracil-resistant sub-lines revealed that high expression of TS and DPDY is associated with poor 5-fluorouracil response[42].

***Targeted therapies in PDAC***

Comprehensive genetic analysis has revealed that pancreatic cancers are a host of numerous genetic mutations[43]. Mutation of *K-ras* is the most frequent genetic alteration observed in more than 90% of pancreatic cancer cases[44]. K-ras protein is a downstream signaling molecule activated by various transmembrane receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR), insulin-like growth factor receptor, and c-met. EGFR, overexpressed in more than 40% of pancreatic cancers, is associated with poor disease prognosis, invasion, and aggressive clinical behavior[45,46]. Given its importance, therapies targeting EGFR have been tested to determine their ability to improve the outcomes of PDAC patients. In one phase III trial, the addition of erlotinib (EGFR tyrosine kinase inhibitor) to gemcitabine-based therapy significantly improved the overall survival of PDAC patients[47]. A recent clinical trial compared the efficacy of gemcitabine + erlotinib in rash-positive pancreatic cancer patients and found similar one-year survival and better quality of life compared to patients on FOLFIRINOX[48]. Some trials however, have failed to show the clinical benefit of adding EGFR targeting drugs to PDAC chemotherapy[49-52]. Therapies targeting other molecular mechanisms active in pancreatic cancer have not shown beneficial effects, and EGFR targeting may have a place in PDAC therapy as precision medicine[53-57].

**FUTURE OPPORTUNITIES TO TARGET PDAC**

***Pancreatic tumor metabolism***

Pancreatic cancer is characterized by a dense stroma surrounding the tumor. This dense stromal region limits vascularization, creating an environment limiting oxygen and nutrient supply[58,59]. Limited oxygen gives rise to hypoxia that is associated with poor patient prognosis[59-61]. In an abundance of oxygen, the non-malignant cells produce most of their energy from mitochondrial oxidative phosphorylation (OXPHOS) while cancer cells exhibit an altered metabolism, first observed in the 1920s by Warburg[62], in which they produce most of their energy from glycolysis. Further, Warburg[62] observed that the majority of the glucose taken up by the cancer cells is converted to lactate rather than CO2, an observation that has since been witnessed and verified by various researchers in various tumors, including PDAC[63-70]. Pancreatic cancer shows upregulation in glycolysis, pentose phosphate pathway (PPP), fatty acid synthesis, and purine/pyrimidine synthesis, and downregulation of enzymes involved in Kreb’s cycle and the OXPHOS.

Analysis of the pancreatic cancer progression model revealed that the metabolic alterations precede tumor formation[71]. Metabolic rewiring in the early stages involves upregulated glycolytic and PPP. The altered metabolic profile allows quick ATP production and provides nucleotides and other metabolic intermediates required for proliferating cancer cells[72]. However, the suppression of OXPHOS can lead to excessive acid build-up within the cancer cells in the form of lactate. To circumvent this, pancreatic cancers express monocarboxylate transporters (MCT1 and MCT4) to efflux out lactate[73,74]. These metabolic adaptations, aided by the upregulation of glucose transporters GLUT1, allow the cancer cells to utilize glucose for their energy and biosynthetic needs. In addition, the molecular biology of pancreatic cancers, such as mutation of KRAS and P53, contribute to the so-called “glycolytic switch” in the PDACs by regulating genes like hexokinase-2, glucose transporters GLUT-1, and PKM2, and by promoting anabolic processes[75-78].

Altered tumor metabolism is also associated with poor therapy response in pancreatic tumors. Acquired gemcitabine-resistant models of pancreatic cancer show a marked increase in aerobic glycolysis that maintains the EMT phenotype and reduced responsiveness to the therapeutic agent[79]. The resistant cells exhibit elevated glycolytic enzymes HK2, LDHA and PKM2, and glucose transporter GLUT1. Below we discuss the central carbon metabolic pathways — namely, glycolysis, tricarboxylic acid (TCA) cycle, and the PPP — as therapeutic targets in pancreatic cancer.

**Glycolysis as therapeutic target:** Analysis of pancreatic tumors reveals that HK2 expression is upregulated in localized tumors as well as metastatic tumors compared to non-malignant tissues[80]. Since HK2 plays a crucial role in pancreatic tumors, efforts have been made to evaluate HK2 as a therapeutic target for pancreatic cancers. We were among the first to show that inhibition of glycolytic enzymes HK2 inhibits the growth and pro-survival signaling in pancreatic cancers[81]. In addition, inhibition of HK2 in pancreatic cancer cells suppresses their anchorage-independent growth and invasion[80]. The role of HK2 has also been implicated in gemcitabine resistance, as HK2 dimerization is enhanced in cells that do not respond to gemcitabine[82]. *In vitro* and *in vivo* analysis revealed that inhibition of HK2 enhanced the sensitivity of PDAC to gemcitabine. Similarly, in another study, inhibition of HK2 using chemical inhibitor 2-deoxyglucose enhanced resistant cells’ sensitivity to gemcitabine[79].

PKM2: Pyruvate kinase (PK) is a glycolytic enzyme that catalyzes the conversion of phosphoenol pyruvate and ADP into pyruvate and ATP. Four isoforms of the enzyme exist in vertebrates: PKR in erythrocytes; PKL in liver and kidney; PKM1 in adult muscle, brain, and heart; and PKM2 in most adult tissues and fetal tissues[83]. Phosphorylation of PKM2 at tyrosine residue 105 (Y105) is associated with reduced PKM2 activity and enhanced tumor growth[84,85]. Analyses of PKM isoform show abundance of isoform M2 in tumor cells compared to high levels of M1 in normal tissues[52,53]. In cancer cell lines, high PKM2 Levels are associated with proliferation, metastasis, and angiogenesis[54-56]. The role of PKM2 in pancreatic tumors is, however, controversial. Using the mice model of PDAC, a recent report demonstrated that although PKM2 expression is elevated in PDAC, the loss of PKM2 does not significantly affect the size of tumors or the survival of mice bearing PDAC[86]. Surgical specimens from 115 PDAC patients show that PKM2 expression is associated with better overall survival[87]. However, others have shown that high PKM2 expression correlates with poor patient outcomes[88,89]. Considering several observations demonstrating a vital role of PKM2 in pancreatic cancer survival, invasion, angiogenesis, metastasis, and drug resistance, we believe the PKM2 serves as an attractive target for the treatment of PDAC, even though its role in pancreatic cancer tumorigenesis is still unproven[90-95].

Lactate dehydrogenase (LDH): LDH is an enzyme that exists as a tetramer and catalyzes the conversion of pyruvate to lactate and *vice versa*. LDHA (LDH gene product) regulates pyruvate’s conversion to lactate, thus preventing the entry of pyruvate into the TCA cycle. Deregulated expression of LDHA is observed in various tumors, including pancreatic, gastric, bladder, cholangiocarcinoma, lung, and endometrial cancers[96-102]. Numerous oncogenic signaling molecules, namely, HIF1 alpha, myc, FOXM1, and tyrosine kinase receptors, can regulate the level or the activity of LDH[96,103-106]. Elevated levels of LDH are associated with unfavorable prognoses for PDAC patient survival, chemotherapy response, and recurrence[107-112]. Preclinical studies have revealed that inhibition of LDH reduces the survival of PDAC cells[113,114].

**PPP as therapeutic target:** The PPP branches from glycolysis and contributes to the cancer phenotype through (1) synthesis of NADPH (oxidative PPP), which is important for redox regulation and fatty acid synthesis, and (2) supplying the proliferating cells with pentose sugar (non-oxidative PPP) for nucleic acid biosynthesis[115]. Accumulating evidence indicates that PPP plays a vital role in pancreatic tumor survival, metastasis, and therapy resistance. Our lab and others have shown that MYC regulates the activity of both oxidative and non-oxidative PPP through the regulation of G6PD and the RPIA (non-oxidative PPP) gene[78,116,117]. The regulation of RPIA *via* MYC appears to be under the directive of KRAS. The MAPK-MYC-RPIA-nucleotide biosynthesis pathway is shown to be important for KRAS-mediated maintenance of PDAC[78,116]. Considering that most PDAC patients (90%) express mutant KRAS, inhibition of PPP is an attractive strategy for developing more efficient pancreatic cancer therapies that would target KRAS-induced metabolic abnormalities. Our recent results found that pancreatic cancer cells resistant to erlotinib express elevated levels of G6PD. The upregulated G6PD prevents the induction of ROS in response to erlotinib, thus protecting the cells from drug-induced cytotoxicity[117]. The non-oxidative PPP has also been implicated in PDAC therapy resistance. Shukla *et al*[118] found that gemcitabine-resistant cells express enhanced carbon flux into the non-oxidative PPP, aided by elevated non-oxidative PPP enzyme levels. This alteration in metabolic flux allows elevated pyrimidine synthesis that contributes to gemcitabine resistance[118].

**TCA cycle and OXPHOS as therapeutic target:** Although cancer cells exhibit an elevated flux of glycolytic intermediate into branched pathways, the TCA cycle is still functional. The TCA cycle continues to provide proliferating cancer cells with energy, macromolecules and maintain the cellular redox balance. Recent reports have demonstrated the importance of the TCA cycle and OXPHOS in pancreatic cancer survival[119-123]. Due to their critical roles, the TCA cycle and OXPHOS have been tested as a therapeutic target for PDAC therapy. Three major approaches have been sought to this end: (1) Targeting TCA cycle enzyme/intermediates; (2) Targeting glutamine-dependent anaplerosis; and (3) Targeting the OXPHOS.

Glutamine, a non-essential amino acid, is considered an important energy source for PDAC along with glucose[124,125]. Accumulating evidence demonstrates that glutamine plays a vital role in PDAC proliferation, invasion, maintenance of redox balance, chemotherapy, and radiotherapy resistance, underlining glutamine metabolism as a potential therapeutic target[126-132]. However, conflicting results show that the presence of glutamine suppresses PDAC growth and invasion, dampening enthusiasm for targeting glutamine metabolism[133-135]. A current clinical trial (NCT04634539) is analyzing whether adding glutamine improves efficacy and reduces the toxicity of PDAC chemotherapy. The results from this trial will shed light on the effect of glutamine on PDAC chemotherapy.

Two additional approaches, targeting the OXPHOS and the TCA cycle, have shown promise in preclinical evaluations, and agents targeting them are currently in clinical trials (Table 2). IACS-010759 inhibits mitochondrial complex one and has recently completed a phase I study in different tumor types, including advanced pancreatic cancers (Table 2). Although the preclinical data regarding the effect of IACS-010759 on pancreatic tumors is lacking, inhibition of OXPHOS complex one appears to be a promising strategy for overcoming drug resistance[136-139]. The anti-diabetic drug metformin has been tested and continues to be tested for its efficacy in PDAC (NCT01210911, NCT02336087, and NCT01666730). Although the experience with metformin in clinical settings has not resulted in improved patient outcomes, a recent meta-analysis indicated survival benefits in patients with PDAC and concurrent diabetes mellitus, highlighting a need for a personalized therapeutic approach for the success of this therapy[140-142].

CPI-613 or Demivistat (Table 2) is a TCA cycle targeting agent that inhibits the activity of pyruvate dehydrogenase and α- ketoglutarate dehydrogenase. In a phase 1 trial, 61% of patients achieved an objective response, and 3 (17%) patients achieved a complete response after receiving CPI-613[143].

***Targeting PDAC DNA repair***

Activating KRAS mutations are major drivers of malignant growth in PDAC and have remained undruggable until recent promising developments. Oncogenic KRAS-induced DNA replication stress drives genomic instability and tumorigenesis in PDAC. Genomic analysis have also revealed that modifications in “DNA damage control” is a prominent genetic alteration observed in PDAC[43]. Recently, genetic alterations in PDAC have been classified into four sub-types by Waddell *et al*[144]: (1) Stable; (2) Locally rearranged; (3) Scattered; and (4) Unstable. The “unstable” phenotype harbors mutations in the DNA damage repair (DDR), such as BRCA1, BRCA2, PALB2, and ATM. Mutations in ATM account for the most frequently occurring somatic mutations in approximately 4% of PDAC cases, followed by BRCA2, STK11, and BRCA1[144-147]. Given the important role these DDR genes play in a significant proportion of human PDACs, patients are likely to benefit from tailored, targeted therapies, including platinums, directed against specific DDR (Table 3). The following paragraphs will discuss these therapies.

**Platinums:** Platinum agents (cisplatin, oxaliplatin) cause DNA damage by forming platinum adducts on the DNA and causing DNA interstrand crosslinks[148]. Oxaliplatin is a component of the standard of care FOLFIRINOX, and platinum compounds alone are well suited in cancers that have a deficiency in the homologous repair (HR) pathway. Many studies have highlighted the advantageous use of platinum compounds for HR-deficient PDAC. Golan *et al*[149] showed a survival benefit (22 mo *vs* 9 mo) in platinum-treated *vs* platinum-naïve BRCA1/2 mutated advanced PDAC. Similarly, platinum improved overall survival in patients with HR-deficient PDACs and in patients with germline BRCA1, BRCA2, and PALB2 mutations[150,151]. Hence careful patient selection depending on the genetic make-up of the tumor would be essential for platinums to succeed.

**Poly (ADP-ribose) glycohydrolase:** Poly (ADP-ribose) glycohydrolase (PARG) is a macrodomain protein with exo- and endo-glycohydrolase activity[152,153]. It critically regulates DNA damage responses by removing poly (ADP-ribose) molecules (PARylation) on modified proteins during the DNA repair process. It is the primary PAR degrading enzyme and reverses poly (ADP ribose) polymerase (PARP) functions by hydrolyzing the ribose-ribose bonds present in PAR molecules. By preventing cytoplasmic PAR accumulation, PARG prevents PAR-mediated apoptosis, termed as parthanatos[154]. Inhibiting PARG causes DNA replication fork collapse, which leads to irreparable DNA damage and cell death. Recent studies have highlighted the benefits of selectively targeting PARG as an anti-cancer therapeutic strategy alone or in combination with other genotoxic therapies[155-157]. Targeting PARG was shown to enhance chemotherapeutic effects of DNA damaging agents, like oxaliplatin and 5-fluorouracil in PDAC, and was also synergistic with mitotic kinase, Wee-1 inhibition. In a siRNA screen with DNA replication factors, PARG inhibition was shown to be synergistic with TIMELESS, HUS1, MCM2, CHK1, and RFC2 proteins in an ovarian cancer model, indicating that combinations of PARGi and DNA replication stress inducers should be evaluated as potential therapeutic strategies for PDAC treatment[158]. A synthetic lethal relationship with PARG inhibition and DDR proteins like BRCA1, BRCA2, ABRAXAS, BARD1, and PALB2 was reported in an MCF7 breast cancer model[159]. Since genomic screens in PDAC have revealed alterations/mutations in similar DDR proteins, it is valuable to target PARG in such DDR-deficient PDAC tumors.

**Wee-1:** WEE1 kinase is an important cell cycle regulator of the G2-M checkpoint and is overexpressed in various cancers, including glioblastoma, breast cancer, osteosarcoma, and hepatocellular carcinoma[160-163]. It phosphorylates and inactivates CDK1 to allow for the repair of damaged DNA before entering mitosis. Wee-1 has regulatory roles in DNA replication stress and HR mechanisms[164-166]. In PDAC, Wee-1 expression is upregulated by a post-transcriptional mechanism regulated by RNA binding protein, HuR[167], and its inhibition has been found to be effective in DNA repair-deficient PDAC cells[168]. In one study, Wee-1 inhibition was found to sensitize PDAC cells to gemcitabine chemo-radiation therapy[165]. Another study showed Wee-1 inhibition was synergistic with gemcitabine in p53-deficient PDAC xenografts[169]. Co-targeting WEE1 and ATM was shown to synergistically reduce cell proliferation and migration *via* downregulation of PDL-1 expression in pancreatic cancers[170]. Recently, it was also published that a combination of Wee-1 with another DNA repair target, PARG, enhances DNA damage and decreases cell survival in PDAC cells[171].

**PARP:** PARP is a DNA repair enzyme that plays a role in inflammation, regulation of cell death, transcription, and modulation of post-transcriptional gene expression. In response to DNA damage, PARP-1 could either promote cell survival and DNA repair or cause cell death when the damage is high[172]. PARP covalently adds Poly (ADP ribose) (PAR) chains onto its target proteins by consuming beta nicotinamide adenine dinucleotide (β NAD+). PAR further recruits other DNA repair proteins in the process of damage repair. Chemical competitive inhibitors of PARP enzymatic activity have gained interest as treatment options for many cancers, like ovarian, breast, uterine, and prostate[173], specifically for patients with tumors harboring somatic or germline defects/mutations in HR genes like *BRCA1/2*. Recent whole-genome sequencing studies done in patients with familial pancreatic cancer show that mutations in *BRCA2* gene accounts for 5%-10% of familial pancreatic cancers. In the Ashkenazi Jewish population with PDAC, this percentage increases to 13.7% and represents a major subgroup of PDAC cases that could benefit from PARP inhibitor (PARPi) therapy. In the context of synthetic lethality, impairment of two DNA repair pathways induces cell death and thus targeting HR deficient cells (*BRCA1/2* mutants or others)with PARP inhibitors was found to be lethal[174,175]. Following the success of POLO trial (Pancreas Cancer Olaparib Ongoing), in 2019 FDA approved olaparib (PARPi) as a maintenance therapy in patients with a germline BRCA mutated metastatic PDAC that had not progressed on first-line platinum therapy[174]. An increasing amount of ongoing preclinical and clinical studies suggest that PARPi in combination with either conventional chemotherapeutics (gemcitabine/nab-paclitaxel) or radiation therapy could benefit patients in the long run[176]. However, recent research suggests that although these respond greatly to PARP inhibitors, there is still 40%-70% of BRCA1/2-mutated cancers that fail to respond to PARPi therapy and in those settings PARPi cannot be used. Novel efforts to create a ’BRCAness-tumors harboring mutations in HR beyond BRCA1/2’ phenotype in the cells by use of other small molecule inhibitors and their combination with PARPi is now being exploited. Bagnolini *et al*[174] discovered a small molecule disruptor of RAD51-BRCA2 interaction synergizes with olaparib in pancreatic cancer cells. Another study showed synthetic lethaility with PARPi therapy and FGFR1 blockade in pancreatic cancer[177]. Failure of PARPi therapy can also be attributed to acquired resistance mechanisms[178]. A study in pancreatic cancer showed a secondary mutation in BRCA2 emerged after the patient’s exceptional response to platinum and PARPi therapy, which likely restored BRCA2 function in PARP inhibitor-resistant tumor cells[179]. Thus, careful evaluation and design of PARPi therapy should be pursued, and novel targets for PARPi beyond BRCA1/2 should be explored.

**Other inhibitors of DDR pathway:** Ataxia telangiectasia mutated (ATM) and RAD-3 related (ATR) are serine/threonine protein kinases that are involved in double/single-strand break repair and modulate DNA replication stress and DDR signaling[180-182]. ATM is one of the most commonly mutated DDR genes, and many whole genomic sequencing studies in PDAC have reported both somatic or germline ATM loss-of-function mutations. ATM loss drives pancreatic cancer progression, angiogenesis, epithelial-to-mesenchymal transition, and stemness[183]. Radiosensitization of cells with ATM loss/inhibition has been well documented in many tumor types, including pancreatic cancers[184-186]. ATM loss can also synergize with platinums and PARP inhibitor therapies, emphasizing its role in DNA repair. Specific to PDAC, two studies have shown that patients with ATM/ATR mutated tumors respond well to oxaliplatin-based chemotherapy, experiencing either improved progression-free survival or a stable disease[187,188].Based on these data, multiple ongoing clinical trials (Phase I/II) involving ATM-deficient solid tumors have been initiated with DNA damage agents like PARP inhibitor therapies (olaparib, talazoparib, and niraparib), some of which accept pancreatic cancer patients. Chemical inhibition of ATM *via* small molecule inhibitors (AZD0156, AZD1390) is also being tested in combination with other agents in early stage clinical trials in patients with advanced solid tumors and brain tumors (NCT02588105, NCT03423628). Lack of ATM function may lead to increased dependence on ATR for DDR, and thus ATR inhibition may be particularly potent in PDACs with somatic mutations in ATM. A recent study employing a multi-DDR interference strategy that included an ATR inhibitor and PARP and DNA-PKC inhibitor was shown to inhibit FOLFIRINOX-induced invasive clones in ATM-deficient PDAC tumors[189]. In 2012, a study tested VX-970, an ATR inhibitor, and found it sensitizes PDAC cells to radiation therapy *in vivo* and *in vitro*[190]. Another study found that a combination treatment of AZD6738 (ATR inhibitor) and gemcitabine induces PDAC regression by preventing checkpoint activation by gemcitabine[191]. The ATR inhibitors (VX-970, AZD6738, BAY18953[43]) are currently in the early stages of clinical development, like ATM inhibitors in patients with advanced solid tumors and lymphomas (NCT03188965, NCT03682289, NCT02595931, and NCT03718091), with or without other chemotherapeutic agents. Although these appear to be promising therapies, their clinical activity in PDAC patients is yet to be shown[183].

*I****mmunotherapy***

Immunotherapy has achieved promising outcomes in certain cancers, however is yet to be realized in PDAC[192-194]. Tumors with high tumor mutation burden (TMB, approximate mutations per megabase), such as melanomas and NSCLC, have shown to respond better to immunotherapy[195-197]. These TMBs are generally associated with mismatch repair (MMR) deficiency. PDACs intrinsically have low MMR deficiencies, which may explain the lower response to immunotherapy approaches such as immune checkpoint inhibitors (ICI)[198]. The immunosuppressive nature and “*T cell exhaustion*” further contributes to the poor response of PDAC to immunotherapy.

The PDAC is characterized by the presence of dense stroma in the tumor microenvironment. The stromal components include T cells (cytotoxic and regulatory) and myeloid cells such as tumor-associated macrophages (TAM). Infiltration with macrophages is observed in early PDAC tumor development stages and is associated with poor prognosis in PDAC patients[199-201]. These macrophages secrete immunosuppressive factors such as arginase and TGFβ, and thereby regulate T-cell mediated cytotoxicity and surveillance[200]. The myeloid-derived suppressor cells are immature myeloid cells that suppress T cell proliferation and promote ROS-induced T cell apoptosis[202,203]. The term “T cell exhaustion” is used for T cells’ differentiation state in chronic antigen exposure. The exhaustion stage is driven by persistent T cell receptor signaling leading to ineffective T cell functioning[204-206]. Recent evidence has shown that the T cells present in the PDAC tumor microenvironment are defective in the production of interferon and tumor necrosis factors following peptide recognition[207,208]. However, the T cells with identical peptide specificity in the spleen retain functionality in tumor-bearing animals[209].

Some approaches that are currently under investigation for improving the immunological response of PDAC include as follow.

**Cancer vaccines and immune checkpoint blockade:** Monotherapies targeting programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) have not shown promising responses in PDAC. However, the therapy showed tumor regression and disease stabilization in other advanced cancers such as NSCLC, melanoma, and renal cancers[193]. Similarly, inhibition of PD-1 or PD-L1 failed to demonstrate a positive response in PDAC animal models[207,210-212]. Similar to ICI inhibitors, vaccine trials using vaccine-GVAX pancreas (granulocyte-macrophage colony-stimulating factor-secreting allogeneic pancreatic tumor cells) failed to improve overall survival in PDAC patients compared to single-agent chemotherapy[213]. Since the vaccines were able to recruit T cells, one approach to improve their efficacy would be to promote the activation of T cells, which may be achieved through the combination of vaccines with ICI[214]. Currently, clinical trials are underway for establishing the safety and efficacy of these GVAX with ICIs (NCT03153410, NCT02451982, and NCT02648282).

**Targeting tumor associated macrophages:** Another way to improve the efficacy of immunotherapies is to inhibit the immunosuppressive signaling that originates from the tumor microenvironment. For this, one strategy being tested is to inhibit myeloid cells. Researchers found that CD11b agonist reduces the total number of myeloid cells and improves survival in PDAC mice. In addition, when CD11b was combined with anti-PD-1, anti-CLTA-4, and gemcitabine, enhanced infiltration of tumor with CD8 T cells was observed[212]. Similarly, other studies have confirmed that targeting TAMs improves therapeutic and T-cell checkpoint immunotherapy response in PDAC models[215-217]. Blockade of Csf1/Csf1R (macrophage colony-stimulating factor 1/receptor) reduces collagen deposits and enhances CD8 T cell infiltration in the PDAC mice model[218]. Currently, a phase II trial is underway to determine the efficacy of cabralizumab (CSF1R inhibitor) in combination with nivolumab and chemotherapy in PDAC (NCT03336216).

***Adoptive T cell therapy***

Adoptive T cell therapy involves isolating T cells from tumors and then engineering, expanding, and infusing them back into the patients[219]. The chimeric antigen receptor (CAR) T cell therapy is an example of adoptive T cell therapy wherein the T cells are manipulated to express CAR to assist tumor recognition[220]. Antigen targets that are being tested for PDAC include mesothelin, prostate stem cell antigen, CEA, MUC1, and HER2[221]. However, the immunosuppressive microenvironment remains a hindrance in CAR-T cell therapy’s success in PDAC[222,223]. Other barrier to the success of adoptive T cell therapy in PDAC include antigen selection and toxicities[224-226]. Still, a few promising outcomes have sustained hope for the use of this approach in PDAC. A phase 1 trial found that treatment of PDAC patients with mesothelin-targeting-CART-T cells stabilized disease in 2 out of 6 patients[227]. Similarly, analysis of efficacy and safety of MUC1-targeting CART-T cells found the therapy to be safe and successfully elevated the levels of CD4+ and CD8+ T cells at the tumor[228]. Currently, clinical trials are underway to determine MUC-1-targeted CAR-T cell therapy’s efficacy and safety in patients with solid tumors, including PDAC (NCT02587689 and NCT02617134).

**CONCLUSION**

The PDAC remains an intractable disease that is slated to be the second leading cause of cancer-related deaths by 2030. Although surgical resection remains the only curative treatment option, late diagnosis, in addition to the patient’s performance status, limits the scope of surgical intervention. Chemotherapeutic regimens such as gemcitabine+ nab-paclitaxel and FOLFIRINOX has shown promise in improving patient survival; however, drug resistance remains a continuing challenge that has limited their efficacy. Two approaches that may improve PDAC patient outcomes include inhibiting the mechanism(s) that promote therapy resistance and targeting the key pathways essential for PDAC survival. The altered metabolism provides the PDAC cells with energy (ATP) and macromolecules essential for tumor growth. Additionally, studies have shown that metabolism plays a key role in PDAC therapy resistance. Similarly, PARP targeting therapies’ success has once again brought the importance of DNA repair mechanisms in PDAC into the center. The limited success of immunotherapy has dampened the enthusiasm for targeting PDAC using this approach. However, the uncovering of mechanisms contributing to poor PDAC’s response to immunotherapy has provided opportunities to test newer approaches. Even though the strategies mentioned above have shown promising pre-clinical results individually, a regimen targeting multiple aspects of PDAC will likely deliver a better clinical outcome in this deadly disease.

**ACKNOWLEDGEMENTS**

We thank Wilson J (Thomas Jefferson University, Philadelphia, PA, United States) for her support in editing this manuscript.

**REFERENCES**

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]

2 **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**: 2913-2921 [PMID: 24840647 DOI: 10.1158/0008-5472.CAN-14-0155]

3 **Burris HA 3rd**, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, Cripps MC, Portenoy RK, Storniolo AM, Tarassoff P, Nelson R, Dorr FA, Stephens CD, Von Hoff DD. 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 [PMID: 9196156 DOI: 10.1200/JCO.1997.15.6.2403]

4 **Conroy T**, Desseigne F, Ychou M, Bouché O, Guimbaud R, Bécouarn Y, Adenis A, Raoul JL, Gourgou-Bourgade S, de la Fouchardière C, Bennouna J, Bachet JB, Khemissa-Akouz F, Péré-Vergé D, Delbaldo C, Assenat E, Chauffert B, Michel P, Montoto-Grillot C, Ducreux M; Groupe Tumeurs Digestives of Unicancer; PRODIGE Intergroup. FOLFIRINOX *vs* gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011; **364**: 1817-1825 [PMID: 21561347 DOI: 10.1056/NEJMoa1011923]

5 **Labori KJ**, Katz MH, Tzeng CW, Bjørnbeth BA, Cvancarova M, Edwin B, Kure EH, Eide TJ, Dueland S, Buanes T, Gladhaug IP. Impact of early disease progression and surgical complications on adjuvant chemotherapy completion rates and survival in patients undergoing the surgery first approach for resectable pancreatic ductal adenocarcinoma - A population-based cohort study. *Acta Oncol* 2016; **55**: 265-277 [PMID: 26213211 DOI: 10.3109/0284186X.2015.1068445]

6 **Oettle H**, Post S, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, Schramm H, Fahlke J, Zuelke C, Burkart C, Gutberlet K, Kettner E, Schmalenberg H, Weigang-Koehler K, Bechstein WO, Niedergethmann M, Schmidt-Wolf I, Roll L, Doerken B, Riess H. Adjuvant chemotherapy with gemcitabine *vs* observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. *JAMA* 2007; **297**: 267-277 [PMID: 17227978 DOI: 10.1001/jama.297.3.267]

7 **Neoptolemos JP**, Stocken DD, Bassi C, Ghaneh P, Cunningham D, Goldstein D, Padbury R, Moore MJ, Gallinger S, Mariette C, Wente MN, Izbicki JR, Friess H, Lerch MM, Dervenis C, Oláh A, Butturini G, Doi R, Lind PA, Smith D, Valle JW, Palmer DH, Buckels JA, Thompson J, McKay CJ, Rawcliffe CL, Büchler MW; European Study Group for Pancreatic Cancer. Adjuvant chemotherapy with fluorouracil plus folinic acid *vs* gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA* 2010; **304**: 1073-1081 [PMID: 20823433 DOI: 10.1001/jama.2010.1275]

8 **Neoptolemos JP**, Palmer DH, Ghaneh P, Psarelli EE, Valle JW, Halloran CM, Faluyi O, O'Reilly DA, Cunningham D, Wadsley J, Darby S, Meyer T, Gillmore R, Anthoney A, Lind P, Glimelius B, Falk S, Izbicki JR, Middleton GW, Cummins S, Ross PJ, Wasan H, McDonald A, Crosby T, Ma YT, Patel K, Sherriff D, Soomal R, Borg D, Sothi S, Hammel P, Hackert T, Jackson R, Büchler MW; European Study Group for Pancreatic Cancer. Comparison of adjuvant gemcitabine and capecitabine with gemcitabine monotherapy in patients with resected pancreatic cancer (ESPAC-4): a multicentre, open-label, randomised, phase 3 trial. *Lancet* 2017; **389**: 1011-1024 [PMID: 28129987 DOI: 10.1016/S0140-6736(16)32409-6]

9 **Dreyer SB**, Chang DK, Bailey P, Biankin AV. Pancreatic Cancer Genomes: Implications for Clinical Management and Therapeutic Development. *Clin Cancer Res* 2017; **23**: 1638-1646 [PMID: 28373362 DOI: 10.1158/1078-0432.CCR-16-2411]

10 **Mini E**, Nobili S, Caciagli B, Landini I, Mazzei T. Cellular pharmacology of gemcitabine. *Ann Oncol* 2006; **17 Suppl 5**: v7-12 [PMID: 16807468 DOI: 10.1093/annonc/mdj941]

11 **Heinemann V**, Hertel LW, Grindey GB, Plunkett W. Comparison of the cellular pharmacokinetics and toxicity of 2',2'-difluorodeoxycytidine and 1-beta-D-arabinofuranosylcytosine. *Cancer Res* 1988; **48**: 4024-4031 [PMID: 3383195]

12 **Mackey JR**, Mani RS, Selner M, Mowles D, Young JD, Belt JA, Crawford CR, Cass CE. Functional nucleoside transporters are required for gemcitabine influx and manifestation of toxicity in cancer cell lines. *Cancer Res* 1998; **58**: 4349-4357 [PMID: 9766663]

13 **Spratlin J**, Sangha R, Glubrecht D, Dabbagh L, Young JD, Dumontet C, Cass C, Lai R, Mackey JR. The absence of human equilibrative nucleoside transporter 1 is associated with reduced survival in patients with gemcitabine-treated pancreas adenocarcinoma. *Clin Cancer Res* 2004; **10**: 6956-6961 [PMID: 15501974 DOI: 10.1158/1078-0432.CCR-04-0224]

14 **Ohhashi S**, Ohuchida K, Mizumoto K, Fujita H, Egami T, Yu J, Toma H, Sadatomi S, Nagai E, Tanaka M. Down-regulation of deoxycytidine kinase enhances acquired resistance to gemcitabine in pancreatic cancer. *Anticancer Res* 2008; **28**: 2205-2212 [PMID: 18751396]

15 **Saiki Y**, Yoshino Y, Fujimura H, Manabe T, Kudo Y, Shimada M, Mano N, Nakano T, Lee Y, Shimizu S, Oba S, Fujiwara S, Shimizu H, Chen N, Nezhad ZK, Jin G, Fukushige S, Sunamura M, Ishida M, Motoi F, Egawa S, Unno M, Horii A. DCK is frequently inactivated in acquired gemcitabine-resistant human cancer cells. *Biochem Biophys Res Commun* 2012; **421**: 98-104 [PMID: 22490663 DOI: 10.1016/j.bbrc.2012.03.122]

16 **Miller AL**, Garcia PL, Gamblin TL, Vance RB, Yoon KJ. Development of gemcitabine-resistant patient-derived xenograft models of pancreatic ductal adenocarcinoma. *Cancer Drug Resist* 2020; **3**: 572-585 [PMID: 33073205 DOI: 10.20517/cdr.2020.35]

17 **Wang C**, Zhang W, Fu M, Yang A, Huang H, Xie J. Establishment of human pancreatic cancer gemcitabine‑resistant cell line with ribonucleotide reductase overexpression. *Oncol Rep* 2015; **33**: 383-390 [PMID: 25394408 DOI: 10.3892/or.2014.3599]

18 **Nakahira S**, Nakamori S, Tsujie M, Takahashi Y, Okami J, Yoshioka S, Yamasaki M, Marubashi S, Takemasa I, Miyamoto A, Takeda Y, Nagano H, Dono K, Umeshita K, Sakon M, Monden M. Involvement of ribonucleotide reductase M1 subunit overexpression in gemcitabine resistance of human pancreatic cancer. *Int J Cancer* 2007; **120**: 1355-1363 [PMID: 17131328 DOI: 10.1002/ijc.22390]

19 **Maftouh M**, Avan A, Funel N, Frampton AE, Fiuji H, Pelliccioni S, Castellano L, Galla V, Peters GJ, Giovannetti E. miR-211 modulates gemcitabine activity through downregulation of ribonucleotide reductase and inhibits the invasive behavior of pancreatic cancer cells. *Nucleosides Nucleotides Nucleic Acids* 2014; **33**: 384-393 [PMID: 24940696 DOI: 10.1080/15257770.2014.891741]

20 **Lu H**, Lu S, Yang D, Zhang L, Ye J, Li M, Hu W. MiR-20a-5p regulates gemcitabine chemosensitivity by targeting RRM2 in pancreatic cancer cells and serves as a predictor for gemcitabine-based chemotherapy. *Biosci Rep* 2019; **39** [PMID: 30777929 DOI: 10.1042/BSR20181374]

21 **Xia G**, Wang H, Song Z, Meng Q, Huang X, Huang X. Gambogic acid sensitizes gemcitabine efficacy in pancreatic cancer by reducing the expression of ribonucleotide reductase subunit-M2 (RRM2). *J Exp Clin Cancer Res* 2017; **36**: 107 [PMID: 28797284 DOI: 10.1186/s13046-017-0579-0]

22 **Vena F**, Li Causi E, Rodriguez-Justo M, Goodstal S, Hagemann T, Hartley JA, Hochhauser D. The MEK1/2 Inhibitor Pimasertib Enhances Gemcitabine Efficacy in Pancreatic Cancer Models by Altering Ribonucleotide Reductase Subunit-1 (RRM1). *Clin Cancer Res* 2015; **21**: 5563-5577 [PMID: 26228206 DOI: 10.1158/1078-0432.CCR-15-0485]

23 **Roman NO**, Samulitis BK, Wisner L, Landowski TH, Dorr RT. Imexon enhances gemcitabine cytotoxicity by inhibition of ribonucleotide reductase. *Cancer Chemother Pharmacol* 2011; **67**: 183-192 [PMID: 20339847 DOI: 10.1007/s00280-010-1306-0]

24 **Mitsuno M**, Kitajima Y, Ohtaka K, Kai K, Hashiguchi K, Nakamura J, Hiraki M, Noshiro H, Miyazaki K. Tranilast strongly sensitizes pancreatic cancer cells to gemcitabine *via* decreasing protein expression of ribonucleotide reductase 1. *Int J Oncol* 2010; **36**: 341-349 [PMID: 20043067 DOI: 10.3892/ijo\_00000505]

25 **Hwang DW**, Shin E, Cho JY, Han HS, Yoon YS. Human equilibrative nucleoside transporter-1 (hENT1) and ribonucleotide reductase regulatory subunit M1 (RRM1) expression; do they have survival impact to pancreatic cancer? *Ann Hepatobiliary Pancreat Surg* 2020; **24**: 127-136 [PMID: 32457256 DOI: 10.14701/ahbps.2020.24.2.127]

26 **Han QL**, Zhou YH, Lyu Y, Yan H, Dai GH. Effect of ribonucleotide reductase M1 expression on overall survival in patients with pancreatic cancer receiving gemcitabine chemotherapy: A literature-based meta-analysis. *J Clin Pharm Ther* 2018; **43**: 163-169 [PMID: 29214667 DOI: 10.1111/jcpt.12655]

27 **Aoyama T**, Miyagi Y, Murakawa M, Yamaoku K, Atsumi Y, Shiozawa M, Ueno M, Morimoto M, Oshima T, Yukawa N, Yoshikawa T, Rino Y, Masuda M, Morinaga S. Clinical implications of ribonucleotide reductase subunit M1 in patients with pancreatic cancer who undergo curative resection followed by adjuvant chemotherapy with gemcitabine. *Oncol Lett* 2017; **13**: 3423-3430 [PMID: 28521448 DOI: 10.3892/ol.2017.5935]

28 **Elander NO**, Aughton K, Ghaneh P, Neoptolemos JP, Palmer DH, Cox TF, Campbell F, Costello E, Halloran CM, Mackey JR, Scarfe AG, Valle JW, McDonald AC, Carter R, Tebbutt NC, Goldstein D, Shannon J, Dervenis C, Glimelius B, Deakin M, Charnley RM, Anthoney A, Lerch MM, Mayerle J, Oláh A, Büchler MW, Greenhalf W; European Study Group for Pancreatic Cancer. Intratumoural expression of deoxycytidylate deaminase or ribonuceotide reductase subunit M1 expression are not related to survival in patients with resected pancreatic cancer given adjuvant chemotherapy. *Br J Cancer* 2018; **118**: 1084-1088 [PMID: 29523831 DOI: 10.1038/s41416-018-0005-1]

29 **Zeng S**, Pöttler M, Lan B, Grützmann R, Pilarsky C, Yang H. Chemoresistance in Pancreatic Cancer. *Int J Mol Sci* 2019; **20** [PMID: 31514451 DOI: 10.3390/ijms20184504]

30 **Arumugam T**, Ramachandran V, Fournier KF, Wang H, Marquis L, Abbruzzese JL, Gallick GE, Logsdon CD, McConkey DJ, Choi W. Epithelial to mesenchymal transition contributes to drug resistance in pancreatic cancer. *Cancer Res* 2009; **69**: 5820-5828 [PMID: 19584296 DOI: 10.1158/0008-5472.CAN-08-2819]

31 **Zheng X**, Carstens JL, Kim J, Scheible M, Kaye J, Sugimoto H, Wu CC, LeBleu VS, Kalluri R. Epithelial-to-mesenchymal transition is dispensable for metastasis but induces chemoresistance in pancreatic cancer. *Nature* 2015; **527**: 525-530 [PMID: 26560028 DOI: 10.1038/nature16064]

32 **Kalser MH**, Ellenberg SS. Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection. *Arch Surg* 1985; **120**: 899-903 [PMID: 4015380 DOI: 10.1001/archsurg.1985.01390320023003]

33 **Moertel CG**, Frytak S, Hahn RG, O'Connell MJ, Reitemeier RJ, Rubin J, Schutt AJ, Weiland LH, Childs DS, Holbrook MA, Lavin PT, Livstone E, Spiro H, Knowlton A, Kalser M, Barkin J, Lessner H, Mann-Kaplan R, Ramming K, Douglas HO Jr, Thomas P, Nave H, Bateman J, Lokich J, Brooks J, Chaffey J, Corson JM, Zamcheck N, Novak JW. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: The Gastrointestinal Tumor Study Group. *Cancer* 1981; **48**: 1705-1710 [PMID: 7284971 DOI: 10.1002/1097-0142(19811015)48:8<1705::aid-cncr2820480803>3.0.co;2-4]

34 **Chevalier H**, Vienot A, Lièvre A, Edeline J, El Hajbi F, Peugniez C, Vernerey D, Meurisse A, Hammel P, Neuzillet C, Borg C, Turpin A. FOLFIRINOX De-Escalation in Advanced Pancreatic Cancer: A Multicenter Real-Life Study. *Oncologist* 2020; **25**: e1701-e1710 [PMID: 32886823 DOI: 10.1634/theoncologist.2020-0577]

35 **Foschini F**, Napolitano F, Servetto A, Marciano R, Mozzillo E, Carratù AC, Santaniello A, De Placido P, Cascetta P, Butturini G, Frigerio I, Regi P, Silvestris N, Delcuratolo S, Vasile E, Vivaldi C, Bianco C, De Placido S, Formisano L, Bianco R. FOLFIRINOX after first-line gemcitabine-based chemotherapy in advanced pancreatic cancer: a retrospective comparison with FOLFOX and FOLFIRI schedules. *Ther Adv Med Oncol* 2020; **12**: 1758835920947970 [PMID: 33062062 DOI: 10.1177/1758835920947970]

36 **Jung JH**, Shin DW, Kim J, Lee JC, Hwang JH. Primary Granulocyte Colony-Stimulating Factor Prophylaxis in Metastatic Pancreatic Cancer Patients Treated with FOLFIRINOX as the First-Line Treatment. *Cancers (Basel)* 2020; **12** [PMID: 33120908 DOI: 10.3390/cancers12113137]

37 **Kang SP**, Saif MW. Pharmacogenomics and pancreatic cancer treatment. Optimizing current therapy and individualizing future therapy. *JOP* 2008; **9**: 251-266 [PMID: 18469437]

38 **Zhang N**, Yin Y, Xu SJ, Chen WS. 5-Fluorouracil: mechanisms of resistance and reversal strategies. *Molecules* 2008; **13**: 1551-1569 [PMID: 18794772 DOI: 10.3390/molecules13081551]

39 **Hu YC**, Komorowski RA, Graewin S, Hostetter G, Kallioniemi OP, Pitt HA, Ahrendt SA. Thymidylate synthase expression predicts the response to 5-fluorouracil-based adjuvant therapy in pancreatic cancer. *Clin Cancer Res* 2003; **9**: 4165-4171 [PMID: 14519641]

40 **Jenh CH**, Geyer PK, Baskin F, Johnson LF. Thymidylate synthase gene amplification in fluorodeoxyuridine-resistant mouse cell lines. *Mol Pharmacol* 1985; **28**: 80-85 [PMID: 2991733]

41 **Ciaparrone M**, Quirino M, Schinzari G, Zannoni G, Corsi DC, Vecchio FM, Cassano A, La Torre G, Barone C. Predictive role of thymidylate synthase, dihydropyrimidine dehydrogenase and thymidine phosphorylase expression in colorectal cancer patients receiving adjuvant 5-fluorouracil. *Oncology* 2006; **70**: 366-377 [PMID: 17179731 DOI: 10.1159/000098110]

42 **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**: 473-482 [PMID: 21617862 DOI: 10.3892/ijo.2011.1058]

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

44 **Smit VT**, Boot AJ, Smits AM, Fleuren GJ, Cornelisse CJ, Bos JL. KRAS codon 12 mutations occur very frequently in pancreatic adenocarcinomas. *Nucleic Acids Res* 1988; **16**: 7773-7782 [PMID: 3047672 DOI: 10.1093/nar/16.16.7773]

45 **Lemoine NR**, Hughes CM, Barton CM, Poulsom R, Jeffery RE, Klöppel G, Hall PA, Gullick WJ. The epidermal growth factor receptor in human pancreatic cancer. *J Pathol* 1992; **166**: 7-12 [PMID: 1538276 DOI: 10.1002/path.1711660103]

46 **Boeck S**, Jung A, Laubender RP, Neumann J, Egg R, Goritschan C, Vehling-Kaiser U, Winkelmann C, Fischer von Weikersthal L, Clemens MR, Gauler TC, Märten A, Klein S, Kojouharoff G, Barner M, Geissler M, Greten TF, Mansmann U, Kirchner T, Heinemann V. EGFR pathway biomarkers in erlotinib-treated patients with advanced pancreatic cancer: translational results from the randomised, crossover phase 3 trial AIO-PK0104. *Br J Cancer* 2013; **108**: 469-476 [PMID: 23169292 DOI: 10.1038/bjc.2012.495]

47 **Moore MJ**, Goldstein D, Hamm J, Figer A, Hecht JR, Gallinger S, Au HJ, Murawa P, Walde D, Wolff RA, Campos D, Lim R, Ding K, Clark G, Voskoglou-Nomikos T, Ptasynski M, Parulekar W; National Cancer Institute of Canada Clinical Trials Group. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 2007; **25**: 1960-1966 [PMID: 17452677 DOI: 10.1200/JCO.2006.07.9525]

48 **Haas M**, Siveke JT, Schenk M, Lerch MM, Caca K, Freiberg-Richter J, Fischer von Weikersthal L, Kullmann F, Reinacher-Schick A, Fuchs M, Kanzler S, Kunzmann V, Ettrich TJ, Kruger S, Westphalen CB, Held S, Heinemann V, Boeck S. Efficacy of gemcitabine plus erlotinib in rash-positive patients with metastatic pancreatic cancer selected according to eligibility for FOLFIRINOX: A prospective phase II study of the 'Arbeitsgemeinschaft Internistische Onkologie'. *Eur J Cancer* 2018; **94**: 95-103 [PMID: 29549862 DOI: 10.1016/j.ejca.2018.02.008]

49 **Van Cutsem E**, Li CP, Nowara E, Aprile G, Moore M, Federowicz I, Van Laethem JL, Hsu C, Tham CK, Stemmer SM, Lipp R, Zeaiter A, Fittipaldo A, Csutor Z, Klughammer B, Meng X, Ciuleanu T. Dose escalation to rash for erlotinib plus gemcitabine for metastatic pancreatic cancer: the phase II RACHEL study. *Br J Cancer* 2014; **111**: 2067-2075 [PMID: 25247318 DOI: 10.1038/bjc.2014.494]

50 **Philip PA**, Benedetti J, Corless CL, Wong R, O'Reilly EM, Flynn PJ, Rowland KM, Atkins JN, Mirtsching BC, Rivkin SE, Khorana AA, Goldman B, Fenoglio-Preiser CM, Abbruzzese JL, Blanke CD. Phase III study comparing gemcitabine plus cetuximab *vs* gemcitabine in patients with advanced pancreatic adenocarcinoma: Southwest Oncology Group-directed intergroup trial S0205. *J Clin Oncol* 2010; **28**: 3605-3610 [PMID: 20606093 DOI: 10.1200/JCO.2009.25.7550]

51 **Katopodis O**, Souglakos J, Stathopoulos E, Christopoulou A, Kontopodis E, Kotsakis A, Kalbakis K, Kentepozidis N, Polyzos A, Hatzidaki D, Georgoulias V. Frontline treatment with gemcitabine, oxaliplatin and erlotinib for the treatment of advanced or metastatic pancreatic cancer: a multicenter phase II study of the Hellenic Oncology Research Group (HORG). *Cancer Chemother Pharmacol* 2014; **74**: 333-340 [PMID: 24930058 DOI: 10.1007/s00280-014-2509-6]

52 **Heinemann V**, Vehling-Kaiser U, Waldschmidt D, Kettner E, Märten A, Winkelmann C, Klein S, Kojouharoff G, Gauler TC, von Weikersthal LF, Clemens MR, Geissler M, Greten TF, Hegewisch-Becker S, Rubanov O, Baake G, Höhler T, Ko YD, Jung A, Neugebauer S, Boeck S. Gemcitabine plus erlotinib followed by capecitabine *vs* capecitabine plus erlotinib followed by gemcitabine in advanced pancreatic cancer: final results of a randomised phase 3 trial of the 'Arbeitsgemeinschaft Internistische Onkologie' (AIO-PK0104). *Gut* 2013; **62**: 751-759 [PMID: 22773551 DOI: 10.1136/gutjnl-2012-302759]

53 **Rich TA**, Winter K, Safran H, Hoffman JP, Erickson B, Anne PR, Myerson RJ, Cline-Burkhardt VJ, Perez K, Willett C. Weekly paclitaxel, gemcitabine, and external irradiation followed by randomized farnesyl transferase inhibitor R115777 for locally advanced pancreatic cancer. *Onco Targets Ther* 2012; **5**: 161-170 [PMID: 22977306 DOI: 10.2147/OTT.S33560]

54 **Kindler HL**, Niedzwiecki D, Hollis D, Sutherland S, Schrag D, Hurwitz H, Innocenti F, Mulcahy MF, O'Reilly E, Wozniak TF, Picus J, Bhargava P, Mayer RJ, Schilsky RL, Goldberg RM. 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 [PMID: 20606091 DOI: 10.1200/JCO.2010.28.1386]

55 **Kindler HL**, Ioka T, Richel DJ, Bennouna J, Létourneau R, Okusaka T, Funakoshi A, Furuse J, Park YS, Ohkawa S, Springett GM, Wasan HS, Trask PC, Bycott P, Ricart AD, Kim S, Van Cutsem E. Axitinib plus gemcitabine *vs* placebo plus gemcitabine in patients with advanced pancreatic adenocarcinoma: a double-blind randomised phase 3 study. *Lancet Oncol* 2011; **12**: 256-262 [PMID: 21306953 DOI: 10.1016/S1470-2045(11)70004-3]

56 **Infante JR**, Somer BG, Park JO, Li CP, Scheulen ME, Kasubhai SM, Oh DY, Liu Y, Redhu S, Steplewski K, Le N. 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 [PMID: 24915778 DOI: 10.1016/j.ejca.2014.04.024]

57 **Chung V**, McDonough S, Philip PA, Cardin D, Wang-Gillam A, Hui L, Tejani MA, Seery TE, Dy IA, Al Baghdadi T, Hendifar AE, Doyle LA, Lowy AM, Guthrie KA, Blanke CD, Hochster HS. 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 [PMID: 27978579 DOI: 10.1001/jamaoncol.2016.5383]

58 **Mahadevan D**, Von Hoff DD. Tumor-stroma interactions in pancreatic ductal adenocarcinoma. *Mol Cancer Ther* 2007; **6**: 1186-1197 [PMID: 17406031 DOI: 10.1158/1535-7163.MCT-06-0686]

59 **Hoffmann AC**, Mori R, Vallbohmer D, Brabender J, Klein E, Drebber U, Baldus SE, Cooc J, Azuma M, Metzger R, Hoelscher AH, Danenberg KD, Prenzel KL, Danenberg PV. High expression of HIF1a is a predictor of clinical outcome in patients with pancreatic ductal adenocarcinomas and correlated to PDGFA, VEGF, and bFGF. *Neoplasia* 2008; **10**: 674-679 [PMID: 18592007 DOI: 10.1593/neo.08292]

60 **Couvelard A**, O'Toole D, Leek R, Turley H, Sauvanet A, Degott C, Ruszniewski P, Belghiti J, Harris AL, Gatter K, Pezzella F. Expression of hypoxia-inducible factors is correlated with the presence of a fibrotic focus and angiogenesis in pancreatic ductal adenocarcinomas. *Histopathology* 2005; **46**: 668-676 [PMID: 15910598 DOI: 10.1111/j.1365-2559.2005.02160.x]

61 **Büchler P**, Reber HA, Lavey RS, Tomlinson J, Büchler MW, Friess H, Hines OJ. Tumor hypoxia correlates with metastatic tumor growth of pancreatic cancer in an orthotopic murine model. *J Surg Res* 2004; **120**: 295-303 [PMID: 15234226 DOI: 10.1016/j.jss.2004.02.014]

62 **Warburg O**. On the origin of cancer cells. *Science* 1956; **123**: 309-314 [PMID: 13298683 DOI: 10.1126/science.123.3191.309]

63 **Cairns RA**, Harris IS, Mak TW. Regulation of cancer cell metabolism. *Nat Rev Cancer* 2011; **11**: 85-95 [PMID: 21258394 DOI: 10.1038/nrc2981]

64 **Christofk HR**, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, Wei R, Fleming MD, Schreiber SL, Cantley LC. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature* 2008; **452**: 230-233 [PMID: 18337823 DOI: 10.1038/nature06734]

65 **Dong X**, Li Y, Chang P, Tang H, Hess KR, Abbruzzese JL, Li D. Glucose metabolism gene variants modulate the risk of pancreatic cancer. *Cancer Prev Res (Phila)* 2011; **4**: 758-766 [PMID: 21411499 DOI: 10.1158/1940-6207.CAPR-10-0247]

66 **Dong X**, Tang H, Hess KR, Abbruzzese JL, Li D. Glucose metabolism gene polymorphisms and clinical outcome in pancreatic cancer. *Cancer* 2011; **117**: 480-491 [PMID: 20845477 DOI: 10.1002/cncr.25612]

67 **Markovets AA**, Herman D. Analysis of cancer metabolism with high-throughput technologies. *BMC Bioinformatics* 2011; **12 Suppl 10**: S8 [PMID: 22166000 DOI: 10.1186/1471-2105-12-S10-S8]

68 **Wei Z**, Cui L, Mei Z, Liu M, Zhang D. miR-181a mediates metabolic shift in colon cancer cells *via* the PTEN/AKT pathway. *FEBS Lett* 2014; **588**: 1773-1779 [PMID: 24685694 DOI: 10.1016/j.febslet.2014.03.037]

69 **Mikuriya K**, Kuramitsu Y, Ryozawa S, Fujimoto M, Mori S, Oka M, Hamano K, Okita K, Sakaida I, Nakamura K. Expression of glycolytic enzymes is increased in pancreatic cancerous tissues as evidenced by proteomic profiling by two-dimensional electrophoresis and liquid chromatography-mass spectrometry/mass spectrometry. *Int J Oncol* 2007; **30**: 849-855 [PMID: 17332923 DOI: 10.3892/ijo.30.4.849]

70 **Zhou W**, Capello M, Fredolini C, Piemonti L, Liotta LA, Novelli F, Petricoin EF. Proteomic analysis of pancreatic ductal adenocarcinoma cells reveals metabolic alterations. *J Proteome Res* 2011; **10**: 1944-1952 [PMID: 21309613 DOI: 10.1021/pr101179t]

71 **Vernucci E**, Abrego J, Gunda V, Shukla SK, Dasgupta A, Rai V, Chaika N, Buettner K, Illies A, Yu F, Lazenby AJ, Swanson BJ, Singh PK. Metabolic Alterations in Pancreatic Cancer Progression. *Cancers (Basel)* 2019; **12** [PMID: 31861288 DOI: 10.3390/cancers12010002]

72 **Martinez-Outschoorn UE**, Peiris-Pagés M, Pestell RG, Sotgia F, Lisanti MP. Cancer metabolism: a therapeutic perspective. *Nat Rev Clin Oncol* 2017; **14**: 11-31 [PMID: 27141887 DOI: 10.1038/nrclinonc.2016.60]

73 **Wu DH**, Liang H, Lu SN, Wang H, Su ZL, Zhang L, Ma JQ, Guo M, Tai S, Yu S. miR-124 Suppresses Pancreatic Ductal Adenocarcinoma Growth by Regulating Monocarboxylate Transporter 1-Mediated Cancer Lactate Metabolism. *Cell Physiol Biochem* 2018; **50**: 924-935 [PMID: 30355947 DOI: 10.1159/000494477]

74 **Kong SC**, Nøhr-Nielsen A, Zeeberg K, Reshkin SJ, Hoffmann EK, Novak I, Pedersen SF. Monocarboxylate Transporters MCT1 and MCT4 Regulate Migration and Invasion of Pancreatic Ductal Adenocarcinoma Cells. *Pancreas* 2016; **45**: 1036-1047 [PMID: 26765963 DOI: 10.1097/MPA.0000000000000571]

75 **Feldmann G**, Beaty R, Hruban RH, Maitra A. Molecular genetics of pancreatic intraepithelial neoplasia. *J Hepatobiliary Pancreat Surg* 2007; **14**: 224-232 [PMID: 17520196 DOI: 10.1007/s00534-006-1166-5]

76 **Shen L**, Sun X, Fu Z, Yang G, Li J, Yao L. The fundamental role of the p53 pathway in tumor metabolism and its implication in tumor therapy. *Clin Cancer Res* 2012; **18**: 1561-1567 [PMID: 22307140 DOI: 10.1158/1078-0432.CCR-11-3040]

77 **Schwartzenberg-Bar-Yoseph F**, Armoni M, Karnieli E. The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. *Cancer Res* 2004; **64**: 2627-2633 [PMID: 15059920 DOI: 10.1158/0008-5472.can-03-0846]

78 **Ying H**, Kimmelman AC, Lyssiotis CA, Hua S, Chu GC, Fletcher-Sananikone E, Locasale JW, Son J, Zhang H, Coloff JL, Yan H, Wang W, Chen S, Viale A, Zheng H, Paik JH, Lim C, Guimaraes AR, Martin ES, Chang J, Hezel AF, Perry SR, Hu J, Gan B, Xiao Y, Asara JM, Weissleder R, Wang YA, Chin L, Cantley LC, DePinho RA. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell* 2012; **149**: 656-670 [PMID: 22541435 DOI: 10.1016/j.cell.2012.01.058]

79 **Zhao H**, Duan Q, Zhang Z, Li H, Wu H, Shen Q, Wang C, Yin T. Up-regulation of glycolysis promotes the stemness and EMT phenotypes in gemcitabine-resistant pancreatic cancer cells. *J Cell Mol Med* 2017; **21**: 2055-2067 [PMID: 28244691 DOI: 10.1111/jcmm.13126]

80 **Anderson M**, Marayati R, Moffitt R, Yeh JJ. Hexokinase 2 promotes tumor growth and metastasis by regulating lactate production in pancreatic cancer. *Oncotarget* 2017; **8**: 56081-56094 [PMID: 28915575 DOI: 10.18632/oncotarget.9760]

81 **Bhardwaj V**, Rizvi N, Lai MB, Lai JC, Bhushan A. Glycolytic enzyme inhibitors affect pancreatic cancer survival by modulating its signaling and energetics. *Anticancer Res* 2010; **30**: 743-749 [PMID: 20392992]

82 **Fan K**, Fan Z, Cheng H, Huang Q, Yang C, Jin K, Luo G, Yu X, Liu C. Hexokinase 2 dimerization and interaction with voltage-dependent anion channel promoted resistance to cell apoptosis induced by gemcitabine in pancreatic cancer. *Cancer Med* 2019; **8**: 5903-5915 [PMID: 31426130 DOI: 10.1002/cam4.2463]

83 **Dayton TL**, Jacks T, Vander Heiden MG. PKM2, cancer metabolism, and the road ahead. *EMBO Rep* 2016; **17**: 1721-1730 [PMID: 27856534 DOI: 10.15252/embr.201643300]

84 **Anastasiou D**, Poulogiannis G, Asara JM, Boxer MB, Jiang JK, Shen M, Bellinger G, Sasaki AT, Locasale JW, Auld DS, Thomas CJ, Vander Heiden MG, Cantley LC. Inhibition of pyruvate kinase M2 by reactive oxygen species contributes to cellular antioxidant responses. *Science* 2011; **334**: 1278-1283 [PMID: 22052977 DOI: 10.1126/science.1211485]

85 **Hitosugi T**, Kang S, Vander Heiden MG, Chung TW, Elf S, Lythgoe K, Dong S, Lonial S, Wang X, Chen GZ, Xie J, Gu TL, Polakiewicz RD, Roesel JL, Boggon TJ, Khuri FR, Gilliland DG, Cantley LC, Kaufman J, Chen J. Tyrosine phosphorylation inhibits PKM2 to promote the Warburg effect and tumor growth. *Sci Signal* 2009; **2**: ra73 [PMID: 19920251 DOI: 10.1126/scisignal.2000431]

86 **Hillis AL**, Lau AN, Devoe CX, Dayton TL, Danai LV, Di Vizio D, Vander Heiden MG. PKM2 is not required for pancreatic ductal adenocarcinoma. *Cancer Metab* 2018; **6**: 17 [PMID: 30386596 DOI: 10.1186/s40170-018-0188-1]

87 **Lockney NA**, Zhang M, Lu Y, Sopha SC, Washington MK, Merchant N, Zhao Z, Shyr Y, Chakravarthy AB, Xia F. Pyruvate Kinase Muscle Isoenzyme 2 (PKM2) Expression Is Associated with Overall Survival in Pancreatic Ductal Adenocarcinoma. *J Gastrointest Cancer* 2015; **46**: 390-398 [PMID: 26385349 DOI: 10.1007/s12029-015-9764-6]

88 **Mohammad GH**, Olde Damink SW, Malago M, Dhar DK, Pereira SP. Pyruvate Kinase M2 and Lactate Dehydrogenase A Are Overexpressed in Pancreatic Cancer and Correlate with Poor Outcome. *PLoS One* 2016; **11**: e0151635 [PMID: 26989901 DOI: 10.1371/journal.pone.0151635]

89 **Ogawa H**, Nagano H, Konno M, Eguchi H, Koseki J, Kawamoto K, Nishida N, Colvin H, Tomokuni A, Tomimaru Y, Hama N, Wada H, Marubashi S, Kobayashi S, Mori M, Doki Y, Ishii H. The combination of the expression of hexokinase 2 and pyruvate kinase M2 is a prognostic marker in patients with pancreatic cancer. *Mol Clin Oncol* 2015; **3**: 563-571 [PMID: 26137268 DOI: 10.3892/mco.2015.490]

90 **Azoitei N**, Becher A, Steinestel K, Rouhi A, Diepold K, Genze F, Simmet T, Seufferlein T. PKM2 promotes tumor angiogenesis by regulating HIF-1α through NF-κB activation. *Mol Cancer* 2016; **15**: 3 [PMID: 26739387 DOI: 10.1186/s12943-015-0490-2]

91 **Calabretta S**, Bielli P, Passacantilli I, Pilozzi E, Fendrich V, Capurso G, Fave GD, Sette C. Modulation of PKM alternative splicing by PTBP1 promotes gemcitabine resistance in pancreatic cancer cells. *Oncogene* 2016; **35**: 2031-2039 [PMID: 26234680 DOI: 10.1038/onc.2015.270]

92 **Chen S**, Chen X, Shan T, Ma J, Lin W, Li W, Kang Y. MiR-21-mediated Metabolic Alteration of Cancer-associated Fibroblasts and Its Effect on Pancreatic Cancer Cell Behavior. *Int J Biol Sci* 2018; **14**: 100-110 [PMID: 29483829 DOI: 10.7150/ijbs.22555]

93 **Cheng TY**, Yang YC, Wang HP, Tien YW, Shun CT, Huang HY, Hsiao M, Hua KT. Pyruvate kinase M2 promotes pancreatic ductal adenocarcinoma invasion and metastasis through phosphorylation and stabilization of PAK2 protein. *Oncogene* 2018; **37**: 1730-1742 [PMID: 29335522 DOI: 10.1038/s41388-017-0086-y]

94 **Kim DJ**, Park YS, Kang MG, You YM, Jung Y, Koo H, Kim JA, Kim MJ, Hong SM, Lee KB, Jang JJ, Park KC, Yeom YI. Pyruvate kinase isoenzyme M2 is a therapeutic target of gemcitabine-resistant pancreatic cancer cells. *Exp Cell Res* 2015; **336**: 119-129 [PMID: 26112218 DOI: 10.1016/j.yexcr.2015.05.017]

95 **Li C**, Zhao Z, Zhou Z, Liu R. PKM2 Promotes Cell Survival and Invasion Under Metabolic Stress by Enhancing Warburg Effect in Pancreatic Ductal Adenocarcinoma. *Dig Dis Sci* 2016; **61**: 767-773 [PMID: 26500118 DOI: 10.1007/s10620-015-3931-2]

96 **Cui J**, Shi M, Xie D, Wei D, Jia Z, Zheng S, Gao Y, Huang S, Xie K. FOXM1 promotes the warburg effect and pancreatic cancer progression *via* transactivation of LDHA expression. *Clin Cancer Res* 2014; **20**: 2595-2606 [PMID: 24634381 DOI: 10.1158/1078-0432.CCR-13-2407]

97 **Giatromanolaki A**, Sivridis E, Gatter KC, Turley H, Harris AL, Koukourakis MI; Tumour and Angiogenesis Research Group. Lactate dehydrogenase 5 (LDH-5) expression in endometrial cancer relates to the activated VEGF/VEGFR2(KDR) pathway and prognosis. *Gynecol Oncol* 2006; **103**: 912-918 [PMID: 16837029 DOI: 10.1016/j.ygyno.2006.05.043]

98 **Jiang W**, Zhou F, Li N, Li Q, Wang L. FOXM1-LDHA signaling promoted gastric cancer glycolytic phenotype and progression. *Int J Clin Exp Pathol* 2015; **8**: 6756-6763 [PMID: 26261559]

99 **Kobari M**, Hisano H, Matsuno S, Sato T, Kan M, Tachibana T. Establishment of six human pancreatic cancer cell lines and their sensitivities to anti-tumor drugs. *Tohoku J Exp Med* 1986; **150**: 231-248 [PMID: 3547771 DOI: 10.1620/tjem.150.231]

100 **Koukourakis MI**, Kakouratos C, Kalamida D, Bampali Z, Mavropoulou S, Sivridis E, Giatromanolaki A. Hypoxia-inducible proteins HIF1α and lactate dehydrogenase LDH5, key markers of anaerobic metabolism, relate with stem cell markers and poor post-radiotherapy outcome in bladder cancer. *Int J Radiat Biol* 2016; **92**: 353-363 [PMID: 27010533 DOI: 10.3109/09553002.2016.1162921]

101 **Thonsri U**, Seubwai W, Waraasawapati S, Sawanyawisuth K, Vaeteewoottacharn K, Boonmars T, Cha'on U. Overexpression of lactate dehydrogenase A in cholangiocarcinoma is correlated with poor prognosis. *Histol Histopathol* 2017; **32**: 503-510 [PMID: 27615379 DOI: 10.14670/HH-11-819]

102 **Yu C**, Hou L, Cui H, Zhang L, Tan X, Leng X, Li Y. LDHA upregulation independently predicts poor survival in lung adenocarcinoma, but not in lung squamous cell carcinoma. *Future Oncol* 2018; **14**: 2483-2492 [PMID: 29756998 DOI: 10.2217/fon-2018-0177]

103 **Semenza GL**, Jiang BH, Leung SW, Passantino R, Concordet JP, Maire P, Giallongo A. Hypoxia response elements in the aldolase A, enolase 1, and lactate dehydrogenase A gene promoters contain essential binding sites for hypoxia-inducible factor 1. *J Biol Chem* 1996; **271**: 32529-32537 [PMID: 8955077 DOI: 10.1074/jbc.271.51.32529]

104 **Shim H**, Dolde C, Lewis BC, Wu CS, Dang G, Jungmann RA, Dalla-Favera R, Dang CV. c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. *Proc Natl Acad Sci U S A* 1997; **94**: 6658-6663 [PMID: 9192621 DOI: 10.1073/pnas.94.13.6658]

105 **Li SS**, Pan YE, Sharief FS, Evans MJ, Lin MF, Clinton GM, Holbrook JJ. Cancer-associated lactate dehydrogenase is a tyrosylphosphorylated form of human LDH-A, skeletal muscle isoenzyme. *Cancer Invest* 1988; **6**: 93-101 [PMID: 3365574 DOI: 10.3109/07357908809077032]

106 **Liu J**, Chen G, Liu Z, Liu S, Cai Z, You P, Ke Y, Lai L, Huang Y, Gao H, Zhao L, Pelicano H, Huang P, McKeehan WL, Wu CL, Wang C, Zhong W, Wang F. Aberrant FGFR Tyrosine Kinase Signaling Enhances the Warburg Effect by Reprogramming LDH Isoform Expression and Activity in Prostate Cancer. *Cancer Res* 2018; **78**: 4459-4470 [PMID: 29891507 DOI: 10.1158/0008-5472.CAN-17-3226]

107 **Faloppi L**, Bianconi M, Giampieri R, Sobrero A, Labianca R, Ferrari D, Barni S, Aitini E, Zaniboni A, Boni C, Caprioni F, Mosconi S, Fanello S, Berardi R, Bittoni A, Andrikou K, Cinquini M, Torri V, Scartozzi M, Cascinu S; Italian Group for the Study of Digestive Tract Cancer (GISCAD). The value of lactate dehydrogenase serum levels as a prognostic and predictive factor for advanced pancreatic cancer patients receiving sorafenib. *Oncotarget* 2015; **6**: 35087-35094 [PMID: 26397228 DOI: 10.18632/oncotarget.5197]

108 **Gan J**, Wang W, Yang Z, Pan J, Zheng L, Yin L. Prognostic value of pretreatment serum lactate dehydrogenase level in pancreatic cancer patients: A meta-analysis of 18 observational studies. *Medicine (Baltimore)* 2018; **97**: e13151 [PMID: 30431587 DOI: 10.1097/MD.0000000000013151]

109 **Ji F**, Fu SJ, Guo ZY, Pang H, Ju WQ, Wang DP, Hua YP, He XS. Prognostic value of combined preoperative lactate dehydrogenase and alkaline phosphatase levels in patients with resectable pancreatic ductal adenocarcinoma. *Medicine (Baltimore)* 2016; **95**: e4065 [PMID: 27399091 DOI: 10.1097/MD.0000000000004065]

110 **Mann JR**, Pearson D, Barrett A, Raafat F, Barnes JM, Wallendszus KR. Results of the United Kingdom Children's Cancer Study Group's malignant germ cell tumor studies. *Cancer* 1989; **63**: 1657-1667 [PMID: 2467734 DOI: 10.1002/1097-0142(19900501)63:9<1657::aid-cncr2820630902>3.0.co;2-8]

111 **Tas F**, Aykan F, Alici S, Kaytan E, Aydiner A, Topuz E. Prognostic factors in pancreatic carcinoma: serum LDH levels predict survival in metastatic disease. *Am J Clin Oncol* 2001; **24**: 547-550 [PMID: 11801751 DOI: 10.1097/00000421-200112000-00003]

112 **Xiao Y**, Chen W, Xie Z, Shao Z, Xie H, Qin G, Zhao N. Prognostic relevance of lactate dehydrogenase in advanced pancreatic ductal adenocarcinoma patients. *BMC Cancer* 2017; **17**: 25 [PMID: 28056913 DOI: 10.1186/s12885-016-3012-8]

113 **Annas D**, Cheon SY, Yusuf M, Bae SJ, Ha KT, Park KH. Synthesis and initial screening of lactate dehydrogenase inhibitor activity of 1,3-benzodioxole derivatives. *Sci Rep* 2020; **10**: 19889 [PMID: 33199724 DOI: 10.1038/s41598-020-77056-4]

114 **Moir JAG**, Long A, Haugk B, French JJ, Charnley RM, Manas DM, Wedge SR, Mann J, Robinson SM, White SA. Therapeutic Strategies Toward Lactate Dehydrogenase Within the Tumor Microenvironment of Pancreatic Cancer. *Pancreas* 2020; **49**: 1364-1371 [PMID: 33122526 DOI: 10.1097/MPA.0000000000001689]

115 **Stanton RC**. Glucose-6-phosphate dehydrogenase, NADPH, and cell survival. *IUBMB Life* 2012; **64**: 362-369 [PMID: 22431005 DOI: 10.1002/iub.1017]

116 **Santana-Codina N**, Roeth AA, Zhang Y, Yang A, Mashadova O, Asara JM, Wang X, Bronson RT, Lyssiotis CA, Ying H, Kimmelman AC. Oncogenic KRAS supports pancreatic cancer through regulation of nucleotide synthesis. *Nat Commun* 2018; **9**: 4945 [PMID: 30470748 DOI: 10.1038/s41467-018-07472-8]

117 **Sharma N**, Bhushan A, He J, Kaushal G, Bhardwaj V. Metabolic plasticity imparts erlotinib-resistance in pancreatic cancer by upregulating glucose-6-phosphate dehydrogenase. *Cancer Metab* 2020; **8**: 19 [PMID: 32974013 DOI: 10.1186/s40170-020-00226-5]

118 **Shukla SK**, Purohit V, Mehla K, Gunda V, Chaika NV, Vernucci E, King RJ, Abrego J, Goode GD, Dasgupta A, Illies AL, Gebregiworgis T, Dai B, Augustine JJ, Murthy D, Attri KS, Mashadova O, Grandgenett PM, Powers R, Ly QP, Lazenby AJ, Grem JL, Yu F, Matés JM, Asara JM, Kim JW, Hankins JH, Weekes C, Hollingsworth MA, Serkova NJ, Sasson AR, Fleming JB, Oliveto JM, Lyssiotis CA, Cantley LC, Berim L, Singh PK. MUC1 and HIF-1alpha Signaling Crosstalk Induces Anabolic Glucose Metabolism to Impart Gemcitabine Resistance to Pancreatic Cancer. *Cancer Cell* 2017; **32**: 71-87.e7 [PMID: 28697344 DOI: 10.1016/j.ccell.2017.06.004]

119 **Viale A**, Pettazzoni P, Lyssiotis CA, Ying H, Sánchez N, Marchesini M, Carugo A, Green T, Seth S, Giuliani V, Kost-Alimova M, Muller F, Colla S, Nezi L, Genovese G, Deem AK, Kapoor A, Yao W, Brunetto E, Kang Y, Yuan M, Asara JM, Wang YA, Heffernan TP, Kimmelman AC, Wang H, Fleming JB, Cantley LC, DePinho RA, Draetta GF. Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature* 2014; **514**: 628-632 [PMID: 25119024 DOI: 10.1038/nature13611]

120 **Sancho P**, Burgos-Ramos E, Tavera A, Bou Kheir T, Jagust P, Schoenhals M, Barneda D, Sellers K, Campos-Olivas R, Graña O, Viera CR, Yuneva M, Sainz B Jr, Heeschen C. MYC/PGC-1α Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells. *Cell Metab* 2015; **22**: 590-605 [PMID: 26365176 DOI: 10.1016/j.cmet.2015.08.015]

121 **Kovalenko I**, Glasauer A, Schöckel L, Sauter DR, Ehrmann A, Sohler F, Hägebarth A, Novak I, Christian S. Identification of KCa3.1 Channel as a Novel Regulator of Oxidative Phosphorylation in a Subset of Pancreatic Carcinoma Cell Lines. *PLoS One* 2016; **11**: e0160658 [PMID: 27494181 DOI: 10.1371/journal.pone.0160658]

122 **Dey P**, Baddour J, Muller F, Wu CC, Wang H, Liao WT, Lan Z, Chen A, Gutschner T, Kang Y, Fleming J, Satani N, Zhao D, Achreja A, Yang L, Lee J, Chang E, Genovese G, Viale A, Ying H, Draetta G, Maitra A, Wang YA, Nagrath D, DePinho RA. Genomic deletion of malic enzyme 2 confers collateral lethality in pancreatic cancer. *Nature* 2017; **542**: 119-123 [PMID: 28099419 DOI: 10.1038/nature21052]

123 **Zarei M**, Lal S, Parker SJ, Nevler A, Vaziri-Gohar A, Dukleska K, Mambelli-Lisboa NC, Moffat C, Blanco FF, Chand SN, Jimbo M, Cozzitorto JA, Jiang W, Yeo CJ, Londin ER, Seifert EL, Metallo CM, Brody JR, Winter JM. Posttranscriptional Upregulation of IDH1 by HuR Establishes a Powerful Survival Phenotype in Pancreatic Cancer Cells. *Cancer Res* 2017; **77**: 4460-4471 [PMID: 28652247 DOI: 10.1158/0008-5472.CAN-17-0015]

124 **Nishi K**, Suzuki M, Yamamoto N, Matsumoto A, Iwase Y, Yamasaki K, Otagiri M, Yumita N. Glutamine Deprivation Enhances Acetyl-CoA Carboxylase Inhibitor-induced Death of Human Pancreatic Cancer Cells. *Anticancer Res* 2018; **38**: 6683-6689 [PMID: 30504377 DOI: 10.21873/anticanres.13036]

125 **Son J**, Lyssiotis CA, Ying H, Wang X, Hua S, Ligorio M, Perera RM, Ferrone CR, Mullarky E, Shyh-Chang N, Kang Y, Fleming JB, Bardeesy N, Asara JM, Haigis MC, DePinho RA, Cantley LC, Kimmelman AC. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature* 2013; **496**: 101-105 [PMID: 23535601 DOI: 10.1038/nature12040]

126 **Chakrabarti G**, Moore ZR, Luo X, Ilcheva M, Ali A, Padanad M, Zhou Y, Xie Y, Burma S, Scaglioni PP, Cantley LC, DeBerardinis RJ, Kimmelman AC, Lyssiotis CA, Boothman DA. Targeting glutamine metabolism sensitizes pancreatic cancer to PARP-driven metabolic catastrophe induced by ß-lapachone. *Cancer Metab* 2015; **3**: 12 [PMID: 26462257 DOI: 10.1186/s40170-015-0137-1]

127 **Chen R**, Lai LA, Sullivan Y, Wong M, Wang L, Riddell J, Jung L, Pillarisetty VG, Brentnall TA, Pan S. Disrupting glutamine metabolic pathways to sensitize gemcitabine-resistant pancreatic cancer. *Sci Rep* 2017; **7**: 7950 [PMID: 28801576 DOI: 10.1038/s41598-017-08436-6]

128 **Jia C**, Li H, Fu D, Lan Y. GFAT1/HBP/O-GlcNAcylation Axis Regulates *β*-Catenin Activity to Promote Pancreatic Cancer Aggressiveness. *Biomed Res Int* 2020; **2020**: 1921609 [PMID: 32149084 DOI: 10.1155/2020/1921609]

129 **Li D**, Fu Z, Chen R, Zhao X, Zhou Y, Zeng B, Yu M, Zhou Q, Lin Q, Gao W, Ye H, Zhou J, Li Z, Liu Y, Chen R. Inhibition of glutamine metabolism counteracts pancreatic cancer stem cell features and sensitizes cells to radiotherapy. *Oncotarget* 2015; **6**: 31151-31163 [PMID: 26439804 DOI: 10.18632/oncotarget.5150]

130 **Lyssiotis CA**, Son J, Cantley LC, Kimmelman AC. Pancreatic cancers rely on a novel glutamine metabolism pathway to maintain redox balance. *Cell Cycle* 2013; **12**: 1987-1988 [PMID: 23759579 DOI: 10.4161/cc.25307]

131 **Raho S**, Capobianco L, Malivindi R, Vozza A, Piazzolla C, De Leonardis F, Gorgoglione R, Scarcia P, Pezzuto F, Agrimi G, Barile SN, Pisano I, Reshkin SJ, Greco MR, Cardone RA, Rago V, Li Y, Marobbio CMT, Sommergruber W, Riley CL, Lasorsa FM, Mills E, Vegliante MC, De Benedetto GE, Fratantonio D, Palmieri L, Dolce V, Fiermonte G. KRAS-regulated glutamine metabolism requires UCP2-mediated aspartate transport to support pancreatic cancer growth. *Nat Metab* 2020; **2**: 1373-1381 [PMID: 33230296 DOI: 10.1038/s42255-020-00315-1]

132 **Wang J**, Wang B, Ren H, Chen W. miR-9-5p inhibits pancreatic cancer cell proliferation, invasion and glutamine metabolism by targeting GOT1. *Biochem Biophys Res Commun* 2019; **509**: 241-248 [PMID: 30591220 DOI: 10.1016/j.bbrc.2018.12.114]

133 **Jeong SM**, Hwang S, Park K, Yang S, Seong RH. Enhanced mitochondrial glutamine anaplerosis suppresses pancreatic cancer growth through autophagy inhibition. *Sci Rep* 2016; **6**: 30767 [PMID: 27477484 DOI: 10.1038/srep30767]

134 **Recouvreux MV**, Moldenhauer MR, Galenkamp KMO, Jung M, James B, Zhang Y, Lowy A, Bagchi A, Commisso C. Glutamine depletion regulates Slug to promote EMT and metastasis in pancreatic cancer. *J Exp Med* 2020; **217** [PMID: 32510550 DOI: 10.1084/jem.20200388]

135 **Roux C**, Riganti C, Borgogno SF, Curto R, Curcio C, Catanzaro V, Digilio G, Padovan S, Puccinelli MP, Isabello M, Aime S, Cappello P, Novelli F. Endogenous glutamine decrease is associated with pancreatic cancer progression. *Oncotarget* 2017; **8**: 95361-95376 [PMID: 29221133 DOI: 10.18632/oncotarget.20545]

136 **Bao B**, Wang Z, Ali S, Ahmad A, Azmi AS, Sarkar SH, Banerjee S, Kong D, Li Y, Thakur S, Sarkar FH. Metformin inhibits cell proliferation, migration and invasion by attenuating CSC function mediated by deregulating miRNAs in pancreatic cancer cells. *Cancer Prev Res (Phila)* 2012; **5**: 355-364 [PMID: 22086681 DOI: 10.1158/1940-6207.CAPR-11-0299]

137 **Cheng G**, Zielonka J, Ouari O, Lopez M, McAllister D, Boyle K, Barrios CS, Weber JJ, Johnson BD, Hardy M, Dwinell MB, Kalyanaraman B. Mitochondria-Targeted Analogues of Metformin Exhibit Enhanced Antiproliferative and Radiosensitizing Effects in Pancreatic Cancer Cells. *Cancer Res* 2016; **76**: 3904-3915 [PMID: 27216187 DOI: 10.1158/0008-5472.CAN-15-2534]

138 **Masoud R**, Reyes-Castellanos G, Lac S, Garcia J, Dou S, Shintu L, Abdel Hadi N, Gicquel T, El Kaoutari A, Diémé B, Tranchida F, Cormareche L, Borge L, Gayet O, Pasquier E, Dusetti N, Iovanna J, Carrier A. Targeting Mitochondrial Complex I Overcomes Chemoresistance in High OXPHOS Pancreatic Cancer. *Cell Rep Med* 2020; **1**: 100143 [PMID: 33294863 DOI: 10.1016/j.xcrm.2020.100143]

139 **Rajeshkumar NV**, Yabuuchi S, Pai SG, De Oliveira E, Kamphorst JJ, Rabinowitz JD, Tejero H, Al-Shahrour F, Hidalgo M, Maitra A, Dang CV. Treatment of Pancreatic Cancer Patient-Derived Xenograft Panel with Metabolic Inhibitors Reveals Efficacy of Phenformin. *Clin Cancer Res* 2017; **23**: 5639-5647 [PMID: 28611197 DOI: 10.1158/1078-0432.CCR-17-1115]

140 **Kordes S**, Pollak MN, Zwinderman AH, Mathôt RA, Weterman MJ, Beeker A, Punt CJ, Richel DJ, Wilmink JW. Metformin in patients with advanced pancreatic cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncol* 2015; **16**: 839-847 [PMID: 26067687 DOI: 10.1016/S1470-2045(15)00027-3]

141 **Reni M**, Dugnani E, Cereda S, Belli C, Balzano G, Nicoletti R, Liberati D, Pasquale V, Scavini M, Maggiora P, Sordi V, Lampasona V, Ceraulo D, Di Terlizzi G, Doglioni C, Falconi M, Piemonti L. (Ir)relevance of Metformin Treatment in Patients with Metastatic Pancreatic Cancer: An Open-Label, Randomized Phase II Trial. *Clin Cancer Res* 2016; **22**: 1076-1085 [PMID: 26459175 DOI: 10.1158/1078-0432.CCR-15-1722]

142 **Shi YQ**, Zhou XC, Du P, Yin MY, Xu L, Chen WJ, Xu CF. Relationships are between metformin use and survival in pancreatic cancer patients concurrent with diabetes: A systematic review and meta-analysis. *Medicine (Baltimore)* 2020; **99**: e21687 [PMID: 32925714 DOI: 10.1097/MD.0000000000021687]

143 **Alistar A**, Morris BB, Desnoyer R, Klepin HD, Hosseinzadeh K, Clark C, Cameron A, Leyendecker J, D'Agostino R Jr, Topaloglu U, Boteju LW, Boteju AR, Shorr R, Zachar Z, Bingham PM, Ahmed T, Crane S, Shah R, Migliano JJ, Pardee TS, Miller L, Hawkins G, Jin G, Zhang W, Pasche B. Safety and tolerability of the first-in-class agent CPI-613 in combination with modified FOLFIRINOX in patients with metastatic pancreatic cancer: a single-centre, open-label, dose-escalation, phase 1 trial. *Lancet Oncol* 2017; **18**: 770-778 [PMID: 28495639 DOI: 10.1016/S1470-2045(17)30314-5]

144 **Waddell N**, Pajic M, Patch AM, Chang DK, Kassahn KS, Bailey P, Johns AL, Miller D, Nones K, Quek K, Quinn MC, Robertson AJ, Fadlullah MZ, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Wani S, Wilson PJ, Markham E, Cloonan N, Anderson MJ, Fink JL, Holmes O, Kazakoff SH, Leonard C, Newell F, Poudel B, Song S, Taylor D, Waddell N, Wood S, Xu Q, Wu J, Pinese M, Cowley MJ, Lee HC, Jones MD, Nagrial AM, Humphris J, Chantrill LA, Chin V, Steinmann AM, Mawson A, Humphrey ES, Colvin EK, Chou A, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Pettitt JA, Merrett ND, Toon C, Epari K, Nguyen NQ, Barbour A, Zeps N, Jamieson NB, Graham JS, Niclou SP, Bjerkvig R, Grützmann R, Aust D, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Falconi M, Zamboni G, Tortora G, Tempero MA; Australian Pancreatic Cancer Genome Initiative, Gill AJ, Eshleman JR, Pilarsky C, Scarpa A, Musgrove EA, Pearson JV, Biankin AV, Grimmond SM. Whole genomes redefine the mutational landscape of pancreatic cancer. *Nature* 2015; **518**: 495-501 [PMID: 25719666 DOI: 10.1038/nature14169]

145 **Bailey P**, Chang DK, Nones K, Johns AL, Patch AM, Gingras MC, Miller DK, Christ AN, Bruxner TJ, Quinn MC, Nourse C, Murtaugh LC, Harliwong I, Idrisoglu S, Manning S, Nourbakhsh E, Wani S, Fink L, Holmes O, Chin V, Anderson MJ, Kazakoff S, Leonard C, Newell F, Waddell N, Wood S, Xu Q, Wilson PJ, Cloonan N, Kassahn KS, Taylor D, Quek K, Robertson A, Pantano L, Mincarelli L, Sanchez LN, Evers L, Wu J, Pinese M, Cowley MJ, Jones MD, Colvin EK, Nagrial AM, Humphrey ES, Chantrill LA, Mawson A, Humphris J, Chou A, Pajic M, Scarlett CJ, Pinho AV, Giry-Laterriere M, Rooman I, Samra JS, Kench JG, Lovell JA, Merrett ND, Toon CW, Epari K, Nguyen NQ, Barbour A, Zeps N, Moran-Jones K, Jamieson NB, Graham JS, Duthie F, Oien K, Hair J, Grützmann R, Maitra A, Iacobuzio-Donahue CA, Wolfgang CL, Morgan RA, Lawlor RT, Corbo V, Bassi C, Rusev B, Capelli P, Salvia R, Tortora G, Mukhopadhyay D, Petersen GM; Australian Pancreatic Cancer Genome Initiative, Munzy DM, Fisher WE, Karim SA, Eshleman JR, Hruban RH, Pilarsky C, Morton JP, Sansom OJ, Scarpa A, Musgrove EA, Bailey UM, Hofmann O, Sutherland RL, Wheeler DA, Gill AJ, Gibbs RA, Pearson JV, Waddell N, Biankin AV, Grimmond SM. Genomic analyses identify molecular subtypes of pancreatic cancer. *Nature* 2016; **531**: 47-52 [PMID: 26909576 DOI: 10.1038/nature16965]

146 **Hoadley KA**, Yau C, Hinoue T, Wolf DM, Lazar AJ, Drill E, Shen R, Taylor AM, Cherniack AD, Thorsson V, Akbani R, Bowlby R, Wong CK, Wiznerowicz M, Sanchez-Vega F, Robertson AG, Schneider BG, Lawrence MS, Noushmehr H, Malta TM; Cancer Genome Atlas Network, Stuart JM, Benz CC, Laird PW. Cell-of-Origin Patterns Dominate the Molecular Classification of 10,000 Tumors from 33 Types of Cancer. *Cell* 2018; **173**: 291-304.e6 [PMID: 29625048 DOI: 10.1016/j.cell.2018.03.022]

147 **Witkiewicz AK**, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, Mollaee M, Wagner KU, Koduru P, Yopp A, Choti MA, Yeo CJ, McCue P, White MA, Knudsen ES. Whole-exome sequencing of pancreatic cancer defines genetic diversity and therapeutic targets. *Nat Commun* 2015; **6**: 6744 [PMID: 25855536 DOI: 10.1038/ncomms7744]

148 **Johnstone TC**, Park GY, Lippard SJ. Understanding and improving platinum anticancer drugs--phenanthriplatin. *Anticancer Res* 2014; **34**: 471-476 [PMID: 24403503]

149 **Golan T**, Kanji ZS, Epelbaum R, Devaud N, Dagan E, Holter S, Aderka D, Paluch-Shimon S, Kaufman B, Gershoni-Baruch R, Hedley D, Moore MJ, Friedman E, Gallinger S. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. *Br J Cancer* 2014; **111**: 1132-1138 [PMID: 25072261 DOI: 10.1038/bjc.2014.418]

150 **Pishvaian MJ**, Blais EM, Brody JR, Rahib L, Lyons E, De Arbeloa P, Hendifar A, Mikhail S, Chung V, Sohal DPS, Leslie S, Mason K, Tibbets L, Madhavan S, Matrisian LM, Petricoin E. Outcomes in Patients With Pancreatic Adenocarcinoma With Genetic Mutations in DNA Damage Response Pathways: Results From the Know Your Tumor Program. *JCO Precis Oncol* 2019; 1-10 [DOI: 10.1200/po.19.00115]

151 **Yu S**, Agarwal P, Mamtani R, Symecko H, Spielman K, O’Hara M, O’Dwyer PJ, Schneider C, Teitelbaum U, Nathanson KL, Domchek SM, Reiss KA. Retrospective Survival Analysis of Patients With Resected Pancreatic Ductal Adenocarcinoma and a Germline BRCA or PALB2 Mutation. *JCO Precis Oncol* 2018; 1-11 [DOI: 10.1200/po.18.00271]

152 **Rack JG**, Perina D, Ahel I. Macrodomains: Structure, Function, Evolution, and Catalytic Activities. *Annu Rev Biochem* 2016; **85**: 431-454 [PMID: 26844395 DOI: 10.1146/annurev-biochem-060815-014935]

153 **Barkauskaite E**, Jankevicius G, Ladurner AG, Ahel I, Timinszky G. The recognition and removal of cellular poly(ADP-ribose) signals. *FEBS J* 2013; **280**: 3491-3507 [PMID: 23711178 DOI: 10.1111/febs.12358]

154 **Harrision D**, Gravells P, Thompson R, Bryant HE. Poly(ADP-Ribose) Glycohydrolase (PARG) vs. Poly(ADP-Ribose) Polymerase (PARP) - Function in Genome Maintenance and Relevance of Inhibitors for Anti-cancer Therapy. *Front Mol Biosci* 2020; **7**: 191 [PMID: 33005627 DOI: 10.3389/fmolb.2020.00191]

155 **Lear AL**, Perkins HR. O-acetylation of peptidoglycan in Neisseria gonorrhoeae. Investigation of lipid-linked intermediates and glycan chains newly incorporated into the cell wall. *J Gen Microbiol* 1986; **132**: 2413-2420 [PMID: 3098911 DOI: 10.1099/00221287-132-9-2413]

156 **Shirai H**, Poetsch AR, Gunji A, Maeda D, Fujimori H, Fujihara H, Yoshida T, Ogino H, Masutani M. PARG dysfunction enhances DNA double strand break formation in S-phase after alkylation DNA damage and augments different cell death pathways. *Cell Death Dis* 2013; **4**: e656 [PMID: 23744356 DOI: 10.1038/cddis.2013.133]

157 **Gravells P**, Neale J, Grant E, Nathubhai A, Smith KM, James DI, Bryant HE. Radiosensitization with an inhibitor of poly(ADP-ribose) glycohydrolase: A comparison with the PARP1/2/3 inhibitor olaparib. *DNA Repair (Amst)* 2018; **61**: 25-36 [PMID: 29179156 DOI: 10.1016/j.dnarep.2017.11.004]

158 **Pillay N**, Tighe A, Nelson L, Littler S, Coulson-Gilmer C, Bah N, Golder A, Bakker B, Spierings DCJ, James DI, Smith KM, Jordan AM, Morgan RD, Ogilvie DJ, Foijer F, Jackson DA, Taylor SS. DNA Replication Vulnerabilities Render Ovarian Cancer Cells Sensitive to Poly(ADP-Ribose) Glycohydrolase Inhibitors. *Cancer Cell* 2019; **35**: 519-533.e8 [PMID: 30889383 DOI: 10.1016/j.ccell.2019.02.004]

159 **Gravells P**, Grant E, Smith KM, James DI, Bryant HE. Specific killing of DNA damage-response deficient cells with inhibitors of poly(ADP-ribose) glycohydrolase. *DNA Repair (Amst)* 2017; **52**: 81-91 [PMID: 28254358 DOI: 10.1016/j.dnarep.2017.02.010]

160 **Iorns E**, Lord CJ, Grigoriadis A, McDonald S, Fenwick K, Mackay A, Mein CA, Natrajan R, Savage K, Tamber N, Reis-Filho JS, Turner NC, Ashworth A. Integrated functional, gene expression and genomic analysis for the identification of cancer targets. *PLoS One* 2009; **4**: e5120 [PMID: 19357772 DOI: 10.1371/journal.pone.0005120]

161 **Masaki T**, Shiratori Y, Rengifo W, Igarashi K, Yamagata M, Kurokohchi K, Uchida N, Miyauchi Y, Yoshiji H, Watanabe S, Omata M, Kuriyama S. Cyclins and cyclin-dependent kinases: comparative study of hepatocellular carcinoma *vs* cirrhosis. *Hepatology* 2003; **37**: 534-543 [PMID: 12601350 DOI: 10.1053/jhep.2003.50112]

162 **Mir SE**, De Witt Hamer PC, Krawczyk PM, Balaj L, Claes A, Niers JM, Van Tilborg AA, Zwinderman AH, Geerts D, Kaspers GJ, Peter Vandertop W, Cloos J, Tannous BA, Wesseling P, Aten JA, Noske DP, Van Noorden CJ, Würdinger T. In silico analysis of kinase expression identifies WEE1 as a gatekeeper against mitotic catastrophe in glioblastoma. *Cancer Cell* 2010; **18**: 244-257 [PMID: 20832752 DOI: 10.1016/j.ccr.2010.08.011]

163 **Wang H**, Huang M, Zhang DY, Zhang F. Global profiling of signaling networks: study of breast cancer stem cells and potential regulation. *Oncologist* 2011; **16**: 966-979 [PMID: 21665913 DOI: 10.1634/theoncologist.2010-0230]

164 **Dreyer SB**, Upstill-Goddard R, Paulus-Hock V, Paris C, Lampraki EM, Dray E, Serrels B, Caligiuri G, Rebus S, Plenker D, Galluzzo Z, Brunton H, Cunningham R, Tesson M, Nourse C, Bailey UM, Jones M, Moran-Jones K, Wright DW, Duthie F, Oien K, Evers L, McKay CJ, McGregor GA, Gulati A, Brough R, Bajrami I, Pettitt S, Dziubinski ML, Candido J, Balkwill F, Barry ST, Grützmann R, Rahib L; Glasgow Precision Oncology Laboratory,; Australian Pancreatic Cancer Genome Initiative, Johns A, Pajic M, Froeling FEM, Beer P, Musgrove EA, Petersen GM, Ashworth A, Frame MC, Crawford HC, Simeone DM, Lord C, Mukhopadhyay D, Pilarsky C, Tuveson DA, Cooke SL, Jamieson NB, Morton JP, Sansom OJ, Bailey PJ, Biankin AV, Chang DK. Targeting DNA Damage Response and Replication Stress in Pancreatic Cancer. *Gastroenterology* 2021; **160**: 362-377.e13 [PMID: 33039466 DOI: 10.1053/j.gastro.2020.09.043]

165 **Kausar T**, Schreiber JS, Karnak D, Parsels LA, Parsels JD, Davis MA, Zhao L, Maybaum J, Lawrence TS, Morgan MA. Sensitization of Pancreatic Cancers to Gemcitabine Chemoradiation by WEE1 Kinase Inhibition Depends on Homologous Recombination Repair. *Neoplasia* 2015; **17**: 757-766 [PMID: 26585231 DOI: 10.1016/j.neo.2015.09.006]

166 **Saini P**, Li Y, Dobbelstein M. Wee1 is required to sustain ATR/Chk1 signaling upon replicative stress. *Oncotarget* 2015; **6**: 13072-13087 [PMID: 25965828 DOI: 10.18632/oncotarget.3865]

167 **Lal S**, Burkhart RA, Beeharry N, Bhattacharjee V, Londin ER, Cozzitorto JA, Romeo C, Jimbo M, Norris ZA, Yeo CJ, Sawicki JA, Winter JM, Rigoutsos I, Yen TJ, Brody JR. HuR posttranscriptionally regulates WEE1: implications for the DNA damage response in pancreatic cancer cells. *Cancer Res* 2014; **74**: 1128-1140 [PMID: 24536047 DOI: 10.1158/0008-5472.CAN-13-1915]

168 **Lal S**, Zarei M, Chand SN, Dylgjeri E, Mambelli-Lisboa NC, Pishvaian MJ, Yeo CJ, Winter JM, Brody JR. WEE1 inhibition in pancreatic cancer cells is dependent on DNA repair status in a context dependent manner. *Sci Rep* 2016; **6**: 33323 [PMID: 27616351 DOI: 10.1038/srep33323]

169 **Rajeshkumar NV**, De Oliveira E, Ottenhof N, Watters J, Brooks D, Demuth T, Shumway SD, Mizuarai S, Hirai H, Maitra A, Hidalgo M. MK-1775, a potent Wee1 inhibitor, synergizes with gemcitabine to achieve tumor regressions, selectively in p53-deficient pancreatic cancer xenografts. *Clin Cancer Res* 2011; **17**: 2799-2806 [PMID: 21389100 DOI: 10.1158/1078-0432.CCR-10-2580]

170 **Jin MH**, Nam AR, Park JE, Bang JH, Bang YJ, Oh DY. Therapeutic Co-targeting of WEE1 and ATM Downregulates PD-L1 Expression in Pancreatic Cancer. *Cancer Res Treat* 2020; **52**: 149-166 [PMID: 31291716 DOI: 10.4143/crt.2019.183]

171 **Agostini LC**, Jain A, Shupp A, Nevler A, McCarthy G, Bussard KM, Yeo CJ, Brody JR. Combined Targeting of PARG and Wee1 Causes Decreased Cell Survival and DNA Damage in an S-Phase-Dependent Manner. *Mol Cancer Res* 2021; **19**: 207-214 [PMID: 33257507 DOI: 10.1158/1541-7786.MCR-20-0708]

172 **Krishnakumar R**, Kraus WL. The PARP side of the nucleus: molecular actions, physiological outcomes, and clinical targets. *Mol Cell* 2010; **39**: 8-24 [PMID: 20603072 DOI: 10.1016/j.molcel.2010.06.017]

173 **Rouleau M**, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. *Nat Rev Cancer* 2010; **10**: 293-301 [PMID: 20200537 DOI: 10.1038/nrc2812]

174 **Bagnolini G**, Milano D, Manerba M, Schipani F, Ortega JA, Gioia D, Falchi F, Balboni A, Farabegoli F, De Franco F, Robertson J, Pellicciari R, Pallavicini I, Peri S, Minucci S, Girotto S, Di Stefano G, Roberti M, Cavalli A. Synthetic Lethality in Pancreatic Cancer: Discovery of a New RAD51-BRCA2 Small Molecule Disruptor That Inhibits Homologous Recombination and Synergizes with Olaparib. *J Med Chem* 2020; **63**: 2588-2619 [PMID: 32037829 DOI: 10.1021/acs.jmedchem.9b01526]

175 **Farmer H**, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 2005; **434**: 917-921 [PMID: 15829967 DOI: 10.1038/nature03445]

176 **Miller AL**, Garcia PL, Yoon KJ. Developing effective combination therapy for pancreatic cancer: An overview. *Pharmacol Res* 2020; **155**: 104740 [PMID: 32135247 DOI: 10.1016/j.phrs.2020.104740]

177 **Lai SW**, Bamodu OA, Chen JH, Wu AT, Lee WH, Chao TY, Yeh CT. Targeted PARP Inhibition Combined with FGFR1 Blockade is Synthetically Lethal to Malignant Cells in Patients with Pancreatic Cancer. *Cells* 2020; **9** [PMID: 32276472 DOI: 10.3390/cells9040911]

178 **Noordermeer SM**, van Attikum H. PARP Inhibitor Resistance: A Tug-of-War in BRCA-Mutated Cells. *Trends Cell Biol* 2019; **29**: 820-834 [PMID: 31421928 DOI: 10.1016/j.tcb.2019.07.008]

179 **Pishvaian MJ**, Biankin AV, Bailey P, Chang DK, Laheru D, Wolfgang CL, Brody JR. BRCA2 secondary mutation-mediated resistance to platinum and PARP inhibitor-based therapy in pancreatic cancer. *Br J Cancer* 2017; **116**: 1021-1026 [PMID: 28291774 DOI: 10.1038/bjc.2017.40]

180 **Hsieh HJ**, Peng G. Cellular responses to replication stress: Implications in cancer biology and therapy. *DNA Repair (Amst)* 2017; **49**: 9-20 [PMID: 27908669 DOI: 10.1016/j.dnarep.2016.11.002]

181 **Maréchal A**, Zou L. DNA damage sensing by the ATM and ATR kinases. *Cold Spring Harb Perspect Biol* 2013; **5** [PMID: 24003211 DOI: 10.1101/cshperspect.a012716]

182 **Ubhi T**, Brown GW. Exploiting DNA Replication Stress for Cancer Treatment. *Cancer Res* 2019; **79**: 1730-1739 [PMID: 30967400 DOI: 10.1158/0008-5472.CAN-18-3631]

183 **Russell R**, Perkhofer L, Liebau S, Lin Q, Lechel A, Feld FM, Hessmann E, Gaedcke J, Güthle M, Zenke M, Hartmann D, von Figura G, Weissinger SE, Rudolph KL, Möller P, Lennerz JK, Seufferlein T, Wagner M, Kleger A. Loss of ATM accelerates pancreatic cancer formation and epithelial-mesenchymal transition. *Nat Commun* 2015; **6**: 7677 [PMID: 26220524 DOI: 10.1038/ncomms8677]

184 **Moding EJ**, Lee CL, Castle KD, Oh P, Mao L, Zha S, Min HD, Ma Y, Das S, Kirsch DG. Atm deletion with dual recombinase technology preferentially radiosensitizes tumor endothelium. *J Clin Invest* 2014; **124**: 3325-3338 [PMID: 25036710 DOI: 10.1172/JCI73932]

185 **Cowell IG**, Durkacz BW, Tilby MJ. Sensitization of breast carcinoma cells to ionizing radiation by small molecule inhibitors of DNA-dependent protein kinase and ataxia telangiectsia mutated. *Biochem Pharmacol* 2005; **71**: 13-20 [PMID: 16293233 DOI: 10.1016/j.bcp.2005.09.029]

186 **Ayars M**, Eshleman J, Goggins M. Susceptibility of ATM-deficient pancreatic cancer cells to radiation. *Cell Cycle* 2017; **16**: 991-998 [PMID: 28453388 DOI: 10.1080/15384101.2017.1312236]

187 **Kondo T**, Kanai M, Kou T, Sakuma T, Mochizuki H, Kamada M, Nakatsui M, Uza N, Kodama Y, Masui T, Takaori K, Matsumoto S, Miyake H, Okuno Y, Muto M. Association between homologous recombination repair gene mutations and response to oxaliplatin in pancreatic cancer. *Oncotarget* 2018; **9**: 19817-19825 [PMID: 29731985 DOI: 10.18632/oncotarget.24865]

188 **Aguirre AJ**, Nowak JA, Camarda ND, Moffitt RA, Ghazani AA, Hazar-Rethinam M, Raghavan S, Kim J, Brais LK, Ragon D, Welch MW, Reilly E, McCabe D, Marini L, Anderka K, Helvie K, Oliver N, Babic A, Da Silva A, Nadres B, Van Seventer EE, Shahzade HA, St Pierre JP, Burke KP, Clancy T, Cleary JM, Doyle LA, Jajoo K, McCleary NJ, Meyerhardt JA, Murphy JE, Ng K, Patel AK, Perez K, Rosenthal MH, Rubinson DA, Ryou M, Shapiro GI, Sicinska E, Silverman SG, Nagy RJ, Lanman RB, Knoerzer D, Welsch DJ, Yurgelun MB, Fuchs CS, Garraway LA, Getz G, Hornick JL, Johnson BE, Kulke MH, Mayer RJ, Miller JW, Shyn PB, Tuveson DA, Wagle N, Yeh JJ, Hahn WC, Corcoran RB, Carter SL, Wolpin BM. Real-time Genomic Characterization of Advanced Pancreatic Cancer to Enable Precision Medicine. *Cancer Discov* 2018; **8**: 1096-1111 [PMID: 29903880 DOI: 10.1158/2159-8290.CD-18-0275]

189 **Roger E**, Gout J, Arnold F, Beutel AK, Müller M, Abaei A, Barth TFE, Rasche V, Seufferlein T, Perkhofer L, Kleger A. Maintenance Therapy for ATM-Deficient Pancreatic Cancer by Multiple DNA Damage Response Interferences after Platinum-Based Chemotherapy. *Cells* 2020; **9** [PMID: 32948057 DOI: 10.3390/cells9092110]

190 **Fokas E**, Prevo R, Pollard JR, Reaper PM, Charlton PA, Cornelissen B, Vallis KA, Hammond EM, Olcina MM, Gillies McKenna W, Muschel RJ, Brunner TB. 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 [PMID: 23222511 DOI: 10.1038/cddis.2012.181]

191 **Wallez Y**, Dunlop CR, Johnson TI, Koh SB, Fornari C, Yates JWT, Bernaldo de Quirós Fernández 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**: 1670-1682 [PMID: 29891488 DOI: 10.1158/1535-7163.MCT-18-0010]

192 **Rosenberg SA**, Restifo NP. Adoptive cell transfer as personalized immunotherapy for human cancer. *Science* 2015; **348**: 62-68 [PMID: 25838374 DOI: 10.1126/science.aaa4967]

193 **Brahmer JR**, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012; **366**: 2455-2465 [PMID: 22658128 DOI: 10.1056/NEJMoa1200694]

194 **Royal RE**, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, Rosenberg SA. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother* 2010; **33**: 828-833 [PMID: 20842054 DOI: 10.1097/CJI.0b013e3181eec14c]

195 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]

196 **Alexandrov LB**, Nik-Zainal S, Wedge DC, Aparicio SA, Behjati S, Biankin AV, Bignell GR, Bolli N, Borg A, Børresen-Dale AL, Boyault S, Burkhardt B, Butler AP, Caldas C, Davies HR, Desmedt C, Eils R, Eyfjörd JE, Foekens JA, Greaves M, Hosoda F, Hutter B, Ilicic T, Imbeaud S, Imielinski M, Jäger N, Jones DT, Jones D, Knappskog S, Kool M, Lakhani SR, López-Otín C, Martin S, Munshi NC, Nakamura H, Northcott PA, Pajic M, Papaemmanuil E, Paradiso A, Pearson JV, Puente XS, Raine K, Ramakrishna M, Richardson AL, Richter J, Rosenstiel P, Schlesner M, Schumacher TN, Span PN, Teague JW, Totoki Y, Tutt AN, Valdés-Mas R, van Buuren MM, van 't Veer L, Vincent-Salomon A, Waddell N, Yates LR; Australian Pancreatic Cancer Genome Initiative; ICGC Breast Cancer Consortium; ICGC MMML-Seq Consortium; ICGC PedBrain, Zucman-Rossi J, Futreal PA, McDermott U, Lichter P, Meyerson M, Grimmond SM, Siebert R, Campo E, Shibata T, Pfister SM, Campbell PJ, Stratton MR. Signatures of mutational processes in human cancer. *Nature* 2013; **500**: 415-421 [PMID: 23945592 DOI: 10.1038/nature12477]

197 **Yarchoan M**, Hopkins A, Jaffee EM. Tumor Mutational Burden and Response Rate to PD-1 Inhibition. *N Engl J Med* 2017; **377**: 2500-2501 [PMID: 29262275 DOI: 10.1056/NEJMc1713444]

198 **Humphris JL**, Patch AM, Nones K, Bailey PJ, Johns AL, McKay S, Chang DK, Miller DK, Pajic M, Kassahn KS, Quinn MC, Bruxner TJ, Christ AN, Harliwong I, Idrisoglu S, Manning S, Nourse C, Nourbakhsh E, Stone A, Wilson PJ, Anderson M, Fink JL, Holmes O, Kazakoff S, Leonard C, Newell F, Waddell N, Wood S, Mead RS, Xu Q, Wu J, Pinese M, Cowley MJ, Jones MD, Nagrial AM, Chin VT, Chantrill LA, Mawson A, Chou A, Scarlett CJ, Pinho AV, Rooman I, Giry-Laterriere M, Samra JS, Kench JG, Merrett ND, Toon CW, Epari K, Nguyen NQ, Barbour A, Zeps N, Jamieson NB, McKay CJ, Carter CR, Dickson EJ, Graham JS, Duthie F, Oien K, Hair J, Morton JP, Sansom OJ, Grützmann R, Hruban RH, Maitra A, Iacobuzio-Donahue CA, Schulick RD, Wolfgang CL, Morgan RA, Lawlor RT, Rusev B, Corbo V, Salvia R, Cataldo I, Tortora G, Tempero MA; Australian Pancreatic Cancer Genome Initiative, Hofmann O, Eshleman JR, Pilarsky C, Scarpa A, Musgrove EA, Gill AJ, Pearson JV, Grimmond SM, Waddell N, Biankin AV. Hypermutation In Pancreatic Cancer. *Gastroenterology* 2017; **152**: 68-74.e2 [PMID: 27856273 DOI: 10.1053/j.gastro.2016.09.060]

199 **Tsujikawa T**, Kumar S, Borkar RN, Azimi V, Thibault G, Chang YH, Balter A, Kawashima R, Choe G, Sauer D, El Rassi E, Clayburgh DR, Kulesz-Martin MF, Lutz ER, Zheng L, Jaffee EM, Leyshock P, Margolin AA, Mori M, Gray JW, Flint PW, Coussens LM. Quantitative Multiplex Immunohistochemistry Reveals Myeloid-Inflamed Tumor-Immune Complexity Associated with Poor Prognosis. *Cell Rep* 2017; **19**: 203-217 [PMID: 28380359 DOI: 10.1016/j.celrep.2017.03.037]

200 **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**: 9518-9527 [PMID: 17909062 DOI: 10.1158/0008-5472.CAN-07-0175]

201 **Diaz-Montero CM**, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. *Cancer Immunol Immunother* 2009; **58**: 49-59 [PMID: 18446337 DOI: 10.1007/s00262-008-0523-4]

202 **Siret C**, Collignon A, Silvy F, Robert S, Cheyrol T, André P, Rigot V, Iovanna J, van de Pavert S, Lombardo D, Mas E, Martirosyan A. Deciphering the Crosstalk Between Myeloid-Derived Suppressor Cells and Regulatory T Cells in Pancreatic Ductal Adenocarcinoma. *Front Immunol* 2019; **10**: 3070 [PMID: 32038621 DOI: 10.3389/fimmu.2019.03070]

203 **Stromnes IM**, DelGiorno KE, Greenberg PD, Hingorani SR. Stromal reengineering to treat pancreas cancer. *Carcinogenesis* 2014; **35**: 1451-1460 [PMID: 24908682 DOI: 10.1093/carcin/bgu115]

204 **Blank CU**, Haining WN, Held W, Hogan PG, Kallies A, Lugli E, Lynn RC, Philip M, Rao A, Restifo NP, Schietinger A, Schumacher TN, Schwartzberg PL, Sharpe AH, Speiser DE, Wherry EJ, Youngblood BA, Zehn D. Defining 'T cell exhaustion'. *Nat Rev Immunol* 2019; **19**: 665-674 [PMID: 31570879 DOI: 10.1038/s41577-019-0221-9]

205 **Martinez GJ**, Pereira RM, Äijö T, Kim EY, Marangoni F, Pipkin ME, Togher S, Heissmeyer V, Zhang YC, Crotty S, Lamperti ED, Ansel KM, Mempel TR, Lähdesmäki H, Hogan PG, Rao A. The transcription factor NFAT promotes exhaustion of activated CD8⁺ T cells. *Immunity* 2015; **42**: 265-278 [PMID: 25680272 DOI: 10.1016/j.immuni.2015.01.006]

206 **Pauken KE**, Sammons MA, Odorizzi PM, Manne S, Godec J, Khan O, Drake AM, Chen Z, Sen DR, Kurachi M, Barnitz RA, Bartman C, Bengsch B, Huang AC, Schenkel JM, Vahedi G, Haining WN, Berger SL, Wherry EJ. Epigenetic stability of exhausted T cells limits durability of reinvigoration by PD-1 blockade. *Science* 2016; **354**: 1160-1165 [PMID: 27789795 DOI: 10.1126/science.aaf2807]

207 **Burrack AL**, Spartz EJ, Raynor JF, Wang I, Olson M, Stromnes IM. Combination PD-1 and PD-L1 Blockade Promotes Durable Neoantigen-Specific T Cell-Mediated Immunity in Pancreatic Ductal Adenocarcinoma. *Cell Rep* 2019; **28**: 2140-2155.e6 [PMID: 31433988 DOI: 10.1016/j.celrep.2019.07.059]

208 **Stromnes IM**, Schmitt TM, Hulbert A, Brockenbrough JS, Nguyen H, Cuevas C, Dotson AM, Tan X, Hotes JL, Greenberg PD, Hingorani SR. T Cells Engineered against a Native Antigen Can Surmount Immunologic and Physical Barriers to Treat Pancreatic Ductal Adenocarcinoma. *Cancer Cell* 2015; **28**: 638-652 [PMID: 26525103 DOI: 10.1016/j.ccell.2015.09.022]

209 **Burrack AL**, Rollins MR, Spartz EJ, Mesojednik TD, Schmiechen ZC, Raynor JF, Wang IX, Kedl RM, Stromnes IM. CD40 Agonist Overcomes T Cell Exhaustion Induced by Chronic Myeloid Cell IL-27 Production in a Pancreatic Cancer Preclinical Model. *J Immunol* 2021; **206**: 1372-1384 [PMID: 33558374 DOI: 10.4049/jimmunol.2000765]

210 **Ma Y**, Li J, Wang H, Chiu Y, Kingsley CV, Fry D, Delaney SN, Wei SC, Zhang J, Maitra A, Yee C. Combination of PD-1 Inhibitor and OX40 Agonist Induces Tumor Rejection and Immune Memory in Mouse Models of Pancreatic Cancer. *Gastroenterology* 2020; **159**: 306-319.e12 [PMID: 32179091 DOI: 10.1053/j.gastro.2020.03.018]

211 **Mirlekar B**, Michaud D, Searcy R, Greene K, Pylayeva-Gupta Y. IL35 Hinders Endogenous Antitumor T-cell Immunity and Responsiveness to Immunotherapy in Pancreatic Cancer. *Cancer Immunol Res* 2018; **6**: 1014-1024 [PMID: 29980536 DOI: 10.1158/2326-6066.CIR-17-0710]

212 **Panni RZ**, Herndon JM, Zuo C, Hegde S, Hogg GD, Knolhoff BL, Breden MA, Li X, Krisnawan VE, Khan SQ, Schwarz JK, Rogers BE, Fields RC, Hawkins WG, Gupta V, DeNardo DG. Agonism of CD11b reprograms innate immunity to sensitize pancreatic cancer to immunotherapies. *Sci Transl Med* 2019; **11** [PMID: 31270275 DOI: 10.1126/scitranslmed.aau9240]

213 **Le DT**, Picozzi VJ, Ko AH, Wainberg ZA, Kindler H, Wang-Gillam A, Oberstein P, Morse MA, Zeh HJ 3rd, Weekes C, Reid T, Borazanci E, Crocenzi T, LoConte NK, Musher B, Laheru D, Murphy A, Whiting C, Nair N, Enstrom A, Ferber S, Brockstedt DG, Jaffee EM. Results from a Phase IIb, Randomized, Multicenter Study of GVAX Pancreas and CRS-207 Compared with Chemotherapy in Adults with Previously Treated Metastatic Pancreatic Adenocarcinoma (ECLIPSE Study). *Clin Cancer Res* 2019; **25**: 5493-5502 [PMID: 31126960 DOI: 10.1158/1078-0432.CCR-18-2992]

214 **Kinkead HL**, Hopkins A, Lutz E, Wu AA, Yarchoan M, Cruz K, Woolman S, Vithayathil T, Glickman LH, Ndubaku CO, McWhirter SM, Dubensky TW Jr, Armstrong TD, Jaffee EM, Zaidi N. Combining STING-based neoantigen-targeted vaccine with checkpoint modulators enhances antitumor immunity in murine pancreatic cancer. *JCI Insight* 2018; **3** [PMID: 30333318 DOI: 10.1172/jci.insight.122857]

215 **Nywening TM**, Belt BA, Cullinan DR, Panni RZ, Han BJ, Sanford DE, Jacobs RC, Ye J, Patel AA, Gillanders WE, Fields RC, DeNardo DG, Hawkins WG, Goedegebuure P, Linehan DC. Targeting both tumour-associated CXCR2+ neutrophils and CCR2+ macrophages disrupts myeloid recruitment and improves chemotherapeutic responses in pancreatic ductal adenocarcinoma. *Gut* 2018; **67**: 1112-1123 [PMID: 29196437 DOI: 10.1136/gutjnl-2017-313738]

216 **Steele CW**, Karim SA, Leach JDG, Bailey P, Upstill-Goddard R, Rishi L, Foth M, Bryson S, McDaid K, Wilson Z, Eberlein C, Candido JB, Clarke M, Nixon C, Connelly J, Jamieson N, Carter CR, Balkwill F, Chang DK, Evans TRJ, Strathdee D, Biankin AV, Nibbs RJB, Barry ST, Sansom OJ, Morton JP. CXCR2 Inhibition Profoundly Suppresses Metastases and Augments Immunotherapy in Pancreatic Ductal Adenocarcinoma. *Cancer Cell* 2016; **29**: 832-845 [PMID: 27265504 DOI: 10.1016/j.ccell.2016.04.014]

217 **Zhu Y**, Knolhoff BL, Meyer MA, Nywening TM, West BL, Luo J, Wang-Gillam A, Goedegebuure 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**: 5057-5069 [PMID: 25082815 DOI: 10.1158/0008-5472.CAN-13-3723]

218 **Candido JB**, Morton JP, Bailey P, Campbell AD, Karim SA, Jamieson T, Lapienyte L, Gopinathan A, Clark W, McGhee EJ, Wang J, Escorcio-Correia M, Zollinger R, Roshani R, Drew L, Rishi L, Arkell R, Evans TRJ, Nixon C, Jodrell DI, Wilkinson RW, Biankin AV, Barry ST, Balkwill FR, Sansom OJ. CSF1R+ Macrophages Sustain Pancreatic Tumor Growth through T Cell Suppression and Maintenance of Key Gene Programs that Define the Squamous Subtype. *Cell Rep* 2018; **23**: 1448-1460 [PMID: 29719257 DOI: 10.1016/j.celrep.2018.03.131]

219 **Stromnes IM**, Schmitt TM, Chapuis AG, Hingorani SR, Greenberg PD. Re-adapting T cells for cancer therapy: from mouse models to clinical trials. *Immunol Rev* 2014; **257**: 145-164 [PMID: 24329795 DOI: 10.1111/imr.12141]

220 **Liu J**, Zhong JF, Zhang X, Zhang C. Allogeneic CD19-CAR-T cell infusion after allogeneic hematopoietic stem cell transplantation in B cell malignancies. *J Hematol Oncol* 2017; **10**: 35 [PMID: 28143567 DOI: 10.1186/s13045-017-0405-3]

221 **Ali AI**, Oliver AJ, Samiei T, Chan JD, Kershaw MH, Slaney CY. Genetic Redirection of T Cells for the Treatment of Pancreatic Cancer. *Front Oncol* 2019; **9**: 56 [PMID: 30809507 DOI: 10.3389/fonc.2019.00056]

222 **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 [PMID: 30319627 DOI: 10.3389/fimmu.2018.02166]

223 **Wu AA**, Jaffee E, Lee V. Current Status of Immunotherapies for Treating Pancreatic Cancer. *Curr Oncol Rep* 2019; **21**: 60 [PMID: 31101991 DOI: 10.1007/s11912-019-0811-5]

224 **Morgan RA**, Yang JC, Kitano M, Dudley ME, Laurencot CM, Rosenberg SA. Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2. *Mol Ther* 2010; **18**: 843-851 [PMID: 20179677 DOI: 10.1038/mt.2010.24]

225 **Parkhurst MR**, Yang JC, Langan RC, Dudley ME, Nathan DA, Feldman SA, Davis JL, Morgan RA, Merino MJ, Sherry RM, Hughes MS, Kammula US, Phan GQ, Lim RM, Wank SA, Restifo NP, Robbins PF, Laurencot CM, Rosenberg SA. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis. *Mol Ther* 2011; **19**: 620-626 [PMID: 21157437 DOI: 10.1038/mt.2010.272]

226 **Thistlethwaite FC**, Gilham DE, Guest RD, Rothwell DG, Pillai M, Burt DJ, Byatte AJ, Kirillova N, Valle JW, Sharma SK, Chester KA, Westwood NB, Halford SER, Nabarro S, Wan S, Austin E, Hawkins RE. The clinical efficacy of first-generation carcinoembryonic antigen (CEACAM5)-specific CAR T cells is limited by poor persistence and transient pre-conditioning-dependent respiratory toxicity. *Cancer Immunol Immunother* 2017; **66**: 1425-1436 [PMID: 28660319 DOI: 10.1007/s00262-017-2034-7]

227 **Beatty GL**, O'Hara MH, Lacey SF, Torigian DA, Nazimuddin F, Chen F, Kulikovskaya IM, Soulen MC, McGarvey M, Nelson AM, Gladney WL, Levine BL, Melenhorst JJ, Plesa G, June CH. Activity of Mesothelin-Specific Chimeric Antigen Receptor T Cells Against Pancreatic Carcinoma Metastases in a Phase 1 Trial. *Gastroenterology* 2018; **155**: 29-32 [PMID: 29567081 DOI: 10.1053/j.gastro.2018.03.029]

228 **You F**, Jiang L, Zhang B, Lu Q, Zhou Q, Liao X, Wu H, Du K, Zhu Y, Meng H, Gong Z, Zong Y, Huang L, Lu M, Tang J, Li Y, Zhai X, Wang X, Ye S, Chen D, Yuan L, Qi L, Yang L. Phase 1 clinical trial demonstrated that MUC1 positive metastatic seminal vesicle cancer can be effectively eradicated by modified Anti-MUC1 chimeric antigen receptor transduced T cells. *Sci China Life Sci* 2016; **59**: 386-397 [PMID: 26961900 DOI: 10.1007/s11427-016-5024-7]

**Footnotes**

**Conflict-of-interest statement:** The authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** May 6, 2021

**First decision:** June 12, 2021

**Article in press:** August 30, 2021

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Li CG, Reshkin SJ **S-Editor:** Gao CC **L-Editor:** A **P-Editor:** Yuan YY

**Table 1 Landmark trials for approved pancreatic ductal adenocarcinoma therapies**

|  |  |  |  |
| --- | --- | --- | --- |
| **Treatment** | **Tumor characteristic** | **Primary endpoint** | **Ref.** |
| Gemcitabine | Advanced PDAC | Median survival, 5.65 mo | Burris *et al*[3] |
| Gemcitabine + Erlotinib *vs* Gemcitabine | Locally Advanced or metastatic PDAC | Overall survival (OS), 6.24 mo *vs* 5.91 mo | Hoffmann *et al*[59] |
| FOLFIRINOX *vs* Gemcitabine | Metastatic PDAC | OS, 11.1 mo *vs* 6.8 mo | Conroy *et al*[4] |
| Gemcitabine + nab-paclitaxel *vs* Gemcitabine | Metastatic PDAC | OS, 8.5 mo *vs* 6.7 mo | Couvelard *et al*[60] |
| Gemcitabine + Capacitabine *vs* Gemcitabine | Resectable PDAC | OS, 28 mo *vs* 25.5 mo | Neoptolemos *et al*[8] |

PDAC: Pancreatic ductal adenocarcinoma.

**Table 2 Pancreatic ductal adenocarcinoma trials involving agents that target tumor metabolism**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Target** | **Trial description** | **NCI trial number** |
| IACS-010759 | OXPHOS inhibitor | Phase I, in advanced cancers | NCT03291938 |
| CPI-613 | PDH/alpha KDH inhibitor | Phase I, combination with Gem + nab-paclitaxel | NCT03435289 |
| CPI-613 | PDH/alpha KDH inhibitor | Phase II, combination with FOLFIRINOX | NCT03699319 |
| CPI-613 | PDH/alpha KDH inhibitor | Phase III, combination with modified FOLFIRINOX | NCT03504423 |
| Metformin and atorvastatin | Metabolic inhibitors | Metformin + Atorvastatin + Doxycycline + Mebendazole in cancers | NCT02201381 |
| L-glutamine | Glutamine analog | Phase I, combination with Gem + nab-paclitaxel | NCT04634539 |

OXPHOS: Oxidative phosphorylation; PDH: Pyruvate dehydrogenase; KDH: Ketoglutarate dehydrogenase.

**Table 3 Pancreatic ductal adenocarcinoma trials involving agents that target DNA repair**

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug** | **Target** | **Trial description** | **NCI trial number** |
| M6620 (VX-970) | ATR | Phase I, M6620 and irinotecan hydrochloride in treating patients with solid tumors that are metastatic or cannot be removed by surgery | NCT02595931 |
| AZD6738/olaparib | ATR/PARP | Phase II, Phase II trial of AZD6738 alone and in combination with olaparib | NCT03682289 |
| BAY1895344 | ATR | Phase I, testing the addition of an anti-cancer drug, BAY 1895344 ATR inhibitor, to the chemotherapy treatment (Gemcitabine) for advanced solid tumors, pancreatic cancer, and ovarian cancer | NCT04616534 |
| Olaparib | PARP | Phase II, a study of pembrolizumab and olaparib for people with metastatic pancreatic ductal adenocarcinoma and homologous recombination deficiency or exceptional treatment response to platinum-based therapy | NCT04666740 |
| Olaparib | PARP | Phase I, targeted PARP or MEK/ERK inhibition in patients with pancreatic cancer | NCT04005690 |
| Olaparib | PARP | Phase II, a phase 2 study of cediranib in combination with olaparib in advanced solid tumors | NCT02498613 |
| Olaparib | PARP | Phase II, olaparib in treating patients with stage IV pancreatic cancer | NCT02677038 |
| Talazoparib | PARP | Phase II, measuring the effects of talazoparib in patients with advanced cancer and DNA repair variations | NCT04550494 |
| Talazoparib | PARP | Phase I/II, a study of avelumab, binimetinib and talazoparib in patients with locally advanced or metastatic RAS-mutant solid tumors | NCT03637491 |
| Niraparib | PARP | Phase II, niraparib in metastatic pancreatic cancer after previous chemotherapy (NIRA-PANC): A phase 2 trial | NCT03553004 |
| Niraparib | PARP | Phase II, niraparib in patients with pancreatic cancer | NCT03601923 |
| Rucaparib | PARP | Phase II, maintenance rucaparib in BRCA1, BRCA2 or PALB2 mutated pancreatic cancer that has not progressed on platinum-based therapy | NCT03140670 |
| MK1775 | WEE1 | Phase I/II, a phase i and randomized phase II study of nab-paclitaxel/gemcitabine with or without AZD1775 for treatment of metastatic adenocarcinoma of the pancreas | NCT02194829 |

PARP: Poly (ADP ribose) polymerase.