Combination D-estramustine and progression-free interval >6 months increase chances of response to D. Prospective clinical trials are needed to confirm these results.

	1st Line D (n = 223)	2nd Line D (n = 223)	3rd Line D (n = 87)	4th Line D (n = 38)
Median progression free interval since last D dose	–	6 mo	5 mo	4 mo
PSA decrease ⩾50%	100%	40%	39%	26%
Clinical improvement	27.8%	17.0%	9.2%	15.8%
Stable disease	69.5%	65.5%	64.4%	60.5%
Non responder	2.7%	17.5%	26.4%	23.7%

7050 POSTER

Multiple Docetaxel (DOC) Re-challenges (ReC) in Castration-resistant Prostate Cancer (CRPC) Patients (pts) – Outcomes and Predictive Factors of Response

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Background: Responder pts to first-line DOC, who have stopped the treatment in absence of progression, usually experience a disease progression within few months. ReC with DOC is now considered as a therapeutic option for these pts, who are potentially able to achieve again a response. In the clinical practice, the possibility of obtaining a new response by a DOC re-challenge may be usually considered on the basis of the response to the previous treatment. The available data usually report on the clinical outcome of pts who have received one or two ReCs, but it is unclear whether more ReCs may be offered to these pts and there are additional factors able to identify pts who may respond to ReC.
Materials and Methods: From March, 2002 to December, 2010, a consecutive series of 45 CRPC pts received at least one ReC after first-line DOC, for a total of 91 ReC courses (median 2, range 1–7). ReCs consisted of 4–6 DOC cycles and were proposed until the appearance of a true resistance to DOC: we consider as DOC-resistant pts showing a clinical and/or biochemical progression during DOC treatment. For each ReC course, we recorded the following parameters: treatment schedule (3 wks vs weekly), estramustine use (yes vs no), PSA response (⩾ 50%) at the previous DOC course, baseline parameters (hemoglobin, alkaline phosphatase, pain presence, ECOG), number of previous DOC courses, PSA parameters (slope LOG, doubling time, velocity) during both previous DOC course and treatment holiday, duration of treatment holiday before ReC. A binary logistic regression analysis was applied. Continuous variables were categorized by quartiles and chosen for the initial model after a univariate chi-square analysis.
Results: In 67% of 91 ReCs we observed a PSA reduction ⩾ 50%. After a median follow-up of 25 mos, the median survival is 32 mos and the projected 2-years overall survival is 77.5%. In our experience, multiple ReCs were well tolerated with no more than grade 1–2 hematological and non-hematological toxicities. Having an interval log-PSA equal to or more than 0.62 [(exp(beta) 8.965; p = 0.020], an interval from the previous cycle equal to or more than 23 weeks [(exp(beta) 8.212; p = 0.002], a response to the previous cycle [(exp(beta) 7.658; p = 0.014], resulted to be independently predictive of a response to ReC.
Conclusions: In our experience multiple DOC ReCs may be administered in DOC-sensitive pts with CRPC. This may provide a long-term disease control with remarkable survival rate and a second line treatment may be retarded until the appearance of a true DOC-resistance. Response to the previous cycle, interval log-PSA ⩾ 0.62 and the interval from the previous cycle of at least 23 weeks are factors able to identify the pts having more probabilities to respond to ReC.

7051 POSTER

Bicalutamide in Combination With Vandetanib or Placebo in Patients With Castration-refractory Metastatic Prostate Cancer Without Any Clinical Symptom Related to Disease Progression – a Randomized, Double-blind Phase II Trial

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Background: Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) are involved in angiogenesis and mechanisms of castration-resistant prostate cancer (CRPC). The study assessed the efficacy of vandetanib (VEGFR and EGFR inhibitor) in combination with bicalutamide in patients (pts) with CRPC.
Materials and Methods: Chemotherapy-naïve, asymptomatic metastatic CRPC pts were randomized to bicalutamide 150 mg orally o.d. + vandetanib 300 mg orally o.d. (bV arm) or matched placebo orally (bP arm) using 1:1 ratio. Primary endpoint was biological progression free rate at 4 months based on prostate specific antigen (PSA) level. Main secondary endpoints were time to biological/clinical symptoms (PSA response rate, time to cancer related clinical progression, tolerability and safety profile) and overall survival (OS).
Results: Ninety-five patients were randomized 1:1 to bV (n = 47) or bP (n = 48). At data cut-off in November 2010, 2 pts were still on treatment and 17 were deceased. The study did not meet its primary objective of an improved PSA progression free rate at 4 months in the bV arm. Of 89 evaluable patients: 8/44 pts in the bV arm were progression-free at 4 months vs 7/45 pts in the bP arm. Secondary objectives were not met either with bV (time to biological/clinical symptoms [hazard ratio = 1.17, 95% CI 0.76–1.81; p = 0.478]). OS data were immature at time of data cut-off.
Common adverse events (any grade) occurring more frequently with bV compared to bP included diarrhea (43.8% vs 10.6%), hypertension (29.2% vs 10.6%), nausea (18.8% vs 0), electrocardiogram QT prolonged (16.7% vs 2.1%) and photosensitivity reaction (10.4% vs 0).
Conclusions: bV showed only limited therapeutic activity in CRPC.

7052 POSTER

Effectiveness of a Second Course of Docetaxel in Metastatic Prostate Cancer

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Background: Docetaxel is a 1st line treatment option for metastatic castration-resistant prostate cancer (mCRPC). We aimed to assess the clinical benefit of rechallenging docetaxel treated mCRPC with that drug upon progression.
Materials and Methods: A retrospective cohort study, in a Portuguese cancer centre, included patients (pts) with mCRPC who underwent a second course of docetaxel upon disease progression. Primary endpoint was overall survival (OS) calculated by the Kaplan–Meier method. Secondary end-point was severe adverse events rate (SAE).
Results: Between 2000 and 2010, 136 pts with mCRPC were treated with docetaxel. A total of 35 (26%) pts were rechallenged with docetaxel. Docetaxel re-treated pts had a median age of 72 years (range 58–83); 43% had a Gleason score of ⩾8 and 45% were metastatic at diagnosis. Age at first docetaxel treatment, Gleason score, AJCC stage and time since prostate cancer diagnosis were comparable between docetaxel rechallenged pts and those that were not. Median time between completion of first course of docetaxel and its rechallenge was 6.5 months (95CI 5–8). Median overall survival was 17.5 months (95CI 12–23). During the second course of docetaxel, 7 pts developed SAE (health status deterioration, 3; metabolic events, 2; infectious events, 2).
Conclusions: Progression after first line docetaxel treatment in mCRPC remains a challenging clinical problem. Cabazitaxel is approved for use in patients previously treated with docetaxel, even though disease progression on docetaxel was observed in only 30% of pts. Our survival results, with a median time of overall survival of 17.5 months, are comparable to those of Cabazitaxel treated pts in its registration trial. Despite the retrospective design and possible selection bias, our results

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.