A review on Pharmacological interventions to mitigate the progression of pancreatic ductal adenocarcinoma

Sana Saeed[1], Noor-ul-Ain2, Irum Fatima[3] Aamina Habib [4]

[1*]Department of pharmacy, The University of Faisalabad, Pakistan

[2]Department of Pharmacology, Government College University Faisalabad

[3]Department of pharmacy, The University of Faisalabad, Pakistan

[4]Department of pharmacy, The University of Faisalabad, Pakistan

*Corresponding author at Department of pharmacy, The University of Faisalabad, Pakistan

Abstract

Pancreatic ductal adenocarcinoma (PDAC) is a type of cancer that starts in the cells of the ducts of the pancreas. It is the most common type of pancreatic cancer and is typically diagnosed in later stages, making it difficult to treat. Risk factors include smoking, age, and family history. Symptoms include abdominal pain, weight loss, and jaundice. Treatment options include surgery, radiation therapy, and chemotherapy. The prognosis for PDAC is generally poor, with a 5-year survival rate of only around 9%. Treatment for pancreatic ductal adenocarcinoma (PDAC) typically involves a combination of surgery, radiation therapy, and chemotherapy. The specific treatment plan depends on the stage of the cancer and the patient's overall health. Surgery is the main treatment for early-stage PDAC and may involve removing part or the entire pancreas. Radiation therapy and chemotherapy are often used together to shrink the tumor before surgery or to help kill any remaining cancer cells after surgery. In advanced stage, chemotherapy and radiation therapy is mainstay of treatment, which may help to slow the progression of the disease and alleviate symptoms, but is not curative. Additionally, newer therapies such as immunotherapy, targeted therapy, and combination therapy are being studied as potential treatments for PDAC. It is important to consult with a medical oncologist who specialized in pancreatic cancer to discuss the most appropriate treatment plan for your individual case.

Key words: Abdominal, surgery, therapy, radiation, chemotherapy

Introduction:

In the next 20 to 30 years, pancreatic cancer, which already has a high mortality rate, is expected to overtake its position among cancers as the second biggest cause of cancer death in the USA. In the USA, the 5-year survival rate upon diagnosis is 10%, with 80-85% of patients having either metastatic or unresectable illness at presentation. Only 20% of patients who undergo surgery for a localized, respectable tumor survive five years after diagnosis, making the prognosis bleak even for this small subset of patients[1][2]. According to statistics, 432,242 people worldwide died in 2018 as a result of the 458,918 new instances of pancreatic cancer that were discovered. By 2030, pancreatic cancer, which currently ranks as the fourth most common cancer-related cause of death in western nations, is expected to overtake lung cancer as the second most common cancer-related death cause. In less developed nations, pancreatic cancer is still a rare disease and used to be a rare type of cancer[3][4][5]. Due to the population's ongoing ageing and the strong age-related nature of its development, it now constitutes a significant burden in more developed nations in terms of sheer numbers. The pancreas is an expanded, auxiliary digestive gland that is located retroperitoneally on the posterior abdominal wall, straddling the bodies of the L1 and L2 vertebrae. Between the spleen on the left and the duodenum on the right, the pancreas is located transversely in the upper belly. The head, neck, body, and tail are four sections of the pancreas[6][7]. The pancreatic head is the larger portion of the gland that is encircled by the duodenum's C-shaped curvature. The pancreas has a short neck. The pancreatic body extends from the neck and crosses the aorta and L2 vertebra. The peritoneum covers the anterior surface of the pancreatic body. The aorta, the superior mesenteric artery (SMA), the left suprarenal gland, the left kidney, and the renal vessels are all in contact with the posterior side of the body, which is free of peritoneum[6][8][9]. The splenic hilum and the left colic flexure are located just anterior to the left kidney where the pancreatic tail is located. Hepatopancreatic ampulla, which empties into the duodenum's descending portion, is formed when the main pancreatic duct delivering pancreatic fluids meets with the bile duct. A noninvasive, secure, and reliable method for assessing the biliary tree and pancreatic duct is magnetic resonance cholangiopancreatography (MRCP). The left hepatic duct (LHD), which drains segments 1 to 4, and the right hepatic duct (RHD), which drains segments 5 to 8, combine to produce the common hepatic duct (CHD) [10][11]. According to Huang et al. classification, the right posterior segmental duct (RPSD), which drains segments 6 and 7, and the right anterior segmental duct (RASD), which drains segments 5 and 8, typically join forces to form the right hepatic duct (RHD). In 57% of the cases, this type of structure is typical.

Additionally, one or more ducts draining segment 4 and the union of segments 2 and 3 constitute the usual LHD [12][13]. 82% of patients typically have this type of structure. Right lateral insertion, anterior spiral insertion, posterior spiral insertion, high or proximal insertion, low medial insertion, and low lateral insertion were used to categories the cystic duct structure. There are many distinct types of pancreatic neoplasms, and they are often categorized as benign, pre-malignant, and malignant neoplasms based on their biological behavior and histological differentiation into epithelial or non-epithelial neoplasms[14][15]. Endocrine or exocrine epithelial neoplasms, both forms exist, and ductal and acinar neoplasms are subcategories of exocrine neoplasm [16][18][19].

Risk factors:

Important risk factors for pancreatic cancer include both controllable and non-controllable factors. Alcohol consumption, diet, obesity, and cigarette smoking comes under the umbrella of controllable risk factors[20][21]. The causes of pancreatic cancer have been the subject of numerous investigations. An established risk factor for pancreatic cancer is cigarette smoking. Smoking is a significant risk factor for pancreatic cancer, accounting for 20–25% of cases. A dose-response analysis of data from 78 research revealed that even smoking a small number of cigarettes per day or for a short period of time significantly raised the chance of developing pancreatic cancer [23][24][25]. Only heavy drinking was linked to a higher risk of pancreatic cancer, according to a meta-analysis of 19 cohort studies. The risk of alcohol-related malignancies is increased in people who have the ALDH2*2 allele [26][27]. The relationship between food and the risk of pancreatic cancer has been the subject of numerous researches, with mixed results. An inverse relationship between increase dietary fiber intake and pancreatic cancer risk was found in a meta-analysis that pooled information from [28][29] 13 case-control studies and one cohort study (OR = 0.52, 95% CI: 0.44-0.61). Additionally, every 10 gram of dietary fiber consumed daily was linked to a 12% decrease in pancreatic cancer risk (OR = 0.88, 95% CI: 0.84-0.92). Obesity raises the risk of developing various cancers, including pancreatic cancer [30][31]. According to a study by Li et al. having a body mass index (BMI) of 25.0 to 29.9 kg/m2 or higher throughout early adulthood is linked to an increased risk of pancreatic cancer.

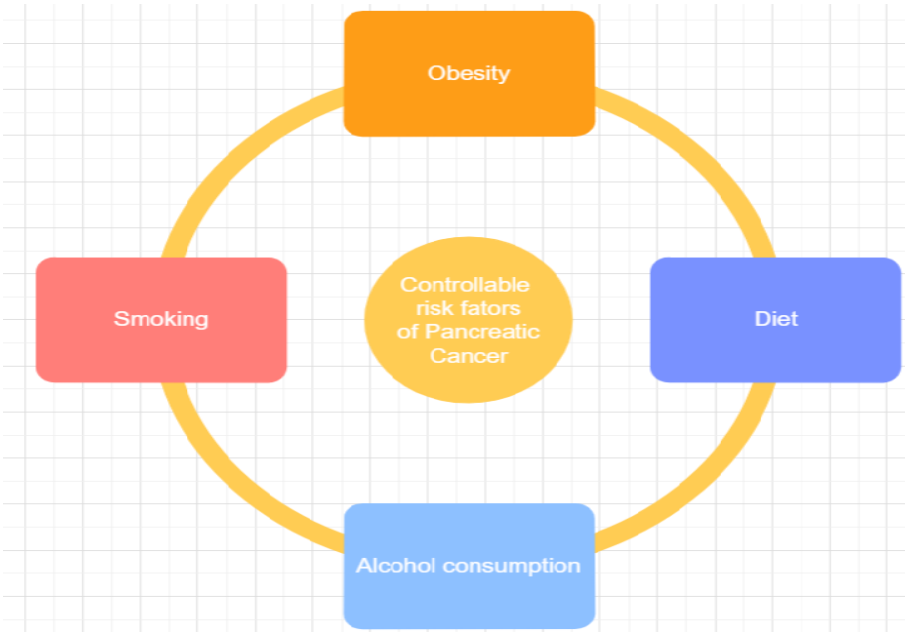

Fig1: controllable risk factors of pancreatic cancer

Gender, age, the presence of newly diagnosed diabetes, ethnicity, genetic variables, and family history are examples of non-controllable risk factors. Men are more likely than women to develop pancreatic cancer. Pancreatic cancer occurs in men at a rate of 5.5 per 100,000 and in women at a rate of 4.0 per 100,000 worldwide [32][33][34]. As people age, their chance of acquiring pancreatic cancer rises, reaching its maximum point between the ages of 60 and 80. African-Americans had greater incidences of pancreatic cancer than Caucasians, but Asian-Americans and Pacific Islanders have the lowest rates of the disease. Although pancreatic cancer is also believed to be a risk factor for acquiring diabetes, there is a long-standing correlation between diabetes and pancreatic cancer development, with a pooled relative risk of 2 to 1. About 1% of those with newly diagnosed diabetes over the age of 50 also have concurrent pancreatic cancer. Similar to this, people with diabetes who have had their diagnosis for less than a year have a 54-fold higher relative risk of getting pancreatic cancer than those with long-term diabetes, who only have a 15-fold higher risk. These findings imply that newly diagnosed diabetes may be a significant risk factor and sign of pancreatic cancer. A long-established risk factor for pancreatic cancer and a significant indicator of disease risk is family history. According to studies, 5–10% of those with pancreatic cancer say they have a close family who also has the disease.

Families with a number of hereditary disorders, for which the risk genes have been discovered,[35][36] such as BRCA1 and BRCA2, linked to hereditary breast and ovarian cancer (HBOC), have higher rates of pancreatic cancer. Third most often occurring malignancy with BRCA1/2 mutations is pancreatic cancer. 22 In BRCA2 carriers and BRCA1 carriers, the risk of pancreatic cancer is approximately 2–6 times higher than in the general population.

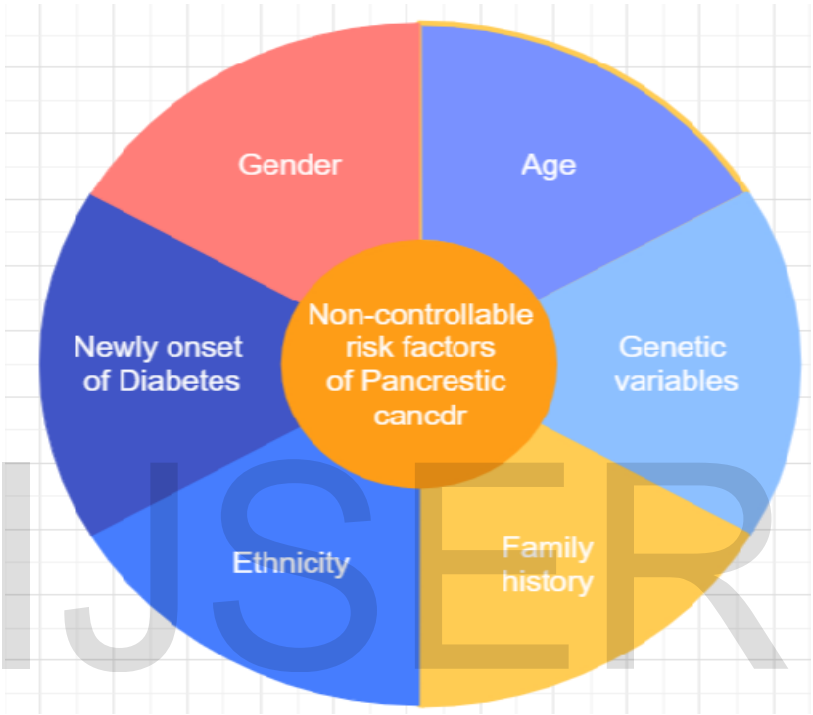

Fig2: Non-controllable risk factors of pancreatic cancer

In 0.4–4% of FPC families, the PALB2 gene was discovered to have pathogenic variants, the bulk of which were found in families with a history of both breast/ovarian and pancreatic cancer. The breast cancer susceptibility gene ATM controls the repair of DNA double-strand breaks. 1-5% of pancreatic cancer patients had ATM mutations[37][38][39]. The majority of HP cases are caused by germline mutations in PRSS1. In HP patients, the risk of pancreatic cancer is almost 69 times higher than in the general population. At age 70, pancreatic cancer would appear in 20–50% of HP patients. 2-5% of all cases of colorectal cancer are hereditary non-polyposis colorectal cancer (HNPCC), often known as Lynch Syndrome. DNA mismatch repair (MMR) gene inactivating mutations, including those in MLH1, MSH2, MSH6, and PMS2, are the cause of pancreatic cancer.

Others observed a roughly 7- to 10-fold increased risk of developing pancreatic cancer among carriers of MMR gene mutations [41][42], despite the fact that other studies revealed no increase in risk of pancreatic cancer in Lynch Syndrome patients.

Microenvironment of tumor:

The development of a thick stroma known as a desmoplastic response is a hallmark of pancreatic cancer. The myofibroblast-like pancreatic stellate cells are essential for the development and turnover of the stroma. These cells release collagen and other elements of the extracellular matrix upon activation by growth factors including TGF1, platelet-derived growth factor (PDGF), and fibroblast growth factor; stellate cells also appear to be in charge of the poor vascularization that is typical of pancreatic cancer [43][44][45]. Stellate cells also control the stroma's absorption and turnover, mostly via producing matrix metalloproteinases. Numerous proteins, including cyclooxygenase-2, PDGF receptor, vascular endothelial growth factor, stromal cell-derived factor, chemokines, integrins, and SPARC (secreted protein, acidic, cysteine-rich) have been linked to a poor prognosis and treatment resistance in stromal cells. These proteins might, however, potentially serve as fresh therapeutic targets. Chemokines and cytokines are increased in PC, according to studies. In fact, compared to healthy serum, the examination of PC serum has shown that it is enriched with greater IL-6, 8-, 10-, and 1RA levels. The function of constitutive STAT3 activation in the development of pancreatic tumors has also been revealed by study, and it has been established that it closely correlates with the overexpression of IL6. IL-8, another signaling component that is aberrantly produced in PC, can drive tumor migration in conjunction with MMP-2 and SDF-1a [46][47]. Through MAPK/ERK cascades, IL-8 overexpression is connected to elevated VEGF release and metastatic dissemination in hypoxic environments. Due to TNF overexpression, the NF-B cascade is one of the most commonly dysregulated pathways in PC, as shown by its elevated levels in patient samples with advanced illness.

Classification of Pancreatic tumors:

Collisson et al. presented the first genetic classification of pancreatic cancers in 2011 and identified three tumor subtypes: 1) classical, 2) quasi-mesenchymal, and 3) exocrine-like tumors, each of which was linked with a specific treatment response and clinical outcome. The adhesion and epithelial genes as well as GATA6, which codes for a TF regulating pancreatic development,

were upregulated in the classical subtype, which had higher survival rates. The lowest survival rates of all three groups were seen in quasi-mesenchymal tumors, which also had higher amounts of mesenchymal genes such CAV1, HK2, and TWIST1[48][49]. Lastly, the overexpression of genes encoding for digestive enzymes and links to exocrine pancreatic function were characteristics of the exocrine-like malignancies. Gene study by Moffitt et al. in 2015 identified two distinct stromal PC subtypes, the "normal" and the "activated," which had a worse prognosis than normal cancers (1 year survival: 60%). According to gene analysis, the active stroma subgroup overexpressed genes related to macrophages (ITGAM), the WNT pathway (WNT 2 and 5A), chemokine signaling (CCL13 and 18), fibroblastic activity, and the WNT pathway (WNT 2 and 5A). In contrast, PSC-specific markers were present in the normal stroma (DES, VIM and ACTA2). Bailey et al. discovered four PC subtypes, which they named as squamous, PC progenitor, immunogenic, and aberrantly differentiated endocrine exocrine subtypes. These four subtypes were connected with diverse molecular pathways. Bailey's squamous subgroup is characterized by a rise in mutations of the genes KDM6A and TP53, as well as those involved in metabolic reprogramming, inflammation, TGF signaling, hypoxia, autophagy, MYC activation, and over expression[50][52][54] of TP63delataN and its target genes. The molecular networks of early PC development TFs (MNX1, PDX1, HNF4A, HNF4G, HNF1A and B, HES1, and FOXA2 and 3) are abundant in pancreatic progenitor tumors [51]. Thirdly, genetic networks such as KRAS, MIST1, NR5A2, NEUROD1, INS, RBPJL, and MAFA are found in Bailey's exocrine-like malignancies, which are thought to affect the advanced stages of exocrine and endocrine PC differentiation and development. Finally, immunological infiltration and increased immune networks linked to antigen presentation, B and T-cell signaling, CD4+ and 8+ T cells, and TLR cascades are characteristics of immunogenic malignancies[54][55].

Pancreatic ductal adenocarcinoma- a major PC

The two primary kinds of pancreatic cancer are (I) adenocarcinoma, which accounts for the great majority of occurrences, and (II) pancreatic endocrine tumors, which account for fewer than 5% of all instances.. The most frequent malignant tumor of the pancreas is pancreatic ductal adenocarcinoma. Due to late diagnosis and fast tumor growth (>50% of patients had metastases at diagnosis), poor prognosis are caused. Different sections of the pancreas can have PDAC localized there, with varying early identification and survival rates. According to recent research,

PDAC that is located in the "head" of the pancreas may fare chances of survival than PDAC that is placed in the "B/T" zone. Due to early identifiable signs such high carbohydrate antigen 19-9 (CA19-9) positive or painless jaundice, it has been postulated that "head" PDAC receives clinical attention before "B/T" PDAC (caused by tumor obstruction of the bile ducts, which pass through the head of the pancreas). Therefore, physicians can deal with "early" stages of PDAC cancers by quickly doing abdominal imaging that will uncover the underlying malignancy [56][57]. Contrarily, tumors of the body and tail do not cause jaundice, and as a result, they typically come to the attention of the medical community after weight loss and/or stomach pain become noticeable [58][59]. Conversely, "B/T" cancer is linked to substantially greater pain, a higher level of serum albumin, a higher level of the antigen carcinoembryonic antigen (CEA), and a higher risk of metastasis. Furthermore, research on PDAC revealed a link between the "B/T" region and the squamous subtype of the disease, the molecular subtype with the worst clinical prognosis [60][61][62]. T he "B/T"PDAC lacks the immunological subtype. This points to a serious problem with leukocyte recruitment within "B/T"PDAC and implies that these tumors are probably not candidates for immune therapy-based treatment. The lack of CD8 γδ- T cells and B cells in "B/T" PDAC was the primary factor in the glaring immune response deficiency [63][64][65].

Diagnosis of PDAC:

Approximately 8% of people over the age of 70 have pancreatic cysts, which can be either intraductal papillary mucinous neoplasms (IPMN) or mucinous cystic neoplasms, both of which are precursors of PDAC, most common form of pancreatic cancer, are earlier signs and can be detected [66][67][68]. Mucinous cystic lesions are simple to spot and are discovered incidentally in 3% of CT participants, in contrast to the third precursor lesion, pancreatic intraepithelial neoplasia, which can only be detected at surgical histology. Many imaging techniques can detect pancreatic cancer at an early stage [69][70][71]. MRI and CT scans with contrast in accordance with Japanese recommendations. Based on clinical symptoms, blood pancreatic enzymes, tumor markers, and transabdominal US, these are the primary techniques used in individuals with suspected PC. In addition to these, endoscopic retrograde cholangiopancreatography (ERCP) is used. For pathological diagnosis, endoscopic ultrasonography guided fine needle aspiration (EUS-FNA) is the standard procedure. The accuracy of EUS-FNA in terms of lesion size is 93.4% for lesions under 20 mm, 83.5% for lesions between 10 and 20 mm, and 82.5% for lesions of 10 mm

or less. Early-stage pancreatic cancers can occasionally go undetected by CT, MRI, and EUS, and EUS-FNA makes it challenging to get specimens [72][73]. Localized stenosis of the primary pancreatic duct is the only imaging finding in this case, particularly with relation to PDAC in situ. The pancreatic duct's thorough examination by ERCP and the following cytology of pancreatic juice become crucial for diagnosis. ERCP has a sensitivity and specificity in this situation of 57.9% and 90.6%, respectively. Pancreatic juice cytology can diagnose PDAC in situ with a sensitivity of 72.2% to 100%. Ikemoto et al. has suggested an approach with a positive long-term prognosis for early detection of PC in stage 0 and IA. Ultrasound should be conducted early in people with risk factors in addition to pancreatic laboratory testing to detect asymptomatic patients. Traditional strategies are used to handle patients who clearly have tumors [74][75]. Patients who exhibit indirect signs such as anomalies of the main pancreatic duct, cystic lesions, or pancreatic atrophy but no overt pancreatic tumor should be assessed by MRI using magnetic resonance cholangiopancreatography. EUS-FNA is carried out if the MRI reveals abnormalities that are indicative of PDAC. The most reliable serum tumor marker for pancreatic cancer in terms of diagnosis, prognosis, and monitoring is CA19-9. Elevated CA19-9 has 79% sensitivity and an 82% specificity to identify PDAC, respectively. Other carbohydrate antigens such CA125, CA72-4, CA50 and CA 242 have been researched for early pancreatic cancer detection. Recent research has a particular interest in multimarker panels combined with CA19-9. Eight proteins (S100A11, ITGB5, PPY, ERBB3, SCAMP3, RET, 5-NT, CEACAM1) were used in combination to fairly accurately differentiate between patients with early stage I/II PC and healthy people [76][77].

Sr.	**Diagnostic techniques**
1	Computed Tomography scan
2	Magnetic Resonance Imaging
3	Endoscopic ultrasonography (EUS)
4	Endoscopic retrograde cholangiopancreatography (ERCP)
5	Endoscopic ultrasonography guided fine needle aspiration (EUS-FNA)
6	Pancreatic tumor markers i.e. CA 19-9, CA 125, CA 72-4, CA 50, CA242

Table 1: Common Pancreatic cancer detection techniques

Treatments for Pancreatic ductal adenocarcinoma:

An innovative approach to cancer treatment is vaccine-associated immunotherapy. Tumor-associated vaccinations can stop cancer cells from migrating by enhancing immune surveillance. The peptide cocktail vaccine OCV-C01 and gemcitabine, the standard first-line chemotherapy, were coupled in a recent multicenter Phase II research with PC patients (n = 30), and the results indicated a median Disease-Free Survival (DFS) of 15.8 months, an improvement above gemcitabine alone (a DFS of 12.0 months). Sialyl Lewis, also known as CA 19-9, is a carbohydrate TAA that is significantly expressed on PC cells. Weitzenfeld et al. effectively prevented mice from developing PC by using CA 19-9-targeted antibodies made from the serum of CA 19-9/keyhole limpet hemocyanin (KLH) vaccine-immunized patients. These findings imply the possibility for clinic-accessible CA19-9-targeted vaccinations. In Phase I clinical studies, the CA 19-9/KLH vaccine in the form of a conjugate vaccination was successful in preventing the development of pancreatic cancer. Dinutuximab, a ganglioside GD2 targeted vaccination, is an FDA-approved medication that has effectively stopped the spread of pancreatic cancer. It is a member of the class of peptides known as dendritic cell vaccines. This kind of vaccination has shown promising results in preventing the spread of pancreatic cancer [78][79]. Anti-PD-L1 or anti-PD-1 mAb therapy dramatically raised the expression of IFN-, granzyme B, and perforin in implanted tumors in a mouse model of pancreatic cancer, enhancing CD8+ T cell infiltration. Blocking PD-L1 facilitated CD8+ T cell infiltration into the tumor site and brought about local immunological activation. For the treatment of patients with stage III, unresectable NSCLC, the FDA authorized durvalumab in 2018. Patients who received durvalumab showed a substantial[80][81] increase in progression-free survival (16.8 months) when compared to patients who received a placebo (5.6 months). A retroviral or lentiviral vector is used to re-inject CAR gene based cultured T cells into the host. Because CAR-T treatment directly promotes cell-mediated immunity, it has a higher potential to trigger an immune response that is more potent against tumors than antibody therapy. Studies using CAR-T therapy and cyclophosphamide to treat pancreatic cancer are currently being conducted. TGF-β is an immunosuppressive cytokine that has been found to aid tumor immune evasion in a variety of tumor forms. Galunisertib (a TGF-inhibitor) in conjunction with gemcitabine was shown to enhance overall survival in a PDAC phase Ib study comparing gemcitabine alone with gemcitabine and Galunisertib in combination with gemcitabine (8.9 vs 7.1 months), with marginally better outcomes. A phase Ib study (NCT02734160) examining the combination of Galunsertib with an anti-PD-L1 inhibitor (Durvalumab) produced one partial

response and 7 out of 32 patients exhibited stable disease (disease control rate: 25%), necessitating additional evaluation for PDAC patients [82].

Oncolytic virus (OV) therapy has attracted increasing attention as a cancer prevention strategy. Utilizing replication-competent viruses, which can reproduce inside of the host and target and kill tumor cells with preference, this strategy may result in a strong and long-lasting immune response. T-VEC (ImlygicTM), a recombinant human herpessimplexvirustype1 (HSV-1), oncolyticviruses have been designed for optimization of tumor selectivity and increased immune activation. This therapy was the first oncolytic viral therapy to get FDA approval. Napabucasin targets the STAT3 signaling pathway in cancer stem cells; this oral inhibitor is able to block cancer stemness genes (c-MYC, ß-CATENIN, TWIST, and others), hence preventing the renewal of cancer stem cells. STAT3 inhibition may potentially influence the genes that control the activation of immunological checkpoints. With a reported objective response rate of more than 35% in a single-arm phase I/II study using napabucasin, gemcitabine, and nab-paclitaxel, the median overall survival was not very outstanding (10.7 months) [83]. Pancreatic cancer has a good case for targeting cyclin kinases since TP53 and CDKN2A mutations are often seen and may prevent the activity of the cyclin D kinase 4/6, which is connected to cyclin D1. The transition of cells from the G1 to the S phase during mitosis is significantly regulated by cyclin D1. In experimental experiments, the multi-cyclin-dependent kinase inhibitor daniciclib inhibited the development of human pancreatic cancer xenografts and seemed to work in synergy with gemcitabine. Numerous trials are now being conducted to determine the effectiveness of these drugs in the management of pancreatic metastatic cancer, including: (1) a phase I/II study of ribociclib with trametinib (NCT02703571); (2) palbociclib + the PI3K/mTOR inhibitor, gedatolisib; and (3) abemaciclib in conjunction with the TGF-ß inhibitor galunisertib or other medications (NCT02981342) [84].

It has been demonstrated that the CXCL12-CXCR4 chemokine signaling pathway is effective in reducing PDAC. Through interaction between stromal cells and immune cells, CXCR4, when coupled to its ligand CXCL12, can control the TME. In animal models, the CXCR4 inhibitors BL-8040 and AMD3100 have increased sensitivity to PD-1/PD-L1 blocking treatment and boosted T cell entry into the TME. A phase II research in PDAC found that BL-8040, both alone and in combination with pembrolizumab, raised the population of T-cells, activated cytotoxic T-cells, reduced the density of MDSCs, caused fast tumor cell death, and was linked with an enhanced

mean overall survival. Talabostat is a fibroblast activation protein (FAP) inhibitor that has demonstrated efficacy in treating PDAC. Talabostat and gemcitabine together were shown to be safe in phase II research. In individuals with metastatic PDAC, there was, however, only a modest clinical effect. The signaling protein insulin-like growth factor (IGF) is overexpressed in PDAC. High IGF-1 levels are linked to aggressive cancers and a bad prognosis. Istiratumab (MM-141) is a bispecific monoclonal antibody that has been developed to bind to both the HER3 and the IGF-1 receptor, blocking the IGF-1R and ErbB3 pathways. It is being studied in a phase II trial [NCT02399137] that is currently recruiting participants. Through the in vivo suppression of AKT phosphorylation, istiratumab (MM-141) has been found to increase gemcitabine and paclitaxel sensitivity. In order to improve the transport of gemcitabine and olaparib to pancreatic cancer cells with BRCA2 mutations, researchers have developed a nanomedicine known as GE11 peptide self-assembly amphiphilic peptide nanoparticle gemcitabine olaparib (GENP-Gem-Ola). Here, the BRCA2 mutant capan-1 cells are suppressed by the synergistic interaction of gemcitabine and PARPi. The usage of GENP-Gem-Ola was explored as a viable strategy for treating pancreatic tumours with mutations in DNA repair pathways. By concentrating ultrasonic waves on a single target tumor, [85] High intensity focused ultrasound (HIFU) therapy works by abrading tissue from external to the body. The vibrational energy of the ultrasonic waves, which are released from various sources inside a semicircular probe, concentrates in the focus area, which is the centre of the curvature. The most current meta-analysis, conducted in 2021, looked at 992 instances of PC from seven researches. High intensity focused ultrasound (HIFU) treatment combined with chemotherapy improved survival compared to chemotherapy alone, with a hazard ratio of 0.40 (95% CI 0.28-0.58). Additionally, the combination treatment group had a substantially better 1-year survival rate (odds ratio 0.35, 95% CI 0.22-0.53, P 0.001) [86].

Conclusion:

There are several pharmacological interventions that are currently being studied to mitigate the progression of pancreatic ductal adenocarcinoma (PDAC) and improve prognosis. These include: Targeted therapies: Drugs that target specific molecules involved in the growth and spread of cancer cells, such as EGFR inhibitors and VEGF inhibitors. Chemotherapy: Drugs that target

rapidly dividing cancer cells, such as gemcitabine and nab-paclitaxel. Immunotherapy: Drugs that help the immune system fight cancer cells, such as checkpoint inhibitors and CAR T-cell therapy. Combination therapies: Using a combination of the above therapies to target multiple pathways involved in cancer growth and spread. It's important to note that these treatments are not universally effective and the choice of treatment depends on the patient's condition, stage of the cancer and overall health status

Acknowledgment: None

Conflict of interest: All authors declare no conflict of interest.

References:

1. Mizrahi, J. D., Surana, R., Valle, J. W., & Shroff, R. T. (2020). Pancreatic cancer. *The Lancet*, *395*(10242), 2008-2020.
2. Rawla, P., Sunkara, T., & Gaduputi, V. (2019). Epidemiology of pancreatic cancer: global trends, etiology and risk factors. *World journal of oncology*, *10*(1), 10.
3. Rahib, L., Smith, B. D., Aizenberg, R., Rosenzweig, A. B., Fleshman, J. M., & Matrisian, L. M. (2014). Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer research*, *74*(11), 2913-2921.
4. Arnold, M., Touillaud, M., Dossus, L., Freisling, H., Bray, F., Margaritis, I., ... & Soerjomataram, I. (2018). Cancers in France in 2015 attributable to high body mass index. *Cancer epidemiology*, *52*, 15-19.
5. Talathi SS, Zimmerman R, Young M. Anatomy, Abdomen and Pelvis, Pancreas. [Updated 2022 Jul 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-.
6. Gupta A, Rai P, Singh V, Gupta RK, Saraswat VA. Intrahepatic biliary duct branching patterns, cystic duct anomalies, and pancreas divisum in a tertiary referral center: A magnetic resonance cholangiopancreaticographic study. *Indian J Gastroenterol.* 2016;35:379–84.

7. Chaib E, Kanas AF, Galvao FH, D'Albuquerque LA. Bile duct confluence: Anatomic variations and its classification. *Surg Radiol Anat.* 2014;36:105–9.
8. Sarawagi R, Sundar S, Gupta SK, Raghuwanshi S. Anatomical variations of cystic ducts in magnetic resonance cholangiopancreatography and clinical implications. *Radiol Res Pract.* 2016;2016:3021484
9. Cascinu S, Falconi M, Valentini V, et al. Pancreatic cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010;21 Suppl 5:v55-58
10. Klein, Alison P. "Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors." *Nature Reviews Gastroenterology & Hepatology* 18.7 (2021): 493-502.
11. Lugo, A.; Peveri, G.; Bosetti, C.; Bagnardi, V.; Crippa, A.; Orsini, N.; Rota, M.; Gallus, S. Strong excess risk of pancreatic cancer for low frequency and duration of cigarette smoking: A comprehensive review and meta-analysis. *Eur. J. Cancer* **2018**, *104*, 117–126.
12. Wang, Y.T.; Gou, Y.W.; Jin, W.W.; Xiao, M.; Fang, H.Y. Association between alcohol intake and the risk of pancreatic cancer: A dose-response meta-analysis of cohort studies. *BMC Cancer* **2016**.
13. Chang, J.S.; Hsiao, J.R.; Chen, C.H. ALDH2 polymorphism and alcohol-related cancers in Asians: A public health perspective. *J. Biomed. Sci.* **2017**, *24*, 19.
14. Mao, Q.Q.; Lin, Y.W.; Chen, H.; Qin, J.; Zheng, X.Y.; Xu, X.; Xie, L.P. Dietary fiber intake is inversely associated with risk of pancreatic cancer: A meta-analysis. *Asia Pac. J. Clin. Nutr.* **2017**, *26*, 89–96.
15. Li D, Morris JS, Liu J, Hassan MM, Day RS, Bondy ML, Abbruzzese JL. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA.* 2009;301(24):2553–2562. doi: 10.1001/jama.2009.886.
16. Rawla, Prashanth, Tagore Sunkara, and Vinaya Gaduputi. "Epidemiology of pancreatic cancer: global trends, etiology and risk factors." *World journal of oncology* 10.1 (2019)
17. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424. doi: 10.3322/caac.21492.
18. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68(1):7–30. doi: 10.3322/caac.21442.
19. American Cancer Society. Cancer Facts and Figures 2014. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2014.html. 2014. Accessed 05 October 2018.
20. Pereira SP, Oldfield L, Ney A, et al. Early detection of pancreatic cancer. Lancet Gastroenterol Hepatol 2020; published online March 2. https://doi.org/10.1016/S2468–1253(19)30416–9.
21. Chen F, Roberts NJ, Klein AP. Inherited pancreatic cancer. Chin Clin Oncol. 2017 Dec;6(6):58. doi: 10.21037/cco.2017.12.04. PMID: 29307198; PMCID: PMC5873957.
22. Shindo K, Yu J, Suenaga M, Fesharakizadeh S, Cho C, Macgregor-Das A, et al. Deleterious Germline Mutations in Patients With Apparently Sporadic Pancreatic Adenocarcinoma. *J Clin Oncol Off J Am Soc Clin Oncol.* 2017 Oct 20;35(30):3382–90.
23. Mocci E, Milne RL, Méndez-Villamil EY, Hopper JL, John EM, Andrulis IL, et al. Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol.* 2013 May;22(5):803–11.
24. Borecka M, Zemankova P, Vocka M, Soucek P, Soukupova J, Kleiblova P, et al. Mutation analysis of the P ALB2 gene in unselected pancreatic cancer patients in the Czech Republic. *Cancer Genet.* 2016 May;209(5):199–204.
25. Chaffee KG, Oberg AL, McWilliams RR, Majithia N, Allen BA, Kidd J, et al. Prevalence of germ-line mutations in cancer genes among pancreatic cancer patients with a positive family history. *Genet Med Off J Am Coll Med Genet.* 2017 Jul 20
26. Masamune A, Kikuta K, Hamada S, Nakano E, Kume K, Inui A, et al. Nationwide survey of hereditary pancreatitis in Japan. *J Gastroenterol.* 2017 Aug 31

27. Møller P, Seppälä TT, Bernstein I, Holinski-Feder E, Sala P, Gareth Evans D, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut.* 2017 Jul 28
28. Chu GC, Kimmelman AC, Hezel AF, DePinho RA. Stromal biology of pancreatic cancer. J Cell Biochem 2007;101:887907.
29. Masamune A, Shimosegawa T. Signal transduction in pancreatic stellate cells. J Gastroenterol 2009;44:249-60.
30. Zhang W, Erkan M, Abiatari I, et al. Expression of extracellular matrix metalloproteinase inducer (EMMPRIN/CD147) in pancreatic neoplasm and pancreatic stellate cells. Cancer Biol Ther 2007;6:21827.
31. Mukherjee P, Basu GD, Tinder TL, et al. Progression of pancreatic adenocarcinoma is significantly impeded with a combination of vaccine and COX-2 inhibition. J Immunol 2009;182:216-24.
32. R. Roshani, F. McCarthy, T. Hagemann, Inflammatory cytokines in human pancreatic cancer, Cancer Lett. 345 (2) (2014) 157–163.
33. A. Scholz, S. Heinze, K.M. Detjen, M. Peters, M. Welzel, P. Hauff, M. Schirner, B. Wiedenmann, S. Rosewicz, Activated signal transducer and activator of transcription 3 (STAT3) supports the malignant phenotype of human pancreatic cancer, Gastroenterology 125 (3) (2003) 891–905.
34. C. Bazzichetto, F. Conciatori, I. Falcone, F. Cognetti, M. Milella, L. Ciuffreda, Advances in tumor-stroma interactions: emerging role of cytokine network in colorectal and pancreatic cancer, J. Oncol. 2019 (2019).
35. E.A. Collisson, A. Sadanandam, P. Olson, W.J. Gibb, M. Truitt, S. Gu, J. Cooc, J. Weinkle, G.E. Kim, L. Jakkula, Subtypes of pancreatic ductal adenocarcinoma and their differing responses to therapy, Nat. Med. 17 (4) (2011) 500.
36. M. Carrasco, I. Delgado, B. Soria, F. Martín, A. Rojas, GATA4 and GATA6 control mouse pancreas organogenesis, J. Clin. Invest. 122 (10) (2012) 3504–3515.
37. E. Karamitopoulou, Tumour microenvironment of pancreatic cancer: immune landscape is dictated by molecular and histopathological features, Br. J. Cancer 121 (July (1)) (2019) 5–14.
38. R.A. Moffitt, R. Marayati, E.L. Flate, K.E. Volmar, S.G.H. Loeza, K.A. Hoadley, N.U. Rashid, L.A. Williams, S.C. Eaton, A.H. Chung, Virtual microdissection identifies distinct tumor-and stroma-specific subtypes of pancreatic ductal adenocarcinoma, Nat. Genet. 47 (10) (2015) 1168.
39. P. Bailey, D.K. Chang, K. Nones, A.L. Johns, A.-M. Patch, M.-C. Gingras, D.K. Miller, A.N. Christ, T.J. Bruxner, M.C. Quinn, Genomic analyses identify molecular subtypes of pancreatic cancer, Nature 531 (7592) (2016) 47.
40. Hidalgo, M.; Cascinu, S.; Kleeff, J.; Labianca, R.; Lohr, J.M.; Neoptolemos, J.; Real, F.X.; Van Laethem, J.L.; Heinemann, V. Addressing the challenges of pancreatic cancer: Future directions for improving outcomes. *Pancreatology* **2015**, *15*, 8–18.
41. Kamisawa T, Wood LD, Itoi T, et al. Pancreatic cancer. *Lancet* 2016;388:73–85.
42. Nowak, N.J.; Gaile, D.; Conroy, J.M.; McQuaid, D.; Cowell, J.; Carter, R.; Goggins, M.G.; Hruban, R.H.; Maitra, A. Genome-wide aberrations in pancreatic adenocarcinoma. Cancer Genet. Cytogenet. 2005, 161, 36–50.
43. Lau, M.K.; Davila, J.A.; Shaib, Y.H. Incidence and survival of pancreatic head and body and tail cancers: A population-based study in the United States. Pancreas 2010, 39, 458–462.
44. Notta, F.; Chan-Seng-Yue, M.; Lemire, M.; Li, Y.; Wilson, G.W.; Connor, A.A.; Denroche, R.E.; Liang, S.B.; Brown, A.M.; Kim, J.C.; et al. A renewed model of pancreatic cancer evolution based on genomic rearrangement patterns. Nature 2016, 538, 378–382.
45. Dreyer,S.B.;Jamieson,N.B.;Upstill-Goddard,R.;Bailey,P.J.;McKay,C.J.;Biankin,A.V.;Chang,D.K.Defining the molecular pathology of pancreatic body and tail adenocarcinoma. Br. J. Surg. 2018, 105, e183–e191.
46. Birnbaum, D. J., Bertucci, F., Finetti, P., Birnbaum, D., & Mamessier, E. (2019). Head and body/tail pancreatic carcinomas are not the same tumors. *Cancers*, *11*(4), 497.

47. Pereira SP, Oldfield L, Ney A, Hart PA, Keane MG, Pandol SJ, Li D, Greenhalf W, Jeon CY, Koay EJ, Almario CV, Halloran C, Lennon AM, Costello E. Early detection of pancreatic cancer. Lancet Gastroenterol Hepatol. 2020;**5**:698–710.
48. Okusaka T, Nakamura M, Yoshida M, Kitano M, Uesaka K, Ito Y, Furuse J, Hanada K, Okazaki K Committee for Revision of Clinical Guidelines for Pancreatic Cancer of the Japan Pancreas Society. Clinical Practice Guidelines for Pancreatic Cancer 2019 From the Japan Pancreas Society: A Synopsis. Pancreas. 2020;**49**:326–335.
49. Kanno A, Masamune A, Hanada K, Maguchi H, Shimizu Y, Ueki T, Hasebe O, Ohtsuka T, Nakamura M, Takenaka M, Kitano M, Kikuyama M, Gabata T, Yoshida K, Sasaki T, Serikawa M, Furukawa T, Yanagisawa A, Shimosegawa T Japan Study Group on the Early Detection of Pancreatic Cancer (JEDPAC) Multicenter study of early pancreatic cancer in Japan. Pancreatology. 2018;**18**:61–67
50. Haba S, Yamao K, Bhatia V, Mizuno N, Hara K, Hijioka S, Imaoka H, Niwa Y, Tajika M, Kondo S, Tanaka T, Shimizu Y, Yatabe Y, Hosoda W, Kawakami H, Sakamoto N. Diagnostic ability and factors affecting accuracy of endoscopic ultrasound-guided fine needle aspiration for pancreatic solid lesions: Japanese large single center experience. J Gastroenterol. 2013;**48**:973–981.
51. Kawamura R, Ishii Y, Serikawa M, Tsuboi T, Tsushima K, Nakamura S, Hirano T, Ikemoto J, Kiyoshita Y, Saeki S, Tamura Y, Miyamoto S, Nakamura K, Furukawa M, Ishida K, Arihiro K, Uemura K, Aikata H. Optimal indication of endoscopic retrograde pancreatography-based cytology in the preoperative pathological diagnosis of pancreatic ductal adenocarcinoma. Pancreatology. 2022;**22**:414–420.
52. Ikemoto J, Serikawa M, Hanada K, Eguchi N, Sasaki T, Fujimoto Y, Sugiyama S, Yamaguchi A, Noma B, Kamigaki M, Minami T, Okazaki A, Yukutake M, Ishii Y, Mouri T, Shimizu A, Tsuboi T, Arihiro K, Chayama K. Clinical Analysis of Early-Stage Pancreatic Cancer and Proposal for a New Diagnostic Algorithm: A Multicenter Observational Study. Diagnostics (Basel) 2021;**11**
53. Sturm N, Ettrich TJ, Perkhofer L. The Impact of Biomarkers in Pancreatic Ductal Adenocarcinoma on Diagnosis, Surveillance and Therapy. Cancers (Basel) 2022;**14**
54. Yu J, Ploner A, Kordes M, Löhr M, Nilsson M, de Maturana MEL, Estudillo L, Renz H, Carrato A, Molero X, Real FX, Malats N, Ye W. Plasma protein biomarkers for early detection of pancreatic ductal adenocarcinoma. Int J Cancer. 2021;**148**:2048–2058.
55. Miyazawa M, et al. Phase II clinical trial using novel peptide cocktail vaccine as a postoperative adjuvant treatment for surgically resected pancreatic cancer patients. Int J Cancer. 2017;140(4):973–82.
56. Weitzenfeld P, Bournazos S, Ravetch JV. Antibodies targeting sialyl Lewis A mediate tumor clearance through distinct effector pathways. J Clin Invest. 2019;129:3952–62.
57. Dhillon S. Dinutuximab: first global approval. Drugs. 2015;75(8):923–7.
58. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/ programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res. 2007;13(7):2151–7
59. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in stage III non–small-cell lung Cancer. N Engl J Med. 2017;377(20):1919–29.
60. Aglietta M, Barone C, Sawyer MB, Moore MJ, Miller WH Jr, Bagala C, et al. A phase I dose escalation trial of tremelimumab (CP-675,206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. Ann Oncol. 2014;25(9):1750–5.
61. R.H. Vonderheide, The immune revolution: A case for priming, not checkpoint. Cancer Cell 33, 563 –569 (2018)
62. G.L. Beatty, D.A. Torigian, E.G. Chiorean, B. Saboury, A. Brothers, A. Alavi, A.B. Troxel, W. Sun, U.R. Teitelbaum, R.H. Vonderheide, P.J. O'Dwyer, A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabineinpatientswithadvancedpancreaticductaladenocarcinoma. Clin. Cancer Res. 19, 6286 – 6295 (2013)

63. H. Jiang, S. Hegde, B.L. Knolhoff, Y. Zhu, J.M. Herndon, M.A. Meyer, T.M. Nywening, W.G. Hawkins, I.M. Shapiro, D.T. Weaver, J.A. Pachter, A. Wang-Gillam, D.G. DeNardo, Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. Nat. Med. 22, 851 –860 (2016)
64. D.R. Principe, B. DeCant, E. Mascarinas, E.A. Wayne, A.M. Diaz, N. Akagi, R. Hwang, B. Pasche, D.W. Dawson, D. Fang, D.J. Bentrem, H.G. Munshi, B. Jung, P.J. Grippo, TGFbeta signaling in the pancreatic tumor microenvironment promotes fibrosis and immune evasion to facilitate tumorigenesis. Cancer Res. 76, 2525 –2539 (2016)
65. Frey NV, Porter DL. CAR T-cells merge into the fast lane of cancer care. *Am J Hematol*. 2016;**91**:146–50.
66. Mariathasan S, Turley SJ, Nickles D, Castiglioni A, Yuen K, Wang Y, Kadel EE, Koeppen H, Astarita JL, Cubas R ***et al*** (2018) TGFbeta attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. ***Nature* 554**: 544–548
67. D. Melisi, A. Hollebecque, D.-Y. Oh, E. Calvo, A.M. Varghese, E.H. Borazanci, T.M. Mercade, F. Simionato, J.O. Park, J.C. Bendell, S.J. Faivre, Y. Zhao, I. Gueorguieva, M. Man, S. Estrem, K.A. Benhadji, M. Lanasa, S.C. Guba, R. GarciaCarbonero, A phase Ib dose-escalation and cohort-expansion study of safety and activity of the transforming growth factor (TGF) β receptor I kinase inhibitor galunisertib plus the anti-PDL1 antibody durvalumab in metastatic pancreatic cancer. 37, 4124–4124 (2019).
68. S.E. Lawler, M.C. Speranza, C.F. Cho, E.A. Chiocca, Oncolytic viruses in cancer treatment: A review. JAMA Oncol. 3, 841 –849 (2017).
69. Valle S, Martin-Hijano L, Alcalá S, Alonso-Nocelo M, Sainz B Jr. The Ever-Evolving Concept of the Cancer Stem Cell in Pancreatic Cancer. Cancers (Basel). 2018 Jan 26;10(2):33.
70. Feldmann G, Mishra A, Bisht S, et al. Cyclin-dependent kinase inhibitor Dinaciclib (SCH727965) inhibits pancreatic cancer growth and progression in murine xenograft models. Cancer Biol Ther 2011;12:598–609.
71. Abel EV, Kim EJ, Wu J, et al. The Notch pathway is important in maintaining the cancer stem cell population in pancreatic cancer. PLoS One 2014;9:e91983
72. Blair A.B., Kim V.M., Muth S.T., Saung M.T., Lokker N., Blouw B., Armstrong T.D., Jaffee E.M., Tsujikawa T., Coussens L.M., et al. Dissecting the Stromal Signaling and Regulation of Myeloid Cells and Memory Effector T Cells in Pancreatic Cancer. Clin. Cancer Res. 2019;25:5351–5363.
73. Seo Y.D., Jiang X., Sullivan K.M., Jalikis F.G., Smythe K.S., Abbasi A., Vignali M., Park J.O., Daniel S.K., Pollack S.M., et al. Mobilization of $CD8^+$ T Cells via CXCR4 Blockade Facilitates PD-1 Checkpoint Therapy in Human Pancreatic Cancer. Clin. Cancer Res. 2019;25:3934–3945.
74. Bockorny B., Semenisty V., Macarulla T., Borazanci E., Wolpin B.M., Stemmer S.M., Golan T., Geva R., Borad M.J., Pedersen K.S., et al. BL-8040, a CXCR4 Antagonist, in Combination with Pembrolizumab and Chemotherapy for Pancreatic Cancer: The COMBAT Trial. Nat. Med. 2020;26:878–885.
75. Nugent F., Cunningham C., Barve M., Fisher W., Patel H., Meiri E., Oza Y., Yang Z., Jurkowski E., Uprichard M. Phase 2 Study of Talabostat/Gemcitabine in Stage IV Pancreatic Cancer. J. Clin. Oncol. 2007;25:4616.
76. Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs. Maintenance Temozolomide alone on Survival in Patients with Glioblastoma: A Randomized Clinical Trial | Neuro-Oncology | JAMA | JAMA Network. [(accessed on 25 October 2021)].
77. Rivera F., Benavides M., Gallego J., Guillen-Ponce C., Lopez-Martin J., Küng M. Tumor Treating Fields in Combination with Gemcitabine or Gemcitabine plus Nab-Paclitaxel in Pancreatic Cancer: Results of the PANOVA Phase 2 Study. Pancreatology. 2019;19:64–72.
78. Tao J., Yang G., Zhou W., Qiu J., Chen G., Luo W., Zhao F., You L., Zheng L., Zhang T., et al. Targeting Hypoxic Tumor Microenvironment in Pancreatic Cancer. J. Hematol. Oncol. 2021;14:14. doi: 10.1186/s13045-020-01030-w.

79. Amanam I, Chung V. Targeted therapies for pancreatic cancer. Cancers (Basel) 2018;10
80. Reni M, Cereda S, Milella M, Novarino A, Passardi A, Mambrini A, Di Lucca G, Aprile G, Belli C, Danova M, Bergamo F, Franceschi E, Fugazza C, Ceraulo D, Villa E. Maintenance sunitinib or observation in metastatic pancreatic adenocarcinoma: a phase II randomised trial. Eur J Cancer. 2013;49:3609–3615.
81. Giordano G, Pancione M, Olivieri N, Parcesepe P, Velocci M, Di Raimo T, Coppola L, Toffoli G, D'Andrea MR. Nano albumin bound-paclitaxel in pancreatic cancer: current evidences and future directions. World J Gastroenterol. 2017;23:5875–5886
82. Lugovskoy AA, Curley M, Baum J, Adams S, Iadevaia S, Rimkunas V, Camblin A, Nie L, Tan G, Johnson B, Mathews S, Horgan K, Louis CU, Czibere AG, Arnedos M, Soria J-C, Bahleda R, Shields A, LoRusso PM, Saleh M, Isakoff SJ. Abstract CT237: preclinical characterization and first-in-human study of MM-141, a dual antibody inhibitor of IGF-1R and ErbB3. Cancer Res. 2015;75:CT237.
83. Camblin AJ, Pace EA, Adams S, Curley MD, Rimkunas V, Nie L, Tan G, Bloom T, Iadevaia S, Baum J, Minx C, Czibere A, Louis CU, Drummond DC, Nielsen UB, Schoeberl B, Pipas JM, Straubinger RM, Askoxylakis V, Lugovskoy AA. Dual inhibition of IGF-1R and ErbB3 enhances the activity of gemcitabine and Nab-paclitaxel in preclinical models of pancreatic cancer. Clin Cancer Res. 2018;24:2873–2885.
84. Lev A, Lulla AR, Wagner J, Ralff MD, Kiehl JB, Zhou Y, Benes CH, Prabhu VV, Oster W, Astsaturov I, Dicker DT, El-Deiry WS. Anti-pancreatic cancer activity of ONC212 involves the unfolded protein response (UPR) and is reduced by IGF1-R and GRP78/BIP. Oncotarget. 2017;8:81776–81793.
85. Du C, Qi Y, Zhang Y, Wang Y, Zhao X, Min H, Han X, Lang J, Qin H, Shi Q, Zhang Z, Tian X, Anderson GJ, Zhao Y, Nie G, Yang Y. Epidermal growth factor receptor-targeting peptide nanoparticles simultaneously deliver gemcitabine and olaparib to treat pancreatic cancer with breast cancer 2 (BRCA2) mutation. ACS Nano. 2018;12:10785–10796.
86. Sofuni, A., Asai, Y., Mukai, S. *et al.* High-intensity focused ultrasound therapy for pancreatic cancer. *J Med Ultrasonics* (2022). https://doi.org/10.1007/s10396-022-01208-4