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Pancreatic cancer treatment with targeted therapies: are we there yet?

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Abstract. – OBJECTIVE: Pancreatic cancer (PaCa) is a disease that is extremely difficult to treat and is associated with a high fatality rate. The majority of patients present to hospitals with metastatic or end-stage cancer, making the ultimate cure impossible. End-stage PaCa has no specific treatment, though surgery, irradiation, and chemotherapy can help patients live longer. Consequently, it is vital to accumulate all information on potential targeted therapies for this cancer into a single report.

MATERIALS AND METHODS: This review has been compiled using relevant keywords and a thorough web search utilising PubMed, ScienceDirect, GoogleScholar, Scopus, MEDLINE, and SpringerLink.

RESULTS: Conventional medicines that target various biological processes have a significant negative impact on normal cells. As a result, targeted therapies are required, which include the use of small-molecule inhibitors and monoclonal antibodies to target cancer cell surface receptors, growth factors, and other proteins involved in disease progression. In this review, we summarize the known targeted PaCa therapies, which include inhibitors of the KRAS, mTOR, and PI3K/AKT signaling pathways, as well as PARP, hedgehog, EGFR/ErbB, and TGF-β signaling pathways, along with inhibitors of the neurotrophic tropomyosin receptor kinase (NTRK).

CONCLUSIONS: An adequate understanding of PaCa pathogenesis and the adoption of tailored medicines can increase patients' overall survival. We believe targeted therapy can help patients with PaCa to have a better prognosis. As such, more research is needed to find appropriate biomarkers to aid in early tumor diagnosis and to discover novel prospective therapeutics based on the drugs listed in this article.

Key Words:
Pancreatic cancer, Chemotherapy, Targeted therapy, Small molecule inhibitor, Monoclonal antibody.

Introduction

Pancreatic cancer (PaCa) is a difficult-to-treat disease and associated with high mortality[1]. About 90% of PaCa cases are adenocarcinomas[2]. Neuroendocrine tumors such as gastrinoma, insulinoma, somatostatinoma, glucagonoma, and non-functional islet cell tumors are less common. PaCa mainly affects the head and neck of the pancreas[3]. Globally, PaCa is the seventh leading cause of cancer-related deaths[4], with the highest incidence rates in Europe, North America, and Australia/New Zealand, and it is estimated to become the third leading cause of cancer death by 2025[5]. As the incidence and mortality rates are following an upward trend, it has been estimated that PaCa will be the fourth leading cause of cancer-associated death in males while in the females, it will be the third in the US by 2040[6].

About 53% of diagnosed patients present with metastatic or end-stage disease[7,8]. PaCa is a very aggressive type of cancer with a low 5-year relative survival rate (5-9%)[9]. In the face of a lack of effective and safe treatments options, late diagnosis in advanced tumor stages and the aggressive behavior of PDAC, there is high mortality of the disease. Therefore, the discovery and development of precision medicine for pancreatic cancer patients has become an urgent research area to address[9]. PaCa usually shows no symptoms at the early stage[10]. As the tumor grows, some symptoms that are not specific to PaCa manifest; these include jaundice, light-colored stool, pain in the abdominal area, reduction in weight, and fatigue[11]. Pre-existing diagnostic tests may appear nonspecific, thereby overlooking patients with onset stages of the disease[7]. There is no specific

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treatment for advanced PaCa, although life is prolonged, and patients' symptoms are reduced using surgery, radiotherapy, and chemotherapy[12].

Although surgical resection may improve the patient's survival, about 80% of patients with PaCa are diagnosed with unresectable (locally advanced and/or metastatic) tumor because symptoms of PaCa manifest at a later stage. This leads to treatment failures and an extremely poor prognosis for advanced PaCa[13]. Chemotherapy is still the mainstay in the treatment of unresectable PaCa[14]; according to the National Comprehensive Cancer Network's recommendation, gemcitabine-based chemotherapy is a standard course for advanced or metastatic PaCa[15]. Recent studies have reported that targeted therapy is a better therapeutic strategy available for advanced or metastatic PaCa[16,17]. In the last 15 years, the treatment of solid tumor has shifted from the use of conventional anticancer chemotherapeutics to more targeted therapies. It has been established that small-molecule epidermal growth factor receptor (EGFR) inhibitors offer improved efficacy and better tumor control in the case of EGFR-mutated cancer compared to traditional anticancer chemotherapy, although it has yet to be established for PaCa[14]. The reasons for poor therapeutic efficacy and the aggressive nature of PaCa include the late presentation of symptoms in patients for diagnosis, cancer-cell-intrinsic alterations, and factors associated with the tumor microenvironment. In 2008, Jones et al[8] conducted a detailed genetic analysis from 24 PaCa cell lines and reported 63 genetic alterations with a fundamental set of 12 cellular signaling pathways that are usually altered in PaCa[1]. Since that discovery, several clinical trials have targeted these altered pathways. This review was planned and conducted to summarize some of these targeted approaches. The specific focus of this review is Pancreatic Ductal Adenocarcinoma (PDAC), which is the commonest subtype of PaCa, accounting for about 90% of all cases.

Materials and Methods

A detailed search has performed through PubMed, ScienceDirect, Google Scholar, Scopus, MEDLINE, and SpringerLink. Research papers were searched using keywords such as pancreatic cancer and pathogenesis, pancreatic cancer, PDAC, treatment for pancreatic cancer and targeted therapy, EGFR inhibitors, PARP inhibitors, NTRK inhibitors, etc. Scientific papers that matched the keywords have reviewed and findings have noted herein.

Pathogenesis

Pancreatic carcinoma majorly originates from lesions associated with pancreatic intraepithelial neoplasia (PanINs), less frequently from intraductal papillary mucinous neoplasm (IPMN), and rarely from mucinous cystic neoplasm[19]. PanIN is a microscopic lesion of dysplasia from which most PDAC arises. The progression of PanIN to invasive ductal adenocarcinoma is caused by the accumulation of genetic changes and progression of the characteristic microenvironment[20] through PanIN-2 (atypical hyperplasia, papillary duct lesion with atypia) and PanIN-3 (grade 3 carcinoma *in-situ*)[21] (Figure 1). The first driver of mutation in PaCa is the oncogenic activation of the Kirsten rat sarcoma (*KRAS*) gene, found in more than

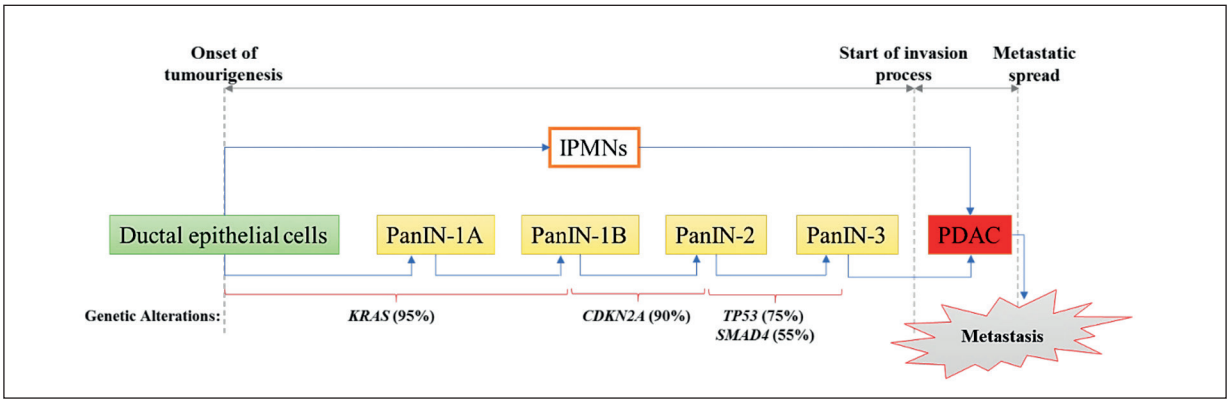

Figure 1. Schematic representation of pathological changes for the initiation of pancreatic carcinoma and changes in associated genes.

90% of tumors[22], which is generally mutated in low-grade PanIN lesions (PanIN-1A) and is the initial incident for PaCa formation[23]. Despite the complication associated with PDAC initiation, *KRAS* mutation has been confirmed as the major driver for cancer progression and maintenance of tumors[7,20,24]. PaCa demonstrates different types of mutations in crucial signaling pathways.

Other commonly occurring mutations include inactivation of cyclin-dependent kinase 2 (CDK2) and mothers against decapentaplegic homolog 4 (SMAD4) protein as well as *BRCA2*, DNA repair associated (BRCA2), MutL homolog 1 (MLH1), or alteration in serine protease 1 (PRSS1) genes. Mutations in tumor protein 53 (TP53) occur later in PanIN, resulting in the progression of PDAC but not its initiation[25]. Based on the complete genome/exome sequencing, Shain and co-workers disclosed that SWI/SNF, an ATP-dependant chromatin-remodeling complex, has tumor suppressor role and is also the fifth leading cause that drives mutations in PaCa[26]. TP53 is involved in DNA damage and regulates cell cycle checkpoints, cell cycle arrest, and apoptosis, and mutation in TP53 inactivates antiproliferative activity, and there is subsequent tumor growth and spread. However, an amazing study recently reported that, in some contexts, mutant p53 could function as a tumor suppressor[27]. Cyclin-dependent kinase 2A (CDK2A) is a regulatory protein responsible for the regulation of the G1/S-phase in the cell cycle. Inactivation by mutation leads to loss of function and, hence, increased cell proliferation. Makohon-Moore et al[28] reported that mutations in SMAD4 abnormally activate the transforming growth factor-beta (TGF-β) signaling pathway, which functions in the growth and differentiation of cells[29]. In addition, it has been reported that several other signaling pathways [e.g., Notch, Wnt, DNA damage response, sonic hedgehog (SHH)] or cellular processes (e.g., stem cell growth and maintenance, apoptosis, and epigenetic regulation) are affected by various mutations. For example, defective pathways and consequent deregulation of DNA damage can occur due to the mutations in epigenetic regulators or deletions in genes [e.g., AT-rich interactive domain-containing protein 1A (*ARID1A*)][30], which can lead to cellular survival and enhanced tumorigenic signals[31].

Targeted Therapies

Conventional therapies are remedies that target various cellular processes; they cannot differentiate between oncogenic cells and normal cells and thereby cause undesirable side effects. Consequently, targeted treatments with small molecule inhibitors (SMIs) and monoclonal antibodies (mAbs) are warranted. These compounds target receptors at the tumor cell surface, growth factors, or other proteins related to disease development and advancement. Targeted therapy can be said to involve drugs that inhibit tumor cell proliferation by interacting with important molecules in the cells needed for cancer development, rather than just interfering with the rapidly dividing cells, as is the case for traditional chemotherapy[32]. Targeted cancer therapy has drawn attention from many researchers because it is expected to take the place of systemic chemotherapy in the future. Researchers and clinicians have hypothesized it will lead to a better therapeutic outcome with less toxicity than systemic chemotherapy.

Targeted therapy inhibits certain pathways useful in cancer initiation and proliferation through apoptosis of tumor cells, which leads to the inhibition of enzymes along with the growth factor receptors essential for the progression of oncogenic cells. With targeted therapy, cancer treatment may move from ‘cure’ to ‘management’ in the future, and hair loss, which is the main side effect of systemic chemotherapy, may be reduced[32]. SMIs and mAbs are examples of targeted therapy[33].

Small Molecule Inhibitors

Small molecules are low-molecular-weight organic compounds that are designed to penetrate the cell membrane, bind specific targets in the cell, and interfere with signaling pathways. The discovery of SMIs was an outstanding achievement in cellular biology research. These compounds allow several cellular pathways to be studied, to improve patient outcomes. For example, protein kinases associated with the initiation and progression of cancer are an important target in cancer therapy because many SMIs target these kinases. Targeting different proteins and signaling or receptor pathways linked to cancer cells can lead to alterations in signal transduction cascades. Several SMIs have been reported so far with potent and efficacious activity; they include proteasome inhibitors, vascular endothelial growth factor (VEGF) blocking molecules, immune system modulating agents, and histone deacetylase (HDAC) inhibitors[34].

Proteasome inhibitors include bortezomib, carfilzomib, and ixazomib (Figure 2). Such inhibitors cause PaCa cell death by induction of apoptosis through endoplasmic reticulum stress[35],

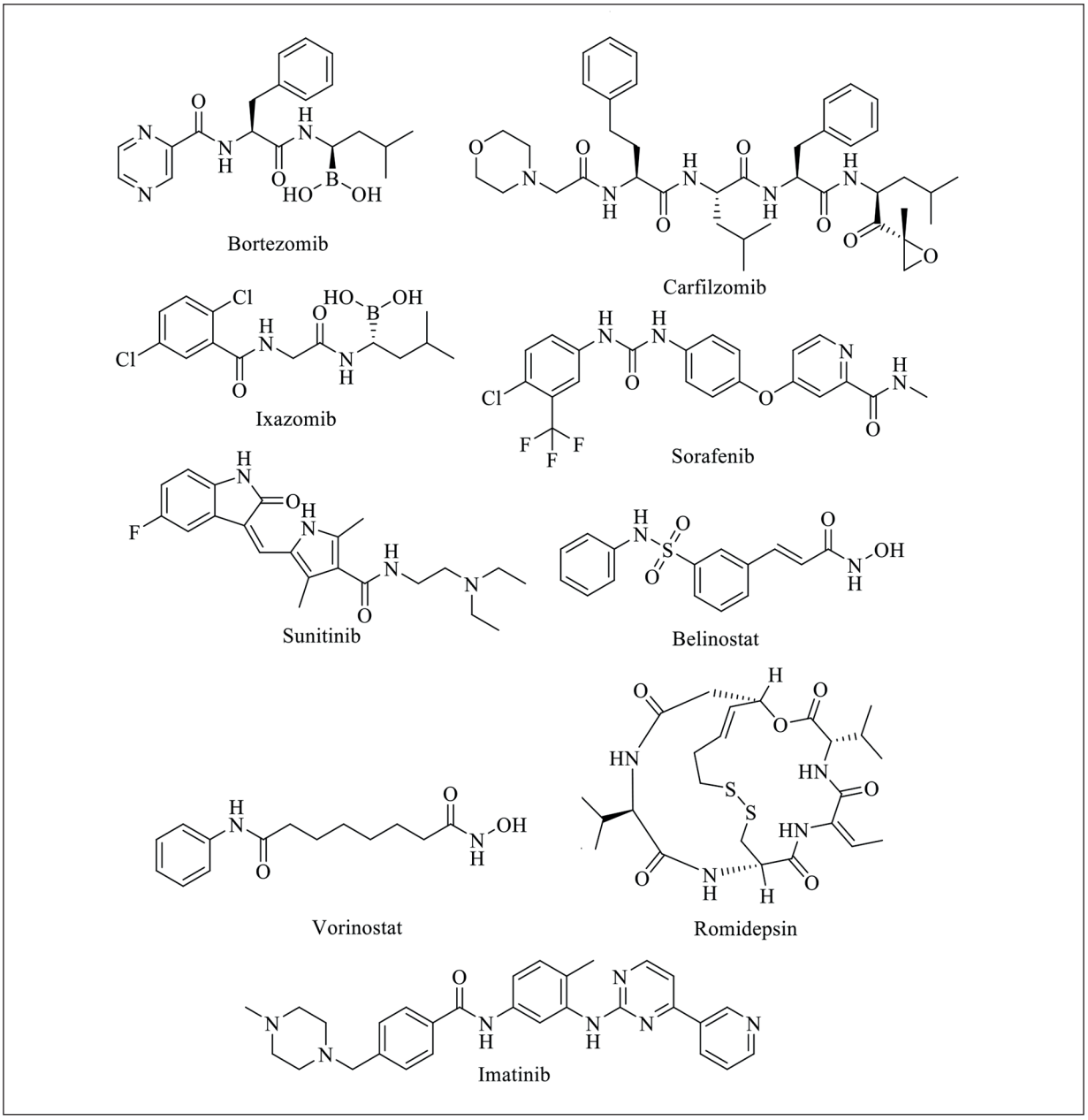

Figure 2. Small molecule inhibitors reported treating pancreatic cancer.

upregulation of proapoptotic proteins (e.g., Noxa, an inhibitor of κB, inhibition of nuclear factor-kappa B (NF-κB) and its anti-apoptotic target genes, and suppression of many anti-apoptotic proteins (e.g., B-cell lymphoma-extra-large (Bcl-xL), B-cell lymphoma 2 (Bcl-2), and Signal transducer and activator of transcription 3 (STAT-3)[36].

VEGF-blocking molecules, including sorafenib and sunitinib (Figure 2), are tyrosine kinase inhibitors (TKIs) and are used in the treatment of PaCa. They have dual effects: blockade of cancer cell proliferation and pro-angiogenic signaling by inhibiting rapidly accelerated fibrosarcoma (RAF) kinase that controls cell division and proliferation, VEGFR-2 and platelet-derived growth factor (PDGF) receptor beta (PDGFR-β) signaling pathway that blocks angiogenesis[37].

HDAC inhibitors include belinostat, vorinostat, and romidepsin (Figure 2). They induce cell growth arrest and apoptosis[38]. There are several advantages of SMIs over chemotherapeutic drugs and RNA interference (RNAi) agents – SMIs al-

low an extensive array for *in vivo* assays through varied temporal and titration designs that yield higher penetration in isolation and are useful in testing the combined effects with existing antitumor drugs[34].

Protein kinases have become important as drug targets due to their crucial role in most signal transduction pathways. A kinase is an enzyme known as a phosphotransferase that mostly catalyzes substrate-level phosphorylation reactions[34]. Research on these enzymes[35] has increased since it was discovered that mutation in and deregulation of protein kinases directly affect the pathophysiology of cancer[39]. Imatinib (Figure 2), a tyrosine kinase inhibitor, is used to treat chronic myeloid leukemia, inhibits the tyrosine kinase activity of BCR-ABL1, a tumor-promoting fusion protein that has been identified as a tumor-initiating genomic event for subtypes of hematological malignancy[39]. Similarly, sunitinib, another TKI, can target several receptors and growth factors, for example, stem cell factor receptor, PDGF receptor, VEGF receptor (VEGFR), glial cell line-derived neurotrophic factor receptor, colony-stimulating factor-1 receptor and Fms-like tyrosine kinase-3 receptor[40]. Sorafenib is the first anti-angiogenic receptor tyrosine kinase inhibitor, targeting VEGFR-1/2/3, PDGFR-β, and c-Kit receptor[41]. In tumor cells, sorafenib can inhibit the Raf/MEK/extracellular signal-regulated kinase (ERK) pathway and subsequently leads to apoptosis through different mechanisms (e.g., blocking phosphorylation of eukaryotic translation initiation factor 4E).

Monoclonal Antibodies (mAbs)

Anti-EGFR and Anti-Human EGFR-2 mAbs

Currently, three anti-EGFR antibodies have been approved by the US Food and Drug Administration (FDA) including cetuximab, panitumumab, and necitumumab. A phase 2 study reported that cetuximab and bevacizumab together with gemcitabine, cisplatin and fluorouracil prolongs overall survival by approximately 6 months and Progression-Free Survival (PFS) by approximately 3 months in patients with advanced pancreatic cancer[42]. Nevertheless, a new systematic review and meta-analysis reports that administration of cetuximab with standard therapy for the treatment of pancreatic cancer is not beneficial[43]. The cetuximab-gemcitabine combination reportedly showed no significant benefit in patients[21]. Trastuzumab, a humanized anti-human epidermal growth factor receptor 2 (HER2) mAb, has been studied in phase I and II clinical trials. In phase II clinical trials using gemcitabine, trastuzumab plus erlotinib as first-line treatment of metastatic pancreatic cancer, the combination showed effectiveness in terms of disease control, PFS and overall survival (OS). The safety profile was acceptable but a larger study to investigate this combination compared to the standard regimen is warranted[44].

Anti-VEGF/VEGFR mAbs

Although the anti-VEGF mAb, bevacizumab, showed great activity in patients with different solid cancers, it was not efficacious in two large phase III studies in advanced PaCa[42]. Bevacizumab binds to VEGF (Figure 3), thereby inhibiting interaction with its receptors and activation of downstream signaling pathways; this inhibition leads to vascular regression and tumor dormancy. It has been approved for PaCa, colorectal cancer, Non-Small Cell Lung Cancer (NSCLC), metastatic renal cancer, and glioblastoma multiform. Cetuximab and nimotuzumab target EGFR, panitumumab targets ABX-EGFR, and trastuzumab targets HER2 in PaCa[45].

Upon binding to the cancer cell, the anticancer drug with a mAb becomes engulfed by the cancer cell, resulting in death. This process targets tumor cells by reducing the potential adverse events caused by anticancer drugs towards normal cells and providing a wider therapeutic range. Based on clinical trials, median overall survival improved with two chemotherapy regimens when compared with gemcitabine. Various preclinical and clinical studies on the effectiveness of many mAbs in PaCa treatment have been carried out[46]. mAbs are crucial to identify novel and overexpressed cell surface antigens in human cancers and mAb-based products show therapeutic and diagnostic ability in cancer, which have not yet been tapped. However, despite the advances made, to date no antibody-based drugs have been approved for the treatment of patients with pancreatic cancer[47].

Mucins (MUCs) involved in PaCa show higher expression of different MUC family members, like MUC1[48]. Overexpression of MUC1 is associated with cancer progression, invasion, and metastasis in breast and PaCa cells[49]. Furthermore, MUC1 expression is related to anti-cancer drug resistance, leading to therapeutic failures[50]. Studies have reported that MUC1 is expressed more

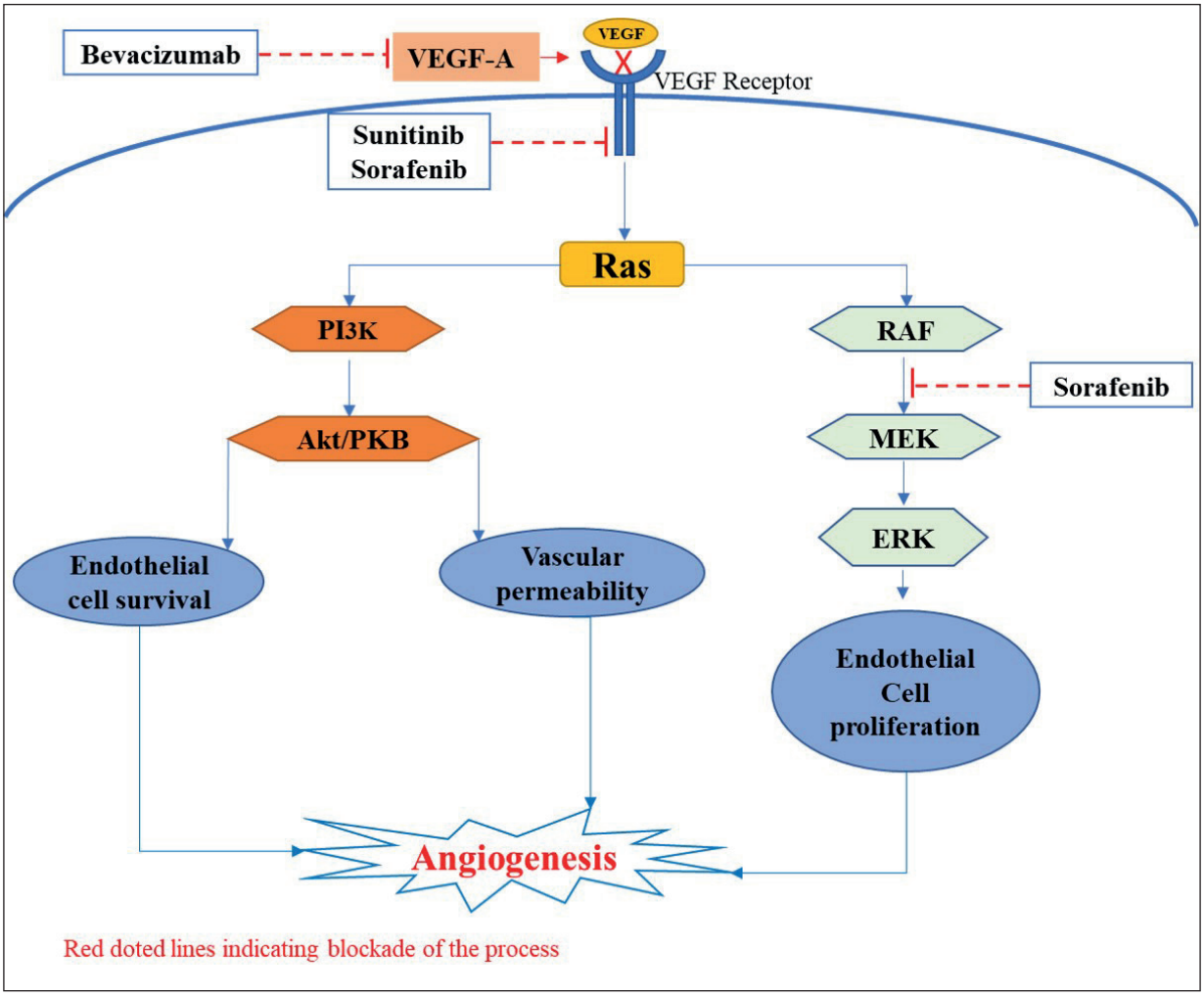

Figure 3. Mechanism of action of bevacizumab, sorafenib, and sunitinib.

in PaCa than on the luminal surface of a normal control pancreas[48,49].

Targeted Therapy in Pancreatic Cancer: Signaling Pathways Involved and Associated Drugs

KRAS Pathway Inhibitors

Kirsten rat sarcoma viral oncogene (KRAS) mutations are common in PaCa. As a matter of fact, more than 90% of the cases show mutation of the *KRAS* gene, which results in carcinogenesis and maintenance of an active state, constantly induces downstream signaling pathways (e.g., mitogen-activated protein kinase (MAPK)/ERK, phosphoinositide 3-kinases (PI3K)/AKT pathways), and thereby increases growth signals, invasiveness, and subsequent inhibition of apoptosis. Since KRAS inhibition did not give the expected result, proteins along the Ras signal transduction pathway can be targeted[14] and used extensively[7]. There has yet to be an effective drug that targets the *KRAS* mutant, although several attempts have been made. Therefore, alternative approaches, like inhibition of Ras downstream signaling pathways (e.g., MAPK and PI3K pathways) have been the focus. With the failure of small molecules to produce an expected result, a new treatment option has been proposed, aiming at a novel 'Achilles heel' in KRAS, specifically the G12C oncoprotein, sadly, *KRAS*-G12C mutation is rather uncommon in pancreatic ductal adenocarcinoma[51]. Optimization of 4-(piperazin-1-yl)quinazoline series of compounds has given rise to a new generation of KRAS-G12C-spe-

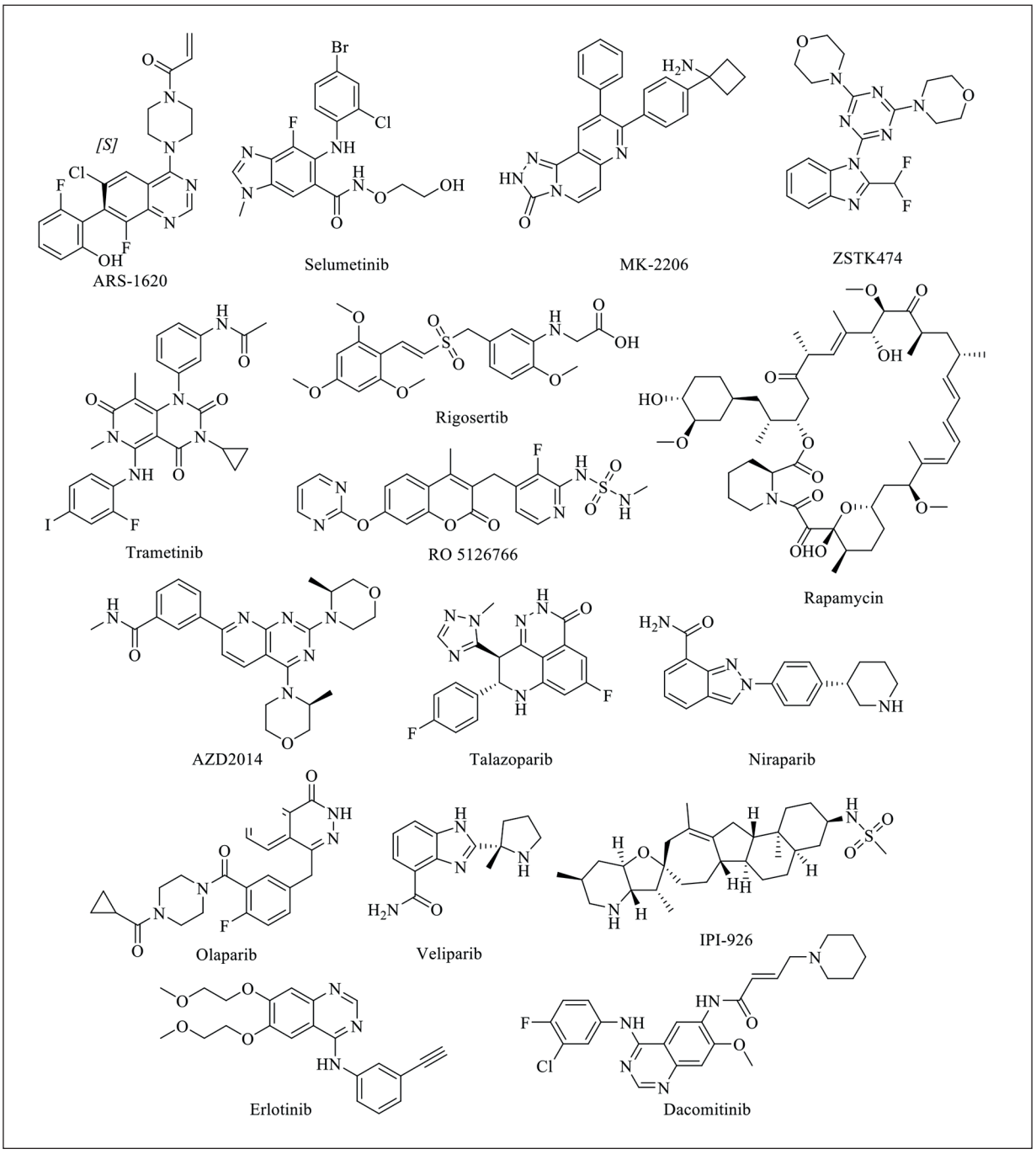

Figure 4. SMIs of the signaling pathway that are being used as targeted therapy in PaCa.

cific inhibitors (e.g., ARS-1620; Figure 4), which possess anticancer activity[52]. Sakamoto et al[53] reported KRAS-G12D-selective inhibitors, KS-58 which selectively binds to KRAS-G12D and exhibited *in vitro* antiproliferative activity on the human lung cancer cell line A427 and the human pancreatic cancer cell line PANC-1, both of which express KRAS-G12D. It also showed *in vivo* anticancer activity.

Most of the efforts in targeting KRAS have failed, and mutated *KRAS* still remains an undruggable target, therefore there is current-

ly no inhibitors used in clinical practice that directly target wild-type (WT) and/or mutated Ras[53,54]. Therefore, researchers have proposed inhibiting downstream targets of KRAS like the protein kinase MEK[55]. Single drugs that target PI3K, AKT, and mechanistic target of rapamycin (mTOR) have not been beneficial in PaCa with Ras mutation. Work is in progress to evaluate the inhibition of the PI3K and RAF/MEK/ERK pathways. A randomized phase II study revealed that MEK inhibitors (e.g., selumetinib; Figure 4) and AKT inhibitor (e.g., MK-2206; Figure 4) were not more beneficial over FOLFIRONIX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) and the toxicity greater in patients in whom gemcitabine-based drugs were not effective[56]. Trametinib (Figure 4), a MEK1/2 inhibitor, combined with gemcitabine[57] and rigosertib (Figure 4), a PI3K inhibitor in combination with gemcitabine[58] have been tested in PaCa.

mTOR and PI3K/AKT Pathway Inhibitors

Deregulation of the PI3K/AKT signaling pathway has been estimated to occur in most pancreatic cancer patients[59]. The PI3K pathway reportedly inhibits cellular apoptosis and thereby stimulates cancer cell proliferation[60]. Generally, the PI3K/AKT pathway stimulates both PDAC in human and PaCa in *KRAS*-driven mouse models[61]. PI3K mutations are more common in other types of cancer than in PaCa and cause tumorigenesis in relatively few PaCa patients[62]. Van et al[63] recently reported that the MAPK/MEK pathway is activated due to suppression of the PI3K/AKT/mTOR pathway. They also reported that a dual-purpose agent ZSTK474 (a PI3K inhibitor; Figure 4) and RO5126766 (a Raf/MEK inhibitor; Figure 4) can inhibit PaCa cell line viability[63]. mTORC1 is a downstream molecule of AKT and is activated by phosphorylated AKT. As a PDK2, mTORC2 fully activates AKT by phosphorylating Ser473[64]. mTOR activation regulates the translation of different proteins, including cyclin D1, which regulates cell cycle progression, and hypoxia-inducible factor 1- α (HIF-1 α), which regulates expression of pro-angiogenic VEGF[59]. Inhibition of mTOR signaling represses PDAC cell progression. Many substances regulate the behaviors of PDAC cells through the mTOR signaling pathway[65], by regulating metabolic pathways like those for glycolysis, amino acid and nucleotide metabolism; the promotion of cyclin synthesis; induction of autophagy and apoptosis in PDAC cells; and inhibition of cyclin synthesis[65].

Rapamycin, an mTOR inhibitor, effectively blocked the proliferation and development of pancreatic cancer cells in mice with *KRAS* activation and PTEN mutation[66]. However, clinical studies have failed to demonstrate efficacy of mTOR inhibitors as a single agent or with chemotherapy in advanced PDA[67]. Feedback pathway upregulation likely mediates acquired resistance to these agents, and furthermore, their use is hindered by toxicities, including hyperglycemia, cytopenia, fatigue, and mucositis/stomatitis[68].

Conway et al[69] used a double PI3K pathway inhibitor, AZD2014 (Figure 4), to inhibit growth and invasion in a particular PDAC model, the KPC (LSL-KRAS-G12D, LSL-Trp53R172H and Pdx1-Cre)-GEM PDAC model.

AZD2014 (Vistusertib®) in combination with paclitaxel (PTX), was reported to effectively inhibit both *in vitro* and *in vivo* ATC cell migration, invasion, and growth. This study supports the result of a phase 1 clinical trial where both AZD2014 and PTX were used in solid tumors[70].

Poly (ADP-ribose) Polymerase (PARP) Pathway and its Inhibitors

Mutation of the tumor suppressor gene BRCA2 leads to a hereditary inclination to breast cancer, ovarian cancer, and PC, thereby inhibiting DNA damage repair, leading to genome instability[71]. DNA damage activates PARP1 and PARP2. Available PARP inhibitors (PARPi) are being tested clinically for efficacy. Phase III trials have reported that talazoparib, niraparib, olaparib, and veliparib (Figure 4) are efficacious and tolerable in cancer, although there is a need for more studies. Olaparib has received accelerated approval due to the effects it has shown clinically[72]. A recent phase II randomized controlled trial investigated cisplatin and gemcitabine with or without Veliparib, a PARP inhibitor in patients with untreated advanced PDAC and a germline mutation of BRCA or PALB2[73]. An unprecedented survival rates, with a 2-year survival rate of 30.6% and a 3-year survival rate of 17.8% and high response rates for both arms of the study (74% with Veliparib, 65.2% without veliparib)[73] were reported. With the success of PARP inhibitors in other BRCA-associated cancers, interest has risen to translating these findings to BRCA-associated PDAC. A phase II study has evaluated the efficacy of PARP inhibitors in PDAC patients with germline BRCA mutations[73].

The clinical use of PARPi has been affected by their resistance, the main mechanism of which is the restoration of homologous recombination repair (HRR)[74].

Hedgehog (Hh) Signaling Pathway Inhibitors

The hedgehog pathway is important in embryonic development and tissue homeostasis. Furthermore, it has been suggested that deviant activation of Hh leads to neoplastic transformations, malignant tumors, and drug resistance in many cancers. Hh signaling encourages cancer by controlling cancer cell growth, malignancy, metastasis, and the expansion of cancer stem cells[75]. The two transmembrane protein receptors, Patched 1 and Patched 2, act as tumor suppressors, slow down downstream signaling proteins (e.g., Smo and Gli), and prevent activation of downstream signaling components and thus transcription of target genes[76].

The dense stroma plays an important role in tumor growth, proliferation, epithelial-mesenchymal transition (EMT), immune evasion and resistance to various therapies[77], therefore, many therapies have been targeted to modulate its interaction with the tumor.

It has been established repeatedly that indiscriminate targeting and near complete depletion of tumor stroma can cause more harm than good[78].

PDAC tumor is characterized by the uncontrolled activity of the Hh pathway[78], which activates pancreatic stellate cells (PSCs) through paracrine effects and controls stromal abundance[79]; this phenomenon is important in maintaining cancer stem cells. In the tumor microenvironment, the Hh ligand is produced by tumor cells; Hh binds to its receptor (Patched 1) on PSCs and thereby activates intracellular signaling by abolishing the inhibitory effects of Smo. Gli1, a transcription factor, is therefore translocated to the nucleus, where it controls various target genes like extracellular matrix proteins.

Activated PSCs then provide an appropriate microenvironment and promote cancer progression by altering four processes in pancreatic cancer models: (1) excessive fibrosis, (2) promoting tumor metastasis, (3) inducting resistance of chemotherapy and radiotherapy and (4) immune modulation. Evidence[80] confirmed the importance of PSCs in pancreatic cancer development. For example, a small molecule inhibitor, IPI-926 (Saridegib®, Figure 4) negatively regulates the Hh pathway and a preclinical study revealed that IPI-926 enhances the perfusion of gemcitabine in pancreatic tumors and improves survival[79].

EGFR/ErbB Signaling Pathway Inhibitor

Studies have demonstrated the EGFR/ErbB effects on normal cell growth, migration, cellular differentiation, adhesion, and apoptosis in the pancreas, heart, muscle, nervous system, and epithelia of various organs. EGFR activation upon malignant transformation can be because of upregulated receptor expression, enhanced autocrine and paracrine production of activating growth factors, and altered intrinsic tyrosine kinase activity because of mutations. EGFR activation is majorly due to combination of many factors, thereby complicating the search for suitable therapy[81]. Although EGFR inhibitors erlotinib and dacomitinib (Figure 4) have been approved for the treatment and improvement of PaCa prognosis, the clinical benefit of EGFR-targeted therapy is still limited[82].

TGF-β Signaling Inhibitor

TGF-β signaling follows SMAD (signal transducers for receptors of the TGF-β superfamily, which is vital for controlling cell development and growth) and non-SMAD pathways, which are linked with several other factors like AKT, ERK-1/2, and MAPK[83]. TGF-β signaling regulates cell cycle progression in pancreatic β-cells by controlling the nuclear localization of CDKI and p27[84]. In the noncanonical TGF-β signaling pathway, TGF-β superfamily ligands activates Rho, extracellular signal-regulated kinase (ERK), Janus kinase/STAT3, and phosphoinositide 3-kinase (PI3K)/AKT pathways in cancer associated fibroblasts[85].

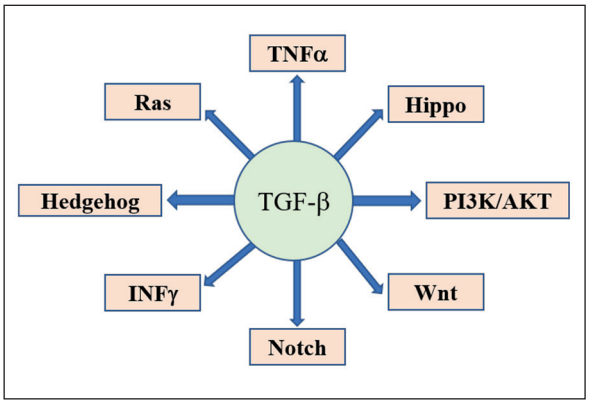

Figure 5. TGF-β and other corresponding signaling pathways.

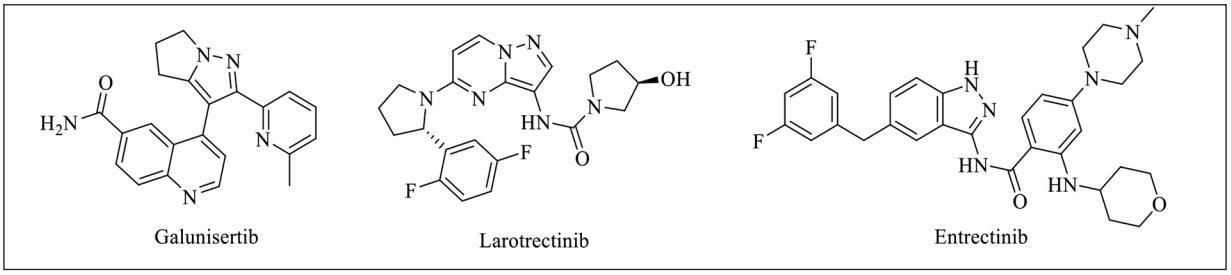

Figure 6. TGF-β signaling and neurotrophic receptor tyrosine kinase (NTRK) inhibitors.

The TGF-β pathway communicates with other signaling pathways and controls carcinogenesis (Figure 5).

Galunisertib (Figure 6) is an oral SMI that binds to TGF-β receptor I (TGFβRI) kinase inhibits its kinase activity, thereby blocking cancer cell proliferation[86]. Galunisertib in combination with checkpoint inhibitors (including nivolumab and durvalumab) is presently undergoing development in patients with NSCLC, hepatocellular carcinoma (HCC), or pancreatic cancer[87]. A phase Ib/randomized phase II study (JBAJ) of galunisertib in combination with gemcitabine showed improved overall survival (OS) *vs.* gemcitabine monotherapy in patients with unresectable pancreatic cancer[88]. Melisi et al[89] reported that the combination of TGFβ and PD-L1 inhibition has the potential to act synergistically to induce immune restoration and improve anti-tumor responses in pancreatic cancer.

Neurotrophic-Tropomyosin Receptor Kinase Inhibitors

Neurotrophic-tropomyosin receptor kinase (NTRK) gene fusions are known for causing a form of PDAC, thereby providing a potential target for therapy with tropomyosin receptor kinase (TRK) inhibitors. NTKR fusions are very rare, observed in less than 1% of cancers; however, such a condition appears in the lung, colorectal, pancreatic, breast, and brain carcinoma as well as cholangiocarcinoma, sarcoma, and melanoma[90]. FDA-approved NTRK inhibitors are larotrectinib (Vitrakvi®) and entrectinib (Rozlytrek®) (Figure 6), which can block the activity of TRK and other proteins that are responsible for driving cancer growth. Targeted TRK inhibition with larotrectinib in PaCa harbouring a CTRC-NTRK1 gene fusion is well tolerated and can improve quality of life[91]. Entrectinib produced striking, rapid, and durable responses in all children with the refractory central nervous system and solid tumors harboring ROS1, NTRK 1/2/3, or ALK fusions[92].

Conclusions

Due to its aggressive nature and late detection, PaCa is extremely difficult to treat. The majority of patients have late-stage disease, making treatment difficult. Although surgery, radiation, and chemotherapy are used to prolong survival and treat patients' symptoms, there is no particular cure for late-stage PaCa. Standard medications that target a variety of cellular pathways are unable to discriminate between cancer and healthy cells, resulting in substantial side effects. As a result, therapeutics based on SMIs and mAbs are required to target cancer cell surface receptors, growth factors, and/or other proteins involved in disease development. Patients with PaCa may have a greater chance of surviving if the problem is identified early and targeted therapy is used. Although several targeted therapies have been tested for the treatment of PaCa, most of them have been shown to be ineffective. This could be due to the disease's high molecular diversity and late discovery. The most crucial goal is to identify PaCa as soon as possible, as this will ensure that focused therapy is as effective as possible. Efforts should be undertaken to find relevant biomarkers to aid in early tumor detection and to expand therapeutic perspectives. To get the most out of these new drug candidates, particularly TGF-β signaling pathway inhibitors, it is critical to keep up with the newest scientific developments and be steered toward a fresh perspective on chemical scaffolds, design, and development of new molecules for chemotherapy. TGF-β signaling is regulated by SMAD, which is required for cell development and proliferation and is related to various other factors such as AKT, ERK-1/2, and MAPK. In addition, immunotherapeutic drugs are projected to play a

larger role in cancer treatment in the near future. By analyzing and documenting existing data, this paper has gathered ideas to design and develop further novel specific drug candidates to treat PaCa, which will aid future researchers.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Nwaefulu wrote the manuscript; Sagineedu proofread it; Islam edited and made necessary corrections within the manuscript, drew and formatted images and chemical structures; and Stanslas generated the concept and edited the manuscript.

References

1) Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. Lancet 2020; 395: 2008-2020.
2) Henley SJ, Ward EM, Scott S, Ma J, Anderson RN, Firth AU, Thomas CC, Islami F, Weir HK, Lewis DR, Sherman RL, Wu M, Benard VB, Richardson LC, Jemal A, Cronin K, Kohler BA. Annual report to the nation on the status of cancer, part I: National cancer statistics. Cancer 2020; 126: 2225-2249.
3) PDQ Adult Treatment Editorial Board. Pancreatic Neuroendocrine Tumors (Islet Cell Tumors) Treatment (PDQ®): Health Professional Version. 2020. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK65870/.
4) Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-249.
5) Huang J, Lok V, Ngai CH, Zhang L, Yuan J, Lao XQ, Ng K, Chong C, Zheng ZJ, Wong MCS. Worldwide burden of risk factors for, and trends in pancreatic cancer. Gastroenterology 2021; 160: 744-754.
6) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.
7) Facts & Figures 2020. American Cancer Society; Atlanta, GA: 2020.
8) National Cancer Institute. Cancer Stat Facts: Pancreatic Cancer. Surveillance, Epidemiology and End Results Program. 2019.
9) Regel I, Mayerle J, Mahajan UM. Current strategies and future perspectives for precision medicine in pancreatic cancer. Cancers 2020; 12: 1024.
10) Lin K, Lin AN, Lin S, Lin T, Liu YX, Reddy M. A Silent asymptomatic solid pancreas tumor in a nonsmoking athletic female: Pancreatic Ductal Adenocarcinoma. Case Rep Gastroenterol 2017; 11: 616-624.
11) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018; 68: 7-30.
12) Mohammed S, Van Buren G 2nd, Fisher WE. Pancreatic cancer: advances in treatment. World J Gastroenterol 2014; 20: 9354-9360.
13) Di B, Pan B, Ge L, Ma J, Wu Y, Guo T. Targeted agents for patients with advanced/metastatic pancreatic cancer: A protocol for systematic review and network meta-analysis. Medicine (Baltimore) 2018; 97: e0115.
14) Amanam I, Chung V. Targeted therapies for pancreatic cancer. Cancers (Basel) 2018; 10: 36.
15) Di Baoshan, Pan Bei, Ge Long, Ma Jichun, Wu, Yiting, Guo Tiankang. Targeted agents for patients with advanced/metastatic pancreatic cancer. Medicine 2018; 97: pe0115.
16) Lee JM, Lee HS, Hyun JJ, Choi HS, Kim ES, Keum B, Seo YS, Jeen YT, Chun HJ, Um SH, Kim CD. Prognostic value of inflammation-based markers in patients with pancreatic cancer administered gemcitabine and erlotinib. World J Gastrointest Oncol 2016; 8: 555-562.
17) Hao J, Yang X, Ding XL, Guo LM, Zhu CH, Ji W, Zhou T, Wu XZ. Paeoniflorin potentiates the inhibitory effects of erlotinib in pancreatic cancer cell lines by reducing ErbB3 phosphorylation. Sci Rep 2016; 6: 32809.
18) Darya J, Amir B, Afshin D, Patrizia L, Nicola S, Vito R, Antonio GS, Behzad B. Pancreatic cancer signaling pathways, genetic alterations, and tumor microenvironment: the barriers affecting the method of treatment. Biomedicines 2021; 9: 373.
19) Kromrey ML, Bülow R, Hübner J, Paperlein C, Lerch MM, Ittermann T, Völzke H, Mayerle J, Kühn JP. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. Gut 2018; 67: 138-145.
20) 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 J, 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.
21) Tanaka S. Molecular Pathogenesis and Targeted Therapy of Pancreatic Cancer. Ann Surg Oncol 2016; 23: S197-205.

22) Hashimoto D, Arima K, Yokoyama N, Chikamoto A, Taki K, Inoue R, Kaida T, Higashi T, Nitta H, Ohmuraya M, Hirota M, Beppu T, Baba H. Heterogeneity of KRAS mutations in pancreatic ductal adenocarcinoma. Pancreas 2016; 45: 1111-1114.

23) Tuveson DA, Shaw AT, Willis NA, Silver DP, Jackson EL, Chang S, Mercer KL, Grochow R, Hock H, Crowley D, Hingorani SR, Zaks T, King C, Jacobetz MA, Wang L, Bronson RT, Orkin SH, DePinho RA, Jacks T. Endogenous oncogenic K-ras (G12D) stimulates proliferation and widespread neoplastic and developmental defects. Cancer Cell 2004; 5: 375-387.

24) Rajbhandari N, Lin WC, Wehde BL, Triplett AA, Wagner KU. Autocrine IGF1 signaling mediates pancreatic tumor cell dormancy in the absence of oncogenic drivers. Cell Rep 2017; 18: 2243-2255.

25) Scarpa A, Capelli P, Mukai K, Zamboni G, Oda T, Iacono C, Hirohashi S. Pancreatic adenocarcinomas frequently show p53 gene mutations. Am J Pathol 1993; 142: 1534-1543.

26) Corces MR, Granja JM, Shams S, Louie BH, Seoane PA, Zhou W, Silva TC, Groeneveld C, Wong CK, Cho SW, Satpathy AT, Mumbach MR, Hoadley KA, Robertson AG, Sheffield NC, Felau I, Castro MAA, Berman BP, Staudt LM, Zenklusen JC, Laird PW, Curtis C, The Cancer Genome Atlas Analysis Network, Greenleaf WJ, Chang HY. The chromatin accessibility landscape of primary human cancers. Science 2018; 362: eaaav1898.

27) Kadosh E, Snir-Alkalay I, Venkatachalam A, May S, Lasry A, Elyada E, Zinger A, Shaham M, Vaalani G, Mernberger M, Stiewe T, Pikarsky E, Oren M, Ben-Neriah Y. The gut microbiome switches mutant p53 from tumor-suppressive to oncogenic. Nature 2020; 586: 133-138.

28) Makohon-Moore A, Iacobuzio-Donahue CA. Pancreatic cancer biology and genetics from an evolutionary perspective. Nat Rev Cancer 2016; 16: 553-565.

29) Ahmed S, Bradshaw AD, Gera S, Dewan MZ, Xu R. The TGF-β/Smad4 signaling pathway in pancreatic carcinogenesis and its clinical significance. J Clin Med 2017; 6: 5.

30) Shen J, Peng Y, Wei L, Zhang W, Yang L, Lan L, Kapoor P, Ju Z, Mo Q, Shih IeM, Uray IP, Wu X, Brown PH, Shen X, Mills GB, Peng G. ARID1A deficiency impairs the DNA damage checkpoint and sensitizes cells to PARP inhibitors. Cancer Discov 2015; 5: 752-767.

31) Witkiewicz AK, McMillan EA, Balaji U, Baek G, Lin WC, Mansour J, Mollaee MK, 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.

32) Zhong L, Li Y, Xiong L, Xiong L, Wang W, Wu M, Yuan T, Yang W, Tian C, Miao Z, Wang T, Yang S. Small molecules in targeted cancer therapy: advances, challenges, and future perspectives. Sig Transduct Target Ther 2021; 6: 201.

33) Walter HS, Ahmed S. Targeted therapies in cancer. Surgery (Oxford) 2018; 36: 122-127.

34) Roskoski R, Jr. Properties of FDA-approved small molecule protein kinase inhibitors. Pharmacol Res 2019; 144: 19-50.

35) Li Y, Dong S, Tamaskar A, Wang H, Zhao J, Ma H, Zhao Y. Proteasome inhibitors diminish c-Met expression and induce cell death in non-small cell lung cancer cells. Oncol Res 2020; 28: 497-507. Epub 2020 Jun 24.

36) Lee HK, Park SH, Nam MJ. Proteasome inhibitor MG132 induces apoptosis in human osteosarcoma U2OS cells. Hum Exp Toxicol 2021; 18: 9603271211017972.

37) Yi M, Jiao D, Qin S, Chu Q, Wu K. Synergistic effect of immune checkpoint blockade and anti-angiogenesis in cancer treatment. Mol Cancer 2019; 18: 60.

38) Li Y, Seto E. HDACs and hdac inhibitors in cancer development and therapy. Cold Spring Harb Perspect Med 2016; 6: a026831.

39) Khera N, Rajput S. Therapeutic potential of small molecule inhibitors. J Cell Biochem 2017; 118: 959-961.

40) Kim S, Ding W, Zhang L, Tian W, Chen S. Clinical response to sunitinib as a multitargeted tyrosine-kinase inhibitor (TKI) in solid cancers: a review of clinical trials. Onco Targets Ther 2014; 7: 719-728.

41) Qin S, Li A, Yi M, Yu S, Zhang M, Wu K. Recent advances on anti-angiogenesis receptor tyrosine kinase inhibitors in cancer therapy. J Hematol Oncol 2019; 12: 27.

42) Tai CJ, Huang MT, Wu CH, Wang CK, Tai CJ, Chang CC, Hsieh CI, Chang YJ, Wu CJ, Kuo LJ, Wei PL, Chen RJ, Chiou HY. Combination of two targeted medications (bevacizumab plus cetuximab) improve the therapeutic response of pancreatic carcinoma. Medicine (Baltim) 2016; 95: e3259.

43) Forster T, Huettner FJ, Springfeld C, Loehr M, Kalkum E, Hackbusch M, Hackert T, Diener MK, Probst P. Cetuximab in pancreatic cancer therapy: a systematic review and meta-analysis. Oncology 2020; 98: 53-60.

44) Assenat E, Mineur L, Mollevi C, Lopez-Crapez E, Lombard-Bohas C, Samalin E, Portales F, Walter T, de Forges H, Dupuy M, Boissière-Michot F, Ho-Pun-Cheung A, Ychou M, Mazard T. Phase II study evaluating the association of gemcitabine, trastuzumab and erlotinib as first-line treatment in patients with metastatic pancreatic adenocarcinoma (GATE 1). Int J Cancer 2021; 148: 682-691.

45) Cai WQ, Zeng LS, Wang LF, Wang YY, Cheng JT, Zhang Y, Han ZW, Zhou Y, Huang SL, Wang XW, Peng XC, Xiang Y, Ma Z, Cui SZ, Xin HW. The latest battles between EGFR monoclonal antibodies and resistant tumor cells. Front Oncol 2020; 10: 1249.

46) Andrikou K, Peterle C, Pipitone S, Salati M, Cascinu S. Emerging antibodies for the treatment of pancreatic cancer. Expert Opin Emerg Drugs 2017; 22: 39-51.

47) Kaplon H, Reichert JM. Antibodies to watch in 2021. mAbs 2021; 13: 1860476.

48) Wang S, You L, Dai M, Zhao Y. Mucins in pancreatic cancer: a well-established but promising family for diagnosis, prognosis and therapy. J Cell Mol Med 2020; 24: 10279-10289.

49) Wu G, Maharjan S, Kim D, Kim JN, Park BK, Koh H, Moon K, Lee Y, Kwon HJ. A novel monoclonal antibody targets mucin1 and attenuates growth in pancreatic cancer model. Int J Mol Sci 2018; 19: 2004.

50) Suh H, Pillai K, Morris DL. Mucins in pancreatic cancer: biological role, implications in carcinogenesis and applications in diagnosis and therapy. Am J Cancer Res 2017; 7: 1372-1383.

51) Hong DS, Fakih MG, Strickler JH, Desai J, Durm GA, Shapiro GI, Falchook, GS, Price, TJ, Sacher, A, Denlinger, CS, Bang, YJ, Dy, GK, Krauss, JC, Kuboki, Y, Kuo, JC, Coveler, AL, Park, K, Kim, TW, Barlesi, F, Munster, PN, Ramalingam, SS, Burns, TF, Meric-Bernstam, F, Henary, H, Ngang, J, Ngarmchamnanrith, G, Kim, J, Houk, BE, Canon, J, Russell Lipford, J, Friberg, G, Lito, P, Govindan, R & Li, BT. KRAS(G12C) inhibition with sotorasib in advanced solid tumors. N Engl J Med 2020; 383: 1207-1217.

52) Xue JY, Zhao Y, Aronowitz J, Mai TT, Vides A, Qeriqi B, Kim D, Li C, de Stanchina E, Mazutis L, Risso D, Lito P. Rapid non-uniform adaptation to conformation specific KRAS(G12C) inhibition. Nature 2020; 577: 421-425.

53) Sakamoto K, Masutani T, Hirokawa T. Generation of KS-58 as the first K-Ras(G12D)-inhibitory peptide presenting anti-cancer activity in vivo. Sci Rep 2020; 10: 21671.

54) Merz V, Gaule M, Zecchetto C, Cavaliere A, Casalino S, Pesoni C, Contarelli S, Sabbadini F, Bertolini M, Mangiameli D, Milella M, Fedele V, Melisi D. Targeting KRAS: The Elephant in the Room of Epithelial Cancers. Front Oncol 2021; 11: 638360.

55) Gillson J, Ramaswamy Y, Singh G, Gorfe AA, Pavlakis N, Samra J, Mittal A, Sahni S. Small molecule KRAS inhibitors: The future for targeted pancreatic cancer therapy? Cancers 2020; 12: 1341.

56) 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.

57) Kawaguchi K, Igarashi K, Miyake K, Lwin TM, Miyake M, Kiyuna T, Hwang HK, Murakami T, Delong JC, Singh SR, Clary B, Bouvet M, Unno M, Hoffman RM. MEK inhibitor trametinib in combination with gemcitabine regresses a patient-derived orthotopic xenograft (PDOX) pancreatic cancer nude mouse model. Tissue Cell 2018; 52: 124-128.

58) O'Neil BH, Scott AJ, Ma WW, Cohen SJ, Aisner DL, Menter AR, Tejani MA, Cho JK, Granfortuna J, Coveler L, Olowokure OO, Baranda JC, Cusnir M, Phillip P, Boles J, Nazemzadeh R, Rarick M, Cohen DJ, Radford J, Fehrenbacher L, Bajaj R, Bathini V, Fanta P, Berlin J, McRee AJ, Maguire R, Wilhelm F, Maniar M, Jimeno A, Gomes CL, Messersmith WA. A phase II/III randomized study to compare the efficacy and safety of rigosertib plus gemcitabine versus gemcitabine alone in patients with previously untreated metastatic pancreatic cancer. Ann Oncol 2015; 26: 1923-1929.

59) Emmanouilidi A, Fyffe CA, Ferro R, Edling CE, Capone E, Sestito S, Rapposelli S, Lattanzio R, Iacobelli S, Sala G, Maffucci T, Falasca M. Preclinical validation of 3-phosphoinositide-dependent protein kinase 1 inhibition in pancreatic cancer. J Exp Clin Cancer Res 2019; 14; 38: 191.

60) Xu F, Na L, Li Y, Chen, L. Roles of the PI3K/AKT/mTOR signaling pathways in neurodegenerative diseases and tumors. Cell Biosci 2020; 10: 54.

61) Eser S, Reiff N, Messer M, Seidler B, Gottschalk K, Dobler M, Hieber M, Arbeiter A, Klein S, Kong B, Michalski CW, Schlitter AM, Esposito I, Kind AJ, Rad L, Schnieke AE, Baccarini M, Alessi DR, Rad R, Schmid RM, Schneider G, Saur D. Selective requirement of PI3K/PDK1 signaling for Kras oncogene-driven pancreatic cell plasticity and cancer. Cancer Cell 2013; 23: 406-420.

62) Payne SN, Maher ME, Tran NH, Van De Hey DR, Foley TM, Yueh AE, Leystra AA, Pasch CA, Jeffrey JJ, Clipson L, Matkowskyj KA, Deming DA. PIK3CA mutations can initiate pancreatic tumorigenesis and are targetable with PI3K inhibitors. Oncogenesis 2015; 4: e169.

63) Van Dort ME, Galbán S, Wang H, Sebolt-Leopold J, Whitehead C, Hong H, Rehemtulla A, Ross BD. Dual inhibition of allosteric mitogen-activated protein kinase (MEK) and phosphatidylinositol 3-kinase (PI3K) oncogenic targets with a bifunctional inhibitor. Bioorg Med Chem 2015; 23: 1386-1394.

64) Khan MA, Jain VK, Rizwanullah M, Ahmad J, Jain K. PI3K/AKT/mTOR pathway inhibitors in triple-negative breast cancer: a review on drug discovery and future challenges. Drug Discov Today 2019; 24: 2181-2191.

65) Li X, Xu H, Li C, Qiao G, Farooqi AA, Gedanken A, Liu X, Lin X. Zinc-doped copper oxide nanocomposites inhibit the growth of pancreatic cancer by inducing autophagy through AMPK/mTOR pathway. Front Pharmacol 2019: 10: 319.

66) Morran DC, Wu J, Jamieson NB, Mrowinska A, Kalna G, Karim SA, Au AY, Scarlett CJ, Chang DK, Pajak MZ; Australian Pancreatic Cancer Genome Initiative (APGI), Oien KA, McKay CJ, Carter CR, Gillen G, Champion S, Pimlott SL, Anderson KI, Evans TR, Grimmond SM, Biankin AV, Sansom OJ, Morton JP. Targeting mTOR dependency in pancreatic cancer. Gut 2014; 63: 1481-1489.

67) Karavasilis V, Samantas E, Koliou GA, Kalogera-Fountzila A, Pentheroudakis G, Varthalitis I,

Linardou H, Rallis G, Skondra M, Papadopoulos G, Papatsibas G, Sgouros J, Goudopoulou A, Kalogeras KT, Dervenis C, Pectasides D, Fountzilas G. Gemcitabine combined with the mTOR inhibitor temsirolimus in patients with locally advanced or metastatic pancreatic cancer. A Hellenic Cooperative Oncology Group Phase I/II Study. Target Oncol 2018; 13: 715-724.

68) Bever KM, Borazanci EH, Thompson EA, Durham JN, Pinero K, Jameson GS, Vrana A, Liu M, Wilt C, Wu AA, Fu W, Wang H, Yin Y, Leal JP, Jesus-Acosta A, Zheng, Laheru DA, Von Hoff DD, Jaffee EM, Powell JD, Le DT. An exploratory study of metformin with or without rapamycin as maintenance therapy after induction chemotherapy in patients with metastatic pancreatic adenocarcinoma. Oncotarget 2020; 11: 929-941.

69) Conway JRW, Warren SC, Herrmann D, Murphy KJ, Cazet AS, Vennin C, Shearer RF, Killen MJ, Magenau A, Mélénec P, Pinese M, Nobis M, Zaratzian A, Boulghourjian A, Da Silva AM, Del Monte-Nieto G, Adam ASA, Harvey RP, Haigh JJ, Wang Y, Croucher DR, Sansom OJ, Pajic M, Caldon CE, Morton JP, Timpson P. intravital imaging to monitor therapeutic response in moving hypoxic regions resistant to PI3K pathway targeting in pancreatic cancer. Cell Rep 2018; 23: 3312-3326.

70) Milošević Z, Banković J, Dinić J, Tsimplouli C, Sereti E, Dragoj M, Paunović V, Milovanović Z, Stepanović M, Tanić N, Dimas K, Pešić M. Potential of the dual mTOR kinase inhibitor AZD2014 to overcome paclitaxel resistance in anaplastic thyroid carcinoma. Cell Oncol (Dordr) 2018; 41: 409-426.

71) 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, 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.

72) Dziadkowiec KN, Gąsiorowska E, Nowak-Markwitz E, Jankowska A. PARP inhibitors: review of mechanisms of action and BRCA1/2 mutation targeting. Prz Menopauzalny 2016; 15: 215-219.

73) O'Reilly EM, Lee JW, Zalupski M, Capanu M, Park J, Golan T, Tahover E, Lowery MA, Chou JF, Sahai V, Brenner R, Kindler HL, Yu KH, Zervoudakis A, Vemuri S, Stadler ZK, Do RKG, Dhani N, Chen AP, Kelsen DP. Randomized, multicenter, phase II trial of Gemcitabine and Cisplatin with or without Veliparib in patients with pancreas adenocarcinoma and a germline BRCA/PALB2 Mutation. J Clin Oncol 2020; 38: 1378-1388.

74) Zhu H, Wei M, Xu J, Hua J, Liang C, Meng Q, Zhang Y, Liu J, Zhang B, Yu X, Shi S. PARP inhibitors in pancreatic cancer: molecular mechanisms and clinical applications. Mol Cancer 2020; 19: 49.

75) Sari IN, Phi LTH, Jun N, Wijaya YT, Lee S, Kwon HY. Hedgehog signaling in cancer: a prospective therapeutic target for eradicating cancer stem cells. Cells 2018; 7: 208.

76) Syed V. TGF-β Signaling in Cancer. J Cell Biochem 2016; 117: 1279-287.

77) Bulle A, Lim KH. Beyond just a tight fortress: contribution of stroma to epithelial-mesenchymal transition in pancreatic cancer. Signal Transduct Target Ther 2020; 30: 5: 249.

78) MF van Laarhoven HWM. Clinical trials targeting the stroma in pancreatic cancer: a systematic review and meta-analysis. van Mackelenbergh MG, Stroes CI, Spijker R, van Eijck CHJ, Wilmink JW, Bijlsma. Cancers (Basel) 2019; 11: 588.

79) Kota J, Hancock J, Kwon J, Korc M. Pancreatic cancer: Stroma and its current and emerging targeted therapies. Cancer Lett 2017; 391: 38-49.

80) Jin G, Hong W, Guo Y, Bai Y, Chen B. Molecular mechanism of pancreatic stellate cells activation in chronic pancreatitis and pancreatic cancer. J Cancer 2020; 11: 1505-1515.

81) Williams M, Lomberk G, Urrutia R. EGFR (ErbB) Signaling pathways in pancreatic cancer pathogenesis. In: Neoptolemos J, Urrutia R, Abbruzzese J, Büchler M, editors. Pancreatic Cancer. New York: Springer 2018; pp. 383-408.

82) Xiaojing Du, Biwei Yang, Quanlin An, Yehuda G. Assaraf, Xin Cao, Jinglin Xia. Acquired resistance to third-generation EGFR-TKIs and emerging next-generation EGFR inhibitors. Innovation (N Y) 2021; 2: 100103.

83) Tzavlaki K, Moustakas A. TGF-β Signaling. Biomolecules 2020; 10: 487.

84) Suzuki T, Dai P, Hatakeyama T, Harada Y, Tanaka H, Yoshimura N, Takamatsu T. TGF-β signaling regulates pancreatic β-cell proliferation through control of cell cycle regulator p27 expression. Acta Histochem Cytochem 2013; 46: 51-58.

85) Erdogan B, Webb DJ. Cancer-associated fibroblasts modulate growth factor signaling and extracellular matrix remodelling to regulate tumor metastasis. Biochem Soc Trans 2017; 45: 229-236.

86) Yingling JM, McMillen WT, Yan L, Huang H, Sawyer JS, Graff J, Clawson DK, Britt KS, Anderson BD, Beight DW, Desaiah D, Lahn MM, Benhadji KA, Lallena MJ, Holmgaard RB, Xu X, Zhang F, Manro JR, Iversen PW, Iyer CV, Brekken RA, Kalos MD, Driscoll KE. Preclinical assessment of

galunisertib (LY2157299 monohydrate), a first-in-class transforming growth factor-β receptor type I inhibitor. Oncotarget 2017; 9: 6659-6677.

87) Holmgaard RB, Schaer DA, Li Y, Castaneda SP, Murphy MY, Xu X, Inigo I, Dobkin J, Manro JR, Iversen PW, Surguladze D, Hall GE, Novosiadly RD, Benhadji KA, Plowman GD, Kalos M, Driscoll KE. Targeting the TGFβ pathway with galunisertib, a TGFβRI small molecule inhibitor, promotes anti-tumor immunity leading to durable, complete responses, as monotherapy and in combination with checkpoint blockade. J Immunother Cancer 2018; 6: 47.

88) Melisi D, Garcia-Carbonero R, Macarulla T, Pezet D, Deplanque G, Fuchs M, Trojan J, Oettle H, Kozloff M, Cleverly A, Smith C, Estrem ST, Gueorguieva I, Lahn MMF, Blunt A, Benhadji KA, Tabernero J. Galunisertib plus gemcitabine vs. gemcitabine for first-line treatment of patients with unresectable pancreatic cancer. Br J Cancer 2018; 119: 1208-1214.

89) Melisi D, Oh DY, Hollebecque A, Calvo E, Varghese A, Borazanci E, Macarulla T, Merz V, Zecchetto C, Zhao Y, Gueorguieva I, Man M, Gandhi L, Estrem ST, Benhadji KA, Lanasa MC, Avsar E, Guba SC, Garcia-Carbonero R. Safety and activity of the TGFβ receptor I kinase inhibitor galunisertib plus the anti-PD-L1 antibody durvalumab in metastatic pancreatic cancer. J Immunother Cancer 2021; 9: e002068.

90) Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. Nat Rev Clin Oncol 2018; 15: 731-747.

91) O'Reilly EM, Hechtman JF. Tumor response to TRK inhibition in a patient with pancreatic adenocarcinoma harbouring an NTRK gene fusion. Ann Oncol 2019; 30: viii36-viii40.

92) Robinson GW, Gajjar AJ, Gauvain KM, Basu EM, Macy ME, Maese LD, Sabnis AJ, Foster JH, Shusterman S, Yoon J, Weiss BD, Abdelbaki M, Farid-Kapadia M, Meneses-Lorente J, Cardenas A, Hutchinson K, Bergthold G, Maneval EC, Fox E, Desai AV. Phase 1/1B trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors. J Clin Oncol 2019; 37: 10009.