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Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma
A Phase 2 Randomized Clinical Trial

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IMPORTANCE New therapeutic options for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) are needed. This study evaluated dual checkpoint combination therapy in patients with mPDAC.

OBJECTIVE To evaluate the safety and efficacy of the anti–PD-L1 (programmed death-ligand 1) antibody using either durvalumab monotherapy or in combination with the anticytotoxic T-lymphocyte antigen 4 antibody using durvalumab plus tremelimumab therapy in patients with mPDAC.

DESIGN, SETTING, AND PARTICIPANTS Part A of this multicenter, 2-part, phase 2 randomized clinical trial was a lead-in safety, open-label study with planned expansion to part B pending an efficacy signal from part A. Between November 26, 2015, and March 23, 2017, 65 patients with mPDAC who had previously received only 1 first-line fluorouracil–based or gemcitabine-based treatment were enrolled at 21 sites in 6 countries. Efficacy analysis included the intent-to-treat population; safety analysis included patients who received at least 1 dose of study treatment and for whom any postdose data were available.

INTERVENTIONS Patients received durvalumab (1500 mg every 4 weeks) plus tremelimumab (75 mg every 4 weeks) combination therapy for 4 cycles followed by durvalumab therapy (1500 mg every 4 weeks) or durvalumab monotherapy (1500 mg every 4 weeks) for up to 12 months or until the onset of progressive disease or unacceptable toxic effects.

MAIN OUTCOMES AND MEASURES Safety and efficacy were measured by objective response rate, which was used to determine study expansion to part B. The threshold for expansion was an objective response rate of 10% for either treatment arm.

RESULTS Among 65 randomized patients, 34 (52%) were men and median age was 61 (95% CI, 37-81) years. Grade 3 or higher treatment-related adverse events occurred in 7 of 32 patients (22%) receiving combination therapy and in 2 of 32 patients (6%) receiving monotherapy; 1 patient randomized to the monotherapy arm did not receive treatment owing to worsened disease. Fatigue, diarrhea, and pruritus were the most common adverse events in both arms. Overall, 4 of 64 patients (6%) discontinued treatment owing to treatment-related adverse events. Objective response rate was 3.1% (95% CI, 0.08-16.22) for patients receiving combination therapy and 0% (95% CI, 0.00-10.58) for patients receiving monotherapy. Low patient numbers limited observation of the associations between treatment response and PD-L1 expression or microsatellite instability status.

CONCLUSION AND RELEVANCE Treatment was well tolerated, and the efficacy of durvalumab plus tremelimumab therapy and durvalumab monotherapy reflected a population of patients with mPDAC who had poor prognoses and rapidly progressing disease. Patients were not enrolled in part B because the threshold for efficacy was not met in part A.

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Invited Commentary
page 1438

Supplemental content

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In the United States, pancreatic cancer is predicted to become the second leading cause of cancer-related deaths by 2030.[1] Pancreatic ductal adenocarcinoma (PDAC) accounts for more than 90% of pancreatic tumors, with a 5-year overall survival (OS) rate of 8%.[2,3] Low survival rates are associated with rapid tumor progression and late presentation owing to the absence of early symptoms.[3] Patients with advanced or metastatic PDAC (mPDAC) have few established therapeutic options beyond initial gemcitabine-based or fluorouracil-based chemotherapy.[4]

The therapeutic potential of immune checkpoint therapy has been of increasing interest.[5-8] Durvalumab is a human anti-programmed death-ligand 1 (anti-PD-L1), IgG class 1 monoclonal antibody (mAb) approved for second-line urothelial carcinoma and unresectable stage III non-small cell lung cancer that has not progressed following concurrent platinum-based chemotherapy and radiotherapy.[9] Increased PD-L1 expression in PDAC correlates with less favorable prognosis.[6-8] Blockade of PD-L1 and its receptors by durvalumab may relieve PD-L1–dependent immunosuppressive effects, potentially enhancing the cytotoxic activity of antitumor T cells.[10,11] Preliminary data from a multi-arm, phase 1 expansion study of durvalumab monotherapy had acceptable safety and showed partial responses in 2 of 29 patients with PDAC who had evaluable data.[12]

Tremelimumab, another immune checkpoint therapy, is a human anticytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), IgG class 2 mAb.[13] Blockade of CTLA-4–associated negative regulation of T-cell activation has been shown to increase immune activation and antitumor activity.[13,14] Monotherapy with another anti-CTLA-4 mAb resulted in delayed response after initial progressive disease in 1 patient with PDAC and had acceptable tolerability.[15]

Immune checkpoint blockade in PDAC as a single-agent therapy was not currently indicated beyond the subgroup of patients with microsatellite instability or mismatch repair deficiency[16]; however, a precedent existed for evaluating a combination of 2 immune checkpoint antagonists in this setting. The mechanisms of action of anti-PD-L1 and anti-CTLA-4 mAbs are nonredundant; thus, the combination may have additive or synergistic activity.[14] In fact, the combination of anti-programmed cell death 1 (anti-PD-1)/anti-PD-L1 and anti-CTLA-4 mAb, including durvalumab with tremelimumab, has shown enhanced activity in certain tumor types.[17-21] Moreover, a clinical trial of patients with PDAC demonstrated that anti-CTLA-4 blockade as part of a combination approach had a positive antitumor effect[22]; therefore, a rationale existed for evaluating the potential of dual immune checkpoint combination therapy in patients with PDAC while also assessing single-agent immune checkpoint blockade.

This phase 2 randomized clinical trial evaluated the safety and efficacy of durvalumab with or without tremelimumab in patients with previously treated mPDAC. The study design consisted of 2 parts, with a planned interim analysis of part A after enrollment of 30 patients in either treatment arm (durvalumab plus tremelimumab therapy or durvalumab monotherapy). Part B of the study was not conducted based on the findings of part A, which are reported herein.

Key Points

Question Does combination immuno-oncology therapy (anti–programmed death–ligand 1 and anticytotoxic T-lymphocyte–associated antigen 4) provide clinical benefit for patients with metastatic pancreatic ductal adenocarcinoma?

Findings In part A of this phase 2 randomized clinical trial of 65 patients, durvalumab plus tremelimumab therapy was tolerated in patients with metastatic pancreatic ductal adenocarcinoma and had an objective response rate of 3.1%, and no patients responded to durvalumab monotherapy. The threshold for continuation to part B of the study was an objective response rate of 10% for either arm (durvalumab plus tremelimumab therapy or durvalumab monotherapy), so part B was not conducted based on the findings of part A.

Meaning The efficacy of immunotherapy in part A of this trial was reflective of a population of patients with metastatic pancreatic ductal adenocarcinoma who had poor prognoses and rapidly progressing disease.

Methods

Study Design

Part A of the study was a multicenter, randomized, open-label, signal-seeking evaluation of durvalumab plus tremelimumab therapy (combination therapy) and durvalumab monotherapy (monotherapy) (eMethods in Supplement 1). Patients were randomized on a 1:1 ratio to receive either durvalumab therapy (1500 mg every 4 weeks) plus tremelimumab therapy (75 mg every 4 weeks) for 4 cycles followed by durvalumab therapy (1500 mg every 4 weeks) or durvalumab monotherapy (1500 mg every 4 weeks) for up to 12 months or until confirmed progressive disease or unacceptable toxic effects. Part B of the study was planned as either a nonrandomized or randomized clinical trial, which would be determined based on efficacy signals from part A. Review and approval of the study and diagnostic testing by an institutional review board or ethics committee were obtained for each site. The full trial protocol is provided in Supplement 2. Written informed consent from participants and additional locally required authorizations were obtained before performing any protocol-related procedures.

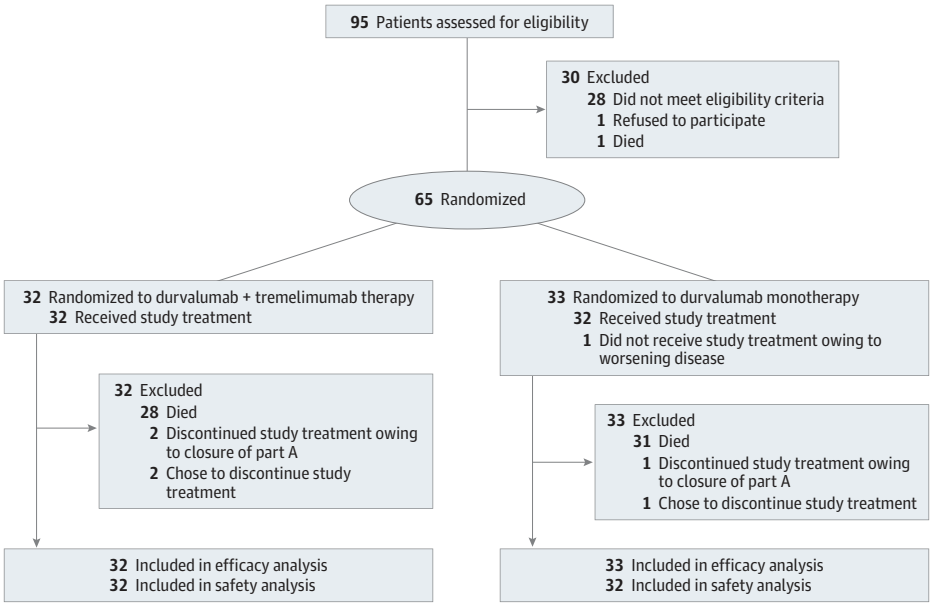
Patients

Patients 18 years or older were eligible to participate if they had histologically or cytologically confirmed mPDAC and tumor progression and had previously received only 1 first-line fluorouracil-based or gemcitabine-based chemotherapy regimen for recurrent PDAC or mPDAC (eMethods in Supplement 1).

Assessments

The primary end point was investigator-assessed objective response rate (ORR) based on the Response Evaluation Criteria in Solid Tumors, version 1.1.[23] Secondary end points included duration of response, disease control rate (DCR) at 3 months (defined after the protocol amendment as complete response or partial response in the first 3 months or stable dis-

Figure 1. CONSORT Diagram



ease for at least 13 weeks following the start of treatment), progression-free survival (PFS), and OS.

Tumor samples, either acquired from recent biopsies performed during screening (preferred) or from existing samples taken less than 3 years before screening, were required for PD-L1 and other biomarker assessments. Testing for PD-L1 was performed by immunohistochemistry using formalin-fixed, paraffin-embedded tumor tissue and the VENTANA PD-L1 (SP263) Assay (Roche Diagnostics). The baseline PD-L1 expression level was summarized for the safety analysis population (eMethods in Supplement 1). A cutoff of 25% or more tumor cells with membrane staining for PD-L1 was chosen to designate PD-L1-high expression.

Adverse events, including treatment-related adverse events (trAEs), were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.[24] Adverse events of special interest included events with a potential inflammatory or immune-mediated mechanism that may have required frequent monitoring and/or intervention with immunosuppressant drugs or hormone therapy.

Statistical Methods

Continuation to part B of the study was determined based on efficacy signals from part A. The prespecified expansion criteria were: (1) part B would be initiated as a nonrandomized clinical trial, and an additional 70 patients per arm enrolled, if an ORR of more than 25% (≥8 responses) was recorded in part A; (2) part B would be initiated as a randomized clinical trial if an ORR of more than 15% (≥5 responses) in at least 1 study arm was recorded in part A; and (3) recruitment for part B would be halted if the predictive probability of either arm achieving minimum criteria for initiating part B was less than 10% for both ORR and DCR at 12 weeks. The primary end point (ORR) for part A was estimated with 95% exact Clopper-Pearson CIs. Kaplan-Meier estimates were used for analyses of PFS and OS.

The efficacy analysis represented the intent-to-treat population and included all randomized patients by assigned treatment regardless of treatment actually received. Patients who received at least 1 dose of study treatment and for whom any postdose data were available comprised the safety analysis population according to treatment actually received.

Results

Patient Disposition and Baseline Characteristics in Part A

The first patient received treatment on November 26, 2015, and the last patient received final treatment on March 23, 2017. Data cutoff was May 26, 2017. Sixty-five patients at 21 sites in 6 countries (Canada, Germany, the Netherlands, South Korea, Spain, and the United States) were randomized to treatment. Thirty-two patients were randomized to the combination therapy arm and 33 were randomized to the monotherapy arm; 1 patient randomized to the monotherapy arm experienced worsened disease and was withdrawn from the study before receiving treatment (**Figure 1**). Median follow-up was 3.2 months (range, 0.4-18.1 months). Among the 65 patients, 34 (52%) were men and 31 (48%) were women, and they had a median age of 61 years (95% CI, 37-81 years). Patient characteristics and demographics were generally distributed evenly for each arm and representative of patients with treatment-refractory mPDAC (eTable in Supplement 1).

Safety

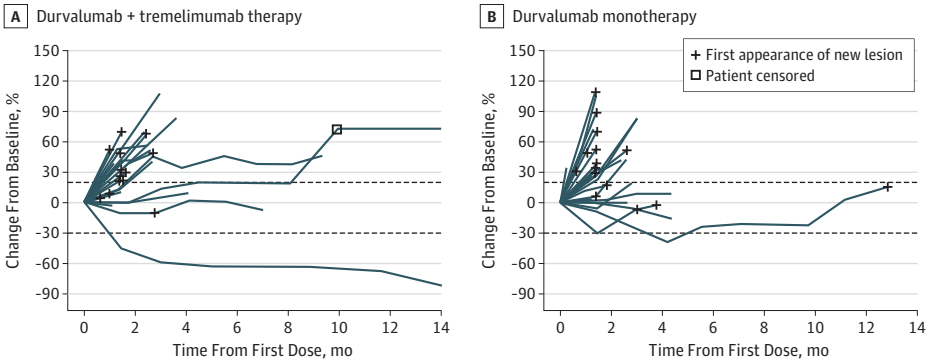
Approximately one-third of patients receiving treatment had at least 1 trAE (11 of 32 patients [34%] in the combination therapy

Table. Common Treatment-Related Adverse Events[a]

	No. (%)					
	Durvalumab + Tremelimumab Therapy (n = 32)		Durvalumab Monotherapy (n = 32)		Total (N = 64)	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any causally related event	11 (34)	7 (22)	10 (31)	2 (6.3)	21 (33)	9 (14)
Hypothyroidism	3 (9)	0	0	0	3 (5)	0
Diarrhea	4 (13)	3 (9)	2 (6)	0	6 (9)	3 (5)
Pruritus	1 (3)	0	2 (6)	0	3 (5)	0
Fatigue	4 (13)	2 (6)	3 (9)	0	7 (11)	2 (3)

[a] The table includes adverse events that occurred in 5% or more of patients and were causally related to treatment, as assessed by the investigator at each study site. Patients with multiple, causally related adverse events were counted once for each system organ class and/or preferred term.

Figure 2. Percentage of Change in Target Lesion Size



Percentage of change was assessed by the investigator at each study site. Dotted reference lines at −30% and 20% denote thresholds for partial response (PR) and progressive disease (PD), respectively. The censored case was of a patient treated with durvalumab plus tremelimumab therapy who maintained stable disease until week 43 (PD on day 302). This patient was re-treated with tremelimumab therapy after PD and survived without appearance of new lesions until data cutoff (day 467).

arm and 10 of 32 [31%] in the monotherapy arm); 7 of 32 patients (22%) in the combination therapy arm and 2 of 32 (6%) in the monotherapy arm had trAEs of grade 3 or higher (eResults in Supplement 1). Common trAEs (ie, occurring in ≥5% of patients) in the combination therapy arm and the monotherapy arm were fatigue (4 of 32 patients [13%] and 3 of 32 [9%], respectively); diarrhea (4 of 32 [13%] and 2 of 32 [6%], respectively); pruritus (1 of 32 [3%] and 2 of 32 [6%], respectively); and hypothyroidism (3 of 32 [9%] in the combination therapy arm only). Grade 3 or higher fatigue (2 of 32 patients [6%]) and diarrhea (3 of 32 [9%]) occurred in the combination therapy arm only (**Table**). Overall, 4 of 64 patients (6%) discontinued treatment because of trAEs. There were no treatment-related deaths.

Efficacy

The ORR was 3.1% (95% CI, 0.08-16.22) for patients treated with combination therapy and 0% (95% CI, 0.00-10.58) for patients treated with monotherapy (eResults in Supplement 1). The DCR at 3 months was 9.4% for patients treated with combination therapy and 6.1% for patients treated with monotherapy; the percentage of change in target lesion size is summarized in **Figure 2**.

Median PFS was 1.5 months in both arms (95% CI, 1.2-1.5 months in the combination therapy arm and 1.3-1.5 months in the monotherapy arm) (**Figure 3**). The 6-month PFS rate was 9.4% (95% CI, 2.4-22.3) in the combination therapy arm and 3.6% (95% CI, 0.3%-15.4%) in the monotherapy arm. Median OS was 3.1 months (95% CI, 2.2-6.1 months) in the combination therapy arm vs 3.6 months (95% CI, 2.7-6.1 months) in the monotherapy arm. The 6-month OS rate was 36.2% (95% CI, 20.0%-52.7%) in the combination therapy arm and 34.9% (95% CI, 19.2%-51.1%) in the monotherapy arm, and the 12-month OS rate was 8.8% (95% CI, 1.8%-22.8%) and 6.3% (95% CI, 1.1%-18.4%), respectively. Three patients experienced long-term survival (ie, patients were alive at data cutoffs during weeks 61-65).

PD-L1 Expression

A cutoff of 25% or more tumor cells was chosen to evaluate PD-L1 expression in PDAC tumor samples, although this cutoff criterion has not been validated in PDAC. The number of respondents was insufficient to establish any association between clinical outcomes and PD-L1 expression. Of 65 samples available for testing, 8 (12%) were from patients with PD-L1-high (≥25% tumor cells) expression and 48 (74%) were from patients with PD-L1-low (<25% tumor cells) expression. The single patient with a confirmed partial response had PD-L1-low/negative expression, with no PD-L1-expressing tumor cells. Of 12 patients with stable disease, 9 had tumors evaluable for PD-L1 expression, and all had PD-L1-low/negative expression, including 6 patients with no tumor cells, 2 patients with 1% or more tumor cells, and 1 patient with 10% or more tumor cells.

Discussion

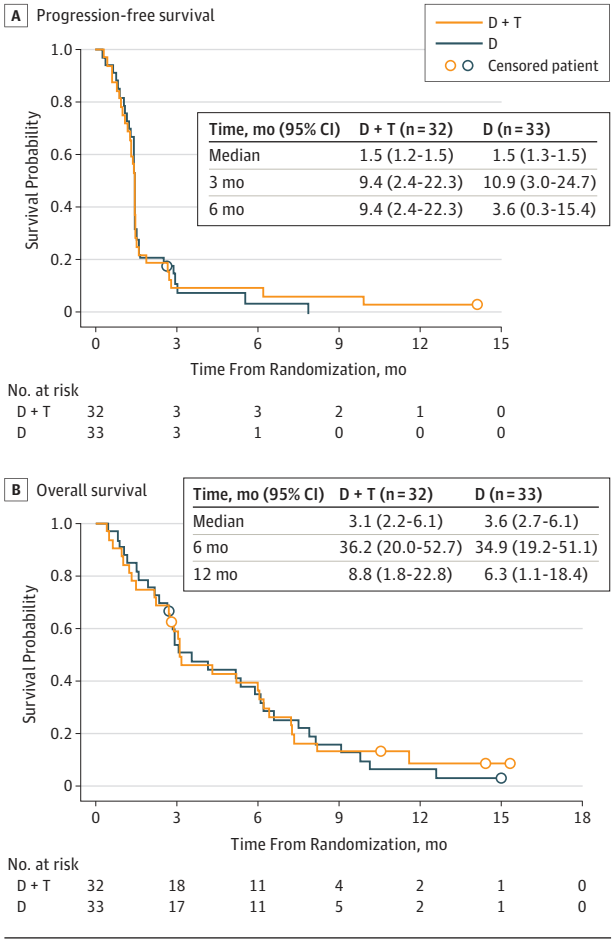
To our knowledge, this study is the first phase 2 randomized clinical trial to evaluate dual immune checkpoint combination therapy in patients with mPDAC. It is important to under-

take studies such as this, even though previous research has reported only modest antitumor activity with immune checkpoint blockade.[12,15] Although combination therapy and monotherapy had modest efficacy (a 3-month DCR of 9.4% and 6.1%, respectively), this result must be interpreted in light of the study's short follow-up time and the ongoing, unmet need for efficacious therapies for patients with mPDAC. The duration of the confirmed partial response in the combination therapy arm was 55 weeks (until data cutoff) and, overall, 15% of patients in this arm had confirmed stable disease lasting more than 6 weeks. The study also provided important toxic effects data related to dual immune checkpoint blockade in the mPDAC setting. Patients in both arms showed acceptable tolerability, and all adverse events were manageable. The observed safety profiles of combination therapy and monotherapy were consistent with profiles in early-phase trials of non-small cell lung cancer.[17,25] The safety profile of durvalumab monotherapy was consistent with the class of anti-PD-1/PD-L1 mAbs.[26,27] Because part A results did not meet the prespecified end point criteria (10% ORR in either arm) to proceed to the part B evaluation, the study was closed.

The tumor microenvironment in PDAC is an immunosuppressive, hypoxic, and fibrotic setting, which may contribute to the failure of conventional and targeted therapies owing to the unusual combination of physical barriers and strong inhibitory immune signaling.[28,29] Early signals may indicate activity, but blockade of immune checkpoints with single-agent therapy has not shown significant and durable responses in patients with mPDAC.[12,15,30,31] The absence of significant activity of durvalumab with or without tremelimumab in patients with mPDAC indicates that combining modes of action in this small study did not sufficiently overcome the immune inhibitory environment known to be a key contributor to poor response in patients with mPDAC.

Accumulating evidence suggests that stromal responses in PDAC contribute to tumor progression through a range of mechanisms involving activated pancreatic stellate cells, myeloid-derived suppressor cells, and regulatory T cells.[32,33] Preclinical data show that dysregulated signaling by pancreatic stellate cells activated within the tumor microenvironment can reduce migration of CD8-positive T cells, preventing their access to tumor cells.[32] In addition, the tumor microenvironment is associated with overexpression of nitric oxide synthase, which can cause active T-cell suppression despite the presence of tumor-specific antigens.[34] Myeloid-derived suppressor cells further contribute to immune suppression and tumor progression following their accumulation in bone marrow and subsequent recruitment to the tumor site; they can produce high amounts of nitric oxide in the tumor microenvironment when activated, further inhibiting antitumor responses.[35] Collectively, these data suggest that immune checkpoint blockade must be part of a comprehensive strategy aimed at reprogramming local immunity toward an effective antitumor response. Preclinical studies continue to support PD-L1/CTLA-4 blockade in conjunction with immunomodulation at the level of antigen-presenting cells to produce tumor regression, even in established tumors.[36,37] One of those studies showed that treatment with a granulocyte-

Figure 3. Progression-Free Survival (PFS) and Overall Survival (OS) in Patients With Metastatic Pancreatic Ductal Adenocarcinoma Treated With Durvalumab Plus Tremelimumab (D + T) Therapy vs Durvalumab Monotherapy (D)



macrophage colony-stimulating factor-secreting PDAC vaccine upregulated PD-L1 membrane expression and, in combination with PD-1 blockade, led to improved survival in tumor-bearing mice.[36] Other novel strategies are also aimed at potentiating immune checkpoint blockade in PDAC.[38-41]

With the exception of data regarding increased CTLA-4 expression on CD8-positive T cells, which is associated with shorter OS in treatment-naive patients,[42] data to derive an association between the expression of immune checkpoint markers and survival in patients with mPDAC are lacking to date. Meaningful evaluation of response and PD-L1 expression in this study was constrained by the low DCR and ORR, which also limited additional biomarker analyses (eg, microsatellite instability status, tumor mutation burden, and breast cancer gene mutations); thus, no conclusions about biomarkers, including tumor mutation burden or microsatellite instability, could be drawn. Nevertheless, microsatellite instability status, tumor mutation burden, and other biomarkers may prove to be important for patients with PDAC. Programmed cell death 1 blockade has shown efficacy in previously treated patients who had unresectable or metastatic solid tumors with microsatel-

lite instability-high status or mismatch repair deficiency.[16,43] In patients with non-small cell lung cancer and high tumor mutation burden, PFS was longer with dual anti-PD-1/anti-CTLA-4 blockade than with chemotherapy as first-line treatment.[44]

Limitations

This study's limitations included the lack of a control arm, which prevented direct comparison of either treatment with another therapeutic option, such as combination chemotherapy. However, patients with mPDAC that is progressing after chemotherapy have few therapeutic options other than enrollment in a clinical trial with no standard of care beyond the second-line setting. Another study limitation was the small number of patients who responded to treatment, which precluded meaningful appraisal of PD-L1 expression or other biomarkers in relation to clinical benefit. The general difficulty in achieving objective responses in the second-line setting points to an inherent challenge for phase 2 studies of patients with mPDAC. In recent years, several targeted therapies and cancer vaccines have been evaluated in PDAC studies, and almost all have failed to demonstrate efficacy in late-stage clinical trials.[45]

Conclusions

The observed efficacy of durvalumab plus tremelimumab therapy and durvalumab monotherapy was reflective of a population of patients with mPDAC who had poor prognoses and rapidly progressing disease; however, treatment was well tolerated. Future studies are needed to evaluate how to best combine immune checkpoint blockade with other agents, including cytotoxic and targeted therapies, with the intention of overcoming the unique immunosuppressive, hypoxic, and fibrotic tumor microenvironment of PDAC. Such studies should evaluate biomarker expression to identify patients most likely to benefit from immune checkpoint blockade.

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Author Contributions: Dr O'Reilly had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: O'Reilly, Sun, Hezel, Takahashi.
Acquisition, analysis, or interpretation of data: O'Reilly, Oh, Dhani, Renouf, Lee, Sun, Fisher, Chang, Vlahovic, Takahashi, Yang, Fitts, Philip.
Drafting of the manuscript: O'Reilly, Oh, Fisher, Takahashi, Yang.
Critical revision of the manuscript for important intellectual content: O'Reilly, Oh, Dhani, Renouf, Lee, Sun, Fisher, Hezel, Chang, Vlahovic, Takahashi, Fitts, Philip.
Statistical analysis: Oh, Yang, Fitts.
Administrative, technical, or material support: O'Reilly, Lee, Chang, Takahashi, Philip.
Supervision: Lee, Chang, Vlahovic, Philip.

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Data Sharing Statement: See Supplement 3.

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Invited Commentary

Dual Checkpoint Inhibition in Pancreatic Cancer
Revealing the Limitations of Synergy and the Potential of Novel Combinations

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Immunotherapy has profoundly altered the treatment landscape in oncology. Immune checkpoint inhibition (ICI) using anti-programmed cell death protein (PD-1) and/or anti-programmed death-ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CLTA-4) has led to significant achievements in numerous malignant diseases. Yet, the success of checkpoint inhibition has not translated to every tumor type. With the notable exception of the 1% to 2% of patients with mismatch repair-deficient metastatic pancreatic cancer where anti-PD-1 therapy alone can lead to significant and durable responses,[1] pancreatic ductal adenocarcinoma (PDAC) has remained refractory to single-agent immunotherapy.

Related article page 1431

The immune resistance of PDACs arises in part from a modest burden of somatic mutations that develop during tumorigenesis (approximately 50-70 expressed neoantigens).[2] As a result, immunotherapy synergy has been an active area of research, with the most rational combinations involving blockade of CTLA-4 and PD-1/PD-L1 pathways. Cytotoxic T-lymphocyte-associated protein 4 regulates T cells early on in the lymph nodes and acts primarily on naïve T cells, whereas PD-1 acts on antigen-experienced T cells at the tumor site.[3]

Preclinical and clinical studies have revealed that the distinct nonredundant mechanistic pathways of combination ICI therapy leads to increased infiltrating T cells, reduction of regulatory T and immunosuppressive myeloid cells, as well as improved clinical outcomes. These data provide the basis to test whether additional ICI may lead to synergy and overcome the limitations of single-agent ICI in tumor types such as PDAC that are considered to be immunologically cold.

In this planned 2-part, phase 2 (part A) multicenter randomized clinical study, O'Reilly et al[4] seek to evaluate the safety and efficacy of an anti-PD-L1 antibody, durvalumab (1500 mg every 4 weeks) randomized 1:1 vs durvalumab plus anti-CTLA-4 antibody, tremelimumab (75 mg every 4 weeks followed by durvaumab 1500 mg every 4 weeks thereafter), in patients with metastatic PDAC previously treated with first-line chemotherapy.[4] Part B was planned as either a nonrandomized or randomized clinical study based on efficacy signals from Part A. This study represents an important opportunity to evaluate the clinical implications, synergy, and potential benefit of dual ICI therapy in patients with PDAC.

The authors show that this combination is safely tolerated. Three patients (9%) in the durvalumab plus tremelimumab arm and 1 patient (3%) in the monotherapy arm discontinued treatment owing to study-defined treatment-related adverse events. There were no treatment-related deaths. The authors report that the objective response rate (ORR) for the durvalumab plus trememilumab arm was 3.1%, whereas there was a 0% response rate in the patients who received durvalumab monotherapy. Overall, this study did not meet the cutoff for ORR to proceed to part B of the study.

Immunology-focused studies in metastatic PDAC remain very challenging in many respects given that, even in the best of circumstances it may take months for an effective immune response to develop.[5] It is likely that the current immunotherapies take too long to induce an effective response in metastatic patients with PDAC who progress quickly, measured in weeks rather than months.

This study clearly and soberly demonstrates that despite the observed clinical benefits of dual ICI therapy appreciated in other tumor types, PDAC remains refractory to standalone dual ICI therapy. The priming of antitumor T-cell responses in the draining lymph nodes by anti-CTLA-4 therapy, tremelimumab, appears to be insufficient in priming T cells in PDAC for the addition of PD-L1 therapy. The authors note that stromal factors in the setting of an immunosuppressive milieu (regulatory T cells [Tregs], myeloid-derived suppressor cells [MDSC], tumor-associated macrophages [TAM], and cancer-associated fibroblasts) in the tumor microenvironment