ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

PD-1–Targeted Immunotherapy: Recent Clinical Findings

Julie R. Brahmer, MD
Associate Professor of Medical Oncology
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University
Baltimore, Maryland

H&O What is known about the role of the programmed death-1 protein (PD-1) pathway in non–small cell lung cancer (NSCLC)?

JB In general, little is known about the role that the PD-1 pathway plays in the control of NSCLC. Based on some small studies, PD-1 expression on tumor-infiltrating lymphocytes has shown to decrease cytokine production and decrease the T-cell effector function. Increased expression of the ligand PD-L1 on tumor cells has been correlated with an increase in the number of tumor-infiltrating lymphocytes in the same region.

H&O What is BMS-936558?

JB BMS-936558 is a fully human IgG4 antibody that blocks the PD-1 protein, overcoming immune resistance and mediating tumor regression. Preliminary data suggest a relationship between PD-L1 expression on tumor cells and objective response.

H&O What was the design of your study involving BMS-936558?

JB In this large phase I multidose study, BMS-936558 was administered once every 2 weeks for 8-week treatment cycles. It was originally a dose escalation trial, starting at a low dose and increasing up to 10 mg/kg. If patients had rapid disease progression or were deteriorating clinically, they went off study. If unacceptable toxicities occurred, the drug was stopped and patients were followed for up to 48 weeks. If patients had response, stable disease, or even disease progression but were clinically stable, they were able to remain on the study until confirmed complete response, confirmed progressive disease, or unacceptable toxicity. Treatment lasted for up to 96 weeks.

Because of the initial activity seen in the dose escalation portion, particularly in NSCLC, expansion cohorts were enrolled in 3 different dose levels. Eligible patients with NSCLC were randomized to 1, 3, or 10 mg/kg, for a total of 32 patients on each dose level. Equal numbers of squamous as well as nonsquamous cell histology were enrolled at each dose level.

H&O What were some baseline characteristics among the patient population?

JB Only patients with melanoma, renal cell carcinoma, NSCLC, colorectal cancer, and castration-resistant prostate cancer who had progression while receiving prior therapy could be enrolled. Patients had received at least 1 and no more than 5 prior therapies. Most patients had good performance status, and up to 55% of patients had at least 3 prior therapies. Patients with a history of chronic autoimmune disease, prior therapy with antibodies that modulate T-cell function, conditions requiring immunosuppressive medications, or chronic infection (eg, human immunodeficiency virus infection and hepatitis B or C) were excluded. The median age was 65 years, 61% of patients were male, 39% had squamous carcinomas, and 60% had nonsquamous histology.

H&O What were the key safety results?

JB In general, the antibody was well tolerated. A maximum tolerated dose was not identified. There was no apparent relationship between drug dose and the frequency of adverse events in either all treated patients or the NSCLC subgroup. Drug-related grade 3 or 4

toxic effects occurred in 14% of all patients, and in only 8% of patients with NSCLC. The most common side effects were fatigue, rash, diarrhea, and elevated aspartate transaminase. However, such events occurred only in approximately 2 patients each and were consistent with the immunogenic activity of BMS-936558. A concerning side effect was early-stage pneumonitis, which was noted in approximately 2% of all patients. There were 3 treatment-related deaths (NSCLC=2 patients, colorectal carcinoma=1 patient) among the 9 patients (3%) who developed pneumonitis. However, we have since developed better ways to identify patients who are at risk for this toxicity, in order to detect it early and treat it aggressively. Only 5% of patients discontinued treatment due to side effects.

H&O What were some interesting findings regarding pretreatment tumor biopsies?

JB In order to assess the role of intratumoral PD-L1 expression in the modulation of the PD-1–PD-L1 pathway, 42 patients were evaluated for PD-L1 expression via immunohistochemical analysis on their pretreatment tumor biopsies. While no objective response occurred in any of the 17 patients with PD-L1–negative tumors, 9 of the 25 patients (36%) with PD-L1–positive tumors had an objective response (P=.006). Of the 10 NSCLC patients evaluated, 5 patients had PD-L1–positive expressing tumors, and 1 of those 5 patients had a response. No responses were seen in the PDL-1–negative NSCLC tumors. Our findings suggest that PD-L1 expression in pretreatment tumor biopsies may correlate with clinical response to anti-PD-1 therapy, but more studies are warranted in order to define the role of PD-L1 as a potential predictive marker of response.

H&O What are the implications of this study?

JB The level of response among patients with advanced lung cancer, which is typically not responsive to immune-based therapies, was unexpected and quite notable in this study. Furthermore, the duration of the responses across multiple tumor types appeared greater than that observed with most chemotherapies or kinase inhibitors. As such, phase II trials involving immunologic and molecular-marker correlates are under way, and phase III studies of anti-PD-1 antibodies for the treatment of NSCLC, melanoma, and renal cell carcinoma are in development.

H&O What does the future hold?

JB In addition to BMS-936558, several blockers of the inhibitory pathways are being studied, and I am hopeful that at least 1 will be available for use in patients with solid tumors. In the future, I think that these types of therapies will be used in combination to harness synergistic antitumor effects. We are now just hitting the tip of the iceberg with such antibodies. If these studies can be confirmed in further analysis, a number of novel avenues for cancer immunotherapy may emerge.

Suggested Readings

Topalian SL, Brahmer JR, Hodi FS, et al. Anti-PD-1 (BMS-936558, MDX-1106) in patients with advanced solid tumors: clinical activity, safety, and a potential biomarker for response. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract CRA2509.

Tykodi SS, Brahmer JR, Hwu W, et al. PD-1/PD-L1 pathway as a target for cancer immunotherapy: safety and clinical activity of BMS-936559, an anti-PD-L1 antibody, in patients with solid tumors. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2012;30: Abstract 2510.

Topalian SL, Hodi S, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443-2454.

Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366:2455-2465.

ClinicalTrials.gov. An exploratory study to investigate the immunomodulatory activity of various dose levels of anti programmed-death-1 (PD-1) antibody (BMS-936558) in subjects with metastatic clear cell renal cell carcinoma (RCC). http://clinicaltrials.gov/ct2/show/NCT01358721. Identifier: NCT01358721.

ClinicalTrials.gov. BMS-936558 (MDX-1106) in subjects with advanced/metastatic clear-cell renal cell carcinoma (RCC). http://clinicaltrials.gov/show/NCT01354431. Identifier: NCT01354431.