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DEVELOPMENTAL THERAPEUTICS-CLINICAL PHARMACOLOGY AND IMMUNOTHERAPY Article Tools

Safety and antitumor activity of biweekly MDX-1106 (Anti-PD-1, BMS-936558/ONO-4538) in patients with advanced refractory malignancies.

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Abstract

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Background: Programmed death-1 (PD-1), a T-cell inhibitory receptor, may suppress antitumor immunity. MDX-1106, a fully human IgG4 PD-1 blocking antibody, has shown antitumor activity and limited toxicity after intermittent dosing (Brahmer et al., ASCO 2009). This multicenter trial evaluates safety, antitumor activity, pharmacokinetics (PK), and immunological correlates of extended biweekly dosing.

Methods: Patients (pts) had treatment refractory metastatic non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), melanoma (MEL), or prostate cancer (CRPC), and no history of autoimmune disease. Escalation of biweekly MDX-1106 dosing at 1, 3, or 10 mg/kg IV was studied. Enrollment at the MTD was expanded to 16 pts in each indication, plus colon cancer. Tumor assessments after every 4 doses (one cycle) used RECIST. Pts received up to 12 treatment cycles, until progression (PD) or complete response (CR). Clinically stable pts with early PD could continue until further PD or deterioration.

Results: Four, 4, and 8 pts accrued at 1, 3, and 10 mg/kg, respectively. MTD was not reached. Grade 1/2 drug-related adverse events in > 2 pts included fatigue (9 pts/56.3%), nausea (4 pts/25.0%), and diarrhea, xerostomia, and pruritus (3 pts/18.8% each). One possibly drug-related SAE, myelodysplastic syndrome, rapidly emerged in a MEL pt previously treated with cytotoxic chemotherapy. As of Dec 2009, 6/16 (37.5%) evaluable pts had objective tumor responses, including 3 at 1 mg/kg (RCC/CR, RCC/PR, MEL/PR), 2 at 3 mg/kg (NSCLC/PR, MEL/PR) and one at 10 mg/kg (MEL/PR). All responses are ongoing (3-13+ mo). Preliminary PK estimates of trough/peak antibody levels after 2 cycles are ~ 25/40, 50/110, 150/300 ug/ml for 1, 3, and 10 mg/kg, respectively. Expansion cohort enrollment at 10 mg/kg is nearly complete, and the 1 and 3 mg/kg cohorts have been expanded with 16 MEL pts each. Grade 3/4 adverse events remain uncommon.

Conclusions: MDX-1106 administered biweekly is well tolerated and has antitumor activity at 1-10 mg/kg. Correlative tumor and immunologic studies

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are underway. Objective responses with limited toxicity in multiple malignancies warrant further investigation of PD-1 blockade.

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