Pancreatic cancer and immune checkpoint inhibitors—still a long way to go

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Despite advances in immunotherapy in multiple solid tumor types, the role of immunotherapy in pancreatic ductal adenocarcinoma (PDAC) remains limited. PDAC has been reported to express a low tumor mutational burden and an immunosuppressive tumor microenvironment, both of which pose challenges to the success of immunotherapy for pancreatic cancer (1,2). Earlier immunotherapy efforts in pancreatic cancer focused on vaccines, but thus far no large scale vaccine trials have demonstrated long-term efficacy. Notable completed pancreatic cancer vaccine studies include the TeloVac, IMPRESS, and ECLIPSE trials.

Telomerase is expressed in pancreatic cancer, and GV1001 is a telomerase peptide vaccine that demonstrated an immune response in phase I/II studies (3). TeloVac was an open-label, randomized, phase III trial evaluating the immunogenic telomerase peptide vaccine GV1001 in combination with gemcitabine and capecitabine in 1,062 patients with locally advanced or metastatic pancreatic cancer. Patients were randomly assigned 1:1:1 to receive chemotherapy alone, chemotherapy and sequential GV1001, or chemotherapy and concurrent GV1001. Median overall survival was 7.9 months with chemotherapy alone, 6.9 months with chemotherapy and sequential GV1001, and 8.4 months with chemotherapy and concurrent GV1001. The trial was terminated early in March 2011 due to decreased survival in the chemotherapy and sequential GV1001 groups (4).

IMPRESS was a phase III study of the pancreatic cancer vaccine algenpantucel-L in 722 patients with surgically resected pancreatic cancer. Algenpantucel-L is a vaccine comprised of allogeneic pancreatic cancer cells modified to express surface alpha-1,3-galactosyltransferase leading to hyperacute rejection of the vaccine allograft with a goal of inducing immune-mediated toxicity towards endogenous pancreatic cancer cells. Study patients received algenpantucel-L in combination with adjuvant gemcitabine with or without 5-FU and radiation versus adjuvant gemcitabine with or without 5-FU and radiation alone. Results were published in May 2016. The study did not reach its primary endpoint of improved overall survival; median overall survival was 30.4 months for the control group and 27.3 months for the study group (5).

A more recently completed pancreatic cancer vaccine trial was a phase IIb, randomized, multicenter study of GVAX pancreas and CRS-207 compared to single-agent chemotherapy in patients with previously treated metastatic pancreatic cancer (ECLIPSE). GVAX is an irradiated, autologous pancreatic cancer vaccine genetically modified to secrete granulocyte-macrophage colony stimulating factor with a goal of stimulating an immune response against pancreatic cancer cells. CRS-207 is a live, attenuated Listeria-based cancer vaccine expressing human mesothelin which can activate an immune response against mesothelin-overexpressing pancreatic cancer cells. ECLIPSE compared low-dose cyclophosphamide/GVAX/CRS-207 (arm A) versus CRS-207 alone (arm B), or single-
agent chemotherapy (arm C). The study rationale for adding low-dose cyclophosphamide was to enhance the immune response by depleting regulatory T cells, based on previously published phase II data (6). Study subjects were divided into a primary cohort of patients who had received two or more lines of therapy (213 patients) and a second-line cohort of patients who had received one prior line of chemotherapy for metastatic disease (90 patients). The study did not meet the primary efficacy endpoint of improved overall survival of arm A compared to arm C in the intention-to-treat (ITT) primary cohort. The median overall survival in the primary cohort of arm A was 3.7 months, 5.4 months in arm B, and 4.6 months in arm C. It should be noted that there was a disproportionate dropout rate in arm C in both primary and secondary cohorts although there was not a significant difference in overall survival between the ITT and full analysis set populations (7).

Attention turned to immune checkpoint blockade following the disappointing results of pancreatic cancer vaccine trials. The anti-programmed death-1 (PD-1) immune checkpoint inhibitor pembrolizumab is the only immunotherapy that is FDA-approved for the treatment of patients with advanced PDAC—provided PDAC is mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H). In May 2017, pembrolizumab was approved for patients with unresectable or metastatic, MSI-H/dMMR solid tumors with progression on prior treatment with no satisfactory alternative treatment options (8). This was the FDA's first tissue/site agnostic approval, and was based on the combined results of five multi-cohort, single-arm clinical trials evaluating pembrolizumab in patients with metastatic or unresectable solid tumors who had received a median of two prior lines of therapy. Of 149 patients with MSI-H/dMMR cancers across all five studies, there were 59 responders for an objective response rate (ORR) of 36.9% and a complete response rate of 7% (9-11). Of the five studies included in the FDA approval summary, the study by Le et al. Science 2017 was the first to demonstrate a benefit of PD-1 blockade in pancreatic cancers. Eight of the 86 patients included in the study had pancreatic cancer, and the ORR among pancreatic cancer patients was 62% (2 patients had complete responses, 3 patients had partial responses, 1 patient had stable disease, and 2 patients were not evaluable) (9).

Subsequent reports on PD-1 inhibition in MSI-H/dMMR solid tumors have demonstrated lower response rates in pancreatic cancer. KEYNOTE-158 was a non-randomized, open-label, multicenter, multi-cohort phase II study evaluating pembrolizumab in a variety of tumor types, including a specific cohort of non-colorectal MSI-H/dMMR solid tumors previously treated with standard therapy. Efficacy results from the non-colorectal MSI-H/dMMR solid tumor cohort of KEYNOTE-158 were recently published (12). Patients were treated with pembrolizumab 200 mg once every 3 weeks for 35 cycles or until disease progression, treatment-limiting toxicity, intercurrent illness, or patient/investigator decision to withdraw from the study. The ORR among 233 patients across 27 tumor types was 34.4%. While these pooled response rates to pembrolizumab in pretreated patients with MSI-H/dMMR cancers were encouraging—the response rate in the subset of patients with MSI-H/dMMR pancreatic cancers was not as robust. Of 22 patients with pancreatic cancer included in the study, 3 partial responses and 1 complete response to pembrolizumab were observed (ORR 18.2%). The median overall survival was 4.0 months in the pancreatic cancer subgroup, although it should be noted that the median duration of response was 13.4 months.

These results from small numbers of patients with MSI-H/dMMR pancreatic cancers are difficult to generalize as the incidence of mismatch repair deficiency in PDAC has been reported to range from 0.8% to 2% (9,13-15). PDAC has long been thought of as an immunologically “cold” malignancy, with multiple barriers to effective immunotherapy in the PDAC tumor microenvironment (16). Attempting to overcome these barriers by utilizing a combination of anti-PD-1/anti-programmed death ligand-1 (PD-L1) checkpoint inhibitors with other immune and targeted therapies is a logical next step.

O’Reilly et al. recently published negative results from the first phase II randomized clinical trial evaluating dual immune checkpoint blockade in patients with advanced PDAC (17). This was a multicenter, two-part, phase II randomized clinical trial of the PD-L1 antibody durvalumab with or without the anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody tremelimumab in patients with recurrent or metastatic PDAC. Study participants had received one prior gemcitabine-based or fluorouracil-based chemotherapy regimen. Sixty-five patients were randomized to part A of the study. The ORR was 3.1% for patients treated with the combination of durvalumab and tremelimumab and 0% for patients treated with durvalumab monotherapy. As part A did not meet the pre-specified threshold for study expansion (10% ORR in either
treatment arm), the study was closed. PD-L1 expression was evaluated, however the low number of responses was inadequate for analysis of PD-L1 and clinical response association. This study highlights some of the challenges of effective immunotherapy in PDAC.

Effective immunotherapy for PDAC that is not MSI-H/dMMR remains elusive and is an area of ongoing clinical research. Studies investigating PD-1/PD-L1 inhibition in combination with other therapies in PDAC are ongoing (16). A recently published phase I study of nivolumab and the anti-CC chemokine receptor 4 antibody mogamulizumab in patients with advanced solid tumors included 15 patients with PDAC (18). The authors reported 1 confirmed partial response and 2 unconfirmed partial responses in patients with PDAC. These results should be interpreted within the limitations of a phase I study. Novel therapies in preclinical development are investigating the use of CAR T-cell therapy against PDAC (19). Selected immunotherapy clinical trials for pancreatic adenocarcinoma are listed in Table 1. We will await the results of these ongoing studies that offer hope for successful pancreatic cancer immunotherapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References


### Table 1: Selected immunotherapy trials for pancreatic adenocarcinoma

<table>
<thead>
<tr>
<th>Study name</th>
<th>Phase</th>
<th>Immunotherapy</th>
<th>Status</th>
<th>ClinicalTrials.gov identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Car T cell immunotherapy for pancreatic cancer (20)</td>
<td>I</td>
<td>huCAR-T meso cells</td>
<td>Recruiting</td>
<td>NCT03323944</td>
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<tr>
<td>LCAR-C182A cells in the treatment of advanced gastric cancer and pancreatic ductal adenocarcinoma (21)</td>
<td>I</td>
<td>LCAR-C182A cells</td>
<td>Recruiting</td>
<td>NCT03890198</td>
</tr>
<tr>
<td>Autologous T-cells in patients with metastatic pancreatic cancer (22)</td>
<td>I</td>
<td>CAR-T meso cells</td>
<td>Recruiting</td>
<td>NCT03638193</td>
</tr>
<tr>
<td>Th-1 dendritic cell immunotherapy plus standard chemotherapy for pancreatic adenocarcinoma (DECIST) (23)</td>
<td>I</td>
<td>Autologous dendritic cell vaccine</td>
<td>Not recruiting</td>
<td>NCT04157127</td>
</tr>
<tr>
<td>Nivolumab and ipilimumab and radiation therapy in MSS and MSI high colorectal and pancreatic cancer (24)</td>
<td>II</td>
<td>Nivolumab and ipilimumab</td>
<td>Recruiting</td>
<td>NCT03104439</td>
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<td>Study of anti-CEA CAR-T + chemotherapy vs chemotherapy alone in patients With CEA+pancreatic cancer &amp; liver metastases (25)</td>
<td>II</td>
<td>Anti-CEA CAR-T cells</td>
<td>Not recruiting</td>
<td>NCT04037241</td>
</tr>
<tr>
<td>Plerixafor and cemiplimab in metastatic pancreatic cancer (26)</td>
<td>II</td>
<td>Cemiplimab</td>
<td>Not recruiting</td>
<td>NCT04177810</td>
</tr>
</tbody>
</table>
25. Study of Anti-CEA CAR-T + Chemotherapy VS Chemotherapy Alone in Patients With CEA+Pancreatic