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Evaluation of Ipilimumab in Combination With Allogeneic Pancreatic Tumor Cells Transfected With a GM-CSF Gene in Previously Treated Pancreatic Cancer

Dung T. Le,† Eric Lutz,* Jennifer N. Uram,* Elizabeth A. Sugar,*‡ Beth Onners,* Sara Solt,* Lei Zheng,* Luis A. Diaz, Jr,†§ Ross C. Donehower,* Elizabeth M. Jaffee,* and Daniel A. Laheru**

Summary: Preclinical reports support the concept of synergy between cancer vaccines and immune checkpoint blockade in nonimmunogenic tumors. In particular, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies have been successfully combined with GM-CSF cell-based vaccines (GVAX). Ipilimumab (anti-CTLA-4) has been tested as a single agent in patients with pancreatic ductal adenocarcinoma (PDA) resulting in a delayed response at a dose of 3 mg/kg. Our study evaluated ipilimumab 10 mg/kg (arm 1) and ipilimumab 10 mg/kg + GVAX (arm 2). A total of 30 patients with previously treated advanced PDA were randomized (1:1). Induction doses were administered every 3 weeks for a total of 4 doses followed by maintenance dosing every 12 weeks. Two patients in arm 1 showed evidence of stable disease (7 and 22 wk) but none demonstrated CA19-9 biochemical responses. In contrast, 3 patients in arm 2 had evidence of prolonged disease stabilization (31, 71, and 81 wk) and 7 patients experienced CA19-9 declines. In 2 of these patients, disease stabilization occurred after an initial period of progression. The median overall survival (OS) (3.6 vs. 5.7 mo, hazards ratio: 0.51, $P = 0.072$) and 1 year OS (7 vs. 27%) favored arm 2. Similar to prior ipilimumab studies, 20% of patients in each arm had grade 3/4 immune-related adverse events. Among patients with OS > 4.3 months, there was an increase in the peak mesothelin-specific T cells ($P = 0.014$) and enhancement of the T-cell repertoire ($P = 0.031$). In conclusion, checkpoint blockade in combination with GVAX has the potential for clinical benefit and should be evaluated in a larger study.

Key Words: CTLA-4, GVAX, pancreatic cancer, vaccine, ipilimumab

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See Commentary by Bajor and Vonderheide on page 362

Even with the recent progress in the treatment of metastatic pancreatic ductal adenocarcinoma (PDA), the median survival in the best performance status patients remains 11 months.[1,2] Progress has been made with immunotherapy for traditionally immunogenic cancers such as melanoma and even in some tolerogenic cancers such as lung and prostate cancer.[3–7] Despite the view that PDA is a particularly nonimmunogenic cancer, data suggest that immune responses and antitumor responses can be induced in PDA.[8–11]

Cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) functions as a negative regulator of T-cell activation. Ipilimumab, a CTLA-4 antagonist antibody, has been tested in patients with advanced PDA.[12] Although single agent ipilimumab at 3 mg/kg was minimally effective, a significant delayed response in 1 patient suggests that immunotherapy could play a role in PDA. Melanoma studies demonstrated a dose-response relationship with ipilimumab, and the dose of 10 mg/kg was selected from prior studies.[4,13] Furthermore, preclinical studies show synergy between anti-CTLA-4 antibodies and granulocyte macrophage-colony stimulating factor (GM-CSF) cell-based vaccines.[14–16] The current PDA trial builds on these observations by evaluating ipilimumab at 10 mg/kg alone or in combination with allogeneic pancreatic tumor cells transfected with a *GM-CSF* gene (GVAX) for the treatment of previously treated, locally advanced, or metastatic PDA.

PATIENTS AND METHODS

Patients

Study protocol (NCT00836407) was approved by the Johns Hopkins institutional review board, institutional biosafety committee, the FDA, and the NIH Recombinant DNA Advisory Committee. Participating patients signed informed consent.

Patients were eligible for enrollment if they had previously treated, locally advanced, or metastatic histologically proven PDA, were ≥18 years of age, had received gemcitabine-based chemotherapy, had Eastern Cooperative Oncology Group performance status 0 or 1 with normal hematologic and renal function, aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase ≤2.5 × upper limit of normal (ULN) (< 5 × ULN for patients with liver metastases), bilirubin <1.5 × ULN, and an expected survival of 9 weeks. Individuals were excluded if they had infection with human immunodeficiency virus, hepatitis B or C, a history of brain metastases, autoimmune disease, prior CTLA-4 inhibitor or agonist use, surgery, radiation, chemotherapy, vaccination, or steroids within 28 days of study initiation.

Study Design and Treatment

This was a phase 1b, open-label, randomized study performed at Johns Hopkins University (Baltimore, MD). The primary objective of the study was to determine the safety profile of ipilimumab alone or in combination with GVAX in patients with previously treated PDA. Secondary

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comparison of OS between treatment groups, measurement of CA19-9 kinetics, exploration of an association of mesothelin-specific T-cell responses with OS, and estimation of overall response rate and immune-related response. Immune-related response criteria (irRC) account for the kinetics of both old and new lesions, given the known for potential delayed responses with ipilimumab.[17] Thirty patients with PDA were enrolled at Johns Hopkins University between March 11, 2009 and December 6, 2010 with follow-up censored as of January 27, 2013. All patients were included in the safety and efficacy analyses. Patients were randomized in a 1:1 manner to ipilimumab alone (arm 1) or ipilimumab + GVAX (arm 2) using a randomized block design. In both arms, ipilimumab (10 mg/kg) was administered intravenously (IV) over 90 minutes. In arm 2, before the ipilimumab infusion, patients received GVAX, which consists of 2 pancreatic tumor cell lines (Panc 6.03 and Panc 10.05), which have been modified with a plasmid vector encoding the cDNA for human *GM-CSF* and subsequently cultured and irradiated.[8] The vaccine consists of Panc 6.03 and Panc 10.05 cells (2.5×10^8 cells each) combined into a single vaccine and administered as intradermal injections, 2 each in the right and left thighs and 2 in the nondominant arm. Biosafety level 2 practices were employed for the containment of GVAX.

Treatments were administered at weeks 1, 4, 7, and 10. Computed tomography (CT) scans (magnetic resonance imaging if CT contraindicated) were performed for tumor assessments at weeks 1, 7, 14, and 22. Patients with progressive disease (PD) without rapid clinical deterioration could continue on study treatment. At week 22 evaluation, patients with evidence of a response or stable disease (SD) were offered maintenance dosing of the originally assigned treatment every 12 weeks. Tumor assessments were performed every 12 weeks during maintenance. Patients with early progression followed by SD or better between weeks 14 and 22 were also eligible for maintenance. Patients were followed by telephone contact every 12 weeks to evaluate survival, disease status, and adverse events (AE).

Patient Monitoring and Toxicity Criteria

AEs were graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0. For purposes of determining unacceptable toxicity during the initial 22-week treatment phase, patients were followed for drug related >grade 4 AE or grade 3 AEs including immune-related AE (IRAE) not improving to <grade 2 under therapy within 2 weeks. In addition, ≥grade 2 eye pain or reduction of visual acuity that did not respond to topical therapy within 2 weeks was also an unacceptable toxicity. A 3 + 3 design was used to determine whether or not the toxicity was acceptable for the first 6 patients in each arm. If the toxicity rate was <33%, then the remaining patients would be enrolled in that arm. The proportion of patients with unacceptable toxicities was continuously monitored. If the toxicity level in the combination arm was ≥2/6, then the dose of ipilimumab could be reduced to 5 mg/kg for the combination arm only. Intrapatient dose deescalations were not permitted. AEs 70 days after the last dose were recorded if possibly related to the investigational agents.

There were no protocol-defined unacceptable toxicities in the first 6 patients in either arm and enrollment con-

Immunologic Assessments

Detection of Mesothelin-specific $CD8^+$ T Cells by Interferon γ-ELISPOT

Synthesis of peptides, ELISA assays for identifying mesothelin peptides, and ELISPOT assays have previously been described.[9–11] Peripheral blood lymphocytes (PBL) were collected at baseline, before each dose, 28 days after maintenance doses, and at the off study visit. PBLs from patients expressing HLA-A*0101 and/or HLA-A*0201 alleles were tested if pretreatment and posttreatment samples were available. T-cell responses to mesothelin peptides were adjusted for background measured against irrelevant melanoma or renal cell carcinoma control peptides. Responses were measured to 8 HLA-A*0101 and 6 HLA-A*0201 mesothelin peptides. The sum of T-cell responses to mesothelin peptides were reported. The size of the mesothelin-specific T-cell repertoire was defined as the percentage of peptides for which an induction was measured. A response was considered to be induced when the frequency of specific T cells was ≥5 in 1×10^5 $CD8^+$ PBL and increased by ≥2-fold compared with baseline.

Clinical Assessments

Radiographic imaging was obtained at the specified time points. Response was assessed by RECIST v1.0 and irRC. CA19-9 serum levels were measured at regular intervals. OS was defined as the time from enrollment until death or loss to follow-up.

Statistical Considerations

Fifteen patients in each arm were enrolled to refine estimates of toxicity and initial efficacy measurements. Comparisons of continuous and categorical characteristics were made using the Wilcoxon rank-sum tests and the Fisher exact tests, respectively. For each arm, the Kaplan-Meier estimates of the survival curve were calculated and used to estimate median OS and the proportion of individuals alive at 1 year with 95% confidence intervals (CI). Comparisons between groups were made using log-rank tests. Differences between pretreatment and posttreatment immune responses were compared using the Wilcoxon signed-rank tests.

RESULTS

Patient Characteristics, Safety, and Tolerability

Patient characteristics are shown in Table 1. Baseline characteristics were similar among patients in each arm with the exception that arm 1 had fewer patients with ≥2 prior therapies (60% vs. 100%, $P = 0.017$). The most common AEs reported for ipilimumab therapy were IRAEs; the most common AEs reported for GVAX vaccines were localized vaccine reactions and self-limiting systemic rashes. Table 2 summarizes IRAEs observed during all treatment cycles by arm and CTCAE grade. The rate of IRAEs attributable to ipilimumab was similar to what has been reported in other studies testing ipilimumab at the 10 mg/kg dose. Seventy-three percent and 80% of patients in arm 1 and 2, respectively, experienced any grade IRAE and 20% of patients in both arms experienced grade 3 and 4 IRAEs (colitis, Guillain-Barre syndrome, nephritis in arm 1; colitis, rash, pneumonitis in arm 2). The case of nephritis was considered an unacceptable toxicity because

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