TPS5123 Poster Session

A randomized, open-label, phase 2b study of the BET bromodomain inhibitor (BETi) ZEN-3694 plus enzalutamide vs. enzalutamide in patients with metastatic castration resistant prostate cancer (mCRPC).

Rahul Raj Aggarwal, Michael Thomas Schweizer, Christopher H. Chay, Omkar Marathe, Emilio Araujo-Mino, David Morris, David M. Nanus, Mohit Narang, Alexander I. Spira, Ian D. Schnadig, Sarah Attwell, Emily Johnson, Philip Wegge, Vandy Xu, Helena Zhu, Alissa McGuire, Margo Snyder, Michael Sweeney, Sanjay Lakhotia, Joshi J. Alumkal; University of California, San Francisco, San Francisco, CA; University of Washington & Fred Hutchinson Cancer Center, Seattle, WA; Messino Cancer Centers, Asheville, NC; The Oncology Institute, Whittier, CA; D&H Cancer Research Center, LLC, Margate, FL; Urology Associates, P.C., Nashville, TN; Weill Cornell Medical Center, NewYork-Presbyterian Hospital, New York, NY; Maryland Oncology Hematology, Columbia, MD; Virginia Cancer Specialists, Fairfax, VA; Northwest Cancer Specialists, P.C., Portland, OR; Zenith Epigenetics, Calgary, AB, Canada; Zenith Epigenetics, San Francisco, CA; Newsoara Biopharma Co., Ltd, Shanghai, China; Tigermed America LLC, Charleston, SC; University of Michigan Rogel Cancer Center, Ann Arbor, MI

Background: Androgen receptor signaling inhibitors (ARSI), such as enzalutamide (Enza), and abiraterone (Abi), are standard therapies for metastatic hormone-sensitive and metastatic castration-resistant prostate cancer (mHSPC, mCRPC). Patients who respond to the initial ARSI are frequently prescribed a 2nd ARSI upon progression. A suboptimal response to first line ARSI, including the ~ 20% treated with an ARSI for mHSPC who progress within 12 months of treatment initiation, may enrich for cancers harboring AR-independent mechanisms of resistance including treatment-emergent neuroendocrine prostate cancer (t-NEPC). BETi have been shown pre-clinically to block the neuroendocrine prostate cancer lineage plasticity program through modulating E2F1, a transcription factor involved in stemness and cell differentiation. Prior results from a mCRPC Ph. 1b/2a trial of ZEN-3694+ Enza support this notion, as lower AR transcriptional activity in baseline tumor biopsies was associated with longer radiographic progression-free survival (rPFS). Additionally, mCRPC patients who were primary refractory to 1st line abiraterone had prolonged rPFS with ZEN-3694 + Enza, suggesting that the patients with primary resistance may benefit from the combination. To test this hypothesis, a Ph. 2b randomized trial was initiated, enriching for mCRPC with suboptimal response to 1st line ARSI. **Methods:** This is a multi-national (USA and China), open-label, randomized, two cohort, Ph. 2b study of ZEN-3694 + Enza vs. Enza in mCRPC patients who have progressed on Abi (NCT04986423). Cohort A (N = 150): Patients with poor response to Abi defined either as progression in $<$ 12 months or failure to achieve PSA nadir of 0.2 ng/mL while taking Abi in HSPC setting, or progression in $<$ 6 months and/or failure to achieve a PSA50 response while taking Abi in the CRPC setting. Cohort B (N = 50): Patients who responded to Abi, defined as $>$ 12 months duration without progression while on Abi in the HSPC setting and achieving a nadir PSA $<$ 0.2 ng/mL, or $>$ 6 months duration without progression while on Abi in the CRPC setting and confirmed PSA50 response. The primary endpoint is radiographic progression-free survival (rPFS) by blinded independent central review (BICR) in Cohort A evaluated by PCWG3. Key secondary endpoints include rPFS by BICR for Cohorts A + B, PFS by investigator assessment, overall survival, PSA50 response rate, objective response rate by RECIST 1.1, efficacy endpoints for only USA patients, and patient-reported health status and quality of life, evaluated in Cohorts A, and Cohorts A + B together. The trial, conducted in collaboration with Newsoara has dosed approximately 150 of 200 patients to date. Astellas is providing enzalutamide for this study. Clinical trial information: NCT04986423. Research Sponsor: Newsoara Biopharma Co., Ltd; Zenith Epigenetics; Astellas Pharma Inc.