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A Phase Ib/IIa Study of the Pan-BET Inhibitor ZEN-3694 in Combination with Enzalutamide in Patients with Metastatic Castration-resistant Prostate Cancer

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Abstract

Purpose: ZEN-3694 is a bromodomain extraterminal inhibitor (BETi) with activity in androgen-signaling inhibitor (ASI)-resistant models. The safety and efficacy of ZEN-3694 plus enzalutamide was evaluated in a phase Ib/IIa study in metastatic castration-resistant prostate cancer (mCRPC).

Patients and methods: Patients had progressive mCRPC with prior resistance to abiraterone and/or enzalutamide. 3+3 dose escalation was followed by dose expansion in parallel cohorts (ZEN-3694 at 48 and 96 mg orally once daily, respectively).

Results: Seventy-five patients were enrolled (*N* = 26 and 14 in dose expansion at low- and high-dose ZEN-3694, respectively). Thirty (40.0%) patients were resistant to abiraterone, 34 (45.3%) to enzalutamide, and 11 (14.7%) to both. ZEN-3694 dosing ranged from 36 to 144 mg daily without reaching an MTD. Fourteen patients (18.7%) experienced grade ≥3 toxicities, including three patients with grade 3 thrombocytopenia (4%). An exposure-dependent decrease in whole-blood RNA expression of BETi targets was observed (up to fourfold mean difference at 4 hours post-ZEN-3694 dose; $P \leq 0.0001$). The median radiographic progression-free survival (rPFS) was 9.0 months [95% confidence interval (CI), 4.6-12.9] and composite median radiographic or clinical progression-free survival (PFS) was 5.5 months (95% CI, 4.0-7.8). Median duration of treatment was 3.5 months (range, 0-34.7+). Lower androgen receptor (AR) transcriptional activity in baseline tumor biopsies was associated with longer rPFS (median rPFS 10.4 vs. 4.3 months).

Conclusions: ZEN-3694 plus enzalutamide demonstrated acceptable tolerability and potential efficacy in patients with ASI-resistant mCRPC. Further prospective study is warranted including in mCRPC harboring low AR transcriptional activity.

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