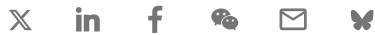


Phase I and Clinical Pharmacology May 01, 2008



Phase I Trial of the Prostate-Specific Membrane Antigen–Directed Immunoconjugate MLN2704 in Patients With Progressive Metastatic Castration-Resistant Prostate Cancer

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Abstract

Purpose

MLN2704 is an immunoconjugate designed to deliver the maytansinoid antimicrotubule agent drug maytansinoid-1 directly to prostate-specific membrane antigen (PSMA)–expressing cells via the PSMA-targeted monoclonal antibody MLN591. This novel immunoconjugate has shown cytotoxic anti–prostate cancer activity. This study investigated the safety profile, pharmacokinetics,

immunogenicity, and preliminary antitumor activity of MLN2704.

Patients and Methods

Patients with progressive, metastatic, castration-resistant prostate cancer received MLN2704 intravenously over 2.5 hours. Dose-limiting toxicity (DLT), maximum-tolerated dose (MTD), pharmacokinetics, immunogenicity, and antitumor activity were assessed.

Results

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RESULTS

Twenty-three patients received MLN2704 at doses of 18 to 343 mg/m². Eighteen of these patients received ≥ three doses at 4-week intervals. Pharmacokinetics of conjugate levels were dose proportional. There was no correlation between clearance and body-surface area. MLN2704 was nonimmunogenic. Study drug-related grade 3 toxicities occurred in three (13%) of 23 patients, including uncomplicated febrile neutropenia (the only DLT) in one patient, reversible elevations in hepatic transaminases, leukopenia, and lymphopenia. No grade 4 toxicities were observed. The most frequent grade 1 or 2 toxicities included fatigue, nausea, and diarrhea. Neuropathy occurred in eight (35%) of 23 patients, including five of six patients treated at 343 mg/m². Two (22%) of the nine patients treated at 264 or 343 mg/m² had sustained a more than 50% decrease in prostate-specific antigen versus baseline, accompanied by measurable tumor regression in the patient treated at 264 mg/m².

Conclusion

Therapeutic doses of MLN2704 can be administered safely on a repetitive basis. An MTD was not defined. MLN2704 is being administered at more frequent intervals in ongoing trials to determine an optimal dosing schedule.

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