PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

Section Editor: Andrew J. Armstrong, MD

STEAP1 as a Potential Target for New Therapies in Prostate Cancer

Wm. Kevin Kelly, DO
Chair, Department of Medical Oncology
Sidney Kimmel Medical College
Thomas Jefferson University
Associate Director of Clinical Research
Sidney Kimmel Cancer Center
Philadelphia, Pennsylvania

H&O What is six-transmembrane epithelial antigen of prostate 1 (STEAP1)?

WKK STEAP1 was first described more than 2 decades ago. It is a cell-surface antigen that is highly expressed in prostate cancer, including more than 80% of prostate cancer with bone and lymph node involvement and 62% of Ewing sarcoma and some other tumors. The expression of STEAP1 is associated with higher Gleason scores and a worse prognosis in prostate cancer patients. STEAP1 is only minimally expressed in normal tissues, including the normal prostate, which makes it an ideal therapeutic target.

H&O How well are prostate-specific membrane antigen (PSMA) and STEAP1 associated with each other?

WKK Both PSMA and STEAP1 are good markers for prostate cancer. Researchers from the University of Washington did a notable study that looked at the differential expression of PSMA and STEAP1.[1] Among patients with metastatic castration-resistant prostate cancer, 87% of tissue samples were positive for STEAP1 and 61% were positive for PSMA, so we see greater sensitivity with STEAP1.

H&O What approaches to STEAP1 therapies have been investigated?

WKK Danila and colleagues from Memorial Sloan Kettering Cancer Center investigated the use of vandortuzumab vedotin (DSTP3086S), an antibody-drug conjugate that targets STEAP1 and is linked to the potent antimitotic agent monomethyl auristatin E.[2] This phase 1 study established that the agent was tolerable, but produced limited clinical activity.

In addition, chimeric antigen receptor T-cell therapies are being developed to target STEAP1 and STEAP2, which is also highly expressed in prostate cancer.[3,4] Other trials are looking at bispecific antigens that bind to STEAP1, such as xaluritamig. Xaluritamig is a 2+1 T-cell engager, designed to engage T cells via CD3 and tumor cells via STEAP1, and to trigger T cell–mediated lysis of STEAP1-positive cells. The 2+1 design of xaluritamig allows for avidity-driven activity, enabling selectivity for tumor cells with high STEAP1 expression and avoiding effects on normal cells with minimal expression.

H&O Could you describe the design of your recent phase 1 study with xaluritamig?

WKK This was the first global trial to look at xaluritamig in patients with metastatic castration-resistant prostate cancer.[5] To be eligible for this trial, patients had to have experienced progression on 1 or 2 androgen receptor axis-targeted agents and up to 2 prior taxane regimens. The main objective was to establish the maximum tolerated dose. We first performed a single-dose escalation phase in patients and found that we could use a dose of up to 0.1 on cycle 1, day 1. Doses higher than that led to

significant toxicity, including cytokine release syndrome (CRS). We subsequently conducted a step-up dosing phase that went up to 1.5 mg weekly, which was safe and tolerable. We reported our initial findings in *Cancer Discovery* based on the experience of 97 patients enrolled in the phase 1 dose escalation study.

H&O Could you describe the results of your study?

WKK We observed responses at all dose levels, which is unusual for a phase 1 trial. Notably, patients treated at higher doses achieved deeper and more consistent prostate-specific antigen (PSA) and measurable disease responses. Specifically, PSA50 responses were observed in 40% of patients in the low-dose cohorts and 59% in the high-dose cohort, which was defined as a target dose of 0.75 mg or greater. It was observed that PSA90 responses occurred in 19% of patients in the low-dose cohorts and 36% in the high-dose cohorts.

In this phase 1 trial, 67 of 97 patients evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) had RECIST responses. Confirmed RECIST responses occurred more often in the high-dose cohorts, with a partial response (PR) rate of 41% vs 3% in low-dose cohorts. Interestingly, responses to xaluritamig were rapid and typically occurred by the first assessment, after 4 weeks of treatment. In addition, many patients had a prolonged duration of response (DOR) to this novel therapy. Nineteen patients remained on treatment at the data cutoff; of these, 13 patients remained on treatment for more than 6 months. Although the preliminary data on the DOR are immature, the median DOR is currently 9.2 months among the 16 patients with confirmed PRs, with 10 patients still in response.

The pharmacokinetic profile demonstrated targeted exposure and predicted efficacious ranges that we saw preclinically. The half-life of the drug was between 3 and 4 days.

H&O What side effects occurred?

WKK The most common treatment-related side effects, which were primarily grade 1 and 2, were CRS (72%), fatigue (45%), muscle pain (34%), fever (32%), rash (28%), decreased appetite (25%), joint pain (24%), and anemia (21%). Although patients were admitted to the hospital for observation owing to the potential of CRS, the CRS that occurred was generally mild and resolved in all cases with standard management. This management typically consisted of corticosteroids and/or tocilizumab along with acetaminophen and intravenous hydration. Grade 3 or higher CRS occurred in 2% of patients. We were not surprised to see anemia and fatigue, which are common in patients with advanced prostate cancer. We were, however, surprised to see that some patients developed muscle and joint pain. We do not understand what caused these side effects, but corticosteroids and tocilizumab improved them. It was observed that 19% of the patients stopped taking xaluritamig because of side effects or dose-limiting toxicities.

H&O Are additional studies looking at this agent?

WKK Currently, phase 3 studies are being planned to study xaluritamig in both early and late castration-resistant prostate cancer. There are also plans to study xaluritamig in earlier-stage prostate cancer and in combination with other agents. As mentioned earlier, researchers are also looking at other ways to target the STEAP family of proteins.

H&O In what ways might the results of this study apply to other agents?

WKK We used to view prostate cancer as a cold tumor, meaning that immunotherapy would not work in advanced stages. This trial makes us stop and think that prostate cancer is not a cold tumor after all; we just need to have the right agents to stimulate the immune system. This trial did not simply show that xaluritamig is an active agent in prostate cancer, it showed that well-designed immunotherapy agents may play an important role in the treatment of prostate cancer in the future.

Disclosures

Dr Kelly has received research funding from and has served as a consultant for Amgen, Johnson & Johnson, and Bayer.

References

1. Bhatia V, Kamat NV, Pariva TE, et al. Targeting advanced prostate cancer with STEAP1 chimeric antigen receptor T cell and tumor-localized IL-12 immunotherapy. *Nat Commun*. 2023;14(1):2041.
2. Danila DC, Szmulewitz RZ, Vaishampayan U, et al. Phase I study of DSTP3086S, an antibody-drug conjugate targeting six-transmembrane epithelial antigen of prostate 1, in metastatic castration-resistant prostate cancer. *J Clin Oncol*. 2019;37(36):3518-3527.
3. Jin Y, Lorvik KB, Jin Y, et al. Development of STEAP1 targeting chimeric antigen receptor for adoptive cell therapy against cancer. *Mol Ther Oncolytics*. 2022;26:189-206.
4. Zanvit P, van Dyk D, Fazenbaker C, et al. Antitumor activity of AZD0754, a dnTGFβRII-armored, STEAP2-targeted CAR-T cell therapy, in prostate cancer. *J Clin Invest*. 2023;133(22):e169655.
5. Kelly WK, Danila DC, Lin CC, et al. Xaluritamig, a STEAP1 × CD3 XmAb 2+1 immune therapy for metastatic castration-resistant prostate cancer: results from dose exploration in a first-in-human study. *Cancer Discov*. 2024;14(1):76-89.