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LETTER TO THE JOURNAL

Evaluation of exposure-response-safety relationship of model-informed low-dose 500 mg abiraterone acetate in prostate cancer patients

Prostate cancer is a common cancer among men worldwide. Large-scale clinical studies of the 1,000 mg daily dosing of abiraterone acetate (AA) have confirmed its antitumor efficacy in patients with metastatic hormone-sensitive prostate cancer (mHSPC) or metastatic castration-resistant prostate cancer (mCRPC), regardless of their cancer's response to androgen deprivation therapy (ADT) or treatment duration. However, this dosage was indirectly justified based on the absence of dose-limiting toxicities (DLTs) in prior phase I dose-escalation trials, where a plateau in the increase of upstream steroids relating to secondary mineralocorticoid excess was observed at doses greater than 750 mg and up to 2,000 mg daily [1, 2]. Notably, prostate specific antigen (PSA) levels declined at all investigated doses (250 to 1,000 mg) [1, 2].

Cytochrome P450 17A1 (CYP17A1) is involved in both adrenal and de novo intratumoural androgen biosynthesis. We previously identified that abiraterone targeted CYP17A1 via a two-step binding mechanism [3]. Our subsequent pharmacokinetic/pharmacodynamic (PK/PD) simulations found that both the 1,000 mg and 500 mg doses of AA achieved comparable > 80% apparent target CYP17A1 enzyme occupancy and equipotent reduction of downstream plasma dehydroepiandrostenedione-sulfate (DHEA-S) levels, despite the difference in systemic exposure of abiraterone [3]. In addition, we developed physiologically-based pharmacokinetic (PBPK) models for AA and abiraterone via a middle-out approach [4], which enabled the prospective prediction of abiraterone systemic exposure at different doses.

List of Abbreviations: AA, abiraterone acetate; ADT, androgen deprivation therapy; AE, adverse event; CYP17A1, cytochrome P450 17A1; DHEA-S, dehydroepiandrostenedione-sulfate; DLT, dose-limiting toxicity; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PBPK, physiologically-based pharmacokinetics; PK, pharmacokinetics; PK/PD, pharmacokinetics/pharmacodynamics; PSA, prostate specific antigen.

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Our research group participated in a global phase II study that demonstrated a 250 mg dose of AA taken with a low-fat meal achieved comparable PSA metrics to the standard 1,000 mg AA dose taken in a fasting state in patients with CRPC [5]. However, the fat content of food could significantly impact the relative bioavailability of abiraterone [4], and controlling food intake poses a challenge in outpatient settings and during the long-term use of abiraterone. By analyzing the PK data, we observed that the systemic exposure of a lower dose of 500 mg of AA (fasted) is comparable to that of a 250 mg dose of AA with a low-fat meal. Furthermore, our modeling studies revealed that 500 mg AA is promising in achieving optimal antitumor efficacy, and diminishing mineralocorticoid-related adverse outcomes simultaneously. In addition, patients will pay less with a half-reduced dose. Currently, data on the administration of 500 mg AA in prostate cancer patients remains insufficient. To address this gap, we conducted a proof-of-concept phase I study in mCRPC and mHSPC patients newly initiated on 500 mg once daily AA. Simultaneous PBPK/PD simulations of the low-dose AA were performed to further support the unique relationship between systemic exposure and pharmacological response of abiraterone.

The clinical cohort study was conducted at National University Hospital (NUH), Singapore. The study was approved by the Domain Specific Review Boards of National Healthcare Group, Singapore, and was conducted in accordance with Declaration of Helsinki. Between November 2021 and September 2023, 7 men with mHSPC and 2 men with mCRPC were enrolled for the final analysis (median age, 72 years; range, 65 to 90). Enrolled patients were initiated on 500 mg AA once daily for 12 weeks, plus oral prednisolone 5 mg twice daily for mCRPC and 5 mg once daily for mHSPC. After this period, patients were reverted to the standard 1,000 mg dose due to ethical considerations and were followed up with routine clinical visits. The primary objectives were to determine

the PK of abiraterone, as well as evaluate the pharmacological response, i.e. percentage change in PSA from baseline to 12 weeks, and safety of 500 mg AA treatment. Secondary objective was the measurement of endocrine biomarkers (testosterone, androstenedione, DHEA-S, and cortisol) to further assess the pharmacological response of our low-dose AA treatment. Details of study design and data analysis are described in Supplementary Materials. Characteristics of enrolled patients are detailed in Supplementary Materials. Population-based ADME simulator Simcyp (version 23, Sheffield, UK) was utilized for simultaneous PBPK/PD simulations of abiraterone PK and time-dependent CYP17A1 enzyme occupancy. Our model-informed 500 mg and clinically approved 1,000 mg AA dosages were simulated. Details of modeling workflow are provided in Supplementary Materials.

Plasma PK of abiraterone at week 2 with available samples from seven patients was analyzed. Observed and simulated plasma concentrations of abiraterone are illustrated in Figure 1A-B. Corresponding PK parameters are provided in Supplementary Materials. PK sampling up to 6 h post-dose was implemented due to ethical considerations, and PBPK simulation for the 24-h PK of abiraterone was utilized as the proxy for further evaluation. Simulated plasma concentrations of abiraterone recapitulated our clinical observations from 0 to 6 h post-dose (Figure 1A). 24-h PK profiles revealed that the systemic exposure of 500 mg AA was comparable with previous results from mCRPC patients under the same dose [1, 2], and was approximately half of that previously observed or simulated with a 1,000 mg dose of AA [4].

Proportion of patients achieving a significant decrease in PSA at early post-treatment stage (usually within 12 weeks) has been frequently used as a hallmark for measuring response to a variety of prostate cancer therapies [6, 7]. Decline in PSA at week 12 was observed in all our nine patients (Figure 1C). Seven patients (78%) demonstrated decrease in PSA levels of ≥ 50% at any visit (Figure 1D). In brief, 6 mHSPC patients achieved PSA decline of ≥ 50% at week 4, and further decreased to ≥ 80% at week 12 (Figure 1D). One mCRPC patient achieved PSA decline of 91.1% at week 12, and another patient exhibited substantial PSA decline at week 8 (90.4%) but a rebound at week 12 (22.1%) (Figure 1D). The PSA rebound might possibly be associated with germline mutations in the DNA damage repair gene, ataxia-telangiectasia mutated (*ATM*), detected in his cancer tissues. These mutations have been found to be associated with attenuated responses to androgen receptor (AR)-targeted therapy [8].

Low-dose AA was safe and well tolerated during the 12-week treatment. Adverse events (AEs) of any cause occurred in 6 out of 9 patients. Details of safety profile are provided in Supplementary Materials. Hypokalemia was previously the only grade 3 or grade 4 AE in the 500 mg AA dosage groups [1, 2]. Consistently, hypokalemia was the most common AE in our study (Supplementary Materials). Other reported AEs were not observed in our study.

Baseline levels of testosterone, androstenedione, DHEA-S and cortisol were similar between 2 types of patients in our study. Circulating testosterone levels at baseline were in the castrate range (median, 14.62 ng/dL; range, 3.57 to 43.15) in all 9 patients (Figure 1E). From Visit 1 onwards, decline of levels of the 4 steroids were well correlated, demonstrating substantial suppression by low-dose AA (Figure 1E-H). The observations were also consistent with findings from previous studies on 1,000 mg AA therapy, which reported that suppression of downstream steroids of CYP17A1 was correlated with PSA decline at week 12 [6, 9, 10]. Therefore, our endocrine profiles broadened the evidence in supporting the pharmacological response of 500 mg AA by including 7 mHSPC patients in addition to 2 mCRPC patients.

Our clinical observations were substantiated via PBPK/PD modeling of daily doses of both our low-dose 500 mg and clinically approved 1,000 mg AA. CYP17A1 enzyme occupancy remained above 80% despite a 50% reduction in systemic exposure to abiraterone after 2 weeks of 500 mg AA treatment (Figure 1B). In addition, free CYP17A1 continued to be slowly released from tight binding, while abiraterone has been eliminated systemically.

Our preliminary research involved a small cohort of patients with mCRPC and mHSPC in the treatment group only, and evaluations were conducted over a relatively short period of 12 weeks. Despite this limitation, our proof-of-concept phase I study and PBPK/PD modeling results underscored the pharmacological response of the low-dose regimen, and were consistent with our hypothesis that a lower dose of AA is promising for achieving optimal antitumor efficacy, reducing adverse outcomes, and alleviating financial burdens simultaneously. A long-term, large-scale, controlled clinical trial is essential to further evaluate and confirm the clinical efficacy of low-dose AA therapy.

DECLARATIONS

AUTHORS' CONTRIBUTIONS

Participated in research design: Edmund Chiong, Eric Chun Yong Chan, and Eleanor Jing Yi Cheong.

Conducted experiments: Edmund Chiong, Ziteng Wang, Sin Mun Tham, Revathi Periaswami, Poh Choo Toh, Ziting Wang, Qing Hui Wu, Woon Chau Tsang, Arshvin Kesavan, Alvin Seng Cheong Wong, Patrick Thomas Wong, and Felicia Lim.

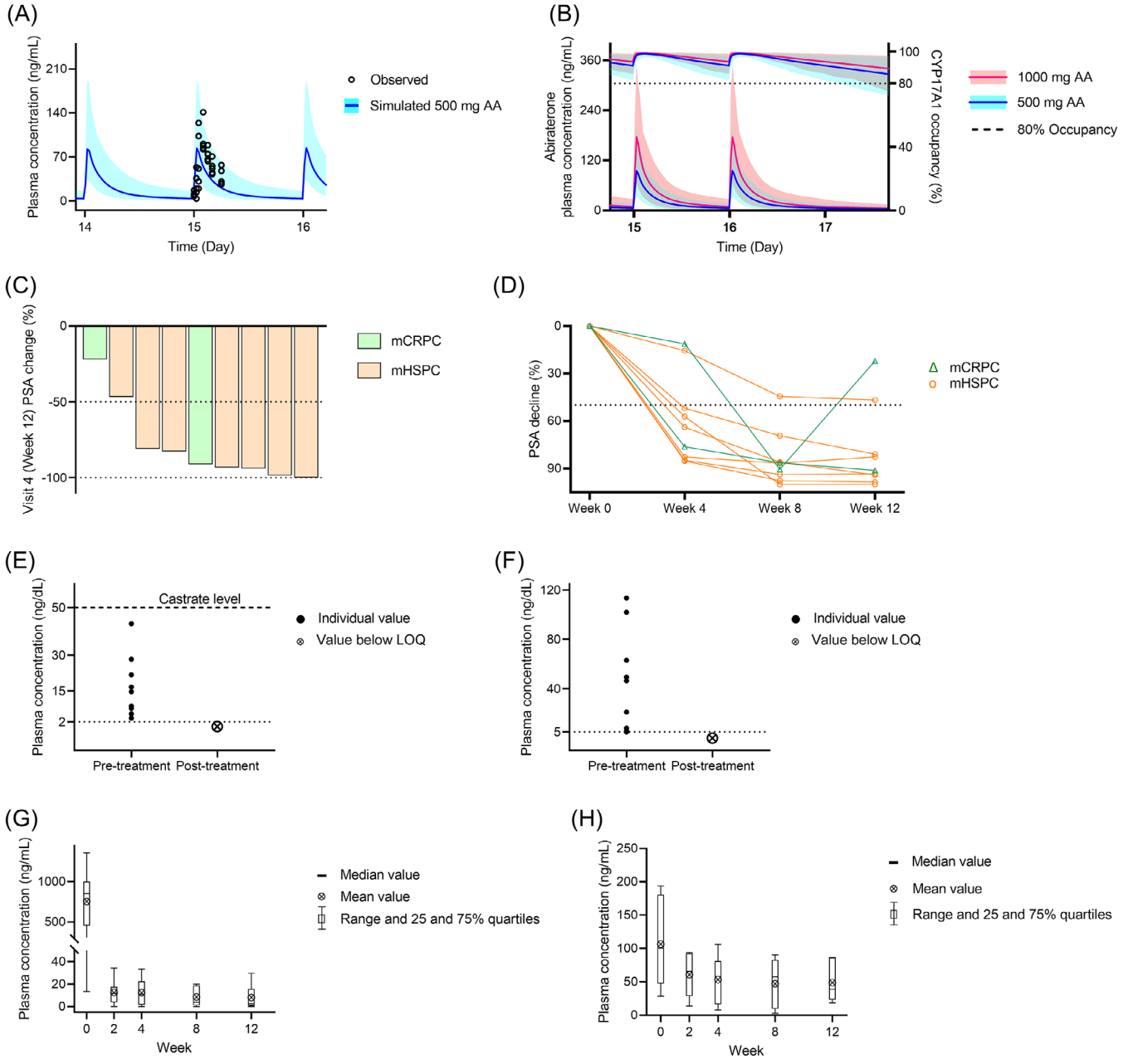

FIGURE 1 PK, pharmacological response and endocrine profiles of abiraterone of low-dose 500 mg AA. (A) Observed plasma concentration versus time profile presented as individual values ($n = 5$), along with simulated profiles via PBPK modeling for 16 days. Solid blue line represents simulated geometric mean concentration of abiraterone, and blue area represents the 5th and 95th percentiles of the simulated concentration. Notably, C_{max} of abiraterone was observed at 4 h post-dose for one patient, and another patient missed 6 h post-dose sample, thus observed data were from five mHSPC patients. **(B)** Simulated plasma concentration of abiraterone and target CYP17A1 enzyme occupancy profiles among cancer patients receiving 500 or 1,000 mg of AA daily for 12 weeks. Blue or red line represents mean plasma concentrations or target occupancy for 500 and 1,000 mg dosage, respectively. Blue or red area represents the area between 5th and 95th percentiles of corresponding simulated mean values. Dotted line represents CYP17A1 occupancy of 80% as reference. **(C)** Waterfall plot showing relative change in PSA levels at Visit 4 (Week 12) of low-dose 500 mg AA therapy in men with mHSPC and mCRPC. One mHSPC patient had PSA levels below the LOQ of 0.03 μg/L, which were recorded as 100% decrease. **(D)** Individual PSA kinetics in mHSPC (°) and mCRPC (△) patients who received low-dose 500 mg AA for 12 weeks. **(E-F)** Individual values for plasma levels of testosterone (**E**) and androstenedione (**F**) at baseline and post-treatment. At every study visit post-treatment, levels of testosterone and androstenedione in all patients were detected but lower than the LOQ of the assay, and were combined as a single point. **(G-H)** Median (line) and mean (circle) levels for plasma levels of DHEA-S (**G**) and cortisol (**H**) at baseline and each study visit. The box and whiskers represent the 25 and 75% quartiles, and range of the data. Abbreviations: AA, abiraterone acetate; CYP17A1, cytochrome P450 17A1; DHEA-S, dehydroepiandrostenedione-sulfate; LOQ, limit of quantitation; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; PBPK, physiologically-based pharmacokinetic; PSA, prostate specific antigen.

Performed data analysis: Ziteng Wang, Yi Chen Yao, Revathi Periaswami, and Shuaibing Liu.

Wrote or contributed to the writing of the manuscript: Ziteng Wang, Eric Chun Yong Chan, and Edmund Chiong.

The corresponding authors, Edmund Chiong and Eric Chun Yong Chan, had full access to all of the data and the final responsibility to submit for publication.

All authors had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST STATEMENT

No author has an actual or perceived conflict of interest with the contents of this article.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Domain Specific Review Boards of National Healthcare Group, Singapore (2020/00258), and was conducted in accordance with Declaration of Helsinki. All patients provided written informed consent.

TRIAL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.