increased in 74% patients. In 3 patients, an increase of preexisting anti-PSA antibody levels was measured. NK-cells showed a tendency for increased activation (CD25 and CD69). Individual patients had prolonged stabilization of PSA-levels after initial rises. One patient had a greater than 85% drop in his PSA-level.
Conclusions: CV9103 was safe and well-tolerated and displayed an unexpectedly high level of cellular immunogenicity.

7047 POSTER

A Phase I Pharmacodynamic Dose Escalation Study of Steroid Sulphatase Inhibitor Irosustat in Patients With Prostate Cancer

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Background: The reservoir of inactive steroid hormones like DHEA-sulphate which are present at plasma concentrations up to 500 times higher than testosterone could potentially play an important role in intracrine androgen synthesis, by serving as a precursor source. Irosustat is an irreversible steroid sulphatase (STS) inhibitor blocking the hydrolysis of sulphated steroids to their biologically active forms.
Methods: A phase I dose escalation study was conducted in castration-resistant prostate cancer (CRPC), chemo-naïve patients with evidence of disease progression. The aim of the study was to evaluate the safety, tolerability and pharmacokinetic (PK) and pharmacodynamic (PD) profiles of irosustat (STS inhibition in peripheral blood mononuclear cells (PBMC), inhibition of Adiol, Adione, Testosterone (T) and ratio of DHEA: DHEAS in the plasma) after 28 days of daily oral administration. The steady-state PKs of irosustat were assessed in all patients. Plasma concentrations of androgens were determined pre-dose, and D28 by HPLC-MS/MS analysis. Six patients were recruited in each of 3 sequential cohorts (20, 40 and 60 mg).
Results: 17 patients were evaluable for safety, PK and PD assessment. Irosustat was well tolerated at all doses and there were no reports of drug related $\geqslant$ grade 3 adverse events. The most common toxicity was grade 1, 2 dry skin and itching observed in all 3 cohorts. Other toxicities included grade 1, 2 pain, headache, cramps and nausea. Irosustat exposure (AUC_{0-24}) increased with dose but proportionality was not seen at the highest concentration. Nearly complete STS enzyme inhibition was observed in the 3 patient cohorts from the first dose. Effect on hormone was similar between 40 and 60 mg cohorts but slightly better as compared to 20 mg. At 40 mg, mean Adiol reduction was −67.4% (range −84.5 to −51.0); T was −30.5% (range −75.5 to +18), DHEA was −52.5% (range −89.0 to +13.3) and DHEA: DHEAS ratio was decreased by 338% (range 4.3 to 472.7%).
Conclusion: Irosustat was well tolerated with dry skin as most common related adverse event and PD proof of concept was demonstrated with a full inhibition of STS enzyme leading to an increase of DHEAS and notable suppression of non sulphated androgens (DHEA, Adiol and testosterone) in CRPC patients with on-going androgen deprivation therapy.

7048 POSTER

Chemotherapy Use in Metastatic Castration Resistant Prostate Cancer (mCRPC) in the UK

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Background: In the UK, NICE guidance (TA101, June 2006) endorsed the use of docetaxel in patients with prostate cancer who progress and become unresponsive to hormone treatment. There has been an increasing acceptance of the role of 2nd and subsequent line chemotherapy following docetaxel failure however until recently there has been a lack of evidence to guide choice of regimen. This evaluation aimed to describe current chemotherapy practice across a number of specialist cancer centres.
Material and Methods: A series of local service evaluations were undertaken in 5 UK NHS cancer centres. Appropriate approvals to conduct the evaluation in each centre were obtained. Data were sourced retrospectively from patients medical records and electronic hospital systems, from the start of chemotherapy for CRPC to the present time or death. Data were analysed and reported for each centre individually. There was no change to the management of patients for the purposes of any part of this review.
Results: A total of 111 patients with a mean age at diagnosis of between 67−72 yrs between centres were included. Patients were initiated on 1st line docetaxel between Nov 2006-Jan 2010.

Table: Outcome data by centre

Centre	No. pts	Mean no. cycles 1st line docetaxel	% (n) pts receiving 2nd line treatment	Median time (months)				
				Diagnosis of CRPC to initiation of 1st line docetaxel	Initiation of docetaxel to progression	Completion of 1st line to initiation of 2nd line	Initiation of docetaxel to death or end of observation period	% complete pathway (patient deceased)
1	22	7.91	41% (9)	3.33	7.67	4.11	12.88	95%
2	24	6.83	25% (6)	2.97	8.03	6.41	14.46	71%
3	22	4.91	9% (2)	2.33	6.57	6.55	21.86	64%
4	22	6.77	73% (16)	3.48	5.57	4.60	19.94	68%
5	21	6.52	52% (11)	2.78	7.16	8.51	22.51	86%

Overall 34% (n = 38) received 2nd line cytotoxic chemotherapy using a number of regimens including mitoxantrone, docetaxel, ECarboF (epirubicin, carboplatin, fluorouracil) and Carboplatin + etoposide. 13 patients (11.7%) received further chemotherapy following 2nd line. The median time from initiation of docetaxel to either death or date of data collection was 17.81 (in 77% of patients complete pathway was available at time of data capture).
Conclusions: There is agreement between healthcare professionals regarding management of patients up to the completion of 1st line docetaxel, but a disparity of clinical opinion regarding care beyond this. A viable percentage of patients are amenable to 2nd line cytotoxic chemotherapy. It will be important to understand how currently available chemotherapy agents are used in practice and their effectiveness to formulate future treatment paradigms as novel therapies become available. The advent of licensed and approved 2nd line therapies will provide an evidence base for future therapeutic decisions.

7049 POSTER

Management of Metastatic Castration-resistant Prostate Cancer (mCRPC) After an Initial Good Response to First-line Docetaxel (D) − a Retrospective Study on 270 Patients (pts)

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Background: To evaluate the potential benefit of reintroducing a docetaxel-based (D) chemotherapy versus a non-taxane based (NT) regimen in mCRPC pts who were good responders to a first-line treatment with D and subsequently progressed.
Material & Methods: Records of 270 consecutive mCRPC pts with good response to first-line D (PSA decrease $\geqslant$50% and/or objective clinical response) were retrospectively collected in 7 European countries (17 centers). Management at progression and outcomes (PSA response, clinical response and overall survival) were analyzed. Impact of selected variables on PSA response to D rechallenge was analyzed by multivariate logistic regression analysis with stepwise procedure.
Results: Median time from last D dose to progression was 6 months. At progression, 47 received NT (mainly mitoxantrone, 40%) and 223 were rechallenged with D [median 6 cycles (range 1−24)], either in monotherapy (82.5%) or combined with estramustine (15.2%) or other drugs (2.3%). Median overall survival was 18.2 months [95% CI: 16.1–22.0] with D and 16.8 months [95% CI 13.4–21.5] with NT (p=ns). PSA decrease $\geqslant$50% was more frequent with D (40.4%) than with NT (10.6%, $p < 0.001$). Clinical improvement (i.e. improved performance status and/or pain relief and/or reduced analgesic consumption) and stable disease were more frequently reported with D than with NT. However, efficacy of D and progression-free interval since last D dose decreased with subsequent rechallenges (table). In multivariate analysis, combination with estramustine (OR 3.8; 95% CI 2.1−6.8) and a progression-free interval >6 months (OR 2.89; 95% CI 1.3−6.3) predicted PSA response to D rechallenge.
Conclusion: This retrospective study suggests that a first D rechallenge in mCRPC pts well responding to first-line D therapy is associated with a greater biochemical and clinical response compared to a non-taxane regimen. However, D efficacy is decreasing with subsequent rechallenges.

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