add to previous information calling for a comparative trial of Cabazitaxel vs Docetaxel rechallenge in docetaxel sensitive mCRPC.

7053 POSTER

Hormonal Impact of Second-line Salvage Chemotherapy With Carboplatin Plus Weekly Docetaxel in Patients With Castration and Docetaxel-resistant Prostate Cancer

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Background: Cabacitaxel has recently been approved by the FDA as standard second-line chemotherapy for patients progressing during or after first-line docetaxel chemotherapy. However, Cabacitaxel treatment is hampered by high costs and toxicity. Recent data suggest that carboplatin may be effective in combination with docetaxel in DRPC. Platinum(II)-complexes have been shown to interfer with steroid biosynthesis lowering testosterone levels by inhibiting the cholesterol side chain cleavage enzyme (CYP11A1), 3β-hydroxysteroid dehydrogenase (HSD3B1,2) and 17α hydroxylase/C17,20-lyase (CYP17A1).
Methods: Docetaxel failure/resistance was defined according to the Prostate Cancer Working Group (PCWG2 2007) criteria. Since February 2005, 63 consecutive DRPC pts were treated with at least two cycles of carboplatin AUC5 iv for 30 min on day 1 every 4 weeks (q4w), docetaxel at a dose of 35 mg/m^2 iv for one hour on days 1, 8, (15) plus prednisone 2x5 mg/day orally after receiving informed consent until disease progression or occurrence of intolerable adverse effects. Efficacy measures were done following PCWG2 recommendations. Free testosterone levels were measured before (n = 36) and during carboplatin/docetaxel chemotherapy (n = 29).
Results: Response of prostate-specific antigen (PSAR; ⩾50% PSA) was observed in 30/63 (47.6%) patients. At the time of the current analysis the median follow-up time was 13.6 months and 40/63 patients had died. Median progression-free survival (PFS) for all patients was 6.9 months (CI 95% 5.9, 7.9) and median overall survival (OS) was 17.1 months (CI 95% 12.5, 21.7). In PSAR, PFS was 15.7 (CI 95% 6.8, 24.6) months versus 4.2 (CI 95% 2.9, 5.6) months in PSANR ($p < 0.001$; hazard ratio HR 0.13, CI 0.06, 0.27) and OS was 27.0 months (CI 95% 19.5, 34.5) versus 7.9 (CI 95% 6.4, 9.4) months ($p < 0.001$; HR 0.19 CI 0.09, 0.38). This regimen was reasonably well tolerated, with leukopenia/neutropenia as the most common reversible grade 3/4 toxicity (44.2/40.4%). Median free testosterone levels were 1.05 pg/ml before and 0.21 pg/ml during carboplatin/docetaxel treatment (testosterone nadir; $p < 0.001$). While free testosterone levels before DC treatment were associated with lower PSAR (HR 5.81 CI 1.32, 25.6; $p = 0.02$), free testosterone nadir levels <0.3 pg/ml during DC treatment were associated with higher PSAR (HR 0.13 CI 0.02, 0.85, $p = 0.034$), PFS (0.17 CI 0.05, 0.57, $p = 0.004$) and OS (HR 0.14 CI 0.03, 0.57).
Conclusion: These data suggest that carboplatin plus weekly docetaxel may be an important second-line treatment option for DRPC patients by inhibiting the testosterone biosynthesis.

7054 POSTER

Concurrent Histone Deacetylase and Mammalian Target of Rapamycin Inhibition Attenuate Androgen Receptor and Hypoxia Signaling Associated With Alterations in MicroRNA Expression

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Background: Limited therapies are available to patients with advanced prostate cancer (PCa) and castrate resistant PCa. Molecular mechanisms involved in PCa have indentified histone deacetylases (HDACs) and the mammalian target of rapamycin complex 1 (mTORC1) as potential therapeutic targets. Moreover, specific inhibitors towards HDACs and mTORC1 have been clinically developed and demonstrate great potential as novel treatments for patients with PCa.
Methods: We have utilized the c-MYC adenocarcinoma cell line from the *c-myc* transgenic mouse with PCa to transplant to wild type male FVB mice to create a transplantable androgen sensitive prostate tumour model (Myc-CaP/AS). Further, we generated a castrate resistant transplantable tumour model through serial passaging of Myc-CaP/AS tumours in castrated wild type male FVB mice (Myc-CaP/CR).for the *in vivo* evaluation of the therapeutic potential of the HDAC inhibitor panobinostat and the mTORC1 inhibitor everolimus in combination for the treatment of PCa.
Results: We demonstrate that panobinostat/everolimus combination treatment results in greater antitumour activity and therapeutic efficacy in an androgen-sensitive and castrate-resistant immuno-competent pre-clinical murine MYC tumour model of PCa. Further, we identified that combinational treatment resulted in the attenuation of androgen receptor, c-MYC and HIF-1α signaling. Inhibition of these signaling pathways was also associated with altered expression of microRNAs involved as effectors or regulators of these transcription factors.
Conclusion: Our results confirm that low dose concurrent panobinostat/everolimus combination is well tolerated and results in greater antitumour activity and therapeutic efficacy in tumour bearing immunocompetent mice. This combinational strategy warrants further clinical development for the treatment of patients with advanced and castrate-resistant PCa.

7055 POSTER

A Phase 1 Single-dose Open-label Pharmacokinetic (PK) Study of Abiraterone Acetate (AA) in Male Subjects With Mild or Moderate Hepatic Impairment

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Background: AA is the prodrug of abiraterone (A), an androgen biosynthesis inhibitor that specifically inhibits CYP17, blocking biosynthesis of androgens including testosterone and dihydrotestosterone. AA has shown improved survival in a Phase 3 study in patients with metastatic castrate-resistant prostate cancer. Primary objective: compare PK profile of AA and abiraterone after a single 1000 mg oral dose of AA in subjects with hepatic impairment or normal hepatic function.
Materials and Methods: In this single-dose, open-label, PK study (COU-AA-011) male subjects with mild or moderate hepatic impairment based on Child-Pugh (CP) classification, or normal hepatic function (mean age and BMI matched) received a single oral dose of AA 1000 mg after ⩾10-hr fast. Serial PK blood samples were collected ⩽ 96 hrs post-dose. Safety was assessed by adverse events (AEs). Subjects were enrolled sequentially as follows: subjects with mild hepatic impairment; moderate hepatic impairment; normal hepatic function. A safety review was performed after the first subject was treated and after all subjects in each cohort had been treated before proceeding to the next cohort.
Results: 24 subjects were enrolled: 8 with mild (CP score 5−6) and 8 with moderate hepatic impairment (CP score 7−9); 8 with normal hepatic function (matched-control cohort). Abiraterone was rapidly absorbed after AA administration. Mean C_{max}, AUC_{0-last}, and $AUC_{0-\infty}$ values were 3.5-, 4.8- and 4.7-fold higher, respectively, in the moderate hepatic impairment vs normal hepatic function cohorts. Median $t_{1/2}$ was ~4.5−5.5 hrs longer in the mild and moderate hepatic impairment vs normal hepatic function cohorts.

PK parameter Mean (SD)	Mild hepatic impairment (n = 8)	Moderate hepatic impairment (n = 8)	Normal hepatic function (n = 8)
T_{max}, hrs, median (range)	2.0 (0.5, 3.0)	1.5 (1.0, 2.0)	1.75 (1.0, 3.0)
C_{max}, ng/mL	71.9 (40.2)	297 (258)	85.7 (46.6)
AUC_{0-last}, ng × hr/mL	355 (191)	1530 (1350)	321 (166)
AUC0-∞, ng × hr/mL	365 (194)	1562 (1389)	330 (166)
$T_{1/2}$, hrs	17.7 (7.91)	18.6 (5.04)	13.1 (4.19)

8/24 subjects reported AEs; grade 1 (n = 6), grade 2 (n = 2). 5 reported 6 treatment-related AEs; 1 grade 2 (pruritus); 5 grade 1 (3 flatulence, 1 dry mouth, and 1 dizziness). There were no serious or grade 3/4 AEs.
Conclusions: Systemic exposure to A after a single 1000 mg dose of AA was comparable in the mild hepatic impairment and normal cohorts, but significantly higher (4.8 fold) in the with moderate hepatic cohort. Tolerability of AA was comparable across groups.