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RECENT FINDINGS IN IMMUNOTHERAPY TREATMENT OF PANCREATIC CANCER - A NARRATIVE REVIEW

Michał Cholewiński[1] ✉, ***Alicja Pełszyk[2]***, ***Daria Marciniak[3]***, ***Justyna Kącikowska[4]***, ***Natalia Rosół[5]***, ***Natalia Ziółkowska[6]***, ***Paweł Szajewski[4]***, ***Justyna Łapicka[2]***, ***Agata Pluta[7]***, ***Natalia Kruszewska[8]***

[1] *Warsaw Southern Hospital, Warsaw, Poland*
[2] *Military Institute of Medicine – National Research Institute, Warsaw, Poland*
[3] *Multidisciplinary Hospital in Warsaw-Międzylesie, Warsaw, Poland*
[4] *Dr. Anna Gostyńska Wolski Hospital, Warsaw, Poland*
[5] *National Medical Institute of the Ministry of Interior and Administration, Warsaw, Poland*
[6] *Central Clinical Hospital of the University Clinical Centre of the Medical University of Warsaw, Poland*
[7] *New Hospital in Olkusz, Poland*
[8] *Provincial Hospital in Poznań, Poland*

✉ ***s.cholewinski@gmail.com***

ABSTRACT

INTRODUCTION

Despite the established role of immunotherapy in several malignancies, pancreatic ductal adenocarcinoma remains largely resistant to these approaches. A highly immunosuppressive tumor microenvironment represents a major barrier to effective immune based treatment. At the molecular level, multiple studies have identified potential targets that may be exploited to modulate immune responses in pancreatic cancer.

AIM

To summarize and critically evaluate recent clinical and translational evidence on the use of immunotherapy in pancreatic cancer published between 2023 and 2025.

METHODS

A narrative literature review was performed using PubMed, focusing on clinical and randomized clinical trials published from January 2023 to October 2025. The search terms included pancreatic cancer and immunotherapy. Only English language publications with available full text were considered.

RESULTS

Preclinical and translational studies consistently demonstrate immune dysfunction within the pancreatic cancer tumor microenvironment, which limits the effectiveness of immunotherapy. Clinical data indicate that immune checkpoint inhibitors do not provide meaningful benefit as monotherapy. Combination strategies with chemotherapy or radiotherapy generally produced inconsistent results, with limited benefit observed only in selected patient subgroups. TGF β based vaccination approaches combined with immune checkpoint inhibitors were associated with prolonged progression free and overall survival in specific settings. Vaccine based strategies, including personalized mRNA vaccines and dendritic cell vaccines, demonstrated durable recurrence free survival or measurable molecular responses in early phase clinical trials.

CONCLUSIONS

Recent literature shows advances in the biological understanding of immunotherapy resistance in pancreatic cancer, but molecular and immunological findings are not consistently translated into clinical benefit. Among the investigated strategies, personalized mRNA vaccines and dendritic cell based immunotherapies currently provide the most consistent positive signals and represent priority directions for further evaluation in controlled clinical trials.

Keywords: Pancreatic cancer, immunotherapy, immune checkpoint inhibitors, pancreatic ductal adenocarcinoma, tumor microenvironment, cancer vaccines

1. INTRODUCTION

Several neoplasms have shifted from being considered fatal diseases to being categorized as chronic illnesses, owing to the new therapies. One of them is immune checkpoint inhibitors (ICIs), whose discovery has ushered in a new era of oncology. Despite the field of oncology grouping an abundance of diseases, they do not all follow the same strategies in terms of etiology, diagnosis, or treatment. Immunotherapy has been successfully implemented in the treatment of advanced melanoma [1], lung cancer [2], or bladder cancer [3]; however, its usefulness in the pancreatic ductal adenocarcinoma (PDAC) has been limited. Currently, the "ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up" implements immunotherapy in the form of pembrolizumab as a second-line treatment in patients with MSI-H/dMMR metastatic pancreatic tumors (FDA approved, but not EMA approved) [4]. The scarce application of ICIs and other immune agents is due to several factors. A major impediment is formed by a highly immunosuppressive tumor microenvironment (TME), which is composed of "a high number of tumor-associated immunosuppressive cells and a uniquely desmoplastic stroma" that renders T cells unable to infiltrate the tumor [5]. Cancer-associated fibroblasts (CAF) are responsible not only for tumor progression but also for drug resistance [6]. Moreover, PD-L1 (programmed death-ligand 1) is found to be overexpressed in PDACs [7].

However, there have been some promising molecular findings that could warrant developing specific targeting agents to address the immune mechanisms. An increased overall survival (OS) has been correlated with the spatial distribution of cytotoxic T cells in proximity to cancer cells [8]. Moreover, an increased amount of evidence confirms that pancreatic cancer is recognized by the immune system; what is hindering its natural function is the tumor's evasion strategies, which in turn also affect immunotherapy efficacy [9].

Pancreatic cancer is predicted to become the second leading cause of cancer-related death by 2030 [10], therefore, novel approaches to its treatment are required. The urgent need to develop new treatment strategies, along with the biochemical implications of targeting the TME with immunotherapy, led us to review the literature on recent advances in the field. We present a comprehensive summary of the latest clinical trials that implement various treatment regimens of immunotherapy that aim to overcome the impasse posed by PDAC's TME.

1.1. NOVELTY OF THE ARTICLE

The novelty of the article lies in the fact that, based on clinical and translational studies from 2023 to 2025, a consistent demonstration is provided of the fundamental limitations of immune checkpoint inhibitor efficacy in PDAC, while simultaneously identifying specific immunotherapeutic approaches for which stable clinical or molecular signals of efficacy have been documented. The article systematically demonstrates that vaccine based and cellular strategies, including personalized mRNA vaccines, dendritic cell vaccines, KRAS targeted vaccines and CAR T therapy, qualitatively differ from ICIs in the nature of their outcomes and constitute an independent direction in the development of immunotherapy for PDAC.

1.2. RELEVANCE OF THE ARTICLE

The relevance of the article is determined by the high lethality of pancreatic cancer and the projected increase in its contribution to cancer related mortality. The text shows that existing standards of treatment, including immunotherapy, are applicable only to a very limited subgroup of patients and do not solve the problem as a whole.

Under these conditions, a systematic analysis of new immunotherapeutic approaches aimed at overcoming the immunosuppressive tumor microenvironment has direct clinical and research significance.

1.3. AIM OF THE ARTICLE

The aim of the article is to analyze and critically evaluate current data on the use of immunotherapy in pancreatic cancer over the period from January 2023 to October 2025, with an emphasis on clinical outcomes, molecular mechanisms of resistance and therapeutic approaches aimed at modifying the tumor microenvironment.

Research objectives of the article

1. To describe the key molecular and cellular mechanisms of immunosuppression within the PDAC tumor microenvironment that influence the effectiveness of immunotherapy.
2. To analyze the results of clinical trials of immune checkpoint inhibitors in various therapeutic combinations and to determine the limits of their clinical efficacy.
3. To identify immunological and molecular factors associated with response to immunotherapy based on the data from the included studies.
4. To evaluate the clinical and molecular outcomes of vaccine based and cellular immunotherapeutic strategies.
5. To determine the directions of PDAC immunotherapy with the greatest potential for further clinical research.

2. METHOD OF LITERATURE SELECTION

A narrative literature review was conducted using PubMed, focusing on trials published between January 2023 and October 2025. The search included the following keywords: "pancreatic cancer" and "immunotherapy". The inclusion criteria were randomized trials and clinical trials written in English and whose full text was available. If a study tackled more than one type of tumor, it was allowed as long as at least some of the data distinguished patients with pancreatic cancer from other experimental groups.

A total of 73 titles and abstracts were identified through the database search. After screening according to the inclusion and exclusion criteria, 23 clinical studies were included in the qualitative analysis. The final reference list comprised 44 sources.

Inclusion criteria:

- Publication date between January 2023 and October 2025
- Language of publication must be English
- Article type: clinical trials or randomized clinical trials

Exclusion criteria:

- Publications with no original data
- Language of publication other than English
- Date of publication before January 2023
- Article type: case reports, meta-analyses, conference abstracts

2.1. DATA COLLECTION

A total of 73 titles and abstracts were found that matched the search criteria. Then, two researchers investigated the abstracts to look for both inclusion and exclusion criteria. If an abstract fulfilled the criteria, then a full publication was retrieved and sent for a thorough analysis. 23 articles fit the inclusion criteria. The data extractions included: patient population, staging, treatment regimen used as an intervention, oncological endpoints, safety and adverse reactions, and molecular outcomes (if a study had a biochemical analysis). The results from the studies were then extracted and put into a table (Table 2) to create a summary of the interventions and oncological outcomes. The review offers a qualitative synthesis, and hence we did not implement any statistical analysis. A section was devoted to phase 1 clinical trials to present the ongoing attempts to introduce new agents, in order to cover the topic broadly.

3. RESULTS AND DISCUSSION

3.1. PRE-CLINICAL DATA

Yousuf et al. carried out a study to explore the tumor microenvironment with the use of single-cell RNA sequencing

(scRNAseq), mass cytometry, spatial transcriptomics, and multiplex fluorescent immunohistochemistry (mfIHC). Combining multiple techniques allowed the research to develop a "spatially resolved multi-omics immune profiling strategy" [11]. The comparison of immune profiling of treatment-naïve surgically resected tumors to nontumor pancreatic tissue and patient blood samples led the researchers to multiple conclusions. Firstly, CD8 T effector cell populations are present within the TME in PDAC, however, their cytotoxic abilities are likely impaired [11]. Secondly, the trajectory analysis of the CD8 T cells demonstrated they have up-regulated signals of exhaustion and immune dysfunction, while their signals of naïveness and cytotoxicity are down-regulated [11], reflecting the defective phenotypes in the TME. Thirdly, peripheral CD8 T cells did not exhibit LAG3 expression, while that was the opposite in the TME, where the majority of the cell population displayed LAG3 expression. LAG3 acts as an immune checkpoint that can inhibit T cell activation [12], further contributing to T cell exhaustion within the tumor. Similarly, natural killer T (NKT) cells expressed higher levels of inhibitory molecules at the tumor site compared to nontumor tissue [11]. Regarding other cell populations: tumor-infiltrating CD4 T cells possess an exceptionally dysfunctional phenotype; B lymphocytes in the TME also express an immunosuppressive phenotype, e.g., through significantly higher levels of *TGFB1*; lastly, macrophages and monocytes in tumor site populations are more prone to exhibit genes involved in angiogenesis and immunoregulation [11]. The researchers then identified a correlation between an immune signature and a survival outcome. Specifically, significantly longer overall survival was correlated with the following profile: "high levels of CD8 T and CD4 T cells together with low levels of alternatively activated macrophages" [11].

The TME of pancreatic cancer expresses a variety of molecules to support fibrosis and a local immunosuppressive environment. One of them is transforming growth factor-β (TGF-β). Mortensen et al. used the findings that TGF-β-specific T cells targeting TGF-β-expressing immune regulatory cells have been identified in patients with cancer, and are especially elevated in patients with PDAC [13]. The researchers have analyzed T-cell responses in 32 patients with metastatic PDAC from CheckPAC – a phase II, single-center trial, that included 84 patients who received ICI combined with stereotactic body radiation therapy (SBRT). Patients from arm A were given nivolumab, while the arm B received nivolumab + ipilimumab. Among the 32 patients analyzed: 7 (22%) experienced a partial response (PR), 12 (37%) exhibited stable disease (SD), and 13 (41%) showed progressive disease (PD) [13]. The exploration began with measuring T-cell responses to a TGF-β epitope called TGF-β-15 peptide before and after treatment. To rule out dysfunctional immune responses from other than a neoplastic reason, they compared the responses to tetanus and flu epitopes. They established a correlation between a strong TGF-β-specific immune response at the beginning of the treatment and longer progression free survival (PFS) and overall survival (OS) [13]. Moreover, the finding remained significant in multivariate analysis [13]. Next, the scientists repeatedly stimulated patients' cells, who exhibited a weak initial response, with the TGF-β-15 epitope in vitro, resulting in enhanced immune response to TGF-β-15 [13]. Thus, they managed to mimic a TGF-β-15 vaccination effect. The data from all of the findings suggest that having TGF-β-specific T cells can be beneficial for patients receiving ICI + SBRT treatment, and that response can be enhanced with a TGF-β-based vaccination [13].

Further analysis of the CheckPAC patient group conducted by Christensen et al. revealed that high levels of FASLG and Gal-1 were associated with checkpoint inhibitor efficacy [14]. Univariable Cox regression analysis demonstrated that high FASLG and Gal-1 were significantly linked with longer PFS [14]. That is a promising finding, displaying that there are predictors for ICIs' efficacy in metastatic PDAC patients.

Boucher et al. discovered that adding losartan to FOLFIRINOX and chemoradiation reduces immunosuppression-associated genes, Tregs, and FOXP3+ cancer cells in locally advanced PDAC [15]. They designed a phase 2 trial comprised of 45 recruits who received losartan + FOLFIRINOX followed by chemoradiation (n = 17), FOLFIRINOX followed by chemoradiation (n = 19), or no neoadjuvant treatment (n = 9). Then they examined surgical tissue samples using gene expression and immunofluorescence (IF) analysis. The group that received the treatment regimen with losartan had downregulated pro-invasion genes, significantly less residual disease in lesions, and lastly, they had decreased levels of immunosuppressive FOXP3+ and Treg cells [15]. These discoveries show that using additional agents to standard treatments can impact the TME, which warrants further research to find the clinical benefits of such additions.

3.2. CLINICAL TRIALS WITH IMMUNE CHECKPOINT INHIBITORS

Multiple studies attempt to implement already registered agents for other tumor types among PDAC patients. In the table below, we summarize the most commonly used drugs in PDAC trials, along with their mechanisms of action and examples of registered indications.

Table 1. Immunotherapy agents and their characteristics.

Drug name	Brand name	Mechanism of action	Exemplary registered indications

Pembrolizumab	Keytruda, Keytruda Qlex	anti-PD-1 monoclonal antibody	melanoma, NSCLC, head and neck squamous cell cancer, urothelial cancer [16]
Ipilimumab	Yervoy	anti-CTLA-4 monoclonal antibody	melanoma, RCC, colorectal cancer, HCC, NSCLC [17]
Nivolumab	Opdivo, Opdivo Qvantig, Opdualag	anti-PD-1 monoclonal antibody	melanoma, NSCLC, RCC, HCC, colorectal cancer [18]
Tocilizumab	Actemra, Avtozma, RoActemra, Tofidence, Tyenne	anti-IL-6R monoclonal antibody	severe rheumatoid arthritis, giant cell arteritis, adults with COVID-19 requiring supplemental oxygen or mechanical ventilation [19]
Atezolizumab	Tecentriq, Tecentriq Hybreza	anti-PD-L1 monoclonal antibody	NSCLC, small cell lung cancer, HCC, melanoma [20]
Durvalumab	Imfinzi	anti-PD-L1 monoclonal antibody	NSCLC, small cell lung cancer, HCC, biliary tract cancer [21]

NSCLC - non-small cell lung cancer, RCC - renal cell carcinoma, HCC - hepatocellular cancer

3.2.1. PEMBROLIZUMAB

During an open-label, randomized, phase 2 trial, a total of 170 patients were randomly assigned to receive stereotactic body radiation therapy (SBRT) plus pembrolizumab and trametinib (MEK inhibitor) - the experimental group; or SBRT and gemcitabine - the control group. 170 patients with locally recurrent PDAC after surgery and chemotherapy were recruited. The experimental arm received SBRT, 200 mg pembrolizumab i.v. every 3 weeks and 2 mg of trametinib p.o. once daily [22]. The control arm SBRT and 1000 mg/m2 of gemcitabine i.v. on day 1 and 8 of each 21-day cycle for 8 cycles [22]. The researchers predicted the response to the treatment regimen might be different depending on whether there is PD-L1 expression in the TME and the presence of infiltration of CD8+ T cells in the tumor. Hence, the results are analyzed with regard to PD-L1 and TILs (tumor-infiltrating lymphocytes) expression. For the group with pembrolizumab, the median OS was 17.2 months (95% CI 14.6–19.8 months) in patients with PD-L1+/TIL+ and 12.7 months (95% CI 10.8–14.6 months) in patients with PD-L1+/TIL- (HR 0.62, 95% CI 0.39–0.97, p = 0.036) [22]. While in the group with gemcitabine, the median OS was 13.1 months (95% CI 10.9–15.3 months) in patients with PD-L1+/TIL- and 12.7 months (95% CI 9.2–16.2 months) in patients with PD-L1+/TIL+ (HR 0.97, 95% CI 0.62–1.52, p = 0.896) [22]. For patients treated with pembrolizumab, the median PFS accounted for 10.5 months (95% CI 8.7–12.3 months) in the PD-L1+/TIL+ group, and 7.1 months (95% CI 4.9–9.3 months) in the PD-L1+/TIL- group [22]. For patients treated with gemcitabine, the median PFS was equal to 5.0 months (95% CI 1.9–8.0 months) and 5.4 months (95% CI 2.6–8.2 months), for PD-L1+/TIL+ and the PD-L1+/TIL- groups respectively [22]. Adverse events of grade 3 or 4 were found among the immunotherapy group in 16 patients (30.8%) in the PD-L1+/TIL- arm and 10 patients (30.3%) in the PD-L1+/TIL+ arm, whereas for the group with gemcitabine, it was 9 (16.7%) in the PD-L1+/TIL- arm and 8 patients (25.8%) in the PD-L1+/TIL+ [22]. The results show a longer survival when pembrolizumab was part of the regimen, however, only in the patients with PD-L1+/TIL+. Moreover, the OS improvement is not associated with a toxicity increase [22].

Chung et al. designed a double-blind, placebo-controlled, randomized phase II trial based on preclinical studies showing that vitamin D receptor agonists (e.g. paricalcitol) can sensitize pancreatic tumors to PD-1 inhibition signals [23]. They recruited patients with metastatic PDAC with "no disease progression after frontline systemic therapy, and achieving maximal cytoreduction" [23] and no prior anti-PD-(L)1 therapy. The patients received pembrolizumab 200 mg i.v. every 3 weeks and either paricalcitol 25 mcg i.v. 3 times per week or placebo [23]. The study's primary objective was 6-month PFS. However, no significant difference between the group pembrolizumab + paricalcitol (6-month PFS = 0.0%) compared to pembrolizumab + placebo (6-month PFS = 16.7%) [23]. The median PFS for the experimental vs control group was 3.1 months vs 4.0 months [23]. Similarly, the median OS for the experimental vs control group was 10.4 months vs 10.2 months [23]. Moreover, no significant difference was found in treatment-related adverse events (TRAEs) between the two arms [23]. This study shows that despite the promising preclinical findings, the clinical significance does not always follow. The authors also note that the 3 times weekly administration of paricalcitol might be enough to exert an effect on calcium levels, but not enough to affect the PTH level, as

paricalcitol's half-life is 5-7 hours, thus yielding little or no impact on TME [23].

Katz et al. designed a study to test the hypothesis that adding an immune checkpoint inhibition to chemoradiotherapy (CRT) would improve TILs' ability to overcome PDAC's resistance against PD-1 blockade [24]. To test that, they created a prospective, open-label, phase Ib/II randomized clinical trial that allocated 37 patients in a ratio of 2:1 to the treatment (arm A, n = 24, receiving CRT + pembrolizumab) or control (arm B, n = 13, receiving CRT) groups. They included patients with resectable or borderline resectable PDAC (according to the Alliance for Clinical Trials in Oncology criteria), but excluded metastatic patients [24]. CRT in both arms consisted of capecitabine (825 mg/m^2 orally two times a day) and external-beam radiation (50.4 Gy in 28 fractions, 5 days per week), starting on day 1 [24]. Patients from arm A additionally received 200 mg of pembrolizumab i.v. every 3 weeks on days 1, 22, and 43 [24]. Then, after completing the neoadjuvant treatment, a pancreatectomy was performed, followed by an adjuvant therapy chosen by a treating oncologist. The primary endpoints included the incidence and severity of adverse events (AEs) and the relative density of CD8+ TILs in resected tumor specimens (using the tissue from surgical resection) [24]. At least one grade 3 or higher AE, possibly related to neoadjuvant treatment, occurred in 9 (38%) patients in arm A and 4 (31%) patients in arm B [24]. When it comes to grade 4 AEs, leukemia was deemed as possibly linked to the treatment and was attributed to chemotherapy [24]. The only AE that was credited to the combination of pembrolizumab and CRT was grade 3 elevation of alanine aminotransferase, and it further qualified as dose-limiting toxicity resulting in treatment cessation [24]. 17 patients from arm A and 7 from arm B underwent pancreatectomy, while the remainder of the patients developed metastasis or local disease progression. Then, out of these 24 participants, 16 (94%) of resected patients from arm A and 7 (100%) of resected patients from arm B had received adjuvant chemotherapy [24]. The median PFS durations were 18.2 (95% CI: 9.4 to 27.0) months for arm A and 14.1 (95% CI: 2.6 to 24.3) months for arm B [24]. While the median OS durations were 27.8 (95% CI: 17.1 to NR) months for arm A and 24.3 (95% CI: 12.6 to NR) months for arm B [24]. The median CD8+ T-cell densities were 67.4 (IQR: 39.3–141.8) in arm A and 37.9 (IQR: 22.9–173.4) cells/mm^2 in arm B (difference in medians: 29.5 (95% CI: −113.7 to 52.6) [24]. No significant differences were observed in the density of CD8+Ki67+, CD4+, or CD4+FOXP3+ regulatory T cells; M1-like and M2-like macrophages; or granulocytes [24]. These findings led to the conclusions that the addition of pembrolizumab to CRT is safe and well-tolerated, although it does not lead to noticeable effects on immune cell populations in the TME. Moreover, it does not provide a clinical effect as median PFS, and median OS were similar for both arms.

3.2.2. IPILIMUMAB + NIVOLUMAB

TRIPLE-R was a phase 2 study of the combination of ipilimumab, nivolumab, and tocilizumab with SBRT among patients with PDAC who experienced progression on at least one systemic chemotherapy. The addition of an IL-6 inhibiting agent was to test the hypothesis of it being able to enhance ICIs' efficacy [25]. 26 patients were recruited. On the first day of a cycle, they received a single-fraction SBRT with 15 Gy, ipilimumab (1 mg/kg) i.v. (then also repeated on week 6), and lastly, nivolumab (6 mg/kg) and tocilizumab (8 mg/kg) i.v. (both every 4 weeks) [25]. The primary endpoint of the study was ORR. All 26 discontinued the treatment, with 23 of them due to progression of the disease, and 3 due to AEs. The median PFS was 1.6 months (95% CI 1.4–1.7), while the median OS was 4.9 months (95% CI 2.3–8.0) [25]. 2 TRAEs of grade 3-4 were observed, which included nausea and increased AST (aspartate aminotransferase) level [25]. The analysis of tumor-infiltrating lymphocytes (TILs) before and during treatment demonstrated no significant differences in TILs' populations. Although no safety signals were noted, no clinically significant efficacy was registered either.

3.2.3. ATEZOLIZUMAB

In a phase Ib/II trial, 108 patients with pancreatic ductal adenocarcinoma were randomized to receive a treatment of atezolizumab plus PEGPH20 (n = 66) or control treatment, i.e. mFOLFOX6 or gemcitabine plus nab-paclitaxel (n = 42). PEGPH20 is a PEGylated recombinant human hyaluronidase PH20, that can degrade hyaluronan, which is an abundant component of TME [26]. Patients in the experimental group were specifically administered atezolizumab 1200 mg intravenously i.v. every 3 weeks plus PEGPH20 3 µg/kg IV on days 1, 8, and 15 of each 21-day cycle [27]. The ORRs (primary endpoint along with safety) for the atezolizumab group were 6.1% (95% CI, 1.68%-14.80%) vs. 2.4% (95% CI, 0.06%-12.57%) for the standard-of-care group [27]. In the experimental group, grade 3/4 AEs accounted for 65.2%, and grade 5 AEs equaled 4.5%, while the respective grades of AEs in the control group were 61.9% and 2.5% [27]. The small study group hinders the ability to draw wider conclusions. Despite a combination with atezolizumab having a similar tolerability to the standard chemotherapy, it did not meet the primary endpoint as it had not reached an improved ORR.

3.2.4. DURVALUMAB

The DAPPER trial recruited 19 patients with PDAC to receive either durvalumab + olaparib (arm A), or durvalumab + cediranib (arm B). It was a phase 2, single-centre, randomized, open-label, multicohort trial [28]. Patients must have progressed on or be ineligible for standard therapies. The drugs were administered with the following specifications: 1500 mg of durvalumab i.v. every 4 weeks; 300 mg of olaparib p.o. (PARP inhibitor) twice a day, on days 1-28; 20

mg of cediranib p.o. (VEGF inhibitor) daily 5 days on and 2 days off. The primary objectives of the study were the safety profiles of the drug combinations along with their immune marker changes in the TME. The median PFS was 1.3 (95% CI, 0.8-NA) months in arm A and 2.1 (95% CI, 1.3-NA) months in arm B [28]. In arm A: 1 patient had a stable disease (SD), 16 patients had a progressive disease (PD); while in arm B 1 patient had a partial response (PR) [28]. The researchers point out one patient with clinical benefit, namely a patient with germline *BRCA* wild type and *KRAS* G12D mutant that progressed after 8 months of receiving durvalumab + olaparib [28]. However, no notable differences in PFS or OS were seen in PDAC patients based on germline *BRCA* status [28]. The results show limited activity in patients with PDAC. Furthermore, the study included an exploration of TME cell composition before and during the treatment. However, no significant changes were found in CD3+/CD8+ immune infiltration in the biopsies from different points of time [28].

3.2.5. SINTILIMAB

A single-arm, phase II clinical trial was designed to combine several agents: S-1, sintilimab and anlotinib to patients with PDAC with liver metastasis as a second-line therapy. S-1 is an oral derivative of 5-fluorouracil that works as dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) [29], while sintilimab is an anti-PD-1 monoclonal antibody. 23 patients were recruited, but only 19 were suitable for analysis. The treatment regimen was administered in 21-days cycles: S-1 p.o. 25 mg/m^2 from day 1 to day 14, 200 mg of sintilimab i.v. at day 1, 12 mg of anlotinib from day 1 to day 14. According to RECISTv1.1 criteria, 2 patients achieved a PR, but 8 patients reached a SD, while the rest 9 patients had a PD [30]. The ORR was 10.5% (95% CI 0.4%–25.7%), while the DCR was 52.6% (95% CI 27.9%–77.4%) [30]. The median PFS was 3.53 (95% CI 2.50–7.50) months, while the median OS was equal to 8.53 (95% CI 4.97–14.20) months [30]. Grade 3 AEs were noted in 26.1% of patients, with the most common ones being leucopenia, neutropenia, and thrombocytopenia [30]. However, grade 4 or 5 AEs were not observed [30]. Furthermore, 16 patients were analyzed using high-throughput genome sequencing to determine homologous recombination deficiency (HRD). 6 patients were categorized as HRD-High, while 10 patients were marked as HRD-Low. A notable observation was shorter PFS for HRD-High patients compared to HRD-Low group (2.43 months vs. 5.45 months; P = 0.043) [30]. Despite, HRD-High group had shorter OS than the HRD-Low patients, but the difference was not statistically significant (4.43 months vs. 9.35 months; P = 0.11) [30]. The research demonstrated a new safe combination, which has some clinical efficacy that should be further confirmed in randomized trials.

3.2.6. NOVEL THERAPIES

Rojas et al. designed a phase I clinical trial of an adjuvant personalized mRNA neoantigen vaccine (called autogene cevumeran) in patients with PDAC. They enrolled 34 patients with surgically resectable PDAC, out of whom 28 underwent surgery. Then 19 of them received atezolizumab, of which 16 patients were administered the personalized vaccine using neoantigens from that person's tumor, and finally 15 of those 16 patients were followed up on treatment with modified mFOLFIRINOX (folinic acid, fluorouracil, irinotecan, and oxaliplatin) [31]. The primary endpoints of the study were as follows: T cell responses induced by autogene cevumeran, 18-month recurrence-free survival (RFS), and oncologic feasibility [31]. None of the 19 patients treated with atezolizumab experienced grade 3 or higher AEs. Out of the vaccinated 16, one patient experienced grade 3 AE (fever and hypertension). High-threshold assays showed that de novo high-magnitude neoantigen-specific T cells were found in 8 out of 16 patients [31]. Following that discovery, the researchers developed CloneTrack – a new mathematical and immunological method to track T cell clones [31]. The method revealed that vaccine-expanded T cells comprised up to 10% of all blood T cells, and their phenotype was vaccine neoantigen-specific polyfunctional CD8+ T cells [31]. After a median of 18 months, patients with vaccine-expanded T cells (the 8 autogene cevumeran responders) had not reached a median RFS yet vs the 8 non-responders with the median RFS equal to 13.4 months (P = 0.003, hazard ratio (HR) = 0.08 (95% confidence interval (CI) 0.01–0.4) [31]. To rule out a difference caused by a dysfunctional immune system, the results between responders and non-responders were compared to humoral and cellular responses to an unrelated mRNA vaccine (SARS-CoV-2), and both groups were deemed to have comparable immunological fitness [31]. This extensive piece of research proved that a personalized mRNA vaccine for PDAC can induce a substantial T cell response in a large proportion of patients [31]. Moreover, that T cell activity might correlate with a delayed recurrence of disease [31].

Another single-center, open-label, single-arm, combined phase I/II trial explored the efficacy of adjuvant dendritic cell (DC) therapy, with the primary end point being the 2-year RFS rate. A 2-year RFS rate of ≥ 60% was defined as a clinically meaningful improvement [32]. They recruited 38 patients who underwent resection and completed standard-of-care treatment. Out of these 38 patients: 28 completed the study protocol (received 5 DC vaccinations). 3 patients received 4 doses of the vaccine, while 7 patients were given 3 doses. The DC vaccine consists of autologous DCs pulsed with an allogeneic mesothelioma tumor cell lysate, comprising antigens also expressed in PDAC [32]. Its administration was well-tolerated, with only one grade 3 possibly related to treatment dyspnea [32]. The flow cytometric analysis revealed a treatment-induced activation of peripheral blood CD4+ T cells [32]. At a median follow-up of 25.5 months (95% CI, 15.6 to 35.5), the 2-year RFS rate was 64% [32], meeting the primary end point. The estimated 2-year OS rate was 83% [32]. The study shows a safe and tolerable treatment that exerts

an effect on the CD4+ T cells and impacts RFS, rationalizing a further randomized trial.

Koido et al. also implemented the use of DC in PDAC treatment regimen. They developed a noncomparative, open-label, phase I study, whose primary endpoints were safety and toxicity [33]. 6 of the recruited patients had stage III (locally advanced) PDAC, 3 patients had stage IV (metastatic) PDAC, while 1 patient had recurrent disease after surgery [33]. The treatment consisted of nab-paclitaxel 125 mg/m^2 and gemcitabine 1,000 mg/m^2 were administered on days 1, 8, and 15 of each 28-day cycle. Along with the start of the second cycle, patients also received a novel Wilms' tumor 1 (WT1) peptide-pulsed dendritic cell (WT1-DC) vaccine [33].

All patients experienced grade 1-4 hematologic adverse events, which include neutropenia, leukocytopenia, lymphopenia, anemia, or thrombocytopenia [33]. No patients reached a CR, but 7 patients had a PR and 3 patients achieved long-term SD [33]. 7 out of 10 patients managed to undergo a surgical resection, including R0 resection (n = 6) and R1 resection (n = 1) [33]. Out of 9 patients (1 patient excluded due to severe complications from surgery), the median PFS was 2.23 years, while the median OS was 3.52 years [33]. Depending on whether the patients were positive WT1-DTH > 6 or ≤ 6 times, they were divided into the long-term WT1-DTH-positive group and the short-term WT1-DTH-positive group, respectively [33]. The results varied for the two groups, as in the long-term group, the median PFS and OS were not reached, while in the short-term group, the median PFS was 1.37 years and OS and 2.56 years [33]. Moreover, the long-term WT1-DTH positivity was observed in 3 patients with locally advanced PDAC who had R0 resection. It was the same 3 patients who had significant infiltration of T cells and programmed cell death protein-1+ cells within the TME [33]. Furthermore, all four long-term WT1-DTH-positive patients exhibited significantly increased levels of IFN-γ or TNF-α production by CD4+ or CD8+ T cells, as well as significantly decreased levels of circulating regulatory T cells and myeloid-derived suppressor cells, compared to short-term WT1-DTH-positive patients [33]. The study proved a TME modification after administration of the WT1-DC vaccine, and even a clinical benefit in the form of enabling to preform resection surgeries in previously unresectable patients. This warrants the trial to be carried out on a bigger population.

AMPLIFY-201 trial was another study that examined the effects of a cancer vaccine on PDAC, however, they narrowed down the focus to KRAS-mutated patients. Namely, it was a phase 1, multi-center, open-label trial of ELI-002 2P, which is a three-component lymph-node-targeted vaccine, containing amphiphile modification peptides (Amph-Peptides-2P) and CpG oligonucleotide adjuvant (Amph-CpG-7909) [34]. They enrolled 20 patients with PDAC and 5 patients with colorectal cancer, with one of the inclusion criteria being the presence of a tumor mKRAS mutation (G12D or G12R) determined by whole-exome sequencing [34]. The primary endpoints were safety and the recommended phase 2 dose. 13 patients had to cease the treatment due to disease progression. Regarding safety, 12 patients experienced AEs owing to ELI-002 2P of grade 1 and 2. No AEs of grade ≥ 3 were noted. Moreover, no dose-limiting toxicities were detected [34]. The recommended phase 2 dose was determined to be 10 mg of Amph-CpG-7909 [34]. Other findings from the study include: 84% of patients experienced a decline from baseline in ctDNA, including 3 patients with PDAC that reached complete biomarker clearance (0 mean tumor molecules per milliliter (MTM/ml)) [34]. Then, peripheral blood mononuclear cells were collected for T cell response assessment at baseline and post-immunization timepoints, showing that ELI-002 2P induced a robust polyfunctional CD4+ and CD8+ T cell response [34]. During an 8.5-month median follow-up, the median OS was 16.33 months, while the median RFS was not reached [34]. The preceding results demonstrate that ELI-002 2P is a safe and well-tolerated cancer vaccine, inducing a considerable response at a molecular level, thus making it a promising agent for future phases of the trial.

Qi et al. assessed the safety and tolerability of CT041 using two multicenter, open-label phase I/Ib trials [35]. CT041 is a chimeric antigen receptor (CAR)-modified T-cell therapy that targets claudin18.2 in solid tumors, including PDAC [35]. The two studies recruited 24 claudin18.2-positive patients with advanced PDAC, who had received at least one line of therapy. 12 patients were administered 2 cycles of CT041 infusion, while 2 patients received 3 cycles [35]. At data cutoff, 23 patients needed to cease the treatment due to disease progression [35]. All of the patients had experienced at least one treatment-emergent adverse event (TEAE) [35]. The most common TEAEs of grade 3 and higher treatment-emergent adverse events were related to preconditioning, and they were hematologic toxicities, e.g., lymphopenia (100% patients), neutropenia (58.3%), anemia (16.7%), thrombocytopenia (12.5%) [35]. The overall response rate (ORR) was 16.7%, while the disease control rate (DCR) was 70.8% [35]. 13 patients (54.2%) have reached SD [35]. Depending on whether the treatment was second-line or third-line, the ORR was 40.0% (95% CI, 5.3 to 85.3) and 15.4% (95% CI, 1.9 to 45.4), respectively [35]. The median PFS was 3.3 months (95% CI, 1.8 to 6.2), while the median OS was 10.0 months (95% CI, 5.5 to 17.6) [35]. The authors observed a reduction in CA19-9 blood levels by at least 30% in 70.8% of patients [35]. The median duration of response (mDoR) was 9.5 months (95% CI, 2.6 to Not reached) [35]. The results from two studies show that CT041 has a good safety profile, as well as a promising antitumor effect, making it a good target for further phases of trials.

Yi et al. enrolled 24 patients for a PDAC cohort in a phase 2 trial to evaluate the efficacy and safety of SHR-1701 [36]. SHR-1701 is "a bifunctional fusion protein composed of an anti-PD-L1 antibody fused with the extracellular domain of TGF-β receptor II, which functions as a "trap' for all three TGF-β isoforms" [36], and that dual nature is supposed to enhance the antitumor effect of ICIs. They have paired the drug with famitinib – "a multi-targeted tyrosine kinase inhibitor (TKI) of VEGFR2/3, PDGFR, and c-Kit", that has shown synergistic effects with ICIs [36]. All

patients recruited were in the metastatic stage of the disease. Only 20 patients from PDAC cohort were assessable for response evaluation. Out of them 3 patients reached an objective response (OR) – including 2 CR and 1 PR [36]. 9 patients achieved a SD [36]. The DCR was 60.0% (95% CI: 36.1-80.9) [36]. The median PFS was 2.1 months (95% CI: 0.7-3.5), while the median OS was 5.3 months (95% CI: 4.0-6.5) [36]. The AEs were considered together for both PDAC and advanced biliary tract cancer cohorts, with grade 3 or 4 TRAEs occurring in 15 patients. The most common ones include anemia (13.7%) and hypertension (7.8%) [36]. What is more, 16 patients experienced potential immune-related AEs, with the most common ones being rash (23.5%) and hypothyroidism (13.7%) [36]. No TRAEs of grade 5 were reported. Multivariate analysis revealed that patients who underwent primary tumor resection correlated with longer OS (HR = 0.11, 95% CI = 0.02–0.45) [36]. Ne Subsequently, peripheral blood immunophenotype analysis demonstrated that a decrease in CD4+CD25+CD127low Tregs meant decreased immunosuppressive function, while an increase in CD3-CD16+CD56+ NK cells was connected with an increased antitumor cytotoxic activity [36]. The following results suggest that SHR-1701 + famitinib is a safe option for treatment, which reflects the anti-tumor activity on the molecular level and has some clinical correlations that can be used as a reference point for further studies.

Bendell et al. used the finding that "CD73 upregulation in tumors leads to local immunosuppression" to determine whether its inhibition by anti-CD73 human IgG1λ monoclonal antibody (oleclumab), either in monotherapy or in combination with durvalumab, could reduce the antitumor effects in PDAC [37]. This was phase I, multicenter, open-label, dose-escalation and dose-expansion study to determine the safety and tolerability of oleclumab. It recruited 42 patients with PDAC that have used at least two prior lines of treatment before. The treatment regimen consisted of oleclumab 40 mg/kg + durvalumab 10 mg/kg i.v. every 2 weeks [37]. 17% patients reported grade 3 and 4 TRAEs, with the most common ones being fatigue (15%), diarrhea (9%), and rash (7%) [37]. 2 patients experienced OR – including 1 CR and 1 PR [37]. 8 patients experienced SD ≥ 8 weeks [37]. For the combination therapy group, the median OS was 5.6 months, while the median PFS was 1.8 months [37]. For the oleculmab monotherapy arm, the median OS was 6.1 months, while the median PFS was 1.8 months [37]. The phase 1 trial showed that the drug combination has a manageable safety profile with a limited clinical activity.

Another manner to modify the TME and increase immune system reactivity against the tumor was done by Agarwal et al. They designed a phase II study, in which 31 patients with borderline resectable PDAC received perioperative mFOLFIRINOX (or gemcitabine/nab-paclitaxel if a patient did not tolerate the mFOLFIRINOX regimen), then they were administered GVAX/cyclophosphamide/nivolumab and received SBRT, followed by a surgical resection. GVAX is "a GM-CSF-secreting vaccine that activates T-cell immunity against tumor-associated antigens" [38]. The primary endpoint of the study was CD8+ T-cell density in surgical specimens that were compared to historic samples treated only with mFOLFIRINOX and SBRT. 18 patients received at least one dose of the immunotherapy combination [38]. 14 patients completed a surgical resection, out of which 1 patient has achieved a pathologic CR [38]. During a median follow-up at 19.5 months, the median OS was 20.4 months (95% confidence interval, 18.2-not achieved) [38]. However, no difference in the mean CD8 T-cell density in the recruited patients compared to the historic control group was found [38]. This treatment regimen did not manage to induce a noticeable TME change that could increase the immune response against the tumor.

3.3. ONGOING STUDIES & PHASE 1 TRIALS

Currently, many studies are still being conducted. Here, we shortly present the summary of the most relevant trials, mainly phase 1, that aim to implement new immunological agents for treatment of pancreatic cancer.

An open-label, multicenter, phase I dose-escalation was designed to determine safety, efficacy and pharmacodynamics of pixatimod in combination with nivolumab. Pixatimod is an activator of TLR9, that is aimed to activate immune system's response to tumor (30). 54 patients who have never been on ICIs with metastatic PDAC (n = 18) or colorectal cancer have been recruited, and the results are reported for both groups combined. The treatment regimen was administered in 28-days cycles: pixatimod i.v. (25 mg at first, escalated to 50 mg) on days 1, 8, 15, and 22, while nivolumab (240 mg) on days 1 and 15 (30). Dose-limiting toxicities (DLTs) were observed in two patients at 50 mg of pixatimod, thus making it the toxic dose (30). The DLTs were multiorgan failure and "pulmonary edema, cardiomyopathy and autoimmune hepatitis" (30). All of the participants have experienced AEs, out of which 67 were severe, 3 were life-threatening (in grading), and 13 deadly (30). Most common TRAEs for pixatimod were diarrhea, nausea, fatigue, and pyrexia (30). The PDAC cohort had 2 patients that achieved a SD for 15 weeks (30). As majority of the results focused on the patients with metastatic colorectal cancer, the study requires more investigation for patients with PDAC to determine its clinical usefulness, as the pixatimod dose was established to be safe at 25 mg (30).

OPTIMIZE-1 is single-arm, multicentre, phase 1b/2 study that examined the combination of mitazalimab with mFOLFIRINOX in previously untreated metastatic PDAC patients. Mitazalimab is a human CD40 agonistic IgG1 antibody, that can simulate dendritic cells to activacte effector T cells, promoting antitumor response (31). The study exhibited fair safety of the combination, warranting the phase 3 of the trial.

Another phase 1b trial focused on untreated patients with PDAC to determine the safety, toxicity, and maximal

tolerated dose of ibrutinib, that was administered in combination with gemcitabine and nab-paclitaxel. The blood was collected before and after ibrutinib monotherapy revealing increased activation of a population of CD4+ T cells, CD8+ T-cells, and monocytes (32). However, when administered along with chemotherapy the immunological changes in the TME were not observed (32). This study shows that synergistic impact of a combination regimen is not always a mere sum of the components' effects, and different combinations with ibrutinib could be tested. Table 2 presents characteristics of the selected trials.

Table 2. Characteristics of reviewed trials

Name of the study	Treatment for experimental group	Number of recruited patients	Setting	median OS [months]	median PFS [months]	other
[22]	SBRT + pembrolizumab + trametinib	170	local recurrence after surgery followed by chemotherapy	17.2 (14.6–19.8) for PD-L1+/ TIL+ 12.7 (10.8–14.6) for PD-L1+/ TIL-	10.5 (8.7–12.3) for PD-L1+/ TIL+ 7.1 (4.9–9.3) for PD-L1+/ TIL-	-
[23]	pembrolizumab + paricalcitol	24	metastatic PDAC with no prior anti-PD-(L)1 therapy	10.4	3.1.	-
[24]	CRT + pembrolizumab	37	resectable or borderline resectable PDAC	27.8 (17.1 to NR)	18.2 (9.4–27.0)	-
[25]	ipilimumab + nivolumab + tocilizumab + SBRT	26	progression on ≥ 1 systemic chemotherapy	4.9 (2.3–8.0)	1.6 (1.4–1.7)	-
[27]	atezolizumab + PEGPH20	108	metastatic PDAC and PD ≤ 6 months after treatment with 1 line chemotherapy	-	-	ORR = 6.1% (1.68%–14.80%)
[28]	durvalumab + olaparib (arm A) durvalumab + cediranib (arm B)	19	must have progressed on standard therapy	2.7 (2.2-8.1)	1.3 (0.8-NA) 2.1 (1.3-NA)	-
[30]	S-1 + sintilimab + anlotinib	23	PDAC with liver metastasis as a second-line therapy	8.53 (4.97–14.20)	3.53 (2.50–7.50)	ORR = 10.5% (0.4%–25.7%) DCR = 52.6% (27.9%–77.4%)

[31]	surgery + atezolizumab + autogene cevumeran + mFOLFIRINOX	34	surgically resectable PDAC	not reached at follow-up of 18 months	-	RFS not reached at follow-up of 18 months
[32]	surgery + chemotherapy + dendritic cell vaccination	38	resectable PDAC with no radiological recurrence	-	-	2-year RFS rate = 64% estimated 2-year OS rate = 83%
[33]	nab-paclitaxel + gemcitabine + WT1-DC vaccine	10	stage III or stage IV or recurrent after surgery	3.52 years	2.23 years	-
[34]	ELI-002 2P	20	mKRAS mutation (G12D or G12R)	16.33 months at follow-up of 18 months	-	RFS was not reached at follow-up of 18 months
[35]	CT041	24	claudin18.2-positive patients with advanced PDAC, who received ≥ 1 line of therapy	10.0 (5.5 to 17.6)	3.3 (1.8 to 6.2)	mDoR = 9.5 months (2.6 to Not reached)
[36]	SHR-1701 + famitinib	24	metastatic PDAC	5.3 (4.0-6.5)	2.1 (0.7-3.5)	DCR = 60.0% (36.1-80.9)
[37]	oleclumab + durvalumab (arm A), oleclumab (arm B)	42	≥ 2 prior lines of treatment before	5.6 (arm A) 6.1 (arm B)	1.8 (arm A) 1.8 (arm B)	-
[38]	mFOLFIRINOX + + GVAX+ cyclophosphamide + nivolumab + SBRT + surgery	31	borderline resectable PDAC	20.4 months (18.2-not achieved) at follow-up of 20.4 months	-	-

OS - overall survival, PFS - progression-free survival, RFS - recurrence-free survival, DCR - disease control rate, SBRT - stereotactic body radiation therapy, TIL - tumor-infiltrating lymphocytes, PD-L1 - programmed death-ligand 1, PDAC - pancreatic ductal adenocarcinoma, CRT - chemoradiotherapy, ORR - objective response rate, mFOLFIRINOX - modified FOLFIRINOX: folinic acid, fluorouracil, irinotecan, and oxaliplatin, WT1-DC - Wilms' tumor 1 peptide-pulsed dendritic cell vaccine, mDoR - median duration of response

4. DISCUSSION

Pancreatic cancer therapy still poses a huge clinical challenge for medical oncologists. While immunotherapy ushered in a new era for a variety of tumors, it has yet to make a breakthrough in treatment for PDAC.

The preclinical data already show that incorporating immunotherapy into PDAC treatment will not be easy [39]. The immune composition of cells at a tumor site exhibits several dysfunctions. For example, CD8 T cells are driven towards exhaustion and their cytotoxicity signals are down-regulated [11]. There are ways to reduce the immunosuppression of the TME. For instance, Boucher et al. have added losartan to FOLFIRINOX and chemoradiation, achieving a reduction in immunosuppressive cells like FOXP3+ and Tregs in locally advanced PDAC [15]. Furthermore, there is some indication that a strong TGF-β-specific immune response during the initiation of a treatment that includes ICIs can prolong patients' PFS and OS - this can be achieved with TGF-β-based vaccinations [13]. On top of that, for patients treated with ICIs, we could use biomarkers to monitor a better response, as higher FASLG and Gal-1 levels were significantly linked with longer PFS [14].

However, these findings do not warrant treating PDAC in a monotherapy setting. Previous trials testing PD-L1 and CTLA-4 antibodies did not prove to be successful [40,41]. Thus, various combinations of regimens were tested. Chung et al. tried to sensitize tumors to PD-1 inhibition signals using paricalcitol (a vitamin D receptor agonist), but no significant difference for any of the study outcomes was observed, with the median OS for the experimental group (pembrolizumab + paricalcitol) was 10.4 months, while for the control group (pembrolizumab monotherapy) it was 10.2 months [23]. However, there are more successful combinations with ICIs. For instance, adding pembrolizumab to SBRT and gemcitabine demonstrated an improved median OS equal to 17.2 months, although only for patients who were PD-L1+ and tumor-infiltrating lymphocytes (TIL) positive [22]. A similar trial compared the addition of pembrolizumab to capecitabine and external-beam radiation, without dividing the patients into PD-L and TIL subpopulations, showing no significant differences (the median OS durations were 27.8 months for the arm with pembrolizumab vs 24.3 months for the chemoradiotherapy only arm) [24]. More interestingly, they did not find any meaningful differences among cell populations in the resection material in terms of TILs [24]. These two trials imply that any improvement achieved by adding pembrolizumab is significant in a small, highly specific population. Defining that population poses another difficulty, as the findings on the molecular level do not remain consistent across two studies.

TRIPLE-R trial tried to test the combination of ipilimumab + nivolumab + tocilizumab with SBRT, however, all 26 patients had to discontinue the treatment, mainly due to the disease progression [25]. The trials that attempted to introduce atezolizumab or durvalumab did not manage to meet satisfactory results [27,28]. However, coupling sintilimab with anlotinib (anti-PD-1 antibody) turned out to be a safe combination with a potential clinical benefit as a second-line treatment, with the ORR being 10.5% [30].

The notable finding was the sheer number of studies evaluating novel therapies, like cancer vaccinations. More remarkably, the trials present promising results. Firstly, patients who responded well to autogene cevumeran (an adjuvant personalized mRNA neoantigen vaccine), who then received subsequent modified mFOLFIRINOX treatment, did not reach a median RFS at the follow-up after 18 months [31]. Secondly, at a median follow-up of 25.5 months, the 2-year RFS rate was 64% for adjuvant dendritic cell (DC) vaccination [32]. Another trial testing a novel Wilms' tumor 1 (WT1) peptide-pulsed dendritic cell (WT1-DC) vaccine combined with nab-paclitaxel and gemcitabine showed the median PFS of 2.23 years [33]. All these three trials had a good safety profile. Next, GVAX was another vaccine that aimed to induce an immune change in the TME, however, the data show it did not manage to do so [38]. In turn, ELI-002 2P was a vaccine designed specifically for KRAS-mutated patients, which also exhibited great safety and a considerable molecular response [34]. CT041 made using CAR-T technology showed the ORR of 16.7% and the median PFS of 3.3 months, as well as a safe profile, making it a potential research target as a second-line treatment option [35]. Pairing SHR-1701 (an anti-PD-L1 antibody fused with the extracellular domain of TGF-β receptor II) with famitinib (TKI-inhibitor) reached the median PFS of 2.1 months in the metastatic setting, while also exhibiting promising aims on the molecular level, warranting further study [36].

The results for many vaccine-based therapies might look promising, but it is important to consider the complexity of cancer vaccines. While the technology to produce neoantigen-derived vaccines is advancing [42], the majority of PDAC patients do not share these antigens [43], hindering mass production. Furthermore, the vaccines' mechanism of action relies on inducing an immune response and immunomodulating the TME. On its own, these can be rendered ineffective by highly immunosuppressive TME [44]. Therefore, the effectiveness should be accompanied by a combination of therapies, so the outcomes could synergize. That suggests we should look at cancer vaccines as an additive to the treatment regimen, while the research for agents combating the tumor more directly is still necessary.

4.1. LIMITATIONS

Most of the discussed immunotherapeutic approaches in PDAC are supported by early-phase clinical trials with limited sample sizes and predominantly single-arm or open-label designs, which restrict statistical power and prevent direct comparison with standard treatments [31–36]. In several studies, conclusions rely mainly on surrogate endpoints, including immunological or molecular responses, which do not necessarily translate into sustained clinical benefit in terms of overall survival [31,32,34–36]. In addition, patient populations differ across trials with respect to disease stage, prior therapies and molecular tumor characteristics, complicating reproducibility and the identification of stable responder subgroups [22–25]. These methodological constraints require cautious interpretation of the reported

results and underline the need for confirmation in adequately powered randomized controlled trials [39,44].

5. CONCLUSIONS

This narrative review confirms that immunotherapy remains a major clinical challenge in the treatment of pancreatic ductal adenocarcinoma. Preclinical and translational data consistently demonstrate profound immune dysfunction within the tumor microenvironment, which provides a biological explanation for the limited efficacy of immune checkpoint inhibitors observed in clinical trials. The available clinical evidence shows that immune checkpoint inhibitors do not achieve meaningful benefit as monotherapy and that most combination strategies produce inconsistent results.

Among combination approaches, the addition of pembrolizumab to stereotactic body radiotherapy and gemcitabine demonstrated clinical benefit only in narrowly defined subgroups of patients characterized by PD L1 expression and the presence of tumor infiltrating lymphocytes. Other combinations, including ipilimumab plus nivolumab, atezolizumab and durvalumab, failed to demonstrate clinical efficacy. Sintilimab combined with anlotinib showed limited benefit in the second line setting.

The most consistent positive signals were observed with vaccine based and cellular immunotherapeutic strategies. Personalized mRNA vaccination with autogene cevumeran and dendritic cell based vaccines were associated with durable recurrence free survival in selected patients. Additional vaccine approaches, including WT1 peptide pulsed dendritic cell vaccines and KRAS targeted vaccination, demonstrated measurable clinical or molecular responses, while GVAX did not achieve its intended immunological effect.

Overall, the reviewed data indicate that molecular and immunological responses do not consistently translate into clinical benefit. Nevertheless, personalized mRNA vaccines and dendritic cell based therapies currently represent the most substantiated immunotherapeutic strategies in pancreatic cancer and warrant further investigation in controlled clinical trials, with continued attention to safety and rigorous assessment of clinical outcomes.

5.1. FURTHER RESEARCH DIRECTIONS

Future studies should focus on the validation of vaccine based immunotherapeutic strategies in adequately powered randomized clinical trials, as current evidence is derived predominantly from early phase studies. Particular attention should be given to TGF-β-based vaccination approaches and to the prospective validation of FASLG and Gal-1 as biomarkers of response to immunotherapy. In addition, further investigation of combined treatment regimens integrating cancer vaccines with standard chemotherapy and radiotherapy is required to assess potential synergistic effects and to define optimal treatment sequences.

6. DISCLOSURE

6.1. AUTHORS' CONTRIBUTIONS

Conceptualization: Michał Cholewiński

Methodology: Natalia Ziółkowska, Paweł Szajewski

Formal analysis: Justyna Łapicka, Agata Pluta

Investigation: Natalia Rosół, Natalia Kruszewska, Michał Cholewiński

Draft preparation: Alicja Pełszyk, Daria Marciniak

Writing - review and editing: Michał Cholewiński, Justyna Kącikowska

Supervision: Michał Cholewiński

All authors have read and agreed with the published version of the manuscript.

6.2. CONFLICT OF INTEREST STATEMENT

Authors declare no conflicts of interest.

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6.4. USE OF ARTIFICIAL INTELLIGENCE (AI)

The following work has used Grammarly to enhance the syntax and flow of parts of the article. The authors have

thoroughly verified the AI's language refinements. No other AI tool has been applied to any other aspect of the work (including data analysis and conclusions).

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