HSD3B1(1245A>C) Variant Regulates Dueling Abiraterone Metabolite Effects in Prostate Cancer

Mohammad Alyamani,[1] Hamid Emamekhoo,[2,3] Sunho Park,[4] Jennifer Taylor,[1] Nima Almassi,[5] Sunil Upadhyay,[6] Allison Tyler,[3] Michael P. Berk,[1] Bo Hu,[4] Tae Hyun Hwang,[4] William Douglas Figg,[7] Cody J. Peer,[7] Caly Chien,[8] Vadim S. Koshkin,[3] Prateek Mendiratta,[3] Petros Grivas,[3] Brian Rini,[3] Jorge Garcia,[3] Richard J. Auchus,[6] and Nima Sharifi[1,3,5]

[1]Department of Cancer Biology, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA. [2]Department of Medicine, University of Wisconsin Carbone Cancer Center, Madison, Wisconsin, USA. [3]Department of Hematology and Oncology, Taussig Cancer Institute,[4]Department of Quantitative Health Sciences, Lerner Research Institute, and [5]Department of Urology, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, Ohio, USA. [6]Division of Endocrinology and Metabolism, Department of Internal Medicine and Department of Pharmacology, University of Michigan Medical School,Ann Arbor, Michigan, USA. [7]Clinical Pharmacology Program, NCI, Bethesda, Maryland, USA. [8]Janssen Research & Development, Spring House, Pennsylvania, USA.

Background Treatment options including the steroidal drug abiraterone are available to treat patients with prostate cancer. However, despite initial responses, treatment resistance occurs and patients often die from their disease. Abiraterone, a CYP17A1 inhibitor, shares the same A, B steroid ring with endogenous dehydroepiandrosterone, which is a substrate for the enzyme, 3β-hydroxysteroid dehydrogenase (3βHSD) and is required for testosterone and dihydrotestosterone (DHT) synthesis to drive prostate cancer.

The common germline variant in *HSD3B1* (1245C) encodes for a hyperactive (3βHSD1) missense that increases DHT synthesis from extragonadal precursor steroids and is a predictive biomarker of resistance to ADT and sensitivity to non-steroidal CYP17A1 inhibition. Abiraterone is metabolized by 3βHSD1 to multiple steroidal metabolites, including 3-keto-5α-abiraterone which stimulates the androgen receptor. The *HSD3B1* (1245C) variant might therefore increase 3-keto-5α-abiraterone synthesis in patients on abiraterone therapy, possibly limiting clinical benefit.

Patients and Methods Part 1: We quantified abiraterone steroidal metabolites in 15 healthy male volunteers who received a single oral dose of 1000 mg abiraterone acetate plus 240 mg of apalutamide. Part 2: We determined the association between serum 3-keto-5α-abiraterone levels and *HSD3B1* genotype in 30 patients treated with abiraterone acetate (AA). Metabolite concentrations were normalized to the 8 hour time point of the pharmacokinetic study.

Results There were 8, 19, and 3 pts with homozygous wild-type, heterozygous, and homozygous variant *HSD3B1* genotypes. Patients who inherit 0, 1 and 2 copies of *HSD3B1* (1245C) have a stepwise increase in 3-keto-5α-abiraterone.

Conclusion Increased generation of 3-keto-5α-abiraterone in patients with *HSD3B1* (1245C) inheritance might partially negate abiraterone benefits in these patients who otherwise benefit from CYP17A1 inhibition.

Conflict of interest: Caly Chien is an employee of Janssen Research & Development.

FUNDING: Prostate Cancer Foundation Challenge Award, National Cancer Institute.