Antitumor activity of PSMA ADC after progression on docetaxel in a mouse xenograft model of human prostate cancer

Author(s): D. Ma, H. Zhang, B. Kennedy, T. Parsons, W. C. Olson; PSMA Development Company, LLC, Tarrytown, NY

Background: Currently, there are no approved therapies for castration-resistant metastatic prostate cancer that has progressed following docetaxel therapy. Prostate-specific membrane antigen (PSMA) is an attractive target for antibody-targeted therapy of prostate cancer due to its abundant and restricted expression on the surface of prostate cancer cells. We have developed a novel antibody-drug conjugate (ADC) by linking a fully human PSMA monoclonal antibody to monomethylauristatin E (MMAE), a potent tubulin inhibitor. Here, we describe the use of PSMA ADC in a mouse model to treat xenografted human prostate tumors that have progressed following docetaxel therapy.

Methods: Nude mice were implanted subcutaneously with $5 \times 10^6$ C4-2 human prostate cancer cells. Animals were first randomized to receive weekly intravenous (IV) doses of either 2 mg/kg docetaxel ($n = 50$) or vehicle ($n = 10$). Docetaxel significantly reduced tumor growth ($p = 0.025$) during the initial phase of the study; however, most of the tumors later progressed. When the tumor volume of an animal in the docetaxel group exceeded 400 mm$^3$, the animal was rerandomized to receive continued docetaxel therapy ($n = 18$) or weekly IV doses of 6 mg/kg PSMA ADC ($n = 18$). Treatment effects were assessed by measuring tumor volume and overall survival. When tumor volume was assessed to be $\geq 2,000$ mm$^3$, animals would be sacrificed.

Results: At 134 days following tumor implantation, the survival rate was 100% for animals in the PSMA ADC treatment group; 94% of these mice had tumor sizes $< 100$ mm$^3$. In the continued docetaxel treatment group, 14 of 18 animals that were sacrificed when their tumors exceeded 2,000 mm$^3$; the survival rate was 22%. Therefore, PSMA ADC treatment significantly shrank tumors and increased overall survival of animals compared to continued docetaxel treatment ($p < 0.0001$).

Conclusions: PSMA ADC had antitumor activity in mice to xenografted human prostate tumors that had progressed following docetaxel treatment. Treatment with PSMA ADC significantly extended survival in this setting.