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Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

ABSTRACT

BACKGROUND

Blockade of programmed death 1 (PD-1), an inhibitory receptor expressed by T cells, can overcome immune resistance. We assessed the antitumor activity and safety of BMS-936558, an antibody that specifically blocks PD-1.

METHODS

We enrolled patients with advanced melanoma, non–small-cell lung cancer, castration-resistant prostate cancer, or renal-cell or colorectal cancer to receive anti–PD-1 antibody at a dose of 0.1 to 10.0 mg per kilogram of body weight every 2 weeks. Response was assessed after each 8-week treatment cycle. Patients received up to 12 cycles until disease progression or a complete response occurred.

RESULTS

A total of 296 patients received treatment through February 24, 2012. Grade 3 or 4 drug-related adverse events occurred in 14% of patients; there were three deaths from pulmonary toxicity. No maximum tolerated dose was defined. Adverse events consistent with immune-related causes were observed. Among 236 patients in whom response could be evaluated, objective responses (complete or partial responses) were observed in those with non–small-cell lung cancer, melanoma, or renal-cell cancer. Cumulative response rates (all doses) were 18% among patients with non–small-cell lung cancer (14 of 76 patients), 28% among patients with melanoma (26 of 94 patients), and 27% among patients with renal-cell cancer (9 of 33 patients). Responses were durable; 20 of 31 responses lasted 1 year or more in patients with 1 year or more of follow-up. To assess the role of intratumoral PD-1 ligand (PD-L1) expression in the modulation of the PD-1–PD-L1 pathway, immunohistochemical analysis was performed on pretreatment tumor specimens obtained from 42 patients. Of 17 patients with PD-L1–negative tumors, none had an objective response; 9 of 25 patients (36%) with PD-L1–positive tumors had an objective response ($P=0.006$).

CONCLUSIONS

Anti–PD-1 antibody produced objective responses in approximately one in four to one in five patients with non–small-cell lung cancer, melanoma, or renal-cell cancer; the adverse-event profile does not appear to preclude its use. Preliminary data suggest a relationship between PD-L1 expression on tumor cells and objective response. (Funded by Bristol-Myers Squibb and others; ClinicalTrials.gov number, NCT00730639.)

From the Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore (S.L.T., J.R.B., C.G.D., D.M.P., W.H.S., R.A.A., J.M.T., T.L.M., H.X.); Dana–Farber Cancer Institute (F.S.H.) and Beth Israel Deaconess Medical Center (D.F.M., M.B.A.) — both in Boston; Yale University School of Medicine and Yale Cancer Center, New Haven, CT (S.N.G., L.C., M.S.); University of Michigan, Ann Arbor (D.C.S.); Carolina BioOncology Institute, Huntersville, NC (J.D.P.); Memorial Sloan-Kettering Cancer Center, New York (R.D.C.); Vanderbilt University Medical Center (J.A.S., L.H.) and Sarah Cannon Research Institute/Tennessee Oncology (D.R.S.) — both in Nashville; Cincinnati Hematology-Oncology, Cincinnati (P.D.L.); H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL (S.J.A.); Bristol-Myers Squibb, Milpitas, CA (A.J.K.); and Bristol-Myers Squibb, Princeton, NJ (M.J.-K., S.A., D.M., G.D.K., A.G., J.M.W.). Address reprint requests to Dr. Topalian at the Department of Surgery, Johns Hopkins University School of Medicine, 1550 Orleans St., CRB 2, Rm. 508, Baltimore, MD 21287, or at stopali1@jhmi.edu.

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Human cancers harbor numerous genetic and epigenetic alterations, generating neoantigens that are potentially recognizable by the immune system.[1] Although an endogenous immune response to cancer is observed in preclinical models and patients, this response is ineffective, because tumors develop multiple resistance mechanisms, including local immune suppression, induction of tolerance, and systemic dysfunction in T-cell signaling.[2-5] Moreover, tumors may exploit several distinct pathways to actively evade immune destruction, including endogenous "immune checkpoints" that normally terminate immune responses after antigen activation. These observations have resulted in intensive efforts to develop immunotherapeutic approaches for cancer, including immune-checkpoint-pathway inhibitors such as anti–CTLA-4 antibody (ipilimumab) for the treatment of patients with advanced melanoma.[6-8]

Programmed death 1 (PD-1) is a key immune-checkpoint receptor expressed by activated T cells, and it mediates immunosuppression. PD-1 functions primarily in peripheral tissues, where T cells may encounter the immunosuppressive PD-1 ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), which are expressed by tumor cells, stromal cells, or both.[9-12] Inhibition of the interaction between PD-1 and PD-L1 can enhance T-cell responses in vitro and mediate preclinical antitumor activity.[11,13] In a dose-escalation study, the anti–PD-1 monoclonal antibody BMS-936558 (also known as MDX-1106 and ONO-4538) was administered as a single dose in 39 patients with advanced solid tumors.[14] A favorable safety profile and preliminary evidence of clinical activity were shown in this pilot study, establishing the basis for the current multiple-dose trial involving patients with diverse cancers. We report clinical results for 296 patients in this trial.

Methods

Study Design

This study was sponsored by Bristol-Myers Squibb, which provided the study drug and worked jointly with the senior academic authors to design, collect, analyze, and interpret the study results. All the authors signed a confidentiality agreement with the sponsor. The protocol, including a detailed statistical analysis plan, is available with the full text of this article at NEJM.org. All drafts of the manuscript were prepared by the authors with editorial assistance from a professional medical writer paid by the sponsor. All the authors vouch for the accuracy and completeness of the reported data and for the fidelity of this report to the trial protocol, and all the authors made the decision to submit the manuscript for publication.

This phase 1 study assessed the safety, antitumor activity, and pharmacokinetics of BMS-936558, a fully human IgG4-blocking monoclonal antibody directed against PD-1, in patients with selected advanced solid tumors. All patients (or their legal representatives) gave written informed consent before enrollment. The antibody was administered as an intravenous infusion every 2 weeks of each 8-week treatment cycle. Response was assessed after each treatment cycle. Patients received treatment for up to 2 years (12 cycles), unless they had a complete response, unacceptable adverse effects, or progressive disease or they withdrew consent. In clinically stable patients, study treatment could be continued beyond apparent initial disease progression until progression was confirmed, as outlined by proposed immune-response criteria.[15] Patients with stable disease or an ongoing objective response (complete or partial response) at the end of treatment were followed for up to 1 year and were offered retreatment for 1 additional year in the event of disease progression.

Safety evaluations (clinical examination and laboratory assessments) were conducted for all treated patients at baseline and regular intervals. The severity of adverse events was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[16]

Dose Escalation

Patients with advanced melanoma, non–small-cell lung cancer, renal-cell cancer, castration-resistant prostate cancer, or colorectal cancer were enrolled. Cohorts of three to six patients per dose level were enrolled sequentially at doses of 1.0, 3.0, or 10.0 mg per kilogram of body weight. Dose escalation proceeded when a minimum of three patients had completed the safety-evaluation period (56 days) at a given dose level, with dose-limiting toxicity in less than one third of patients. Intrapatient dose escalation was not permitted.

COHORT EXPANSION

A maximum tolerated dose was not reached. Initially, five expansion cohorts of approximately 16 patients each were enrolled at doses of 10.0 mg per kilogram for melanoma, non–small-cell lung cancer, renal-cell cancer, castration-resistant prostate cancer, and colorectal cancer. On the basis of initial signals of activity, additional expansion cohorts of approximately 16 patients each were enrolled for melanoma (at a dose of 1.0 or 3.0 mg per kilogram, followed by cohorts randomly assigned to 0.1, 0.3, or 1.0 mg per kilogram), lung cancer (patients with the squamous or nonsquamous subtype, randomly assigned to a dose of 1.0, 3.0, or 10.0 mg per kilogram), and renal-cell cancer (at a dose of 1.0 mg per kilogram).

PATIENTS

Eligible patients had documented advanced solid tumors; an age of 18 years or older; a life expectancy of 12 weeks or more; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 (on a scale from 0 to 5, with 0 indicating that the patient is asymptomatic, 1 that the patient is restricted in strenuous activity, and 2 that the patient is ambulatory but unable to work)[17]; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0,[18] with modification (see Methods S1 in the Supplementary Appendix, available at NEJM.org; and the protocol); adequate hematologic, hepatic, and renal function; and a history of one to five systemic treatment regimens. Patients with radiographically stable treated brain metastases were enrolled. Patients with a history of chronic autoimmune disease, prior therapy with antibodies that modulate T-cell function (e.g., anti–CTLA-4, anti–PD-1, and anti–PD-L1), conditions requiring immunosuppressive medications, or chronic infection (e.g., human immunodeficiency virus infection and hepatitis B or C) were excluded.

IMMUNOHISTOCHEMICAL ANALYSIS FOR PD-L1

Immunohistochemical analysis for PD-L1 was performed on archival or newly obtained pretreatment formalin-fixed, paraffin-embedded tumor specimens with the use of the murine antihuman PD-L1 monoclonal antibody 5H1.[11,19] The percentage of tumor cells exhibiting cell-surface staining for PD-L1 was scored by two independent pathologists who were unaware of outcomes. PD-L1 positivity was defined per specimen by a 5% expression threshold[19,20]; patients with multiple specimens were considered PD-L1–positive if any specimen met this criterion.

PHARMACOKINETICS AND PHARMACODYNAMICS

For pharmacokinetic analysis, serum concentrations of anti–PD-1 antibody were quantified with the use of an enzyme-linked immunosorbent assay. For pharmacodynamic analysis, peripheral-blood mononuclear cells (PBMCs) were isolated from patients at baseline and after the first treatment cycle to estimate PD-1–receptor occupancy by the antibody on circulating CD3+ T cells by means of flow cytometry.[14]

STATISTICAL ANALYSIS

Data on all 296 patients treated as of the date of analysis for this report (February 24, 2012) were used for summaries of baseline characteristics and adverse events. Pharmacokinetic and molecular-marker analyses included treated patients with available data as of February 24, 2012. The efficacy analysis included the 236 patients who could be evaluated for a response and who began treatment by July 1, 2011. Adverse events were coded with the use of the Medical Dictionary for Regulatory Activities (MedDRA), version 14.1. Adverse events of special interest, with a potential immune-related cause, were identified with the use of a predefined list of MedDRA terms. The best responses in individual patients were derived from investigator-reported data per modified RECIST, version 1.0. Objective responses were confirmed by at least one sequential tumor assessment, and objective response rates were calculated as [(complete responses + partial responses) ÷ number of patients] × 100. Fisher's exact test was used to assess the association between PD-L1 expression and objective response.

RESULTS

BASELINE PATIENT CHARACTERISTICS

A total of 296 patients with advanced solid tumors, including melanoma (104 patients), non–small-cell lung cancer (122), renal-cell cancer (34), castration-resistant prostate cancer (17), and colorectal cancer (19), began treatment with anti–PD-1 antibody between October 2008 and February 24, 2012. The majority of patients were heavily pretreated; 47% had received at least three prior regimens (Table S1-A in the Supplementary

Appendix). Notable prior therapies included immunotherapy and BRAF inhibitors in patients with melanoma (64% and 8% of patients, respectively); platinum-based chemotherapy and tyrosine kinase inhibitors in patients with lung cancer (94% and 34%, respectively); and nephrectomy, immunotherapy, and antiangiogenic therapy in patients with renal-cell cancer (94%, 59%, and 74%, respectively) (Tables S1-B, S1-C, and S1-D in the Supplementary Appendix). Baseline characteristics of the total treated population (296 patients) were similar to those of the efficacy population (236 patients).

SAFETY

A maximum tolerated dose was not defined at the doses tested in this study. A relative dose intensity (the proportion of administered doses relative to planned doses) of 90% or more was achieved in 86% of patients (Table S2-A in the Supplementary Appendix). Fifteen of 296 patients (5%) discontinued treatment owing to treatment-related adverse events (Tables S2-B and S3-A in the Supplementary Appendix). As of the date of analysis, 62 patients (21%) had died; disease progression was the most common cause of death (Table S2-C in the Supplementary Appendix).

The most common adverse events, regardless of causality, were fatigue, decreased appetite, diarrhea, nausea, cough, dyspnea, constipation, vomiting, rash, pyrexia, and headache (Table S3-A in the Supplementary Appendix). Common treatment-related adverse events included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea (Tables S3-A and S3-B in the Supplementary Appendix). Grade 3 or 4 treatment-related adverse events were observed in 41 of 296 patients (14%). Drug-related serious adverse events (as defined in Table S4 in the Supplementary Appendix) occurred in 32 of 296 patients (11%). The spectrum, frequency, and severity of treatment-related adverse events were generally similar across the dose levels tested. Drug-related adverse events of special interest (e.g., those with potential immune-related causes) included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (Table 1 and Fig. 1C).

Hepatic or gastrointestinal adverse events were managed with treatment interruption and, as necessary, with the administration of glucocorticoids. These events (e.g., diarrhea in 33 patients, including three grade 3 or 4 events and elevated alanine aminotransferase levels in 11 patients, including two grade 3 or 4 events) were reversible in all cases. Endocrine disorders were managed with replacement therapy. At the discretion of the treating physician, treatment with anti–PD-1 antibody was reinitiated once the adverse event had been successfully managed. Drug-related pneumonitis occurred in 9 of the 296 patients (3%). Grade 3 or 4 pneumonitis developed in 3 patients (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early-grade pneumonitis in 6 patients was reversible with treatment discontinuation, glucocorticoid administration, or both. In 3 patients with pneumonitis, infliximab, mycophenolate, or both were used for additional immunosuppression; however, given the small number of patients and variable outcomes, the effectiveness of such treatment was unclear. There were three drug-related deaths (1%) due to pneumonitis (two in patients with non–small-cell lung cancer and one in a patient with colorectal cancer).

CLINICAL ACTIVITY

Antitumor activity was observed at all doses tested. Objective responses were observed in a substantial proportion of patients with non–small-cell lung cancer, melanoma, or renal-cell cancer (Table 2 and Fig. 1) and in various sites of metastasis, including the liver, lung, lymph nodes, and bone. At the time of data analysis, two patients with lung cancer who received 10 mg per kilogram had unconfirmed responses, and eight additional patients (with melanoma, lung cancer, or renal-cell cancer) had a persistent reduction in baseline target lesions in the presence of new lesions (a finding consistent with an immune-related response pattern[15]). None of these patients were categorized as having had a response for the purpose of calculating objective-response rates. Objective responses, prolonged disease stabilization, or both were observed in patients who had received a variety of prior therapies. No objective responses were observed in patients with colorectal or prostate cancer.

In patients with lung cancer, 14 objective responses were observed at doses of 1.0, 3.0, or 10.0 mg per kilogram, with response rates of 6%, 32%, and 18%, respectively. Objective responses were observed across non–small-cell histologic types: in 6 of 18 patients (33%) with squamous tumors, 7 of 56 (12%) with nonsquamous tumors, and 1 of 2 with tumors of unknown type.

Table 1. Treatment-Related Adverse Events of Special Interest That Occurred in at Least 1% of All Treated Patients.

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