A CASE REPORT OF METASTATIC CASTRATION RESISTANT PROSTATE CANCER PATIENT WITH AR F877L MUTATION TREATED WITH KPG-121 IN COMBINATION WITH ENZALUTAMIDE

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Background KPG-121 is a novel modulator of the Cerebron (CRBN) E3 ubiquitin ligase complex CRL4 CRBN targeting rapid ubiquitination and degradation of casein kinase 1A1 (CK1α) and transcription factors Aiolos and Ikaros. KPG-121 promotes anti-proliferation and anti-angiogenesis activities. KPG-121 significantly improves anti-tumor efficacies when combined with androgen-receptor antagonists including enzalutamide, abiraterone acetate, apalutamide, or darolutamide in xenograft models when compared to the androgen-receptor antagonist therapy alone. KPG-121 is more potent in degrading CK1α than lenalidomide in vitro.1 CK1α is considered a novel target to overcome enzalutamide resistance in prostate cancer.2

The patient reported here was a 79-year-old white male with metastatic castration resistant prostate cancer (mCRPC) who has the AR F877L mutation and prior enzalutamide treatment.

Methods The mCRPC patient with radiographic progression of bone and lymph node metastases and rising level of prostate-specific antigen (PSA) presented to the Phase 1, open-label, dose finding, first-in-human study to evaluate KPG-121 in combination with enzalutamide, abiraterone, or apalutamide in patients with non-metastatic or metastatic CRPC (NCT03569280). The patient had a medical history of osteoarthritis and his prior treatments included bicalutamide, leuprorelin, sipuleucel-T, enzalutamide, and intensity-modulated radiotherapy. The patient’s ongoing treatments included denosumab since Aug 2014, degarelix since Jul 2016, and enzalutamide Oct 2019 with baseline PSA level of 1.63 ng/mL at the time of enrollment in Jan 2022. The patient’s AR F877L mutation had been documented since Dec 2021.

The patient was initially treated with KPG-121 at 5 mg for 10 days continuously, followed by 4 resting days in combination with 160 mg enzalutamide once daily starting 26 Jan 2022. The patient experienced Grade 3 neutropenia, and the KPG-121 dose was reduced to 2.5 mg on 25 Apr 2022. The patient’s PSA level increased to 5.64 ng/mL after dose interruption and stabilized at the range of 1.77 to 3.08 ng/mL ever since the dose resumed at 0.5 mg on 08 Aug 2022. The patient continues his treatment under the single patient expanded access study and has been treated for over 15 cycles without disease progression with PSA level of 2.96 ng/mL on 08 Jun 2023 as of the data cut.

Conclusions KPG-121 in combination with enzalutamide could potentially overcome enzalutamide resistance in prostate cancer. A trial of larger and longer duration of KPG-121 in combination with enzalutamide is needed to further evaluate the efficacy and safety of KPG-121 in enzalutamide resistant patients.

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REFERENCES