An investigator-initiated phase I study of crizotinib in combination with enzalutamide in metastatic castration-resistant prostate cancer (mCRPC) before or after progression on docetaxel

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Background: Inhibition of the androgen receptor (AR) may de-repress c-Met, which may play a role in progression to CRPC, metastasis, and therapeutic resistance. Preclinical work has shown that crizotinib, a multi-kinase inhibitor including c-Met receptor tyrosine kinase, ROS1, and anaplastic lymphoma kinase, can inhibit prostate cancer growth in cell lines and mouse models. To capitalize on the established efficacy of enzalutamide in CRPC while counteracting induction of c-Met due to AR inhibition, we investigated the combination of crizotinib plus enzalutamide.

Methods: A phase 1, standard 3+3 dose-escalation design was executed to assess the safety, tolerability, and pharmacokinetics of the combination in patients with mCRPC. The primary objective was to identify the maximally tolerated dose (MTD). A fixed standard dose of enzalutamide 160 mg daily plus escalating doses of crizotinib (250 mg daily, 200 mg bid, 250 mg bid) were administered in Cohorts 1, 2 and 3, respectively. The dose limiting toxicity (DLT) period was the first cycle (28 days).

Results: The dose escalation phase has completed. 16 men with ECOG PS 0 or 1 were enrolled in this phase. Median age was 69.5 years. Median baseline PSA was 18.9 ng/dL (range: 0.91-822.2). Visceral disease was present in 31%. The majority (56%) had prior docetaxel. The MTD was full doses of both agents. Cohorts 2 and 3 each had 1 of 6 patients with a grade 3 DLT of transaminitis. The most common, all grade treatment-related AEs were: elevated ALT (10), fatigue (9), elevated AST (9), nausea (6), hypertension (5), diarrhea (4), vomiting (4), constipation (3), edema (2), and dysgeusia (2). There were 6 grade 3/4, at least possibly treatment-related adverse events (AEs): increased ALT (2), hypertension (1), cardiac (3 AEs in same event: cardiac arrest, Vfib, prolonged QTC). Most AEs were grade 1 or 2. All transaminase elevations occurred in the same 4 patients. The dose expansion phase has completed accrual at the MTD. 5 patients remain on study.

Conclusions: Full doses of crizotinib and enzalutamide can be combined in mCRPC. The potential for hepatotoxicity exists with both agents but dose limiting toxicity is low. (NCT number: 02207504)

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