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Abiraterone acetate (AA), an irreversible inhibitor of CYP17, has significant and durable anti-tumor activity in both chemotherapy-naive and docetaxel treated castration-resistant prostate cancer (CRPC)

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Introduction: AA is an oral irreversible inhibitor of CYP17 (17alpha-hydroxylase/C17,20-lyase), a key enzyme in androgen and estrogen synthesis, and is under phase III evaluation for the treatment of CRPC patients (pts) progressing after established therapies.
Methods: CRPC pts were enrolled into 2 parallel trials of AA: (i) A Phase I/II study in chemo-naive CRPC and (ii) A Phase II study in CRPC post-docetaxel. Both Phase II trials utilized a 2-stage design with Ho of 10% and Ha of 30%, alpha = 0.05; beta = 0.14 and PSAWG criteria for response. To investigate predictors of response and mechanism of resistance, target steroids were measured and blood for enumeration and fluorescence in situ hybridization (FISH) studies of circulating tumor cells (CTC), utilizing the CellSearch™ system, was collected at baseline, on study and at progression (PD).
Results: 89 pts have been treated with AA; 54 chemo-naive and 35 post-docetaxel. 35/54 (65%) chemo-naive and 17/35 (48%) post-docetaxel pts had a decline in PSA $\geqslant$50%, rejecting the null hypothesis in both studies. Radiological regression, symptomatic improvements and normalization of raised LDH and ALP were observed. Treatment with AA resulted in significant suppression of androgenic and estrogenic steroids downstream of CYP17. Using Spearman-Rank correlation, pre-treatment androstenedione and estradiol levels were significant predictors of a PSA decline $\geqslant$50% (p values: 0.01079 and 0.0299) but baseline DHEA and testosterone (T) levels were not. Using a super-sensitive LC/MS/MS assay, T declined to <0.05 ng/dl in 5 pts and to a median of 0.23 ng/dl (range: 0.646–0.08 ng/dl) in the other 15 pts studied. There was no association between T nadir of pts who responded compared to those who did not respond to AA. Importantly, there was no rise in hormones at PD. 39/89 pts had $\geqslant$5 CTCs at baseline; 18/39 pts had a decline to <5 CTCs on AA. 16/39 pts had a *TMPRSS2-ERG* fusion in their CTCs idenitifed by FISH. Patients with a decline from $\geqslant$5 CTCs to <5 CTCs had an improvement in survival compared to pts with no decline in CTCs; 14/18 pts with a decline in CTCs to <5 had a *TMPRSS-ERG* fusion. Only 2 pts with a *TMPRSS2-ERG* did not have a decline in CTC to <5 but both had loss of *PTEN*. Gain of *AR* in CTCs at PD on AA compared to baseline was observed in 5 pts.
Conclusions: These results support emerging preclinical data indicating that CRPC frequently remains hormone driven despite progression following all available treatment options. They confirm that the anti-tumor activity of AA is attributable to suppression of androgenic and estrogenic hormones and suggest that pts with a *TMPRSS2-ERG* fusion constitute a tumor sub-group with increased sensitivity to CYP17. Loss of *PTEN* and gain of *AR* are potential mechanisms of resistance.

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Re-inducing sensitivity to abiraterone acetate, a novel CYP17 inhibitor with a high level of anti-tumour activity in castration resistant prostrate cancer

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Introduction: Abiraterone acetate (AA) has been developed as a novel 17alpha-hydroxylase/C17−20, lyase (CYP17) inhibitor, the key enzyme in androgen synthesis. Phase II studies of AA report a PSA decline by $\geqslant$50% in 60% of castration-resistant prostate cancer (CRPC) patients. However, AA causes a rise in ACTH which drives excess synthesis of steroids upstream of CYP17, such as deoxycorticosterone, which can activate a mutated androgen receptor (AR).
Methods: To investigate whether suppression of ACTH would re-induce sensitivity to AA, dexamethasone 0.5 mg/day was added to CRPC patients progressing on AA. Steroids upstream and downstream of CYP17 were measured prior to and after starting dexamethasone.
Results: Addition of dexamethasone to AA resulted in suppression of ACTH, corticosterone and deoxycorticosterone to below the lower limit of sensitivity of the assays used.
Group I: 19/54 pts received dexamethasone at progression on AA and had not received dexamethasone previously: 5/19 (26%) had a decline in PSA $\geqslant$50%. Duration of response (days): 252+, 84+, 140+, 259+, and 280+.
Group II: 11/54 pts had dexamethsone after AA and had previously failed dexamethasone at the same dose and schedule. The duration of response on AA and AA + dexamethasone for this sub group (days) is shown in *table 1*. 4/11 (36%) pts had a decline in PSA $\geqslant$50% and 1/11 pt had a decline in PSA >90% after addition of steroids. Duration of response on dexamethasone + AA (days): 469+, 81+, 231, and 202. One pt did not have a $\geqslant$50% PSA decline but stable disease for 552+ days.
Conclusion: Preliminary data suggests that resistance to AA can occur secondary to activation of a promiscuous AR by hormones upstream of CYP17. This has been reversed by addition of steroids to decrease ACTH drive and upstream steroids and has resulted in re-induction of sensitivity to AA in 30% of patients, regardless of prior treatment with same dose corticosteroids.

Table 1

patients	1	2	3	4	5	6	7	8	9	10	11
Duration (days) on											
AA	509	534	36	112	119	65	56	72	168	49	245
AA + steroids	222	202	21	552+	469+	196	276	151	231	172	81+
PS A response (%) on											
AA	>50%	>50%	PD	>50%	SD	SD	SD	>50%	>50%	>50%	>50%
AA + steroids	PD	>50%	PD	SD	>50%	PD	SD	>30%	>50%	PD	>50%

PD: progressive disease; SD: stable disease.

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Phase I-II study of MDV3100 in castration resistant prostate cancer. The Prostate Cancer Clinical Trials Consortium

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Background: Experimental models and molecular profiles of human prostate cancers show that the androgen receptor (AR) is activated in castration-resistant prostate cancers.. MDV3100 is a novel small molecule AR antagonist engineered for activity in models with AR overexpression. MDV3100 blocks nuclear translocation of AR, DNA binding, and has no agonist activity when AR is overexpressed. In July 2007, a multi-center first-in-man Phase 1−2 trial was initiated to determine safety, pharmacokinetics (PK), and antitumor activity including effects on prostate-specific antigen (PSA), circulating tumor cells (CTC), bone and soft tissue metastases, and in selected patients (pts) fluorodeoxyglucose (FDG) and fluorodihydrotestosterone (FDHT) uptake by positron emission tomography (PET).
Material and Methods: Pts are administered MDV3100 orally, once daily. Dose-escalation cohorts include 3−6 pts starting at 30 mg/day with sequential escalations to 60, 150, 240, and 360 mg/day. Enrollment has been expanded at 60 mg/day and above to further recruit approximately 12 chemotherapy-naive and 12 post-chemotherapy pts, once the safety of a dose has been established.
Results: Enrollment has been completed at doses up to 240 mg/day. Recruitment for the dose-escalation cohort at 360 mg/day is currently ongoing. 22 pts at 60 mg/day, 23 pts at 150 mg/day, and 28 pts at 240 mg/day have been followed for 12+ weeks. To date, MDV3100 has been generally well-tolerated with no reports of serious adverse events deemed related to study drug. PK were dose-linear with a half-life of approximately one week. Available PSA data demonstrate effective AR blockade by MDV3100. PSA declines from basline at week 12 are summarized in the table.
Of the 42 and 31 chemo-naive and post-chemotherapy pts across the three dose levels, 23 (55%) and 13 (42%) had a >50% decline in PSA at week 12 compared to baseline, respectively.