**HSD3B1**(1245A>C) Variant Regulates Duelling 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,2 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 Sharifi1,3,5

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

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