7056 POSTER

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

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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

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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

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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

phosphatase. No serious AEs, deaths, or discontinuations due to AEs were reported.
Conclusions: These results demonstrate the potential for AA to inhibit the CYP2D6 metabolic pathway and caution should be used when AA is coadministered with medications that are known CYP2D6 substrates. There was no apparent DDI between AA and T, a CYP1A2 substrate. The safety profile of AA was consistent with known toxicities.

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Incidence and Outcomes of Brain and Meningeal Metastases (BMm) in Patients With Castration-resistant Prostate Cancer (CRPC) in the Era of Docetaxel (DOC)

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Background: The occurrence of BMm has been usually viewed as an exceptional event in the history of prostate cancer (PC) patients (pts). In two large retrospective series the incidence of BMm in PC pts was about 0.5%. Since the recent introduction of DOC as first line treatment has improved survival of CRPC pts, we have retrospectively evaluated the occurrence of BMm in such setting of pts, to explore whether this survival prolongation has changed the incidence of BMm.
Materials and Methods: The clinical records of a consecutive series of 943 pts with CRPC treated in our Institutions from 2002 to 2010 were reviewed. All pts met the definition of CRPC according to international guidelines: all pts received or were eligible for DOC-based treatment.
Results: We collected a series of 31 pts with BMm (incidence 3.3%). The median age at the diagnosis of PC was 62 yrs (range 51−78). Twenty-one pts had a median number of 1 brain metastases (range 1−8) and neurological symptoms were present in 16 cases. Ten cases presented meningeal metastases: in this case all but one pt were symptomatic. After BMm diagnosis, local treatment were proposed in 16 pts: 5 pts underwent metastasectomy (M) + external brain irradiation (BI), 1 M alone, 9 BI alone, 1 gamma-knife. Eleven pts received chemotherapy after BMm, while the remaining received only best supportive care. The median interval from the PC diagnosis and the achievement of castration resistance was 23 mos (range 7–141) while the appearance of BMm was documented after 6–173 mos (median 43.5) The median survival after BMm was 4 mos (range 1−29) with 6 pts surviving more than 1 year. These long-term survivors had brain metastases in 5 cases and meningeal metastases in 1 case and were managed with surgery in 3 cases, radiotherapy in 2 cases and DOC in 1 case.
Conclusions: It appears from our data that in the DOC era 1) the incidence of BMm in CRPC pts is higher than in the historical reports; 2) the interval from PC diagnosis and the appearance of BMm is clearly longer (43.5 mos) compared to that reported in historical series (28 mos). These findings could be related to the changes in survival of CRPC, produced by DOC introduction in the clinical practice. A special attention should be reserved to the appearance of neurological symptoms in a long-term CRPC survivor due to a possible relation with BMm.

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Assessment of Angiogenic Factors and Hematopoietic Stem Cells and Their Relevance as Prognostic Factors for Overall Survival (OS) in Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients (pts): a Prospective Study

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Background: Circulating biomarkers identification could be useful in predicting early response to sunitinib in pts with mCRPC, especially whole blood circulating endothelial (CEC), progenitors (EPC: CD34+45-) and hematopoïetic stem (HSC: CD34+45low) cells, as well as plasma levels of angiogenic factors (AF) VEGF-A, bFGF, SDF-1, sVEGFR-1&2 (soluble form).
Materials and Methods: A single arm phase 2, multicentre study, continuous regimen of sunitinib (37.5 mg once daily), was subject to CEC, EPC, HSC and AF level assessment at baseline (bsl). CEC, EPC, AF were respectively assessed by immunomagnetic isolation, flow cytometry and ELISA. This abstract presents results of bsl prognostic factor for OS. Multivariate analysis was performed using a Cox stepwise regression model. Bsl ECOG-performance status, hemoglobin, polymorphonuclear neutrophil and platelets were considered as adjustment factors.
Results: Upon 50 patients accrued, AF and CEC/EPC/HSC were available for 40 and 14 pts, respectively. Median OS (months, [CI95%]) for AF sub-group was 15.4 (10.9–23.5). Bsl ECOG: 0=18 and 1−2=22. In univariate analysis, VEGFR-1, HSC and HSC/KDR+ were predictive of OS (respectively $p = 0.02$, $p = 0.016$ and $p = 0.01$), a high level of sVEGFR-1 and high count of HSC or HSC/KDR+ were associated with poor prognosis (3 pts with bsl HSC/KDR+ count >80 presented with the shortest survival). sVEGFR-1 and VEGF-A levels were correlated ($r = 0.41$, $p = 0.009$, Spearman); a VEGFR-1/VEGF-A ratio >1.5 (median) was associated with longer OS (HR = 0.4, CI95%:0.16−1.0). In multivariate analysis sVEGFR-1 and HSC were the main prognostic factors for OS (respectively $p = 0.001$ and $p = 0.01$), a HSC count of less than 1250 (median) being related to good prognosis (HR = 0.16 CI95%:0.03−0.8).
Conclusions: Baseline HSC, HSC/KDR+ and sVEGFR-1 were independent factors associated with poor prognostic in mCRPC pts. Analysis of these markers for early prediction of response to sunitinib is ongoing.

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Assessment of Bone Remodeling Markers and Their Relevance as Prognostic Factors for Overall Survival (OS) in Metastatic Castration-resistant Prostate Cancer (mCRPC) Patients (Pts) Treated With Sunitinib (S) After Docetaxel Failure − a Prospective Study

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Background: Circulating biomarkers identification could be useful in establishing prognostic for survival and prediction of early response in mCRPC pts treated with S. Three bone remodeling markers (BM) were assessed: P1NP, Tartrate-Resistant Acid Phosphatase 5b isoform (TRAP) and beta Collagen 1 carboxy terminal telopeptide (CTX).
Materials and Methods: A single arm phase 2, multicentre study, S continuous regimen (37.5 mg once daily), was subject to BM level assessment at baseline (bsl) and after 3 months of S (% change from bsl). Data also considered at bsl were: ECOG-performance status, total alkaline phosphatases (PAL), bone metastasis (BO), bisphosphonates received within 6 months prior to S (PH6). Total serum calcium, 25-OH Vit D and PTH levels were considered as potential confusion factors in multivariate analysis.
Results: Upon the 50 pts accrued, BM levels at bsl and after 3 months of S were available for 35 and 29 pts, respectively. Observed: 26/35 deaths, median (md) survival 15.4 months [CI95%: 7.3–24.2]. Bsl ECOG 0: N = 13 and 1−2: N = 22, BO N = 30 and PH6 N = 6. P1NP (md = 100 μg/l), CTX (md = 3.3nmol/l) and TRAP (md = 1.55UI/l) were correlated ($r = 0.7$, $p < 0.0001$, Spearman), both at bsl and after 3 months. In univariate analysis, factors associated ($p < 0.1$) with good prognostic were PAL ⩽130UI/l (HR = 0.26), P1NP <100 μg/l (HR = 0.38), TRAP <1.55UI/l (HR = 0.4), ECOG=0 (HR = 0.55), no BO (HR = 0.28), no PH6 (HR = 0.51), CTX <3.3 nmol/l (HR = 0.47). Multivariate analysis (stepwise Cox regression) was performed excluding bsl total PAL which was correlated to P1NP ($r = 0.8$, $p < 0.0001$, spearman) and not specific of bone formation. P1NP was the only independent factor associated with OS (HR = 0.39 [CI95%:0.17, 0.90]). No BM was predictive of response to S at 3 months, this time lapse could be too short with regard to the mean cycle time of bone remodeling.
Conclusions: Baseline P1NP ⩾100 μg/l is associated with poor prognostic and should be taken into account for treatment of mCRPC patients and could considered as a possible stratification factor for future studies.

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Patients' Perception of Information During and After Radiotherapy for Localized Prostate Cancer

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Background: There is a lack of studies on patients' perception of information during and after radiotherapy for localized prostate cancer. Knowledge about areas where patients perceive the information to be sparse can help in improving information to this patient group. Patients' perception of received information and its relation to quality of life were studied as well as information needs and satisfaction with information at different time points from diagnosis.
Material and Methods: Between February 8 and April 15 in 2010, the EORTC QLQ-C30 and QLQ-INFO25 were sent to 660 patients with