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QT/QTc Studies of Abiraterone Acetate in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) − Analysis of 3 Phase 1/2 Studies

C.J. Ryan[1], D.C. Danila[2], A. Tolcher[3], K.N. Chi[4], N. Tran[5], R. Knoblauch[6], T. Kheoh[5], C.M. Haqq[5], H.I. Scher[7], A. Molina[5]. *[1]UCSF Comprehensive Cancer Center, University of California-San Francisco, San Francisco CA, USA; [2]Memorial Sloan Kettering Cancer Center, Genitourinary Medical Oncology, New York NY, USA; [3]South Texas Accelerated Research Therapeutics, START Center for Cancer Care, San Antonio TX, USA; [4]British Columbia Cancer Agency, Medical Oncology, Vancouver BC, Canada; [5]OrthoBiotech Oncology Research & Development (A Unit of Cougar Biotechnology), Los Angeles CA, USA; [6]Johnson & Johnson Pharmaceutical Research & Development, Clinical Research, Raritan NJ, USA; [7]Memorial Sloan Kettering Cancer Center, Genitourinary Oncology Service, New York NY, USA*

Background: Abiraterone acetate (AA) is the prodrug of abiraterone (A), an androgen biosynthesis inhibitor that specifically inhibits CYP17, blocking biosynthesis of androgens, including testosterone and dihydrotestosterone. In a phase 3 study (COU-AA-301), AA + prednisone demonstrated survival benefit in post-docetaxel mCRPC patients (de Bono ESMO, 2010). A median QTc interval prolongation of 9−21 ms has been associated with luteinizing hormone-releasing-hormone-based androgen deprivation therapy (Garnick ASCO 2004). Here we review ECG data from 3 phase 1/2 studies of AA in patients with mCRPC.
Materials and Methods: ECGs were collected in triplicate using 12-lead Holter monitor across 3 phase 1/2 studies of AA + prednisone in mCRPC (Table) at screening, during study, and at end of study for Studies 002 and 004, and at baseline, Cycle 1 Day 1 (C1D1), and C2D1 for Study 006. All ECGs were analysed at a central ECG laboratory. Safety was assessed during each study by monitoring for adverse events (AEs).
Results: 124 mCRPC patients were treated with AA 1000 mg QD + prednisone 5 mg BID across these studies (Table). After AA administration, no patients had a QTcF interval >500 ms; no patients had a change from baseline in QTcF interval $\geqslant$ 60 ms, and 2 patients (2.5%) had a change from baseline in QTcF interval $\geqslant$ 30 and <60 ms. Across all 3 studies, AEs related to cardiac safety included fluid retention (all grades: 32/124 patients [25.8%]; grade 3: 2 [1.6%]) and hypokalaemia (all grades: 12/124 patients [9.7%]; grade 3: 1 [0.8%]). No grade 4 hypokalaemia or fluid retention was reported.
Conclusions: Across 3 phase 1/2 AA studies, QT prolongation was not observed. Cardiac-related AEs occurred in <10% of patients. The phase 3 Study 301 safety database is currently being analysed for differences in cardiac events in the placebo and AA arms. No association between hypokalaemia and QT prolongation, or any cardiac AEs, has been observed.

Table. Study design and ECG results

	COU-AA-002 (Phase 2) (n = 33)	COU-AA-004 (Phase 2) (n = 58)	COU-AA-006 (Phase 1b) (n = 33)	
Patients	Chemo-naïve mCRPC	Post-docetaxel mCRPC[a]	mCRPC failed GnRH therapy, PSA $\geqslant$2 ng/mL and $\leqslant$1 prior chemo	
End of study[b] QTcF interval (ms)	N = 12[c]	N = 13[c]	N = 33[c]	Total (N = 80)
>480 and $\leqslant$500, n (%)	1 (8.3)	0	0	1 (1.3)
>500, n (%)	0	0	0	0

[a]Patients with >2 previous chemotherapy regimens were excluded; [b]C2D1 in COU-AA-006. GnRH, gonadotropin-releasing hormone; PSA, prostate-specific antigen; [c]Number available for QTcF interval analysis.

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A Phase 1 Single Dose Open-label Reduced/staged Pharmacokinetic (PK) and Safety Study of Abiraterone Acetate (AA) in Men With Impaired Renal Function

T. Marbury[1], R. Stonerock[1], N. Tran[2], M. Gonzalez[3], J. Jiao[3], J. Breeding[2], C.M. Haqq[2], A. Molina[2], M. Acharya[3]. *[1]Orlando Clinical Research Center, Clinical Research, Orlando FL, USA; [2]OrthoBiotech Oncology Research & Development (A Unit of Cougar Biotechnology), Los Angeles CA, USA; [3]Johnson & Johnson Pharmaceutical, Research & Developlment, Raritan NJ, USA*

Background: AA is the prodrug of abiraterone (A), an androgen biosynthesis inhibitor that selectively inhibits CYP17. AA improves overall survival in post-docetaxel metastatic castrate-resistant prostate cancer (Scher, ASCO GU 2011). Primary objective: determine PK profile of AA and abiraterone after single 1000 mg oral dose of AA in subjects with impaired renal function and matched-control subjects with normal renal function.
Materials and Methods: In this open-label reduced/staged design PK study (COU-AA-012), subjects with end-stage renal disease (ESRD) on dialysis and mean age and BMI matched-control cohort received single oral dose of AA 1000 mg after $\geqslant$6-hr fast and remained fasting 4 hrs post-dose. Stage 2 − evaluation of subjects with mild/moderate impairment − would only have been triggered if: (1) occurrence of a treatment-related SAE or (2) geometric means, PK exposure parameters (C_{max}, AUC_{0-last}, $AUC_{0-\infty}$) for ESRD >2 times control. Serial PK blood samples were collected over 96 hrs post-dose. Neither occurred, thus Stage 2 was not needed. In the ESRD cohort, AA was administered ~1 hr after dialysis completion. 72-hr PK blood sample was collected before next dialysis session.
Results: 16 male subjects were enrolled: 8 ESRD and 8 matched controls. Control cohort was well matched (age and BMI) to ESRD cohort: mean ages 47 and 51 yrs; mean BMI 29.0 and 29.7 kg/m^2, respectively. After AA administration, A was rapidly absorbed in ESRD and control cohorts, with median tmax values of 3 and 1.5 hrs, and mean $t_{1/2}$ of 16.0$\pm$2.0 and 19.0$\pm$4.0 hrs, respectively. Systemic exposure to A (based on geometric mean C_{max}, AUC_{0-last}, $AUC_{0-\infty}$), was ~35−45% lower in ESRD vs matched controls (Table). One subject in control cohort had grade 1 rhinorrhea; no ESRD subjects had AEs.

Geometric mean and ratio for PK parameters, ESRD vs normal cohorts

Parameter	Geometric Mean, ESRD (n = 8) vs Normal (n = 8)	Geometric Mean Ratio (90% CI)
C_{max} (ng/mL)	38.8 vs 73.0	0.53 (0.27, 1.05)
AUC_{0-last} (ng$\times$hr/mL)	228 vs 363	0.63 (0.32, 1.22)
$AUC_{0-\infty}$ (ng$\times$hr/mL)	243 vs 373	0.65 (0.34, 1.23)

Conclusions: Systemic exposure to A following a single 1000 mg dose of AA in subjects with ESRD was not higher than that of matched controls with normal renal function. Tolerability of AA was comparable in the two cohorts.

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Abiraterone Acetate Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer (mCRPC) − a Drug–Drug Interaction (DDI) Study With Dextromethorphan HBr and Theophylline

K.N. Chi[1], A. Tolcher[2], P. Lee[3], P. Rosen[3], A. Molina[4], J. Jiao[5], A. Bernard[5], N. Tran[4], M. Acharya[5]. *[1]British Columbia Cancer Agency, Medical Oncology, Vancouver BC, Canada; [2]South Texas Accelerated Research Therapeutics, START Center for Cancer Care, San Antonio TX, USA; [3]Tower Cancer Research Foundation, Clinical Trials, Beverly Hills CA, USA; [4]OrthoBiotech Oncology Research & Development (A Unit of Cougar Biotechnology), Los Angeles CA, USA; [5]Johnson & Johnson Pharmaceutical, Research & Development, Raritan NJ, USA*

Background: Abiraterone acetate (AA) is the prodrug of abiraterone, an androgen biosynthesis inhibitor that specifically inhibits CYP17. AA + prednisone (P) demonstrated survival improvements in a phase 3 study in post-docetaxel mCRPC patients. Abiraterone is a potent inhibitor of CYP2D6 and CYP1A2 in vitro. As many commonly prescribed drugs are metabolised through CYP2D6 or CYP1A2, it is important to assess the potential for DDI.
Materials and Methods: COU-AA-15 is a multicentre open-label study conducted in mCRPC patients to evaluate the effects of multiple doses of AA + P on the pharmacokinetics (PK) of a single dose of dextromethorphan HBr (D) and theophylline (T) as probes for CYP2D6 (Group A) and CYP1A2 (Group B), respectively. Groups A (n = 18) and B (n = 16) received 2 single doses of D 30 mg or T 100 mg, respectively, on Days −8 and +8 Cycle 1 under fasting conditions, and continuous daily oral AA 1000 mg + P 10 mg starting on Day 1 Cycle 1. PK was assessed by blood sampling and safety assessed via adverse event (AE) reporting.
Results: Systemic exposure of D was approximately 100% higher with D + AA + P vs D alone based on mean values for C_{max} (7.12 [4.99] vs 3.49 [4.82] ng/mL) and AUC_{24} (70.0 [73.2] vs 35.5 [56.0] h*ng/mL). A comparable increase in D exposure was observed for other exposure parameters assessed (AUC_{last} and AUC_{∞}); mean T_{max} and $t_{1/2}$ values for D were similar with D + AA + P vs D alone. For D + AA + P vs D alone, exposure (AUC) of dextrorphan, the active metabolite of D, was approximately 33% higher while mean T_{max} and $t_{1/2}$ values for dextrorphan were similar. Mean exposure parameter values for T were comparable with T + AA + P vs T alone. Treatment-emergent AEs (TEAEs) were reported in 14 (78%) patients in Group A and 12 (75%) in Group B; most were grades 1−2. One (7%) patient had a TEAE of grade 3 increased alkaline