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Cabazitaxel Plus Prednisone for Patients With Metastatic Castration-resistant Prostate Cancer Previously Treated With a Docetaxel-containing Regimen − Interim Analysis Results From an Ongoing Compassionate-use Programme

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Background: The TROPIC trial (NCT00417079) demonstrated that cabazitaxel plus prednisone (CbzP) improves overall survival compared with mitoxantrone plus prednisone (MP) in patients with metastatic castration-resistant prostate cancer (mCRPC) who progressed during or after docetaxel (D)-based therapy (hazard ratio 0.70; $P < 0.0001$) (de Bono J, *et al. Lancet* 2010; 376:1147–1154). This survival benefit supported establishing a compassionate-use programme (CUP) to provide patients with mCRPC the opportunity to receive treatment with CbzP after therapy with a D-containing regimen in countries where cabazitaxel is not yet licensed.
Material and Methods: This single-arm CUP includes 13 countries and 71 centres, and enrolled patients with mCRPC who were previously treated with a D-containing regimen to receive treatment with CbzP (25 mg/m^2 every 3 weeks plus oral prednisone or prednisolone 10 mg daily given throughout the cycle).
Results: We report baseline characteristics and safety data from the first 123 patients who participated in this programme and received up to two cycles of CbzP in five active countries July 2010–February 2011. The median age (interquartile range [IQR]) was 67 years (63−71), 93% of patients had an ECOG PS 0−1 and 7% had a PS of 2. Patients had previously received a median cumulative dose (IQR) of D of 750 mg/m^2 (525–1200) and a median of 10 (6−15) cycles of D. During treatment with D, 46% of patients progressed. The median time from last dose of D to progression for those progressing after D was 1.4 months. The median time from last dose of D to inclusion was 3.2 months. A quarter of patients had measurable lesions and half had at least three metastatic sites, including bone 91%, regional lymph nodes 44%, distant lymph nodes 34%, pelvis 17%, liver 13% and lung 13%. Of patients included in the interim analysis, 94% received two cycles of CbzP. Adverse events associated with the first two cycles of CbzP occurred in 66% of patients. Rates of grade 3−4 haematological toxicities (adverse events) were: neutropenia 4%, febrile neutropenia 4% and leukopenia 2%. Prophylactic and therapeutic use of G-CSF was permitted in the CUP. All-grade non-haematological toxicities (in >10% patients) were: nausea 18%, diarrhoea 16% and fatigue 14%. Two treatment-related deaths were reported (one myelosuppression with complications and one sudden death).
Conclusion: The CUP interim analysis provides additional safety information about cabazitaxel for the treatment of mCRPC previously treated with a docetaxel-containing regimen in a more representative real-life patient population.

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Docetaxel and Curcuminoids Combination in Patients With Hormone Resistant Prostate Cancer − a Phase II Study

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Background: Prostate cancer is one of the major medical problems in the male population. Docetaxel, the first-line reference treatment in hormono-resistant prostate cancer (HRPC) induces a prostate-specific antigen (PSA) response in 45% of treated patients and an objective tumour response in 12%. Otherwise, some preclinical studies suggested that curcuminoids can inhibit tumour metastasis, invasion and angiogenesis and could reverse mechanisms involved in the acquisition of drug resistance. We wanted to potentiate docetaxel by curcuminoïds for HRPC in first line. Our previous phase I study showed the safety and the tolerability of curcuminoids in association with docetaxel for advanced breast cancers. For this reason, we have conducted a phase II study to assess the response of HRPC to docetaxel/curcuminoids combination.
Methods: Patients (n = 30) with progressing HRPC and rising PSA were enrolled to receive the experimental treatment. Docetaxel was given in standard conditions (75 mg/m^2 + prednisolone, 1h i.v infusion every 3 weeks for 6 cycles) in combination with curcuminoids orally at the dose of 6 g/day according to the schedule previously defined (7 days by cycle: d −4 to d +2). The primary endpoint was the response rate assessed by biological and paraclinical examinations. The secondary end points included safety, time to progression and compliance. Twenty nine patients were evaluable on PSA assessment and 15 on RECIST criteria.
Results: Twenty six patients received the treatment totality and 4 withdrew prematurely. No patient withdrew for toxicity (2 deaths and 2 PSA progression). A PSA response was observed in 17/29 patients (59%) (4 complete response and 13 partial response) observed rapidly (before the 3rd cycle) for 15 patients. The median time to subsequent PSA progression (TTP) was 6.0 months (n = 23/29). Six patients (40%) had a partial objective response and 9 (60%) a stable disease. The median TTP on targets was 6.87 months (n = 9/15). The regimen was well tolerated, with uncommon grade 3/4 toxicity; no adverse event was attributed to curcuminoids. Of 169 cycles, 150 (89%) were completed with perfect compliance.
Conclusions: These preliminary results are promising to improve the response rate of docetaxel in terms of both PSA decrease and objective response, with good tolerability and patient acceptability of curcuminoids. This justify the interest to conduct a randomized trial.

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Final Analysis of a Phase I/IIa Study With CV9103, an Intradermally Administered Prostate Cancer Immunotherapy Based on Self Adjuvanted mRNA

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Background: Safety and Efficacy Trial of a RNActive®-Derived Prostate Cancer Vaccine in Castrate-resistant Disease (CV-9103–001) sponsored by CureVac GmbH. A prostate cancer (PCA) vaccine containing the four antigens PSA, PSCA, PSMA and STEAP1 as self-adjuvanted full-length mRNAs (EudraCT No.: 2008–003967-37).
Material and Methods: 44 castrate resistant prostate cancer patients with metastatic disease and rising PSA were enrolled into a first-in-man phase I/II open, uncontrolled, multi-center, international, prospective, in-patient study. Study objectives in Phase I were determination of the recommended dose (RD) for exploration in the phase II part, assessment of safety of the trial regimen and evaluation of induction of immune response, in Phase II assessment of safety of the trial regimen, evaluation of induction of immune response and assessment of anti-tumour activity. Over a period of 23 weeks 5 vaccinations with CV9103 were administered.
Blood samples were taken before the first and two weeks after the 2nd to 4th vaccination. Immune response was assessed by ELISPOT (IFN-g), intracellular cytokine staining (IFN-g, TNFa), tetramer analysis (all ex vivo) or ELISA (PSA).
Recruitment is completed.
Results: In phase I, one dose limiting toxicity, urinary retention, was observed at the high dose level. A maximum tolerated dose was not defined. Overall, 389 AEs were reported, 282 were classified as related. Of these, most were injection site reactions or flu-like symptoms such as chills and fever. Of 21 serious adverse events, 7 were classified as related. In phase II, the high dose level was expanded by 32 patients. Immunomonitoring was possible in 33 of the 38 patients enrolled at the high dose level. Antigen-specific T-cells were detected in 79% patients. Importantly, 58% of the immunological responders reacted against multiple antigens. Immune responses were detected against all antigens regardless of cellular localization. The frequency of antigen-unspecific B-cells was

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.

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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.

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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.

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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.