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Pancreatic cancer: analysis of disease and treatment options

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PANCREATIC CANCER:

ANALYSIS OF DISEASE AND TREATMENT OPTIONS

by

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ABSTRACT

Pancreatic cancer is a lethal disease with very poor prognosis as it is one of the leading causes of cancer related deaths worldwide. Pancreatic cancer may manifest in different ways and there are a number of different genetic mutations that can lead to carcinomas of the pancreas. This study reviewed some of the genetic alterations seen in pancreatic cancer and how they appear in the context of disease progression. While progress has been made in identifying genetic mutations that may contribute to pancreatic cancer, more work has to be done to solidify biomarkers and potentially contribute to early detection of the disease.

Pancreatic cancer is often asymptomatic until late stages of disease, which is why it is often diagnosed at such a progressed state. Late detection contributes to its poor prognosis as it unlikely to have curative potential at such a late stage. Approach to treatment generally depends on the stage at diagnosis. This study reviewed a number of different treatment options including surgical resection, chemotherapy, and targeted therapy. Surgical resection is currently considered the only cure for pancreatic cancer. The other treatment options may be helpful in reducing recurrence of cancer and/or increasing survival. Targeted therapy is a very recent approach that is currently used as a treatment to manage pancreatic cancer with fairly positive outcomes. Hopefully, with

further exploration into this individualized approach and modification of current targeted agents we are able to discover a cure for this devastating disease.

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LIST OF ABBREVIATIONS

CA 19-9 ..... cancer antigen 19-9

CEA ..... carcinoembryonic antigen

CT ..... computerized tomography

EGFR ..... epidermal growth factor receptor

EUS ..... endoscopic ultrasound

IPMN ..... intraductal papillary mucinous neoplasm

MCN ..... mucinous cystic neoplasm

MIC-1 ..... macrophage inhibitory cytokine-1

MRI ..... magnetic resonance imaging

NSCLC ..... non-small cell lung cancer

OPN ..... osteopontin

PaNET ..... pancreatic neuroendocrine tumor

PanIN ..... pancreatic intraepithelial neoplasia

PARP ..... poly-ADP ribose polymerase

PDAC ..... pancreatic ductal adenocarcinoma

PET ..... positron emission tomography

PHYSIOLOGY:

The pancreas is essential to human survival, as it is an organ that demonstrates both endocrine and exocrine function. Function depends on the different cell types that are found in the pancreas. The endocrine component is arranged into discrete Islets of Langerhans, which are surrounded by the exocrine cells[1].

The endocrine function of the pancreas works to regulate and maintain blood sugar levels. There are 5 different endocrine cells that are found in the islet of Langerhans. These cells are responsible for secreting the hormones that control blood sugar[2]. The two most important hormones in regulating blood sugar include insulin and glucagon. Insulin is secreted by the beta cells of the pancreas and decreases blood sugar levels by facilitating the uptake of glucose into the cell to be utilized for energy[3]. Glucagon is secreted by the alpha cells of the pancreas and works to increase blood sugar levels by increasing the processes of glucose metabolism. The other hormones of the pancreas include somatostatin, ghrelin, and pancreatic polypeptide. Somatostatin is an inhibitory hormone which prevents the release of insulin and glucagon[4]. Ghrelin is involved in orexigenic effect, control of energy expenditure, and peripheral gastroenteropancreatic actions[5]. Pancreatic Polypeptide works to suppress exocrine pancreatic secretions and can be considered a satiety hormone.

One of the major pathologies of the endocrine pancreas is Diabetes Mellitus. This is a chronic disease that occurs when the pancreas cannot produce insulin or cannot utilize insulin effectively. This leads to unregulated and high blood sugar levels which causes damage to the tissues of the body overtime. There are two common types of

diabetes mellitus. Type 1 diabetes is considered to be autoimmune, where the beta-cells of the pancreas are destroyed and therefore insulin cannot be produced sufficiently. Type 1 diabetes is present in about 5–10% of Diabetes Mellitus cases and generally has an earlier onset, being diagnosed in children, teens, and young adults[6]. Type 2 diabetes is commonly characterized by insulin resistance along with hyperglycemia and insulin deficiency. Consistently high levels of sugar in the blood lead to serious health problems that effect many other organs including the heart and kidneys. Type 2 diabetes accounts for a majority of diabetes mellitus cases and results from an interaction of genetic, environmental, and behavioral risk factors[7].

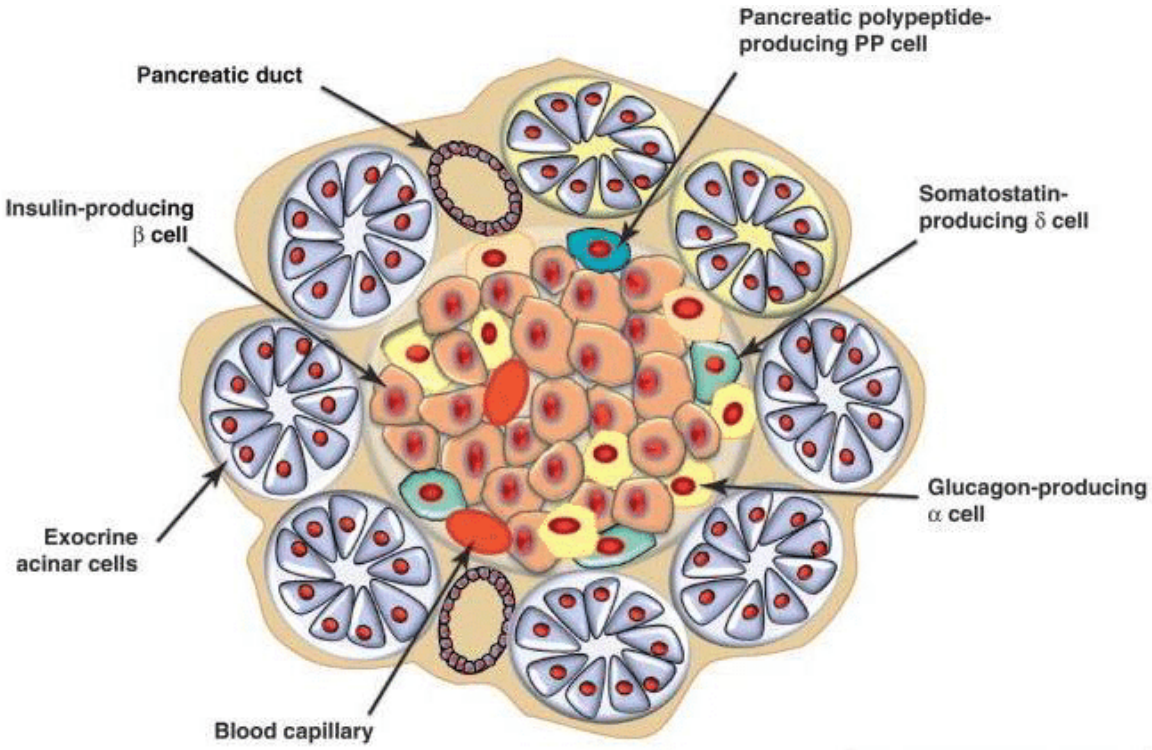
The exocrine function of the pancreas produces enzymes that are critical for digestion and also secretes bicarbonate-rich fluid that neutralizes gastric secretions in order to optimize pH levels for duodenal digestion[8]. The exocrine pancreas contains two major cell types: acinar cells and duct cells. The acinar cells are responsible for synthesizing, storing, and transporting digestive enzymes. These crucial enzymes include proteases, amylase, lipase, and nucleases. The duct cells are responsible for secreting bicarbonate and mucins which neutralize gastric secretions. They also form a network of tubules which are involved in delivering enzymes produced by the acinar cells to the duodenum. Interestingly, many tumor cells of pancreatic cancer share properties similar to the pancreatic ductal cells.

Pathologies of the exocrine pancreas can lead to insufficient breakdown and absorption of nutrients which can cause malnutrition. A major pathology of the exocrine pancreas is pancreatic ductal adenocarcinoma; the most common and fatal form of

pancreatic cancer. Additional pathologies of the pancreas include: acute pancreatitis, chronic pancreatitis, and cystic fibrosis; which all lead to an increased risk of pancreatic cancer. Cystic fibrosis can affect the pancreas by thickening pancreatic secretions and clogging the ducts of the pancreas, which can lead to significant pancreatic disease[9]. Acute pancreatitis is inflammation of the pancreas that lasts less than 3 weeks and is often caused by gallstones or alcohol abuse. Acute pancreatitis can lead to chronic pancreatitis[10]. Chronic pancreatitis is a progressive fibroinflammatory disease that can occur in the ducts of the pancreas. It can be caused by an interaction of environmental and genetic factors. It can also be hereditary or autoimmune. Pancreatitis can lead to scarring and permanent damage of the pancreas. This damage impairs pancreatic function and can also lead to diabetes and pancreatic cancer. Chronic pancreatitis increases the risk of pancreatic cancer by two to three times that of the general population[11].

Figure 1: Cells of The Pancreas[12]

This figure shows the different cells of the pancreas and an example of how they may be arranged. The endocrine cells produce insulin, glucagon, somatostatin, pancreatic polypeptide, and ghrelin (not shown). The exocrine cells are acinar and duct cells and they produce gastric secretions and enzymes for digestive processes.



EPIDEMIOLOGY:

Pancreatic cancer is a lethal disease with a poor prognosis as it is currently the fourth leading cause of death from cancer worldwide. It has a higher death rate in more developed countries and is the third most common cause of death from cancer in the United States[13]. It has a higher incidence in males than in females. Interestingly, pancreatic and kidney cancers are the only two cancers where white patients have lower survival rates than black patients[14]. The incidence of pancreatic cancer is increasing, which could be due to the fact that people are living longer, as pancreatic cancer rarely occurs before the age of 40 and mostly frequently occurs between the 6th and 8th decades of life[15]. Over 90% of individuals who develop pancreatic cancer die from the disease and the 5-year survival rate is one of the lowest of all cancers at just 9%[14].

The cause of pancreatic cancer is multifactorial, with family history and cigarette smoking being dominant. Individuals with a first-degree relative with pancreatic cancer are at a 2.3 fold increased risk of developing pancreatic cancer[16]. Other risk factors for pancreatic cancer include diabetes mellitus, obesity, alcohol abuse, dietary factors, chronic pancreatitis, and H. pylori infection[17]. There is currently no efficient screening procedure for pancreatic cancer and symptoms don't typically show up until the cancer is past the curative stage. Pancreatic cancer presents in the clinic most commonly as severe abdominal pain. Other common symptoms include jaundice, back pain, weight loss, diabetes mellitus, glucose intolerance, and acute pancreatitis.

There are two main types of pancreatic cancer: pancreatic adenocarcinoma and pancreatic neuroendocrine tumor (PaNET). PaNET occurs in the endocrine tissue of the

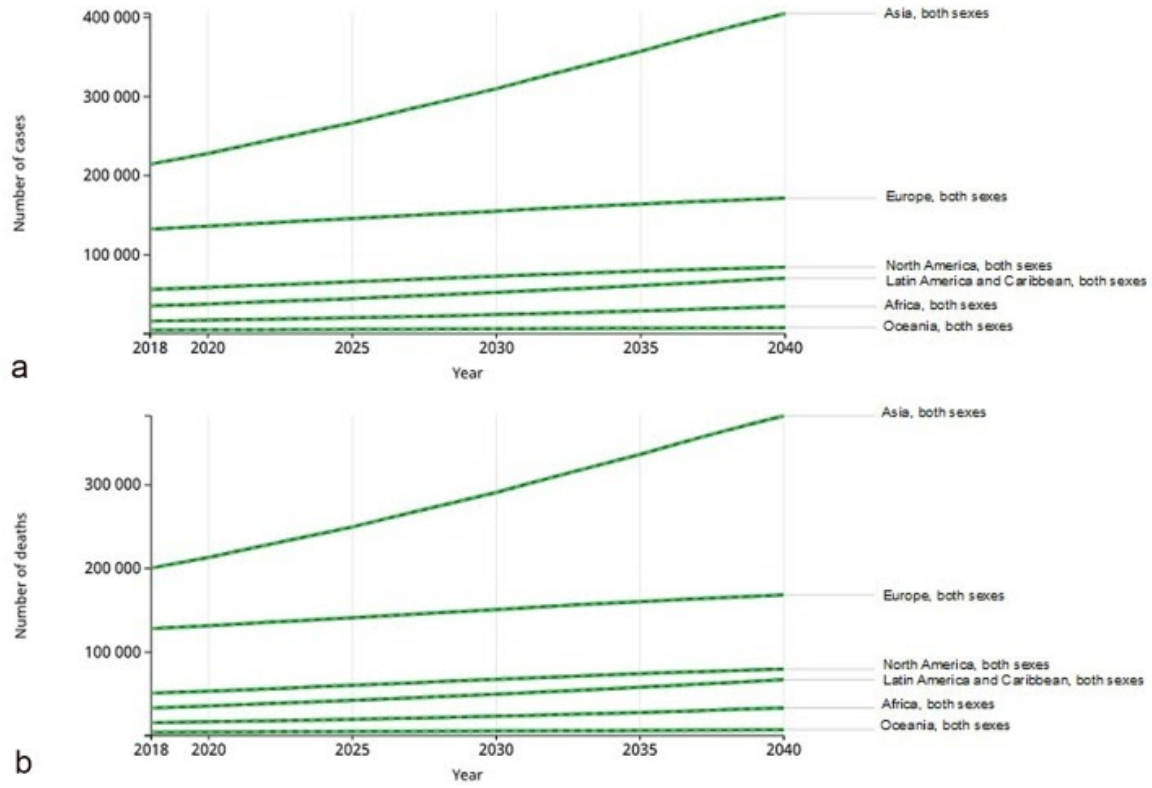
pancreas and is much less common, accounting for only about five percent of cases of pancreatic cancer[18]. Pancreatic adenocarcinoma, which arises from the exocrine function of the pancreas, is the most common type of pancreatic cancer. It accounts for about 85% of cases and has extremely poor prognosis with the 1-year survival rate after diagnosis being about 24%. Pancreatic adenocarcinoma has such poor prognosis in comparison to PaNET because it typically does not present until stage III or IV, at which point some cases are not even candidates for surgical treatment[19]. Diagnosis is often missed and pancreatic cancer is the most common tumor found during autopsies[20].

The therapies explored in this paper will focus on targeting pancreatic adenocarcinoma, as it is the most common and lethal form of pancreatic cancer. Advances in treatment for pancreatic cancer are challenging because of such late stage diagnosis. Temporal trends illustrate increases in both the incidence and mortality of pancreatic cancer from 2018-2040 (Figure 2).

Figure 2: Predicted Trends[13]

This figure represents a prediction of pancreatic cancer incidence and mortality for the years 2018 to 2040 for different continents. It is expected that incidence and mortality for pancreatic cancer will increase in almost every population.

Reproduced from http://globocan.iarc.fr/



GENETICS:

Pancreatic cancer demonstrates both inherited (germ line) mutations and somatic gene mutations. Genetic mutations found in pancreatic cancer are commonly found in other types of cancers, including breast, lung, and colon cancers. Determining which genetic mutation(s) are present in a case of pancreatic cancer can help guide treatment options, specifically targeted therapies.

About 3% to 7% of individuals who present with pancreatic ductal adenocarcinoma, harbor a mutation in BRCA1 or BRCA2[21]. These are pathogenic germline alterations that can increase an individual's risk of developing pancreatic cancer. Specifically, BRCA2 is found in about 7.3% of familial pancreatic cancer patients and can increase risk of pancreatic cancer up to 20-fold. BRCA2 is a tumor suppressor gene that is also involved in repairing double strand breaks of DNA during the cell cycle. BRCA2 has additional roles in cytokinesis, centrosome duplication, and cell death[22]. BRCA2 has been found in breast, ovarian and prostate cancers. BRCA2 mutations are particularly sensitive to therapies that include radiation and Mitomycin C, as these produce double strand breaks and DNA cross-linking[23]. The use of poly-ADP ribose polymerase (PARP) inhibitors is currently being explored as an option of treatment in patients with pancreatic cancer who harbor mutations in the BRCA1 and BRCA2 genes.

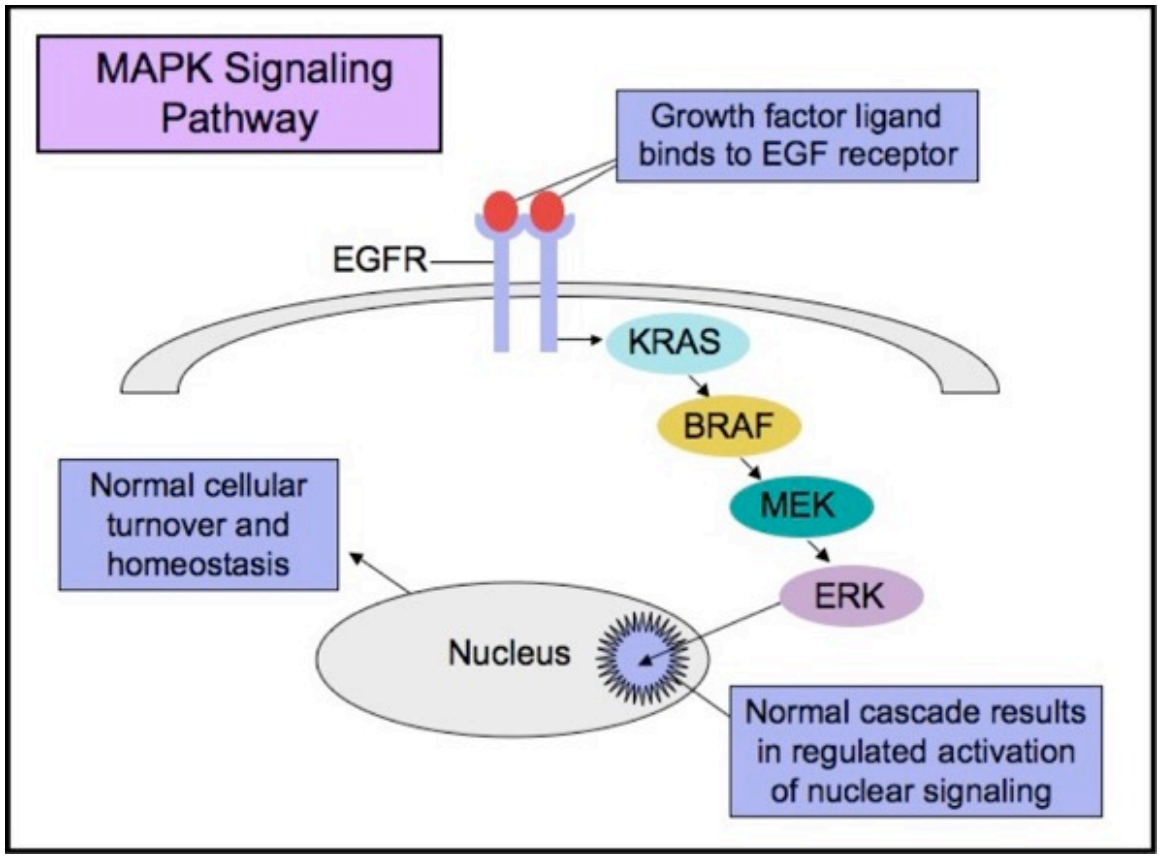
Potentially the most common mutation present in patients with pancreatic ductal adenocarcinoma (PDAC) is the KRAS2 oncogene. This is an activating mutation that is found in approximately 90-95% of pancreatic cancer cases[23]. KRAS is a GTPase that is part of the RAS/MAPK signaling pathway. When it is bound to GTP it is able to bind and

activate RAF family kinases. This can lead to regulation of transcription factors and signal for cell growth and proliferation. When KRAS is mutated, it can cause constitutive activation and lead to uncontrolled cell proliferation which leads to the development of cancer[24].

A high frequency of KRAS2 mutations are also found in pancreatic intraepithelial neoplasias (PanINs), which are precursor lesions of pancreatic cancer[23]. This supports the mutation of KRAS2's role as an initiating event in pancreatic cancer. In addition, constitutive RAS signaling allows the maintenance of pancreatic cancer. Current therapies aimed at targeting this pathway include EGFR inhibitors. The epidermal growth factor receptor (EGFR), is a transmembrane receptor that is involved in initiating the MAPK pathway (Figure 3).

<u>Figure 3:</u> MAPK Signaling Pathway[25]

This figure demonstrates the MAPK signaling pathway. The MAPK signaling pathway mediates extracellular signals to produce a cascade that reaches the nucleus and elicits a response. The signal is communicated from the receptor on the cell surface. This pathway plays a role in cell turnover, proliferation differentiation, survival, and apoptosis.



KRAS2 is generally found in combination with an accumulation of other mutations. These include inactivating mutations in tumor suppressor genes p16/CDK2NA, TP53, and SMAD4/DPC. The gene p16/CDKN2A is a cyclin dependent kinase inhibitor that keeps cell division in check by slowing the progression of the cell cycle from the G1 phase to the S phase[26]. The loss of function of the p16/CDKN2A is

present in about 90% of pancreatic cancer cases[23]. TP53 is a protein with various roles including controlling the checkpoints of the cell cycle, activating DNA repair, and regulating apoptosis. When TP53 loses its function, cells are able to survive and proliferate regardless of damage to its DNA. This leads to an accumulation of damage and an increase of mutations. Inactivation of TP53 is common to many cancers and is seen in approximately 50-75% of cases of pancreatic cancer[27]. SMAD4/DPC is a protein that mediates the transforming growth factor- beta (TGF-B) pathway. It plays significant roles in inhibiting cell growth and regulating apoptosis[28]. SMAD4 is inactivated in about 55% of cases of pancreatic cancer[23].

Additional mutations that can be common to cases of pancreatic cancer are mutations in the hMLH1 and hMSH2 genes[23]. These mutations cause microsatellite instability and lead to defects in DNA mismatch repair[29]. Individuals with these germline mutations can be at an increased risk for pancreatic cancer as well as an elevated risk for earlier onset of pancreatic cancer[30]. Tumors involving these mutations appear to have very distinct histologies and growth patterns.

DISEASE PROGRESSION:

While early detection of PDAC has been quite challenging, there are precursor lesions that can be identified. Some of the common precursor lesions include pancreatic intraepithelial neoplasias (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs)[31]. PanINs are microscopic and the most prevalent precursor lesions found in PDAC. While IPMNs and MCNS are macroscopic and can be detected using radiation[31].

MCNs are lined by mucin-producing epithelial cells. They generally occur in the body or tail of the pancreas and are not connected to the pancreatic ductal system. MCNs are particularly found in women and up to 16% are found in association with invasive carcinomas[31]. MCNs are much less likely than the other precursor lesions to progress to cancer.

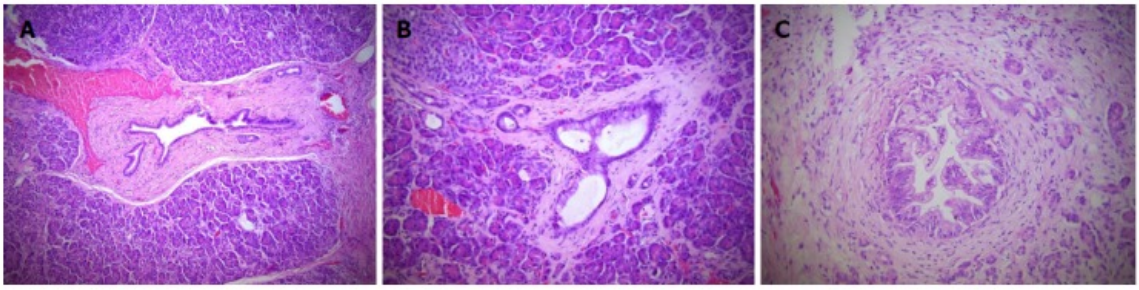
IPMNs are papillary structures that project into the main pancreatic duct. These are generally mucinous tumors found in the head of the pancreas. These lesions are found in up to 40% of cases and occur equally in both men and women. As IPMNs progress they accumulate more genetic abnormalities and exhibit a higher degree of dysplasia[32].

The most common precursor lesions, PanINs, can be found anywhere in the pancreas and have a combination of flat and papillary structures as part of their histology. There are 3 stages of PanINs that progress to metastatic carcinomas. PanIN-1 is classified as a low grade lesion and contains mutations in the KRAS2 gene[23]. This further supports the role of the KRAS2 gene mutations as an initiating event in the formation of pancreatic cancer. PanIN-1 lesions may also contain telomere shortening which enable

more chromosomal abnormalities to accumulate. These lesions can progress to intermediate PanIN-2 lesions which contain inactivating mutations of the p16/CDKN2A genes. This can further progress to more advanced Pan-IN-3 lesions with inactivating mutations in TP53, SMAD4, and BRCA2 genes[23]. The accumulation of these mutations along with the histological progression of the lesions can lead to the initiation and maintenance of PDAC. While these lesions are microscopic, being able to identify them could have significance in detecting pancreatic cancer in its early stages and be fundamental in developing a method for screening. It has also been estimated that it could take up to 12 years for PanIn-3 lesions to transform into pancreatic cancer[33]. This further illustrates the impact a screening protocol can achieve as this is a moderate window for early detection.

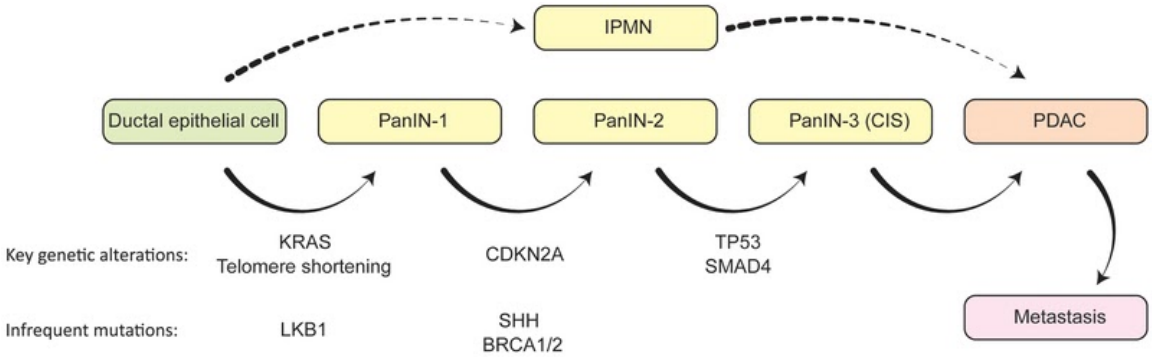
Figure 4: Histology of PanIN lesions[34]

This figure shows the pathogenesis of pancreatic lesions by histological characteristics. (A) represents a normal duct. (B) represents a low grade pancreatic intraepithelial neoplasia (PanIN). (C) represents a high grade PanIN.



<u>Figure 5:</u> Disease Progression Model of Pancreatic Cancer[24]

This figure illustrates the accumulation of genetic mutations and how they are associated with the progression of precursor lesions. As the number of mutations increase, the disease progresses and the prognosis with each stage becomes worse.



DIAGNOSIS

Pancreatic cancer is often not diagnosed until it is in its late stages. This has contributed to the challenge of successful treatment. Early detection has proved difficult because the pancreas is not palpable and there is a lack of identifiable biomarkers. Additionally, pancreatic cancer is often asymptomatic until a very advanced stage. Symptoms can also vary based on the location of the tumor. A tumor in the head of the pancreas can cause a blockage of the common bile duct and lead to symptoms including: weight loss, jaundice, nausea, vomiting, dark urine, and light colored stools[34]. A tumor in the body or tail of the pancreas produces severe abdominal pain that radiates to the back or down the sides of the body.

A biomarker that has been routinely used for the management of pancreatic cancer is serum cancer antigen 19-9 (CA 19-9)[35]. This is an antigen that is released by cancer cells of the pancreas and it thus considered a tumor marker. High levels of CA 19-9 have been found in individuals who have already been diagnosed with pancreatic cancer. However, it appears to have a low positive predictive value in asymptomatic individuals and therefore its ability to screen in an asymptomatic population cannot be determined effective. Due to this, CA 19-9 is more commonly used to monitor cancer progression and tumor response to therapy[36]. While CA 19-9 is the only tumor marker that is FDA approved for the management of pancreatic cancer, others are currently being explored including: carcinoembryonic antigen (CEA), osteopontin (OPN), and macrophage inhibitory cytokine 1 (MIC-1)[35]. With more research, these markers have the potential to be used for the early detection of pancreatic cancer in the future.

Reliable imaging techniques are important in order to detect and stage pancreatic cancer accurately. Some imaging techniques that are currently used are abdominal ultrasound, computerized tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and endoscopic ultrasound (EUS)[37]. CT is the most used imaging technique as it is the most available relative to EUS and MRI. CT demonstrates good sensitivity and specificity for tumors greater than 2cm in size[38]. This limits its effectiveness for early detection of PDAC. MRI may exhibit more accuracy in evaluating smaller tumors but it's use is limited by its higher cost. Furthermore, EUS has demonstrated the most effective technique for diagnosing and staging pancreatic cancer as it is able to identify lesions as small as 2-5mm. It exhibits an accuracy of over 90%. EUS has a significant role in staging the tumor prior to operation and determining the possible resectability[37]. EUS is also unique from other imaging techniques as it provides an opportunity to obtain a cytological sample and analyze the tumor tissue.

STAGING:

Identifying the stage of pancreatic cancer can guide an individual in choosing a treatment approach. The stage of pancreatic cancer is generally determined using the tumor-node-metastasis (TNM) classification system. The size, dimensions, and extension of the primary tumor are classified by (T) and range from TX to T4[39]. TX represents a stage where no primary tumor can be assessed. T4 represents an unresectable tumor that is greater than 2cm in size and involves major blood vessels[40]. The nodal classification ranges from NX to N1 and assesses whether or not the cancer has spread to regional lymph nodes. The metastatic classification ranges from M0 to M1 and indicates whether or not the tumor has spread to other organs. Pancreatic cancer most commonly metastasized to the liver but also commonly spreads to the lungs, bones, and brain[41].

Stage I is confined to the pancreas with no spread to lymph nodes or other organs and is generally a small primary tumor. Stage II involves the growth of the primary tumor into nearby tissues but does not demonstrate any metastasis. Stage I and Stage II are usually resectable and have a better prognosis[34]. Stage III tumors are greater than 2cm in size and have spread to nearby lymph nodes with the propensity to spread to distant organs. Stage IV tumors involve some growth into other organs and possible metastasis into other organs as well. Stage III and Stage IV can present as borderline resectable or unresectable tumors and radiation or chemotherapy are considered at these stages.

Table 1: TNM Classification for Pancreatic Cancer[40]

This table illustrates how pancreatic cancer is classified in terms of the primary tumor, lymph nodes, and metastasis. These classifications are further used to determine the stage of pancreatic cancer.

Table 1. TNM Classification for Pancreatic Cancer[a]

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery; unresectable primary tumor
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Note. Adapted from National Cancer Institute (2014).
[a]American Joint Committee on Cancer staging system.

Table 2: Staging of Cancer[34]

This table represents how TNM categorization would be used to evaluate the stage of cancer. Identifying the stage can help to guide treatment approach.

UICC DISEASE STAGE	T staging	N staging	M staging
STAGE 0	Tis	N0	M0
STAGE IA	T1	N0	M0
STAGE IB	T2	N0	M0
STAGE IIA	T3	N0	M0
STAGE IIB	T1–3	N1	M0
STAGE III	T4	Any N	M0
STAGE IV	Any T	Any N	M1

TREATMENT

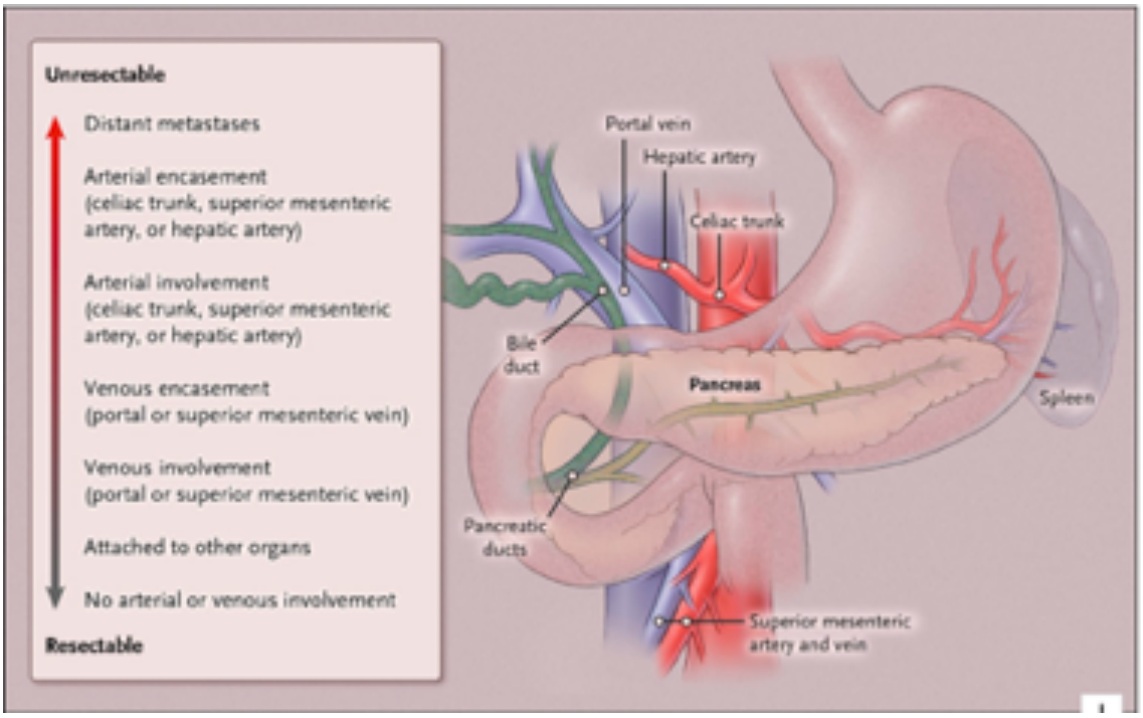
Despite various treatment options for the management of pancreatic cancer, prognosis and survival of the disease still remains quite poor. Current treatment options for pancreatic cancer include: surgical resection, radiation therapy, chemotherapy, targeted therapy, and immunotherapy. Approaches to treatment are dependent on where the tumor is located and what stage the cancer presents as in the patient. While surgical resection is currently considered the only cure for pancreatic cancer, it can be used in combination with previous or subsequent use of chemotherapy[42]. Targeted therapies, such as the use of EGFR inhibitors and PARP inhibitors, are currently being explored and becoming more common in the management of pancreatic cancer. While these have not exhibited the ability to cure pancreatic cancer, they have demonstrated an increase in survival span. With further study and fine-tuning, these therapies may have the capacity to cure pancreatic cancer and become the standard of care in the future.

SURGICAL RESECTION

While surgical resection is considered the only possible cure for pancreatic cancer, it still has poor prognosis and survival. Only about 20% of PDAC cases are able to be operated on[34]. This is generally because at the time of diagnosis the cancer has already spread to distant sites and thus it is not advised to operate. Surgical resectability depends on the tumor size, location and stage.

<u>Figure 6:</u> Anatomy and Surgical Resectability of Pancreatic Cancer[15]

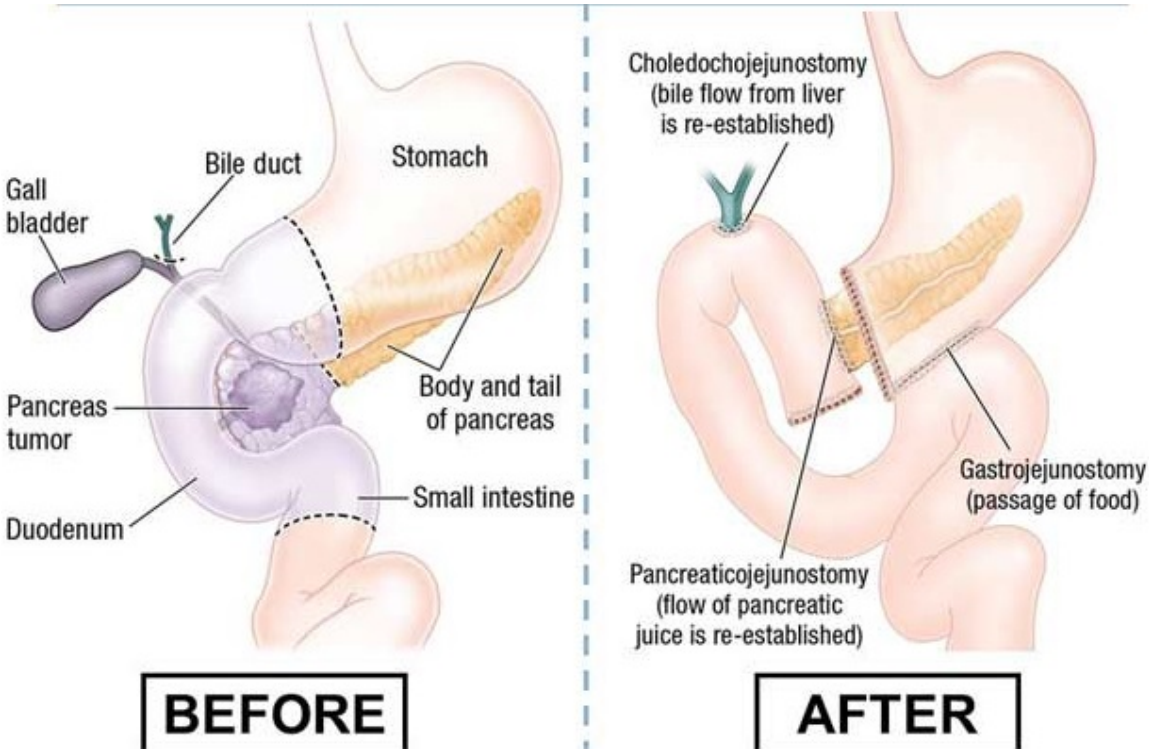
This figure shows the anatomy of the pancreas as well as the structures associated with it. Pancreatic cancers are categorized on a continuum from resectable to unresectable depending on the involvement of adjacent structures and metastases.



About 98% of tumors that arise in the area of the pancreas are malignant and have the potential to metastasize. Of these tumors, about 65% are found in the area around the head or neck of the pancreas[43]. These cancers may be subject to surgical resection by a pancreaticoduodenectomy, also known as the Whipple procedure. However, the tumor is less likely to be resected if it has involvement with major arteries, including the celiac trunk, superior mesenteric artery, and the hepatic artery[15]. The Whipple procedure is a complex surgery that removes the head of the pancreas, the curve of the duodenum, the gallbladder, and the common bile duct. The biliary system and digestive tract are then reconnected so that the digestive process is still able to occur (Figure 7).

<u>Figure 7</u>: The Whipple Procedure

The illustration represents the pancreas before and after the Whipple procedure. This procedure is used when a tumor is able to undergo surgery for resection and is located near the head of the pancreas.



Around 15–20% of the tumors are found at the tail of the pancreas and are subject to surgical procedure by distal pancreatectomy[3]. These procedures are also limited if the tumor involves major arteries. A distal pancreatectomy removes the body and tail of the pancreas along with the spleen[44]. This resection tends to be more uncommon than the Whipple procedure because tumors located in the body or tail of the pancreas usually present at a later stage with a bigger tumor with respect to carcinomas found in the head of the pancreas. Due to this late stage diagnosis, resection is generally not recommended as a treatment option.

And in some cases, if the cancer has spread or occurring in multiple parts of the pancreas, a total pancreatectomy can be done. This usually consists of removal of the entire pancreas, the common bile duct, a portion of the abdomen, a portion of the small intestine, the gallbladder, and the spleen. This is the rarest pancreatic resection surgery. It is followed by endocrine and exocrine insufficiency and it has the highest mortality rate of all pancreatic surgeries[45].

Surgical resection of the pancreas has made many advancements over time and the morbidity and mortality from the surgical procedure itself has decreased drastically as it is now quite low[46]. However, survival after surgical resection is still not very promising with very low 5-year survival rates. In one study done, median survival following pancreatic resection was about 27 months. Survival time after resection is associated with the stage of pancreatic cancer. Factors that lead to favorable prognosis include: absence of lymph node metastasis, absence of portal vein invasion, absence of extra neural pancreatic invasion, and tumor sizes less than 20mm[47].

Despite the idea that surgical resection is the only cure for PDAC, it is realistically not a cure for many patients. Even with the curative surgery, most patients experience a recurrence of cancer and metastasis which leads to fatality. And thus surgery may not be a cure but an option to increase survival time.

SURGICAL RESECTION WITH COMBINATION THERAPY:

The goal of a resection is to completely excise the primary tumor as well as any nearby lymph nodes that could contain remnants of metastasis. Pancreatic cancers that are resectable or borderline resectable can be used in combination with therapies in an

effort to decrease the chances of recurrence and metastasis and thus increase the length of survival. This could include therapeutic treatment before and/or after surgery. Overall, using multiple forms of therapy has demonstrated an improved rate of survival in patients who present with operable PDAC[48].

Therapies used prior to surgery, neoadjuvant therapies, are used in an effort to shrink a tumor. This would help to increase the chances of completely excising a tumor with clear margins during resection. The methods used include chemotherapy and radiation therapy[49]. Treatment is generally a short time period of about 2-3 months of chemotherapy before surgical resection. This time period enables the opportunity to explore the cytology of the tumor. This can help assess if targeted therapy would be beneficial as a treatment approach. Neoadjuvant therapy may also eliminate micro metastases which were not detected by imaging[49]. Targeting these micro metastases early on can decrease their propensity to spread further and cause fatality.

If a tumor is borderline resectable, neoadjuvant therapy may also be considered as a treatment option as shrinking the tumor and sharpening the margins may transition a tumor to a more resectable categorization. However, there is approximately a 20% chance that a tumor will progress and become unresectable in the neoadjuvant therapy period[49]. Therefore, it is important to evaluate if a tumor is rapidly progressing or has already metastasized. In these cases, neoadjuvant therapies are not viable options.

While the neoadjuvant therapy approach has exhibited survival success in other gastrointestinal cancers, it is still at the experimental phase for pancreatic cancer. Neoadjuvant therapy has shown beneficial effects on the T stage, lymph nodes, and

resectable margins. In one clinical trial done with neoadjuvant chemoradiation therapy, the median survival following resection was 34 months and 5-year survival with complete absence of disease occurrence was approximately 33%[50]. This is a promising approach as life expectancy without neoadjuvant therapy is about 26.7 months. Neoadjuvant therapy has also been associated with a higher quality of life expectancy[51].

The current standard of care for resectable PDAC is surgical resection followed by adjuvant therapy. This approach relies on excising the tumor and then using chemotherapy to suppress the growth of any secondary tumors or metastases. Adjuvant therapy is typically given for about 6 months and begins about 8–12 weeks after resection depending on the health of the patient post-surgery[52]. Adjuvant therapy has demonstrated an improvement in 5-year survival to 20–25% and has shown an increase in the disease-free survival period[52].

Chemotherapy drugs that have been approved by the US Food and Drug Administration and are commonly used for the treatment of PDAC are Gemcitabine, Capecitabine, Fluorouracil, Paxlitexil, and Oxaliplatin[34]. These drugs can be used individually or in combination with each other. These are given either intravenously or orally. They are generally given in 2 to 3-week cycles for 3–6 months. Chemotherapy is generally more effective when drugs are used in combination. However, for those who are not healthy enough for combination therapy, single agents are used for management of PDAC.

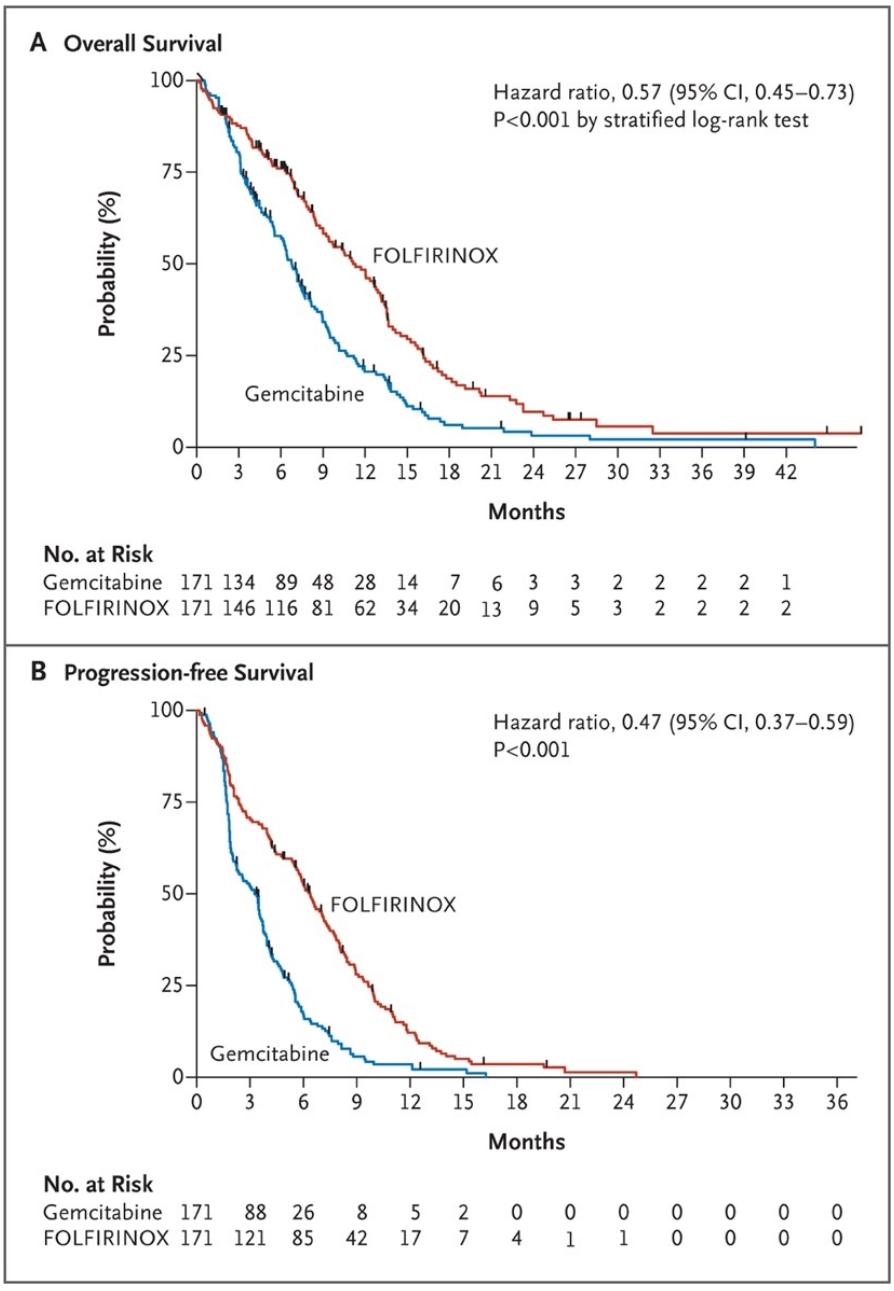
Gemcitabine (Gemzar) has been considered the standard of care for advanced pancreatic cancer since 1997[53]. This is a pyrimidine analog that interferes throughout the

process of DNA replication and works to arrest the cell cycle[24]. It can be used as adjuvant therapy after resectional surgery or for cases that are unresectable. In patients who are healthy enough to tolerate combination therapy, gemcitabine is used with other agents including nab-paclitaxel, oxaliplatin, and capecitabine[54]. Combining with these agents, enhances the sensitivity of germatacibe. In comparison to monotherapy of gemcitabine, combination therapy has consistently displayed an increase in median overall survival when used in cases of resectable pancreatic cancer[42].

FOLFIRINOX, a consolidation of multiple agents, is another standard chemotherapy treatment option. FOLFIRINOX consists of fluorouracil, leucovorin, irinotecan, and oxaliplatin[55]. These work to interfere with the processes of DNA replication and transcription[24]. FOLFIRINOX has shown an overall increase in survival and efficacy in studies where it is compared to gemcitabine nab-paclitaxel. However, this increase in overall survival has come at the expense of higher toxicity and greater experience of side effects. Due to the severe side effects that can impede on quality of life, use of FOLFIRINOX should be approached with caution and only recommended in patients with carcinomas with good performance[55].

<u>Figure 8:</u> FOLFIRINOX vs. Gemcitabine[56]

This figure shows a Kaplan-Meier curve that estimates overall survival and progression-free survival in two different treatment groups. There is significance when FOLFIRINOX is used in comparison to when gemcitabine is used alone. A shows overall survival; the median was 11.1 months in the group receiving FOLFIRINOX (oxaliplatin, irinotecan, fluorouracil, and leucovorin). Panel B shows progression-free survival; the median was 6.4 months in the FOLFIRINOX group and 3.3 months in the gemcitabine group.



While chemotherapy is used in the treatment of pancreatic cancer, it is often not successful. There are frequently dense desmoplastic reactions associated with the disease and pancreatic tumors are surrounded by dense, fibrous tissue growth. This growth can make it resistant to chemotherapy[34]. The first line of treatment for patients who present with advanced pancreatic cancer is combination chemotherapy drugs described above, FOLFIRINOX and gemcitabine/nab-paclitaxel. If a patient is not healthy enough to tolerate the above combination treatments, gemcitabine alone can be used[57]. A limiting factor in the use of stronger combination chemotherapy agents could be age, as some patients who are above the age of 75 could be deemed not fit enough for the side effects that can be endured by these agents.

If the disease progresses to a worse state or severe side effects are experienced by the first-line treatment options, second-line treatment options may be attempted. If FOLFIRINOX has been tried, a treatment option containing gemcitabine either in combination or alone should be attempted. However, FOLFIRINOX is only recommended after gemcitabine combination therapy if a patient is suspected to be healthy enough to tolerate it because it is a more aggressive treatment with more severe side effects. If FOLFIRINOX and gemcitabine/nab-paxlitaxel have already been tried, the next options considered can be fluorouracil (5-FU) and leucovorin in combination with other agents. If a case is not suitable to receive multiple agents, then capecitabine may be used alone. Currently, 5-FU/liposomal irinotecan has demonstrated the strongest level of evidence for second-line treatment[57].

If multiple lines of therapy have been exhausted and a case does not seem to

respond successfully, recovery from pancreatic cancer may be unlikely. If this is the case, palliative care may be the next step considered. The goal of palliative care is to manage symptoms and pain towards the end of life for patients. Cases with a higher intensity of pancreatic cancer receive less aggressive treatment in the last days of life. Some palliative care options for advanced pancreatic cancer patients include surgical palliation, radiation therapy, anesthetics, and chemotherapy for pain management[58].

TARGETED THERAPY:

Targeted therapy is a form of treatment that works by targeting specific genes, proteins, and tissues that contribute to the growth and maintenance of cancer cells. The drugs utilized in targeted therapy are unique because they aim to identify and attack specific cancer cells while minimizing the harm to normal healthy cells. This is different from chemotherapy alone which aims to block all rapidly dividing cells instead of interfering with molecules associated with carcinogenesis and tumor. Targeted therapy is suspected to be more effective and less harmful than chemotherapy. Targeted therapy can be used alone or in association with chemotherapy for the treatment of pancreatic cancer[59].

Targeted therapy is at the core of precision medicine, which strives to optimize efficiency of therapy options for a patient by tailoring treatment based on genetic or molecular profiling of each individual. The goal of this is to identify which molecular markers are present and then assess which treatment a patient would benefit from most[59]. This enables better efficacy and less toxicity of the drug to the patient. This relies on successfully identifying which cells and receptors should be targeted during therapeutic treatment.

There are two categories of targeted therapy: small molecule drugs and monoclonal antibodies. Small molecule drugs work by penetrating the cell membrane and interfering with signaling pathways and target proteins inside the cells. Monoclonal antibodies are not able to penetrate the cell membrane and they work by binding to

cancer cell-specific antigens found on the outside of the cell[59]. The current forms of targeted therapy that have been approved by the FDA for the treatment of pancreatic cancer are in the small molecule drug category. These two approved therapies are Erlotinib and Olaparib, which will be discussed below.

ERLOTINIB:

Erlotinib (Tarceva) is a small molecule drug that is a selective EGFR tyrosine kinase inhibitor. It works by reversibly binding to the adenosine triphosphate (ATP) binding site on the intracellular domain of the EGFR[60]. By doing so it blocks the phosphorylation and initiation of the cascade of transduction signals inside the cell. It can specifically interfere with the MAPK and RAS signaling pathways[61]. These pathways have key functions in the regulation of cell processes including proliferation, apoptosis, and angiogenesis. When Erlotinib is able to successfully block these processes it limits the growth, survival, and metastasis of tumors.

When EGFR is mutated it causes a constitutive, growth-factor independent activation of the downstream pathway that is found in malignant diseases. Deregulation of activity can be a result of EGFR gene mutation as well as an increase in the copies of this gene and EGFR protein overexpression[61]. Erlotinib is used in the treatment of cancers that demonstrate deregulation in EGFR processes. Mutations in EGFR and KRAS are considered predictive biomarkers for the use of Erlotinib[60]. Pathways that overexpress these mutations are commonly found in pancreatic cancers. Erlotinib is currently approved as an orally active agent by the FDA for the treatment of non-small

cell lung cancer (NSCLC) and pancreatic cancer. Erlotinib has shown impressive response rates in NSCLC cases and has shown higher success rates than cytotoxic chemotherapy. While Erlotinib has shown a statistical significance in the increase of survival of individuals with pancreatic cancer, it requires further modification to demonstrate as successful of a response relative to NSCLC cases.

Erlotinib is approved for the treatment of metastatic NSCLC tumors that exhibit deletion or substitution mutations in EGFR. It was FDA approved in 2013 as first-line treatment for metastatic NSCLC with these specific mutations after comparing targeted therapy, Erlotinib, to the standard chemotherapy treatment[62]. Similar to pancreatic cancer, the majority of patients with NSCLC present at the time of diagnosis in the advanced stages of III and IV. The predicted median survival of these patients is approximately three to six months. Using the standard chemotherapy treatment, there is about a 30% response rate to treatment and only about a 10-month median survival[63].

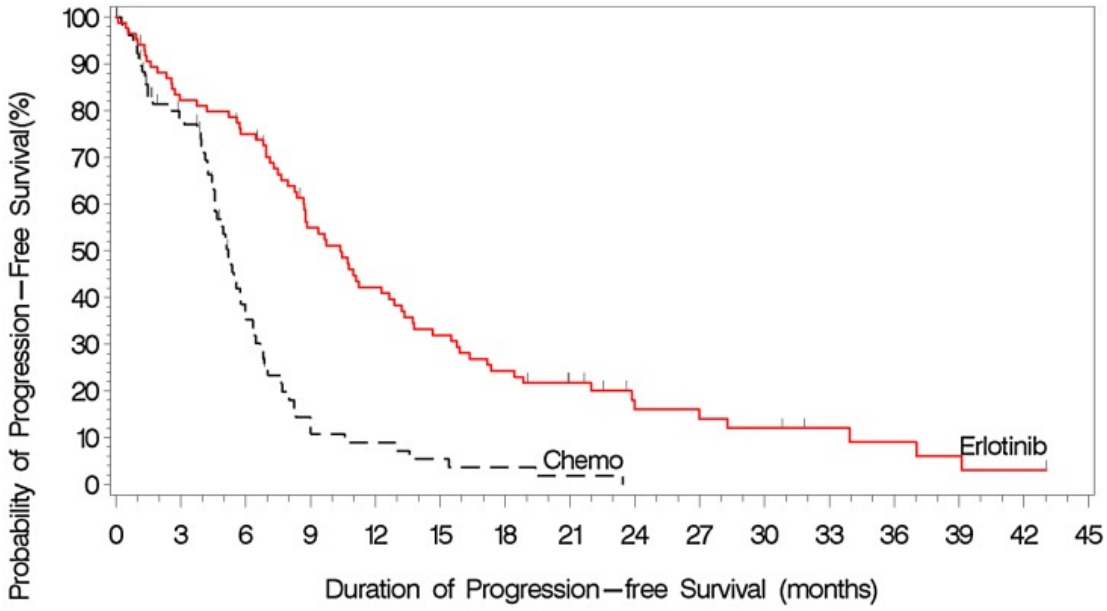
The "European Tarceva versus Chemotherapy" (EURTAC) was the trial reviewed by the FDA that led to the approval of Erlotinib as first-line treatment for NSCLC in the United States. This was a randomized trial in patients with NSCLC who harbored EGFR mutations and were divided into groups given treatment of either chemotherapy or Erlotinib. The chemotherapy used was standard for patients with NSCLC who have EGFR mutations, which is platinum-based doublet chemotherapy[64]. Patients were genotyped prior to receiving treatment therapy and only patients with EGFR exon 19 deletions or exon 21 substitution mutations were included in the trial[65]. Patients also had

to exhibit suitable performance for treatment and the absence of use of any prior therapies. Prior to this study, erlotinib was only approved by the FDA as a treatment option for patients with locally or advanced metastatic NSCLC who had already tried at least one other first-line chemotherapy treatment[66]. Approval was based on progression-free survival, response rate, and toxicity.

The results found in EURTAC showed a significant response rate to the use of Erlotinib in relative to chemotherapy. The median progression-free survival was 10.4 months in patients who received treatment with erlotinib and 5.2 months in patients who received treatment with chemotherapy. The median overall survival was not shown to be statistically significant though as it was 22.9 months in the erlotinib group and 19.5 months in the chemotherapy group[62]. The objective response rate, which demonstrates a shrinkage in tumor size, was 65% in the erlotinib group and 16% in the chemotherapy group. Additionally, more patients had to modify treatment, by either reduction or delay, in the chemotherapy group than the erlotinib group due to adverse response events to treatment. Although more serious adverse events occurred in the erlotinib group.

<u>Figure 9</u>: Chemotherapy vs Erlotinib in NSCLC

This figure demonstrates a Kaplan-Meier curve for NSCLC that compares the progression-free survival in patients who received erlotinib targeted therapy treatment versus patients who received standard chemotherapy treatment. Standard chemotherapy treatments include cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus gemcitabine, and carboplatin plus docetaxel.



Chemo	88	53	22	8	5	3	2	1	0	0	0	0	0	0	0	0
Erlotinib	86	69	62	43	33	25	19	14	8	7	6	4	3	2	1	0

Currently, erlotinib is FDA approved for first-line treatment or second-line treatment following chemotherapy in NSCLC cases who demonstrate an EGFR mutation. Its efficacy and treatment in the use of treatment for NSCLC cases without an EGFR mutation has not been established and is not recommended. Erlotinib is also not recommended for use in combination with chemotherapy in NSCLC.

Erlotinib in combination with gemcitabine chemotherapy is currently FDA approved for patients who present with locally advanced, unresectable, and metastatic

pancreatic cancer. In 2004, the FDA approved erlotinib in combination with concurrently administered gemcitabine after a randomized clinical trial that compared treatment of gemcitabine plus erlotinib to gemcitabine plus placebo (gemcitabine alone)[67]. This was a phase III clinical trial conducted by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) in cooperation with multiple investigators. The study included 569 patients and took place in 18 countries. The patients chosen for this study had to demonstrate locally advanced or metastatic pancreatic cancer. Patients who received prior chemotherapy were not included in the study.

The results of this clinical trial were shown to be statistically significant but still low. The patients who received gemcitabine plus erlotinib exhibited a median progression-free survival of 3.8 months and a median overall survival of 6.4 months. This was compared to the patients who received gemcitabine alone with a median progression-free survival of 3.5 months and median overall survival of 6.0 months. When stratification factors were adjusted for the median survival for gemcitabine plus erlotinib vs gemcitabine alone, was 6.24 months versus 5.91 months, respectively. Additionally, the 1-year survival of patients who received gemcitabine plus erlotinib was 23.8% versus 19.4% for patients who received gemcitabine alone. While progression-free survival was demonstrated to be statistically significantly longer in this study; the objective response rates did not show any significant difference between the two treatment groups[68]. More adverse events occurred in the gemcitabine plus erlotinib group, but they were deemed to be mild, low grade events.

While the NCIC-CTG study demonstrated significant survival benefits of gemcitabine plus erlotinib, it did not show benefit in the context of EGFR mutations. However, later studies did show that gemcitabine plus erlotinib was able to better treat pancreatic cancer with EGFR mutations than gemcitabine alone[60]. A clinical study done in Taiwan was able to demonstrate a significance of gemcitabine plus erlotinib in metastatic pancreatic cancer when EGFR mutations were present[69]. Patients who received gemcitabine plus erlotinib with EGFR mutations had a higher disease control rate than patients receiving the same therapy but without EGFR mutations, 85% versus 33%, respectively. Patients who received gemcitabine plus erlotinib with EGFR mutations also had a significantly longer median progression-free survival of 5.9 months and median overall survival of 8.7 months. This can be compared to patients who received gemcitabine plus erlotinib without EGFR mutations who had a median progression-free survival of 2.4 months and a median overall survival of 6.0 months[60]. Additionally, this study demonstrated consistency with the survival benefit of the combination therapy, such that regardless of whether EGFR mutations were present, the group receiving gemcitabine plus erlotinib had a higher overall survival than the group who received gemcitabine alone.

It is clear that erlotinib is more effective for overall survival in NSCLC in comparison to pancreatic cancer. However, erlotinib does show significant survival effects when used to treat pancreatic cancer when compared to other treatment options for pancreatic cancer. The mechanism for how EGFR inhibitors works to increase survival in pancreatic cancer is poorly understood. One suspected mechanism is that

EGFR is overexpressed and this leads to increased EGFR signaling which leads to growth and metastasis of cancer and decreases the survival of patients with pancreatic cancer[67]. By targeting this signaling pathway, growth and metastasis may be slowed and survival may be extended. Another suspected mechanism is that there is autocrine stimulation of the EGFR and this contributes to pathogenesis of pancreatic cancer by sustaining cell proliferation[67]. Inhibiting EGFR tyrosine kinase activity may contribute to slowing the replication of cells and therefore prolonging the metastasis.

Eventually in patients with both NSCLC and pancreatic cancer overtime resistance is acquired to erlotinib and all patients progress to fatal disease states[70]. While it may slow the progression of carcinomas, resistance is eventually acquired to the targeted inhibition of kinases.

This modest increase in survival of patients with pancreatic cancer when treatment with erlotinib is utilized is promising though. It establishes a need for further research into EGFR mutations and the pathways it involves in association with pancreatic cancer. This increase in survival with this targeted treatment shows progress and is a small step in the direction towards finding a cure for pancreatic cancer. More research is also needed for biomarkers that can establish efficacy of erlotinib.

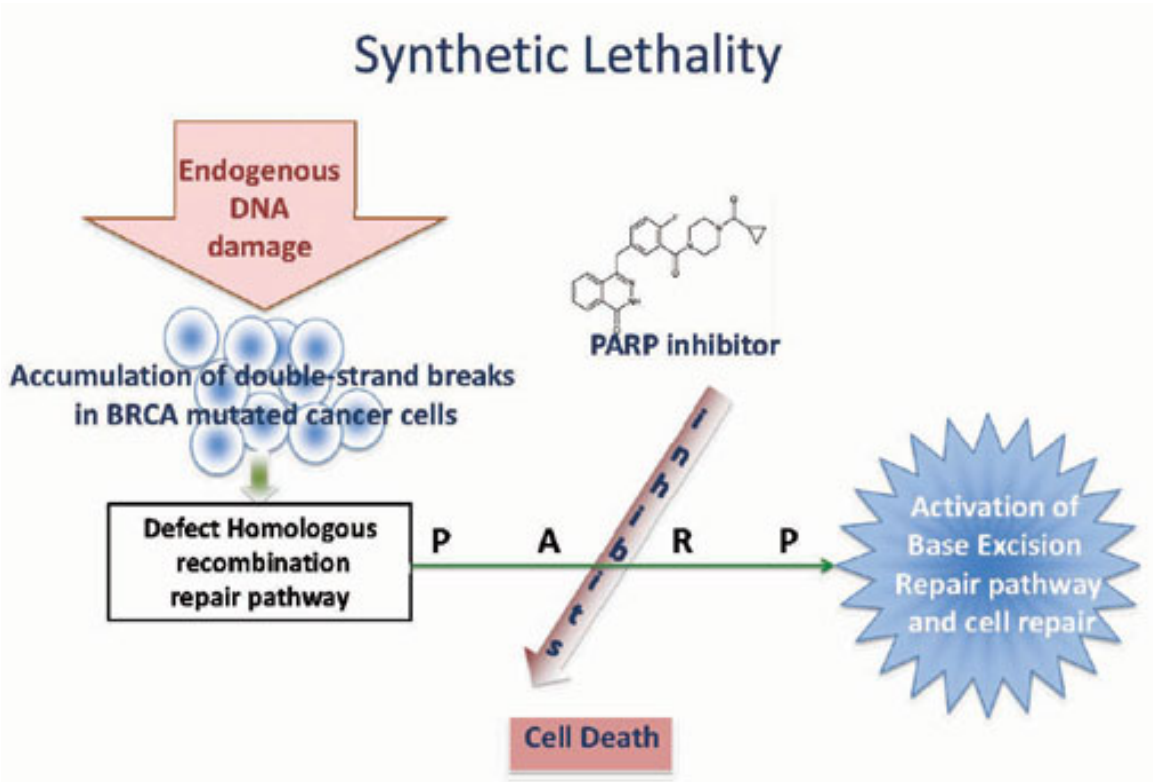
OLAPARIB

Olaparib (Lynparza) is a small drug molecule that is a poly ADP ribose polymerase (PARP) inhibitor. PARPs are a family of enzymes that have a critical role in

a number of cellular processes. These include the processes of structuring chromatin, transcription, replication, recombination, and DNA repair[71]. PARP is involved in the base excision repair pathway and repairing DNA when it becomes damaged, this is of interest for targeted therapy utilized to treat cancer[59]. It is suspected that certain tumor cells may rely on PARP-mediated DNA repair mechanisms for continued survival and growth. These tumors could be sensitive to the inhibition of PARP. When used as a targeted therapy, a PARP inhibitor can block PARP and may stop the cancer cells from repairing their damaged DNA which then leads to apoptosis of the cancer cells.

<u>Figure 10</u>: PARP Inhibitor Action[72]

This figure demonstrates how a PARP inhibitor interferes with the process of DNA repair to cause apoptosis of cancer cells.



BRCA1 and BRCA2 are tumor suppressor genes that are commonly found in cancers, including familial pancreatic cancer. These genes are involved in the repair of DNA. These are the genes that are targeted by PARP inhibitors. This suggests BRCA1 and BRCA2 as genetic markers for targeted therapy. A deleterious germline mutation of BRCA1 and/or BRCA2 can demonstrate loss of expression of these genes and thus loss of tumor suppressor function[73]. Thus this mutation can be used as a valid predictive biomarker for targeted therapy by PARP inhibitors[71].

PARP inhibitors are currently FDA approved as oral agents in the treatment of ovarian, breast, and pancreatic cancer that harbor or are suspected to harbor germline BRCA mutations. Some studies have even demonstrated that PARP is upregulated in certain cancers that express BRCA1 mutations.

Olaparib was first approved in 2014 by the FDA to treat advanced ovarian cancer with defective BRCA genes. This can be used as a first-line maintenance treatment for patients with advanced ovarian cancer following first-line platinum-based chemotherapy. The study that was evaluated for FDA approval was a randomized clinical trial where patients were split into groups receiving either olaparib or placebo. While the study is not complete yet and thus the data is immature, there was a statistical significance in progression-free survival when olaparib was compared to placebo. In another clinical trial, patients who had recurrent ovarian cancer and BRCA mutations were studied. They were again divided into 2 groups receiving either olaparib or placebo. The results were immature but demonstrated significant improvement in progression-free survival.

Patients in the group receiving olaparib had a median progression-free survival of 19.1 months in comparison to the group receiving the placebo who had a median progression-free survival of 5.5 months[74]. In another study evaluated by the FDA for olaparib use in ovarian cancer, the study group had a BRCA mutation and been treated with two prior lines of therapy. The patients who received olaparib had significant results with a median progression-free survival of 8.4 months. The median overall survival of the olaparib group was 29.8 months. The placebo group had a median progression-free survival of 4.8 months and a median overall survival of 27.8 months. In a study where patients had received three prior lines of therapy, patients in the olaparib group demonstrated a significant objective response rate of 34% with a median duration of response of 7.9 months. These results in advanced ovarian cancer with BRCA mutations do show promising response rates of tumors and a significant increase in survival rates using targeted therapy PARP inhibitors.

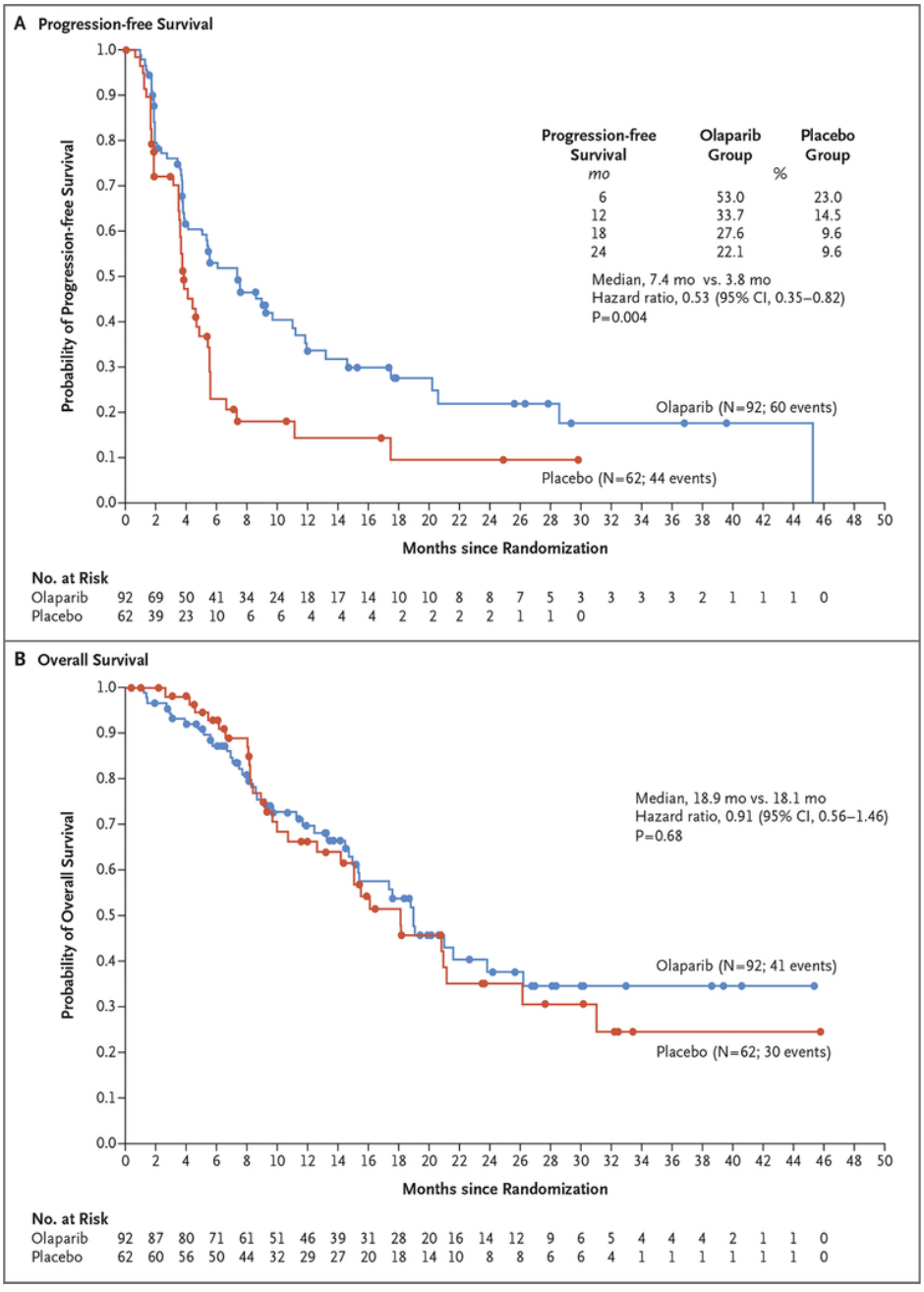
Olaparib has also been evaluated and approved by the FDA for treatment of metastatic breast cancer in patients with germline BRCA mutations who have already had a form of chemotherapy treatment. In a randomized clinical trial, patients were divided into groups receiving either olaparib or chemotherapy. The patients who received olaparib exhibited a significant improvement in progression-free survival with a median of 7.0 months compared to the placebo group who had a median progression free survival of 4.2 months[74]. The olaparib group also showed an objective response rate of 52% compared to the placebo of 23%. These results demonstrate an increase in disease free

survival with olaparib and can possibly correlate to an increase in quality of life for patients with metastatic breast cancer.

The FDA just recently approved olaparib as a treatment option for patients with pancreatic cancer in December 2019[75]. This treatment is reserved for patients who present with metastatic pancreatic cancer who have a BRCA mutation and whose disease has not progressed after at least 16 weeks of first-line chemotherapy treatment. The study that was evaluated for efficacy was a global, randomized phase 3 trial of 154 patients who were divided into groups receiving either PARP inhibitor targeted therapy or placebo tablets. The patients who participated in the trial had mutations in BRCA1, mutations in BRCA2, or mutations in both BRCA1 and BRCA2. Patients in the group receiving treatment with olaparib had significant survival results as the median progression-free survival was 7.4 months compared to the 3.8 months found in the placebo group. The Kaplan-Meier curve between the two trial groups support evidence of a 47% reduction in risk of disease progression or death with treatment of olaparib compared to placebo treatment[75]. At the 6-month point in the study, there were approximately twice as many patients alive and free from disease progression in the olaparib group as there were in the placebo group. At the 2 year point in the study, disease progression was absent in 22.1% of patients in the olaparib group versus 9.6% of patients in the placebo group[75].

<u>Figure 11</u>: Olaparib Survival Curves for PDAC Patients[75]

This figure demonstrates progression-free survival and overall survival estimates of the clinical trial that compared treatment with olaparib to placebo treatment. Panel A shows Kaplan–Meier is an estimate of progression-free survival in the olaparib group and the placebo group. Panel B shows Kaplan–Meier estimates of overall survival in the olaparib group and the placebo group.



While the effects of overall survival cannot be determined with significance yet, pancreatic cancer with BRCA mutations has certainly demonstrated a positive response to PARP inhibitor targeted therapy. Of course, this therapy is of best benefit to the PDAC cases who present with BRCA mutations. The significant survival results that were indicated by previous clinical studies of patients with ovarian and breast cancers using olaparib are hopeful for the potential survival benefit of patients with pancreatic cancer. Olaparib was evaluated and FDA approved for ovarian and breast cancers a few years prior to its approval for pancreatic cancer. The approval for PARP inhibitors in pancreatic cancer is very recent as it was just instated in December 2019. With time and some more research, it is possible that some modifications can improve the efficacy of this targeted therapy and potentially improve survival benefit even further for patients with pancreatic cancer. Olaparib is definitely progress in the field of targeted therapy for pancreatic cancer and with more research and modifications could one day even contribute to a targeted cure for pancreatic cancer.

DISCUSSION AND CONCLUSION

Receiving a diagnosis of pancreatic cancer can be very difficult news. It can be a challenge to choose the best treatment option. There are a number of variables that have to be considered when choosing an approach to treatment. These include stage at diagnosis, the size and location of the tumor, and whether or not metastasis has occurred. Genetic profiling can also be done to assess whether or not the patient would benefit from any targeted therapy options.

If the patient is diagnosed at an earlier stage and the tumor is considered to be resectable than surgical resection should be highly considered and should most likely be done. Surgical resection is still considered the only option that has the potential to cure pancreatic cancer. Based on where the tumor is located, at the head or tail or body of the pancreas, the patient may have a choice between the Whipple procedure or a distal pancreatectomy. Chemotherapy can also be considered along with surgery. The patient may opt to do neoadjuvant chemotherapy to try and shrink the tumor and increase the success of the surgery. This may be considered a little bit riskier but can be done for a short period of time if it is suspected that the tumor isn't progressing rapidly. After the surgery, the patient should also choose an adjuvant chemotherapy to prevent the recurrence of tumor.

If a patient is diagnosed at a stage of pancreatic cancer that is borderline resectable there may be a different approach to treatment. Neoadjuvant therapy may be considered before the surgery if there is a chance that shrinking the tumor could make it more likely to be resectable and increase the chances of completely excising the tumor

during surgery. If the cancer is suspected to be rapidly progressing, then there may not be enough time to do neoadjuvant therapy and surgical resection should be done as soon as possible. The patient's overall health should be evaluated before the surgery is performed on a borderline resectable tumor to see if the individual is a suitable candidate for major surgery. Adjuvant chemotherapy should also be considered after surgery to decrease the likelihood of cancer recurrence. If surgery is not performed, then the patient must consider what treatment options would be most preferred for them. There options may include chemotherapy, targeted therapy, or a combination of both. Genetic profiling would have to be done to evaluate if a patient would benefit from targeted therapy and if so which targeted therapy to choose, erlotinib or olaparib.

A patient may also be diagnosed at an advanced stage where surgical resection is not recommended. At this point the surgery may be too much of a risk, there may have been too much metastasis, or the patient may not be a suitable candidate because of poor health. The patient may consider therapies for management to increase survival: overall survival and/or progression-free survival. Another option the patient may consider is palliative care. To increase management efficacy, genetic profiling may be done to see if the patient would benefit from a targeted therapy option.

While there has been progress made in the treatment of pancreatic cancer, it still remains a very challenging disease with poor prognosis and limited options. Personalized medicine has ignited some hope though as it has provided some targeted therapy options for patients with pancreatic cancer.

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