REVIEW ARTICLE

# From Screening to Treatment of Pancreatic Cancer: A Comprehensive

**Muhammad Wasif Saif**

Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine, Feinstein Institute for Medical Research, Lake Success, NY, USA

**ABSTRACT**

**Introduction** Pancreatic adenocarcinoma is a devastating malignancy, associated with a grim prognosis, due to its silent presentation and lack of diagnostic tests. In addition, treatment options are limited to few agents, such as 5-FU, irinotecan, oxaliplatin, gemcitabine and nab-paclitaxel. **Methods** We performed a literature search for relevant published clinical trials, abstracts of trials in progress and ongoing or planned trials for the treatment of APC using Pubmed.com, ClinicalTrials.gov and American Society of Clinical Oncology (ASCO) abstract search as sources. We present an in-depth analysis of the phase I-III clinical trials determining the role and efficacy of different modalities. We also describe rationale for future investigation. **Discussion** Despite advances in first-line and second-line therapies for APC, median OS remains short of a year. We need collaborative efforts between the cooperative groups, institutions, community practices and industry to work together in enrolling these patients in clinical trials. In addition to use new technologies, such as organoids, we must pay attention to the palliative aspect of care for these patients from the beginning including nutritionist, social worker and supportive care health providers to assist with goals of care, symptom management and end of life discussions.

## INTRODUCTION

Pancreatic cancer (PC) carries a poor prognosis and now ranks as the third leading cause of cancer-related deaths in the United States [1]. Unfortunately, due to lack of any diagnostic tools and non-specific symptomatology, majority of the patients are diagnosed with advanced disease with an abysmal 5-year-overall survival (OS) rate of only 7% [1]. Surgery is feasible in approximately 15–20% of the patients, and even if resected the 5-year survival remains only about 10% [2]. Therefore, it is considered the most fatal malignancy of all major cancers. The disease is rare before the age of 45, but the incidence increases intensely thereafter. Incidence and death rates vary by sex and race [3]. The incidence is greater in males than females (male-to-female ratio 1.3:1) and in blacks than in whites (14.8 per 100,000 in black males compared with 8.8 per 100,000 in the general population) [4].

To date, only two chemotherapy combination regimens, namely FOLFIRINOX (folinic acid, 5-fluorouracil, irinotecan, oxaliplatin) and gemcitabine plus nab-paclitaxel (nabPGem) have shown OS benefit in patients with metastatic disease but both regimens are associated with increased toxicity [5, 6]. Patients with APC refractory to first-line therapy have a dismal prognosis and limited therapeutic options, with only one option consisting of nanoliposomalirinotecan in combination with fluorouracil and folinic acid which was approved by FDA based upon results of the phase III NAPOLI-1 study [7]. Currently, FOLFIRINOX is probably the most widely used regimen in the first-line treatment of APC, hence, how this regimen fits in the algorithm of the treatment is not clear. At present time, screening for pancreatic cancer is not recommended by any society and national practice guidelines in the general population [8]. However, with better understanding of human genetics, recognition of risk factors, and development of diagnostic tools, it is generally recommended to perform endoscopic ultrasound (EUS), multi-detector computed tomography (MDCT), magnetic resonance cholangiopancreatography (MRCP), magnetic resonance imaging (MRI), and endoscopic retrograde cholangiopancreatography (ERCP) in high-risk individuals [9] as summarized in **Figure 1**. It is important to remind here that currently the application of these diagnostic tests is very limited for the general population.

We performed a literature search for relevant published clinical trials, abstracts of trials in progress and ongoing or planned trials for the treatment of APC using Pubmed.com, ClinicalTrials.gov and American Society of Clinical Oncology (ASCO) abstract search as sources. We present an in-depth analysis of the phase I-III clinical trials determining the role and efficacy of different modalities. We also describe rationale for future investigation.

- Sequential therapy
- apply metastatic regimens to earlier stages
- Precision Medicine

Received February 23rd, 2021 - Accepted April20th, 2021
**Keywords** Carcinoma; Drug Therapy; Gemcitabine; Neoplasm Metastasis; Pancreas; Pancreatic Neoplasms; Therapeutics; Early Detection of Cancer; Endosonography; Mucins
**Correspondence** Muhammad Wasif Saif
Deputy Physician-in-Chief & Medical Director, Northwell Health Cancer Institute
Department of Medical Oncology, Donald and Barbara Zucker School of Medicine
Lake Success, NY 11042, USA
**Tel** 516-321-2238
**Fax** 516-321-2272
**E-mail** wsaif@northwell.edu

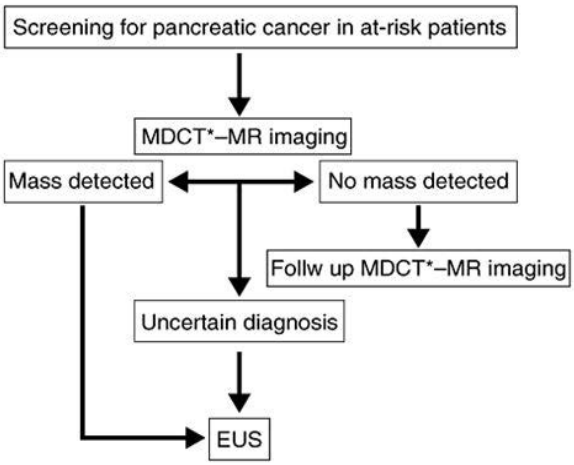


**Figure 1.** Screening in patients at risk of pancreatic cancer.

- Pharmacogenetic and metabolic markers of Chemotherapeutic agents commonly used in PC
- Stromal Targeting agents
- Inflammatory Response
- Other agents
- Immunotherapy
- Surgical resection of hepatic metastases
- Radiation Therapy
- Liver-directed Therapy

**Sequential chemotherapy**

As mentioned earlier, the current guidelines recommend nabPGem or FOLFIRINOX as first-line treatment, followed by nal-IRI depending on the patient's PS. There is no randomized study III performed to date. Ramanathan et al performed a phase II study of induction therapy with gemcitabine and nab-paclitaxel followed by consolidation with modified FOLFIRINOX (mFOLFIRINOX with omission of bolus 5-FU and addition of growth factor every 2 weeks given for a maximum of 6 months) in patients with APC [10]. The study patients received *induction* therapy (gemcitabine and nab-paclitaxel weekly x 3 every 4 weeks for up to 6 cycles or earlier if progressive cancer followed by *consolidation* therapy (mFOLFIRINOX). The primary endpoint was to increase 1-year survival to more than 70%. The results were presented in an annual meeting in 2014 at which time the study had only accrued 26 patients. Among the 20 patients treated with the induction phase, 75% have had a significant decrease in CA 19-9 levels and achieved a 50% partial response (PR) but at the cost of grade ≥3 adverse events, including neutropenia, fatigue, thromboembolic events, and peripheral neuropathy. Other possible sequences of chemotherapy that were tested in small clinical trials or can be utilized in appropriate patients may include:

- Gemcitabine and nab-paclitaxel →nal-IRI with 5-FU and leucovorin versus mFOLFOX-6/OFF versus capecitabine
- mFOLFIRINOX→ gemcitabine and nab-paclitaxel versus gemcitabine if patient has existing neuropathy

The absence of direct comparison of the two first-line regimens at present leaves the choice up to the treating physician and the patient depending on PS and toxicities associated with these regimens. In our experience, the sequence FOLFIRINOX followed by nab-Paclitaxel and Gemcitabine or vice versa lead to an equal OS outcome.

**Metastatic to Earlier Stage: Can we apply metastatic regimens to earlier stages (Locally advanced, adjuvant, and Neo-adjuvant therapy) to enhance the cure rate in pancreatic cancer?**

Until recently, the standard adjuvant therapy for PC following surgery was either 6 months of adjuvant gemcitabine alone or withcapecitabineor 5-FU leucovorin or S-1 [11-14]. Role of radiation therapy in this setting remains to be confirmed based on the conflicts from many studies in the adjuvant setting [11, 15]. Moreover, the notion that pancreatic cancer is a systemic disease and R0 resection is not achieved in majority of the patients undergoing surgery, further underlines the importance of developing better therapies to improve the cure rate of those patients who are able to undergo surgery as well as selecting the right patient who should undergo surgery. These challenges and questions lead us to consider testing intensive regimens such as those proven to be beneficial in the metastatic setting: FOLFIRINOX or gemcitabine with nab-paclitaxel in earlier stages with a hope that the use of these regimens may enhance the cure rate if they are used in earlier stages of pancreatic cancer patients. PRODIGE/ ACCORD study showed an impressive survival benefit with FOLFIRINOX over gemcitabine [15]. However, APACT study did not reach its end point to improve survival with addition of nab-paclitaxel to gemcitabine [16].

Similarly, nab-paclitaxel combination with gemcitabine was recently reported in LAPACT study for patients with locally advanced disease [17]. Median time to treatment

failure (TTF) was 9·0 months (90% CI 7·3-10·1), median progression-free survival (PFS) was 10·9 months (90% CI 9·3-11·6), and median OS was 18·8 months (90% CI 15·0-24·0). Overall, the disease control rate was 77·6% (90% CI 70·3-83·5), including 33·6% PR. Toxicities were similar to previous studies and 15% were converted to resectable disease and underwent surgery. Though curative-intended surgical resection and adjuvant chemotherapy represents the current standard of care for pancreatic cancer, sadly these patients still have an unfavorable prognosis secondary to high risk of relapse. Borrowed from the data other resectable gastrointestinal cancers, especially esophagus and gastric cancer in which neoadjuvant or perioperative multimodal therapies have substantially improved the outcome, it seems very reasonable to postulate that use of the newer and intense chemotherapy regimens, such as FOLFIRINOX or nab-paclitaxel to gemcitabine may improve the outcome inresectableand borderline pancreatic cancer. Recent studies are aiming to investigate the benefit for obvious reasons enumerated below:

1. Potential downsizing of the tumor with subsequent higher proportion of R0 resections,
2. Neoadjuvant chemotherapy may be more effective than adjuvant treatment secondary to preserved anatomy and vasculature,
3. Pancreatic cancer is a systemic disease as these patients are likely to havemicrometastases even at the time of diagnosis of a mall primary tumor, hence, there is benefit of the systemic effect of neoadjuvant chemotherapy,
4. Neoadjuvantchemotherapy also offers a "window of opportunity" to test the biology of the tumor, and
5. Finally, most patients can receive neoadjuvant chemotherapy compared to adjuvant therapy which can be achieved in approximately 60 – 70% due to perioperative morbidity.

**Precision Medicine**

**BRCA2 and Pancreatic Cancer** Patients with BRCA-1 and BRCA-2 germ line mutations are at an increased risk of developing pancreatic adenocarcinoma, especially BRCA-2 mutation [18]. A recent study of whole genome sequencing of 638 patients with familial pancreatic cancer showed mutations in the **BRCA2** gene accounted for the largest fraction of known familial pancreatic cancer genes and was found in 5–10% of the families [19]. Among patients with no family history of PDAC, **BRCA2**mutation is found in 2% and **BRCA1** mutation is found in 1% of the patients or less. In the Ashkenazi Jewish population with PDAC, a much higher incidence of **BRCA** mutations are found and seen in up to 13.7% of unselected cases.

Studies have revealed that the BRCA-2 protein is involved in repair of double-stranded DNA breaks and such tumors deficient in deoxyribonucleic acid (DNA) damage repair mechanisms such as *BRCA* mutants show better responses to DNA alkylators such as irinotecan, cisplatin, oxaliplatin, mitomycin [20]. However, such tumors can utilize the poly(adenosine diphosphate [ADP]-ribose) polymerase (PARP) pathway as a salvage mechanism. Therefore, inhibition of PARP pathway could lead to tumor destruction and synthetic lethality in presence of *BRCA* mutation [21]. Various PARP inhibitors have been approved for treatment of patients with germline or somatic *BRCA* mutant breast and ovarian cancer. This provides basis of using PARP inhibitors in patients with pancreatic cancer that harbor *BRCA* mutation. A recent phase III Pancreas Cancer Olaparib Ongoing (POLO) study showed impressive results with near doubling of progression free survival compared to placebo (7.4 *vs* 3.8 months) [22]. These results highlight the importance of germline testing for all patients with pancreatic cancer and inclusion of additional deficiencies in homologous recombination repair (*ATM* and *PALB2*) including *BRCA* variants of uncertain significance should be further explored.

***HER2*-amplified pancreatic cancers**

*HER2* amplification occurs in 2% of pancreatic adenocarcinoma [23]. Studies have shown that *HER2*-amplified pancreatic cancers demonstrated a mRNA expression profile which clustered with the HER2-amplified intrinsic subtype of breast cancer using the PAM50 classifieron a molecular level, and clinically, these tumorsfollowed an atypical metastatic pattern characterized by sparing the liver and metastasizing to the lungs and brain – a finding similar one seen in *HER2*-amplified breast cancer [24]. Based on these data, the investigators explored the role of anti-HER2 therapy in *HER2*-amplified pancreatic cancers.

Three single arm phase II studies investigated anti-Her2 agents active in combination with cytotoxic agents in pancreatic cancer (**Table 1**). As evidenced from the table above, only 2 of the trials selected patients based on Her2 status, and utilized immunohistochemistry alone to detect *HER2* overexpression.

**Pharmacogenetic and metabolic markers of Chemotherapeutic agents commonly used in PC**

Predicting response and limiting drug-induced toxicity for patients with any tumor type including pancreatic cancer are also critical. Inter-patient differences in tumor response and drug toxicity are common during chemotherapy. Genomic variability of key metabolic enzyme complexes, drug targets and drug transport molecules are important contributing factors, such as hent-1, DPYD, TYMS, TP, UGT1A1, CDA, DCK, MSI, etc. [28,29,30].

Currently, there is inconsistent use of these pharmacogenetic markers in the clinical setting secondary to both the lack of robust evidence as well as limit of financial resources. Patients' selection and tailored treatments by the introduction of genetic testing in future studies is mandated. One such example is outline in **Figure 2**, with a proposed schema for such a study that will

**Table 1:** Studies that investigated anti-Her2 agents active in combination with cytotoxic agents in pancreatic cancer.

| Anti-HER2 agent | Cytotoxic agent | HER2 status required | Method used to test HER2 | Reference |
|---|---|---|---|---|
| Trastuzumab | Gemcitabine | Yes | IHC* | 25 |
| Trastuzumab | Capecitabine | Yes | IHC* | 26 |
| Lapatinib | Gemcitabine | No | NA | 27 |
| *IHC: immunohistochemistry | | | | |

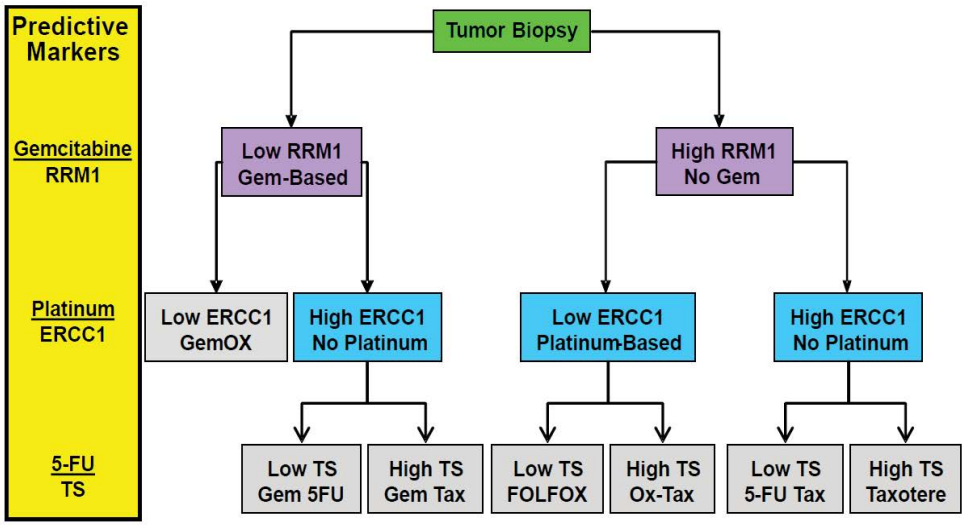


**Figure 2.** Role of Pharmacogenetic Markers in development of Future clinical studies in pancreatic cancer.

hopefully allow better response prediction and limit drug-induced toxicity leading to improved patient outcomes in the most cost-effective way.

### Stromal targeting agents

It has been suggested that the tumor microenvironment, such as desmoplastic reaction and stromal neighborhood in pancreatic cancer may act as a hindrance to chemotherapeutic agents, raising the possibility to develop agents that can target the environment and improve the delivery of chemotherapy [31]. Recently, multiple efforts have been made as well as undergoing on developing stroma-depleting agents into the treatment of pancreatic cancer, such as strategies targeting:

- Transforming growth factor (TGF-β),
- Hedgehog (Hh) pathway,
- Tumor necrosis factor (TNF) receptors,
- Degrading hyaluronic acid (HA) in the stroma, and
- Heparan sulfate proteoglycans (HSPGs).

**Table 2** summarizes the stromal targeting agents either recently underwent evaluation or currently under evaluation to improve outcome of patients with PC:

**Transforming growth factor β (TGF-β)** Kano et al. investigated the effect of inhibiting TGFβ signaling with a low-dose TGFβ type 1 receptor inhibitor in preclinical studies and observed reduction in the pericyte coverage of tumor vessels and enhancement of the accumulation of macromolecular nanomedicines in the area of the tumor [32]. However, this strategy did not reduce the abundant fibrous tissue in the tumor. Further studies are required to further investigate this pathway and develop more effective targets to demolish this pathway.

**Hedgehog (Hh) pathway** Hh signaling cascade regulates embryonic development and pathological activation of this pathway have shown to be oncogenic in many tumor types, including pancreatic cancer. Hh binds to the extracellular receptor, Patched, which releases Smoothened, which then acts to activate transcription factors which is considered as a possible mechanism involved in carcinogenesis [33]. Interestingly, Hh signaling in pancreatic cancer is *limited to the stromal compartment and Sonic Hedgehog (SHh)* and has been shown to produce a desmoplastic reaction in mice, which is not only a scintillating feature of pancreatic cancer but also associated with metastatic potential and pharmacologic barrier [34]. Olive et al. showed that inhibition of *SHh* resulted in improved gemcitabine delivery, depletion of the dense stroma, and increased vascularization of the tumors in preclinical studies [35]. This data led to a testing of Hh inhibitors in clinical setting. IPI-926, a small molecule SHh inhibitor was combined with gemcitabine 1000 mg/m2 IV in a phase I/II study (ClinicalTrials.gov Identifier: NCT01130142). Unfortunately, the trial was closed after preliminary interim analysis showed decreased survival in the IPI-926 plus gemcitabine arm, with median overall survival less than the historical median survival of gemcitabine alone of approximately 6 months [36]. Final results have not been published yet along with translational correlates.

Another agent, GDC-0449 (vismodegib) showed an acceptable toxicity profile and indicated some antitumor effects in a variety of solid tumors in a phase I study. Recently, the results of a study combining vismodegib with

**Table 2:** Summary of Stromal Targeting agentsundergoing evaluation in Pancreatic Cancer.

| **Stromal Targeting agents** | | |
|---|---|---|
| **Notch/Hedgehog pathway** | Sonic Hedgehog has been shown to produce a desmoplastic reaction | • IPI-926<br>• GDC-0449 |
| **Transforming growth factor-β (TGF-β)** | Reduction in pericyte coverage of tumor vessels and enhancing accumulation of macromolecular nanomedicines in the area of tumor | • TGF-β type 1 receptor inhibitor |
| **Tumor necrosis factor receptors (TNF)** | CD40 agonists shrunk stroma in PC models; probably mediated by activation of the tumor-associated macrophages | • CP-870,893 |
| **Hyaluronic acid (HA) of Stroma** | HA is a major component of the stroma; presence of HA in tumors is associated with enhanced tumor growth, increased metastatic potential, rapid tumor progression, and elevation in tumor interstitial fluid pressure (IFP) | • PEGPH20 |
| **Heparan sulfate proteoglycans (HSPGs)** | HSPGs are polysaccharide molecules bound to proteins associated with cell membrane of cells including tumor cells; contribute to tumor microenvironment by binding to factors that support tumor growth | • M402 |
| **Anti-diabetic** | • Insulin receptor-dependent mechanism<br>• Mitochondrial complex I | • Metformin |

*nab*-paclitaxel and gemcitabine showed a disease control rate in over 80% of the patients [37].

**Tumor necrosis factor (TNF) receptors** CD40 superfamily of tumor necrosis factor receptors have been found in pancreatic stroma and preclinical studies have indicated that CD40 agonists shrunk stroma in pancreatic tumor models [38]. It is postulated that this effect is probably mediated by activation of the tumor-associated macrophages. A pilot study combined CD40 agonist (CP-870,893) with gemcitabine and showed PR of 19% among 21 evaluable patients. One dose-limiting toxicity was grade 4, cerebrovascular accident which occurred at the 0.2 mg/kg dose level, and was estimated as the MTD [39]. The most common adverse event included cytokine release syndrome, usually grade 1 and 2. In addition, changes in FDG uptake detected on PET/CT imaging were intriguing. Phase II studies are warranted.

**Hyaluronic acid of the stroma** HA, a glycosaminoglycan is a major component of the stroma and frequently overproduced by various tumor types. In addition, presence of HA in tumors is associated with correlates with enhanced tumor growth, increased metastatic potential, rapid tumor progression, and elevation in tumor interstitial fluid pressure (IFP); hence acting as a barrier to chemotherapeutic agents [40]. PEGylated recombinant human hyaluronidase (PEGPH20) has shown to degrade HA in stroma and leading to better chemotherapy delivery to the tumor cells [41]. Based on the safety profile of the combination of PEGPH20 with gemcitabine, this agent underwent testing both with gemcitabine and nab-paclitaxel as well as FOLFIRINOX.

Encouraged by the preliminary data from phase I/II studies [42], the phase III HALO-109–301 compared PEGPH20 in combination with nab-paclitaxel/gemcitabine to nab-paclitaxel/gemcitabine alone in previously untreated patients with pancreatic tumors confirmed high expression of HA. Patients were randomized in 2:1 manner to receive the experimental arm [43]. The primary endpoint was overall survival. Five hundred patients were enrolled but sadly the study did not meet its primary endpoint of OS (11.2 months compared to 11.5 months (hazard ratio of 1.00 and **p**=0.096). Since this announcement, all future development of PEGPH20 has been halted. Prior to the announcement of the results of HALO study, Ramanathan et al, presented similar negative data of Southwest Oncology Group (SWOG) 1313 that was conducted to determine the safety and efficacy of PEGPH20 in combination with modified version of FOLFIRINOX [44].

**Heparan sulfate proteoglycans** HSPGs are polysaccharide molecules bound to proteins associated with cell membrane of cells including tumor cells. It is believed that HSPGs also contribute to the tumor microenvironment by binding to factors that support tumor growth [45]. M402, a mimetic of heparan sulfate was developed to inhibit the multiple interactions associated with heparan sulfate. Preclinical data from Harvard group has revealed that M402 appears to inhibit stromal activation within the tumor microenvironment, resulting in reduction in desmoplasia with improved tumor perfusion, delivery of gemcitabine, and subsequent tumor shrinkage [46]. These and other promising nonclinical data support the rationale for the ongoing Phase 1/2 study evaluating the safety and tolerability of M402 in combination with nab-paclitaxel and gemcitabine in patients with APC (NCT01621243).

### Agents targeting the inflammatory response

The rationale for this strategy arises from a few observations [47]:

- Inflammatory cytokine signaling does appear to be important both in disease initiation and progression in preclinical models of pancreas cancer,
- Majority of the patients with APC have both laboratory and clinical evidence of systemic inflammation, such as weight loss, decreased muscle mass, poor performance status (cachexia), and
- Patients who have an elevated C-reactive protein, a marker of systemic inflammation, have a worse prognosis.
- Given this rationale for disrupting systemic inflammation, many agents have undergone testing (**Table 3**).

**Table 3:** Agents targeting the Inflammatory Response.

| | | |
|---|---|---|
| **Arachidonic acid Pathway (Lipoxygenase [LOX] Pathway)** | • LTB4 receptor antagonist | • LY293111 |
| **JAK/STAT Pathway** | • JAK1 and JAK2 inhibitor | • Ruxolitinib |

## Arachidonic acid Pathway (Lipoxygenase [LOX] Pathway)

Arachidonic acid is metabolized to leukotrienes and other inflammatory compounds via 5-lipooxgenase. Upregulation of 5-lipoxygenase has been reported in several cancer types, including pancreatic cancer [48] Preclinical studies have revealed that lipoxygenase inhibitors inhibit cell proliferation and induce apoptosis [49]. Tong *et al.* 2012, suggesting that an inhibitor of 5-lipoxygenase may arrest the tumor growth. Unfortunately, a phase II randomized, double blind study compared LY293111, a LTB4 receptor antagonist, with gemcitabine to gemcitabine plus placebo, showed no difference in 6-month survival ($p$> 0.2) or PFS ($p$> 0.05) [50].

### JAK1 and JAK2

A randomized double-blind Phase II study the ***RECAP study***, investigated Ruxolitinib, JAK1 and JAK2 inhibitor that blocks the stat transcription factor pathway and inflammatory cytokines versus placebo in combination with capecitabine in patients with metastatic pancreas cancer. Overall the study did not meet the end point but when they looked at the patient population with elevated C-reactive protein levels, the investigators observed a strong efficacy signal [51]. The survival at 6 months was 42% with ruxolitinib versus 11% for placebo.

These results provide us the proof of the principle with survival benefit in those patients with evidence of systemic inflammation. A randomized phase III study is underway to confirm these results.

### Immunotherapy and pancreatic cancer

Secondary to the relative lack of efficacy of traditional chemotherapy in patients with pancreatic cancer, investigators have also approached to other treatment modalities such as immunotherapy as it worked out in other chemo-refractory tumors such as melanoma. **Table 4** summarizes selected immunotherapy in PC.

### Immune checkpoint inhibitors

Approximately 1% of pancreatic cancers are associated with defective mismatch repair (dMMR/MSI-high) [52]. In the KEYNOTE-016 phase II trial of pembrolizumab for patients with advanced solid tumors with dMMR, 5 of 6 patients with pancreatic cancer responded to pembrolizumab [53]. Other agents in this class, such as ipilimumabare also undergoing investigation in pancreatic cancer [54]. A phase II study of FOLFIRINOX followed by ipilimumab with an allogeneic tumor vaccine is underway in patients with APC [NCT01896869].

### Tumor vaccines

Whole tumor vaccines are promising cancer immunotherapies. Allogeneic pancreatic tumor vaccines are vaccines created from the tumor cells of one patient and given to another patient, with the hope that specific tumor antigens will be expressed and recognized by the new host's immune system, creating an immune response directed toward the host's own tumor cells [55]. **CRS-207** is a pancreatic cancer vaccine which uses a live-attenuated strain of *Listeria monocytogenes* that expresses mesothelin, a cell surface glycoprotein that is overexpressed in pancreatic tumors. The proposed mechanism of action is that the bacteria will invade phagocytes, produce mesothelin and, in turn, activate cytotoxic T cells against mesothelin, resulting in cell death of the mesothelin-expressing tumor cells.A recently completed phase II trial investigated the use of CRS-207 in conjunction with GVAX, a whole-cell vaccine expressing human granulocyte macrophage-colony stimulating factor. This study showed a statistically significant OS benefit in patients receiving the combination of GVAX and CRS-207 immunotherapies compared to patients receiving GVAX immunotherapy alone, with a mOS of 6.1 months compared with 3.9 months, respectively ($p$ = 0.011) [56].

### Tumor-specific antibodies

Yttrium Y-90 clivatuzumabtetraxetan is a radio-immunoconjugate made of a monoclonal antibody directed against the pancreatic tumor antigen MUC 1 conjugated to the chelating agent tetra-azacyclodecanetetra-acetic acid and radiolabeled with the radioisotope yttrium Y90 [56]. A phase I trial showed promising activity with a good safety profile [57]and this agent is currently being investigated in a phase III trial.

### Modified lymphocytes

Another approach to immunotherapy is to use T cells that have been engineered to have a T-cell receptor (TCR) that recognizes a specific antigen by fusing the TCR to the antibody-binding domain of an immunoglobulin (Ig) [58]. IgCD28TCR is a T cell designed with an Ig portion that recognizes carcinoembryonic antigen (CEA), allowing T cells to recognize and destroy cells expressing CEA [59]. A phase II clinical trial is currently recruiting participants with any CEA expressing adenocarcinoma, including pancreatic adenocarcinoma.

### Other targets

Table 5 summarizes few other agents which have been tested or undergoing testing in pancreatic cancer.

### Surgical resection of hepatic metastases

Researchers have investigated to determine the benefit of metastatectomy such as simultaneous pancreatic and partial hepatic resection. An analysis of 109 patients with pancreatic adenocarcinoma was performed [64]. These patients were divided into two groups:

**Table 4:** Immunotherapy in PC.

| | |
|---|---|
| Immune checkpoint inhibitors | Ipilimumab |
| Whole tumor vaccines | GVAX and CRS-207 |
| Tumor-specific antibodies | Yttrium Y-90 clivatuzumabtetraxetan |
| Modified lymphocytes | IgCD28TCR |

**Table 5:** summarizes few other agents which have been tested or undergoing testing in pancreatic cancer.

| Agent | Pathway | Study (I,II,III) | Outcome | Reference |
|---|---|---|---|---|
| Evofosfamide | Hypoxia-activated prodrug of bromo-isophosphoramide mustard (Br-IPM) that is preferentially activated under hypoxic conditions. | MAESTRO is an international, randomized, double-blind, placebo-controlled phase III trial of Evofosfamide/Gemcitabine vs Placebo/Gemcitabine (Clinical trial information: NCT01746979). | No survival benefit. | 60 |
| PHY906/Yiv906 | Chinese herbal drug that inhibits of NFK-b, VEGF and MMP. | II | Met the end point and improved 6-months survival. | 61 |
| Metformin | AMPK-pathway and mTOR. | I | Proof of principle. | 62,63 |

Group 1 consisted of 33 patients with liver metastasis:

- Group 1-A: 11 patients to aggressive surgery, consisting of pancreatoduodenectomy and partial liver resection.
- Group 1-B: 22 patients to palliative bypass surgery.
- Group 2 consisted of 76 patients without liver metastasis:
- Group 2-A: 37 patients to pancreatoduodenectomy.
- Group 2-B: 39 patients to bypass surgery.

The researchers did not find any statistical differences in the median OS (6 months versus 4 months) between Group 1-A and Group 1-B. All the patients in Group 1-A patients succumbed todeath within a year due to multiple recurrent liver metastases. Also, patients in the Group 1-A had significantly poorer survival compared to those in the Group 2-A.

However, as we evolved in the novel chemotherapeutic agents, newer data is showing a trend towards survival in selected patients with hepatectomy [65]. Cases of metachronous liver metastasis or synchronous liver oligometastasesof pancreatic cancer after radical surgery, in which patients exhibit long-term survival without recurrence after hepatectomy, are reported from major cancer centers [66,67]. Hepatectomy may confer long-term survival, and the time to postoperative recurrence and the number of liver metastases may be useful criteria for deciding whether to perform hepatic resection.It mandates a careful selection of patients after primary chemotherapy in a multidisciplinary approach.

## Radiation therapy

In comparison to conventional radiotherapy, stereotactic body radiation therapy (SBRT)may provide the opportunity to administer radiation in a shorter time frame with similar efficacy and reduced toxicity. In addition, SBRT involves more accurate patient immobilization and greater attention to accurate replication of the simulation position for treatment delivery, allowing for sub-centimeter precision [68]. The target tumor and the normal tissue avoidance structures are stereotactically registered to the treatment machine. Multiple non-coplanar fixed beams or arc fields are used in order to minimize normal tissue exposure and provide rapid fall-off of the radiation dose outside of the target area [69]. Finally, an ablative dose of ionizing radiation is delivered to the tumor, typically in one to five sessions. Many of the same principles are employed during stereotactic radiosurgery for brain lesions, but radiation oncologists are now adapting them to the treatment of extra-cranial tumors, such as pancreatic cancer. Multiple retrospective and prospective studies have explored the safety and efficacy of SBRT with and without chemotherapy in locally advanced pancreatic cancer and showed encouraging results with respect to local control of locally advanced pancreatic cancer [68,69,70]. Future studies are needed to address strategies for reducing long-term toxicities associated with SBRT, such as duodenal ulcer or perforation.

## Liver-directed therapy

With the improvement in technology in other modalities, researchers have also investigated the role of chemo- or radio-embolization to the liver metastasis in patients with APC [71].

## Trans-arterial chemoembolization

In one study, repetitive transarterial chemoembolization (TACE) in 34 patients of APC with liver metastases led to an overall disease control in 81 % of the patients (9.37% partial response (PR) + 71.87% stable disease) with an overall median OS of 16 months [72].

## Radio-embolization with Yttrium-90 microspheres (SIRT)

Others have looked in the role of radio-embolization with Yttrium-90 microspheres (SIRT) in APC patients with liver metastases and found an objective response up to 47% and a median OS of 9.0 months (range 0.9-53.0) [73]. Most acute toxicities such as nausea, vomiting, fatigue, fever and abdominal pain did not exceed grade 3. However, liver abscesses, gastroduodenal ulceration, cholestasis and cholangitis, ascites and spleen infarction were noticed as delayed complications secondary to Y-90

radio-embolization [74]. Our group also experienced benefit in selected cases [71]. It is mandatory that such an approach should be undertaken with the guidance of a multi-disciplinary team of experts.

## DISCUSSION

It is evident that there are many challenges related to pancreatic adenocarcinoma ranging from its environment, relative chemo-resistance, to lack of screening tools, delayed diagnosis, diagnosis at an advanced stage, patient's poor quality of life, lack of biomarkers (predictive or prognostic), variation in the management of patients across the globe, such as attitudes towards second-line therapy and use of radiotherapy especially for earlier stage patients. Access and funding for clinical trials remains limited and varied across the globe. So, to overcome these barriers and improve the outcome in patients with pancreatic cancer, we have made significant advances in our understanding of the biology of pancreas cancer, and many novel drugs and biologics are now in the practice such as olaparib while others in pipeline as a result of those advances. I am hopeful that we will see a number of promising novel treatments for pancreas cancer move into the clinic to benefit patients over the next few years. There is a long list of potential biomarkers, beyond pharmacogenetic markers that need to be validated not only to select the therapy but prognostic value too. Circulating tumor cells and circulating tumor DNAmay provide an early signal of treatment response or recurrence, and hence must be adapted immediately in the management of these patients. Future is also dependent on the organoids as well as tumor and patient profiling to evolve patient care in the era of precision medicine.

## Conflicts of Interest

The authors report no conflict of interest.

## REFERENCES


1. American Cancer Society. Cancer Facts & Statistics. American Cancer Society. 2020.

2. Ahmad NA, Lewis JD, Ginsberg GG, Haller DG, Morris JB, Williams NN, et al. Long term survival after pancreatic resection for pancreatic adenocarcinoma. Am J Gastroenterol. 2001; 96:2609-2615. [PMID: 25574100].

3. Zhang J, Dhakal I, Ning B, Kesteloot H. Patterns and trends of pancreatic cancer mortality rates in Arkansas, 1969-2002: A comparison with the US population. Eur J Cancer Prev 2008; 17:18. [PMID: 18090906].

4. Ma J, Siegel R, Jemal A. Pancreatic cancer death rates by race among US men and women, 1970-2009. J Natl Cancer Inst 2013; 105:1694. [PMID: 24203988].

5. Conroy T, Desseigne F, Ychou M, Bouche O, Guimbaud R, Becouarn Y, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. N Engl J Med. 2011; 364:1817-1825. [PMID: 21561347].

6. Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med*. 2013; 369:1691–1703.

7. Von Hoff D. NAPOLI-1: Randomized phase 3 study of MM-398 (nal-IRI), with or without 5-fluoruracil and leucovorin versus 5-fluoruracil and leucovorin, in metastatic pancreatic *cancer* progressed on or following gemcitabine-based therapy [abstract O-0003]. Ann Oncol. 2014; 25:ii105–ii117.

8. Saif MW. Screening of pancreatic cancer. JOP. 2018; 19:109-112. [PMID: 30057517].

9. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, et al. International cancer of the pancreas screening (caps) consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013; 62:339. [PMID: 23135763].

10. Ramesh K Ramanathan, Peter Lee, John E Seng, Stephen Patrick Anthony, Peter J Rosen, Raul R Mena, et al. Phase II study of induction therapy with gemcitabine and nab-paclitaxel followed by consolidation with mFOLFIRINOX in patients with metastatic pancreatic cancer. J Clin Oncol. 2014; 32:3.

11. Neoptolemos JP, Stocken DD, Friess H, Bassi C, Dunn JA, Hickey H et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med*. 2004; 350:1200-1210. [PMID: 15028824].

12. Oettle H. Adjuvant chemotherapy with gemcitabine vs. observation in patients undergoing curative-intent resection of pancreatic cancer. JAMA. 2007; 297:267-277. [PMID: 17227978].

13. Conroy T, Hammel P, Hebbar M, Abdelghani MB, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as adjuvant therapy for pancreatic cancer. N Engl J Med. 2018; 379:2395-2406. [PMID: 30575490].

14. Uesaka K, Boku N, Fukutomi A, Okamura Y, KOnishi M, Matsumoto I, et al. Adjuvant chemotherapy of S-1 versus gemcitabine for resected pancreatic cancer: A phase 3, open-label, randomised, non-inferiority trial (JASPAC 01). Lancet. 2016; 388: 248-257. [PMID: 27265347].

15. Regine WF, Winter KA, Abrams RA, Safran H, Hoffman JP, Konski A, et al. Fluorouracil *vs* gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: A randomized controlled trial. *JAMA*. 2008; 299:1019-1026. [PMID: 18319412].

16. Margaret A Tempero, Michele Reni, Hanno Riess, Uwe Pelzer, Eileen Mary O'Reilly, Jordan Michael, et al. APACT: phase III, multicenter, international, open-label, randomized trial of adjuvant *nab*-paclitaxel plus gemcitabine (*nab*-P/G) vs gemcitabine (G) for surgically resected pancreatic adenocarcinoma. J Clin Oncol 2019; 37:4000-4000.

17. Philip PA, Lacy J, Portales F, Sobrero A, Pazo-Cid R, ManzanoMozo JL, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): A multicentre, open-label phase 2 study. Lancet Gastroenterol Hepatol. 2020; 1253:30327-9. [PMID: 31953079].

18. Lowery MA, Kelsen DP, Stadler ZK, Yu KH, JanJigian YY, Ludwig E, et al. An emerging entity: Pancreatic adenocarcinoma associated with a known BRCA mutation: Clinical descriptors, treatment implications, and future directions. *Oncologist*. 2011; 16:1397-402. [PMID: 21934105].

19. Roberts NJ, Norris AL, Petersen GM, Bondy ML, Brand R, Gallinger S, et al. Whole genome sequencing defines the genetic heterogeneity of familial pancreatic cancer. Cancer Discov. 2016; 6:166-75. [PMID: 26658419].

20. Vyas O, Leung K, Ledbetter L, Kaley K, Rodriguez T, Garcon MC, et al. Clinical outcomes in pancreatic adenocarcinoma associated with BRCA-2 mutation. *Anticancer Drugs*. 2015; 26:224-6. [PMID: 25304989].

21. Lowery MA, Lee A, Tobias E, Sung P, Bhanot U, Shakya R, et al. Evaluation of PARP inhibition as a platinum sparing strategy in BRCA2-deficient pancreatic tumors. *J ClinOncol*. 2014; 32-e15237.

22. Golan T, Hammel P, Reni M, Cutsem EV, Macarulla T, Hall MJ, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med. 2019; 381:317–327. [PMID: 31157963].

23. Bittoni A, Mandolesi A, Andrikou K, Santoni M, Alfonsi S, Lanese A, et al. HER family receptor expression and prognosis in pancreatic cancer. Int J Biol Markers. 2015; 30:e327-32. [PMID: 26109364].

24. Chou A, Waddell N, Cowley MJ, Gill AJ, Chang Dk, Patch AM, et al. Clinical and molecular characterization of HER2 amplified-pancreatic cancer. *Genome Med*. 2013; 5:78. [PMID: 24004612].

25. Safran H, Iannitti D, Ramanathan R, Schwartz JD, Steinhoff M, Nauman C, et al. Herceptin and gemcitabine for metastatic pancreatic cancers that overexpress HER-2/neu. Cancer Invest. 2004; 22:706-712. [PMID: 15581051].

26. Harder J, Ihorst G, Heinemann V, Hofheinz R, Moehler M, Buechler P, et al. Multicentre phase II trial of trastuzumab and capecitabine in patients with HER2 overexpressing metastatic pancreatic cancer. Br J Cancer. 2012; 106:1033-1038. [PMID: 22374460].

27. Safran H, Miner T, Bahary N, Whiting S, Lopez CD, Sun W, et al. Lapatinib and gemcitabine for metastatic pancreatic cancer. A phase II study. Am J ClinOncol. 2011; 34:50-52. [PMID: 24757739].

28. Strimpakos AS, Syrigos KN, Saif MW. The molecular targets for the diagnosis and treatment of pancreatic cancer. Gut Liver. 2010; 4:433-49. [PMID: 21253292].

29. Sugarman R, Patel R, Sharma S, Plenker D, Tuveson D, Saif MW. Pharmacokinetics and pharmacodynamics of new drugs for pancreatic cancer. Expert Opin Drug MetabToxicol. 2019; 15:541-552. [PMID: 31241371].

30. El Hassouni B, Li Petri G, Liu DSK, Cascioferro S, Parrino B, Hassan W, et al. Pharmacogenetics of treatments for pancreatic cancer. Expert Opin Drug MetabToxicol. 2019; 15:437-447. [PMID: 31100206].

31. Merika EE, Syrigos KN, Saif MW. Desmoplasia in pancreatic cancer. Can we fight it? Gastroenterol Res Pract. 2012; 2012:781765. [PMID: 23125850].

32. Kano MR, Bae Y, Iwata C, Morishita Y, Yashiro M, Oka M, et al. Improvement of cancer-targeting therapy, using nanocarriers for intractable solid tumors by inhibition of TGF-beta signaling. Proc Natl Acad Sci USA. 2007; 104:3460-5. [PMID: 17307870].

33. Dimou A, Syrigos K, Saif MW. Rationale for inhibition of the hedgehog pathway paracrine loop in pancreatic adenocarcinoma. JOP. 2011; 12:1-5. [PMID: 21206093].

34. Steg A, Vickers SM, Eloubeidi M, Wang W, Eltoum IA, Grizzle WE, et al. Hedgehog pathway expression in heterogeneous pancreatic adenocarcinoma: implications for the molecular analysis of clinically available biopsies. *Diagn Mol Pathol* 2007; 6:229-37. [PMID: 18043287].

35. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, McIntyre D, Honess D, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science. 2009; 324: 1457-1461. [PMID: 19460966].

36. Antonio Jimeno, Glen J Weiss, Wilson H Miller, Scott Gettinger, Bernard JC Eigl, Anne Lynne S. Chang, et al. Phase i study of the hedgehog pathway inhibitor ipi-926 in adult patients with solid tumors. Clin Cancer Res 2013; 19:2766-2774. [PMID: 23575478].

37. De Jesus-Acosta A, O'Dwyer P, Ramanathan R, Von Hoff D, Maitra A, Rasheed Z, et al. A phase II study of vismodegib, a hedgehog (Hh) pathway inhibitor, combined with gemcitabine and nab-paclitaxel (nab-P) in patients (Pts) with untreated metastatic pancreatic ductal adenocarcinoma (PDA). Br J Cancer. 2020; 122:498-505. [PMID: 31857726].

38. Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, *et al*. CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. *Sci.* 2011; 331:1612–16. [PMID: 21436454].

39. Beatty GL, Torigian DA, Chiorean EG, Saboury B, Brothers A, Alavi A, et al. A phase I study of an agonist CD40 monoclonal antibody (CP-870,893) in combination with gemcitabine in patients with advanced pancreatic ductal adenocarcinoma. Clin Cancer Res. 2013; 19:6286-95. [PMID: 23983255].

40. Jacobetz MA, Chan DS, Neesse A, Bapiro TE, Cook N, Frese KK, *et al*. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut*. 2013; 62:112-20. [PMID: 22466618].

41. Hingorani SR, Harris WP, Beck JT, Berdov BA, Wagner SA, Pshevlotsky EM, et al. Phase Ib study of PE-Gylated recombinant human hyaluronidase and gemcitabine in patients with advanced pancreatic cancer. Clin Cancer Res. 2016; 22:2848-2854. [PMID: 26813359].

42. Hingorani SR, Zheng L, Bullock AJ. HALO 202: Randomized Phase II study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J ClinOncol. 2018; 36:359-366.

43. Hakim N, Patel R, Devoe C, Saif MW. Why HALO 301 failed and implications for treatment of pancreatic cancer. Pancreas (Fairfax). 2019; 3:e1-e4. [PMID: 32030361].

44. Ramanathan RK, McDonough SL, Philip PA, Hingorani SR, Lacy J, Kortmansky JS, et al. Phase IB/II randomized study of FOLFIRINOX plus pegylated recombinant human hyaluronidase versus FOLFIRINOX alone in patients with metastatic pancreatic adenocarcinoma: SWOG S1313. J ClinOncol. 2019; 37:1062–1069. [PMID: 30817250].

45. Onyeisi JOS, Ferreira BZF, Nader HB, Lopes CC. Heparan sulfate proteoglycans as targets for cancer therapy: a review. Cancer BiolTher. 2020; 21:1087-1094. [PMID: 33180600].

46. Birgit CorinnaSchultes, Chia Lin Chu, Alison Long, Elaine Sun, Elma Kurtagic, Daniela Beccati, et al. The effect and mechanism of M402 on gemcitabine uptake into pancreatic tumors. J Clin Oncol 2014.

47. Saif MW. Novel Drug Targets Based on Association between Inflammation and Pancreatic Ductal Adenocarcinoma. *JOP.* 2010; 11:403-4. [PMID: 20601821].

48. Boger PC, Shutt JD, Neale JR, Wilson SJ, Bateman AC, Holloway JW, et al. Increased expression of the 5-lipoxygenase pathway and its cellular localization in Barrett's adenocarcinoma. Histopathology. 2012; 61:509-517. [PMID: 22690932].

49. Tong WG, Ding XZ, Witt RC, Adrian TE. Lipoxygenase inhibitors attenuate growth of human pancreatic cancer xenografts and induce apoptosis through the mitochondrial pathway. Mol Cancer Ther. 2002; 1:929-935. [PMID: 12481414].

50. Saif MW, Oettle H, Vervenne WL, Thomas JP, Spitzer G, Visseren-Grul C, et al. Randomized double-blind phase II trial comparing gemcitabine plus LY293111 versus gemcitabine plus placebo in advanced adenocarcinoma of the pancreas. Cancer J. 2009; 15:339-343. [PMID: 19672152].

51. Hurwitz H, Van Cutsem E, Bendell J, Hidalgo M, Li Pi C, Salvo MG, et al. Ruxolitinib + capecitabine in advanced/metastatic pancreatic cancer after disease progression/intolerance to first-line therapy: JANUS 1 and 2 randomized phase III studies. *Invest New Drugs*. 2018; 36:683-695. [PMID: 29508247].

52. Ahmad-Nielsen SA, Bruun Nielsen MF, Mortensen MB, Detlefsen S. Frequency of mismatch repair deficiency in pancreatic ductal adenocarcinoma. Pathol Res Pract. 2020; 216:152985.

53. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372:2509-20. [PMID: 26028255].

54. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, et al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother*. 2010; 33:828-833. [PMID: 20842054].

55. Kotteas E, Saif MW, Syrigos K. Immunotherapy for pancreatic cancer. J Cancer Res ClinOncol. 2016; 142:1795-805.

56. Dung T Le, Andrea Wang-Gillam, Vincent Picozzi, Tim F Greten, Todd S Crocenzi, Gregory M Springett, et al. A phase 2, randomized trial of GVAX pancreas and CRS-207 immunotherapy versus GVAX alone in patients with metastatic pancreatic adenocarcinoma: Updated results. J Clin Oncol. 2014; 32: 3.

57. Ocean AJ, Pennington KL, Guarino MJ, Sheikh A, Bekaii-Saab T, Serafini AN, et al. Fractionated radioimmunotherapy with (90) Y-clivatuzumabtetraxetan and low-dose gemcitabine is active in advanced pancreatic cancer: A phase I trial. Cancer. 2012; 118:5497-5506. [PMID: 22569804].

58. Liu F, Saif MW. T cell optimization for the treatment of pancreatic cancer. Expert Opin Biol Ther. 2017; 17:1493-1501. [PMID: 28835191].

59. Emtage PC, Lo AS, Gomes EM, Liu DL, Gonzalo-Daganzo RM, Junghans RP. Second-generation anti-carcinoembryonic antigen designer T cells resist activation-induced cell death, proliferate on tumor contact, secrete cytokines, and exhibit superior antitumor activity in vivo: a preclinical evaluation. Clin Cancer Res. 2008; 14:8112-22. [PMID: 19088026].

60. Eric Van Cutsem, Heinz-Josef Lenz, JunjiFuruse, JosepTabernero, Volker Heinemann, Tatsuya Ioka, et al. MAESTRO: A randomized, double-blind phase III study of evofosfamide (Evo) in combination with gemcitabine (Gem) in previously untreated patients (pts) with metastatic or locally advanced unresectable pancreatic ductal adenocarcinoma (PDAC). J Clin Oncol. 2016; 34:4007-4007.

61. Saif MW, Li J, Lamb L, Kaley K, Elligers K, Jiang Z, et al. First-in-human phase II trial of the botanical formulation PHY906 with capecitabine as second-line therapy in patients with advanced pancreatic cancer. Cancer Chemother Pharmacol. 2014; 73:373-80. [PMID: 24297682].

62. Godara A, Siddiqui NS, Hachem H, Tsichlis PN, Martell RE, Saif MW. Prospective evaluation of effect of metformin on activation of amp-activated protein kinase (ampk) and disease control in a sub-group analysis of patients with gi malignancies. J Cell Signal. 2020; 1:35-41. [PMID: 32601620].

63. Ferrari C. Phase II trial of metformin and paclitaxel for patients with gemcitabine-refractory advanced adenocarcinoma of the pancreas. J Clin Oncol. 2014; 32:4022.

64. Gleisner AL, Assumpcao L, Cameron JL, Wolfgang CL, Choti MA, Herman JM, et al. Is resection of periampullary or pancreatic adenocarcinoma with synchronous hepatic metastasis justified? Cancer. 2007; 110:2484-92. [PMID: 17941009].

65. Saif MW. Is liver resection in metastases of exocrine pancreatic carcinoma justified? JOP. 2011;12:68-9.

66. Takada T, Yasuda H, Amano H, Yoshida M, Uchida T. Simultaneous hepatic resection with pancreato-duodenectomy for metastatic pancreatic head carcinoma: does it improve survival? Hepatogastroenterology. 1997; 44:567-73. [PMID: 9164539].

67. Crippa S, Cirocchi R, Weiss MJ, Partelli S, Reni M, Wolfgang CL, et al. A systematic review of surgical resection of liver-only synchronous metastases from pancreatic cancer in the era of multiagent chemotherapy. Updates Surg. 2020; 72:39-45. [PMID: 31997233].

68. Azizi A, Naguib NN, Mbalisike E, Farshid P, Emami AH, Vogl TJ. Liver metastases of pancreatic cancer: role of repetitive transarterial chemoembolization (TACE) on tumor response and survival. Pancreas. 2011; 40:1271-5. [PMID: 21975434].

69. Michl M, Haug AR, Jakobs TF, Paprottka P, Hoffmann RT, Bartenstein P, et al. Radioembolization with Yttrium-90 microspheres (SIRT) in pancreatic cancer patients with liver metastases: efficacy, safety and prognostic factors. Oncology. 2014; 86:24-32. [PMID: 24401529].

70. Cao C, Yan TD, Morris DL, Bester L. Radioembolization with yttrium-90 microspheres for pancreatic cancer liver metastases: results from a pilot study. Tumori. 2010; 96:955-8. [PMID: 21388058].

71. Goyal SP, Jyothi Jose, Craig R Greben, Igor Lobko, Gregory Michael Grimaldi, MagedGhaly, et al. Liver-directed therapy (LDT) and systemic chemotherapy for pancreatic adenocarcinoma with liver metastases (PCLM): Experience of 12 years. J Clin Oncol. 2020; 38: e16768-e16768.

72. Schellenberg D, Kim J, Christman-Skieller C, Chun CL, Columbo LA, Ford JM, et al. Single-fraction stereotactic body radiation therapy and sequential gemcitabine for the treatment of locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys. 2011; 81:181-8. [PMID: 21549517].

73. Chang BW, Saif MW. Stereotactic body radiation therapy (SBRT) in pancreatic cancer: Is it ready for prime time? JOP. 2008; 9:676-82. [PMID: 18981547].

74. Gurka MK, Collins SP, Slack R, Tse G, Charabaty A, Ley L, et al. Stereotactic body radiation therapy with concurrent full-dose gemcitabine for locally advanced pancreatic cancer: A pilot trial demonstrating safety. Radiat Oncol. 2013; 8:44. [PMID: 23452509].