

# PROSTATE CANCER: AN UNMET MEDICAL NEED

Approximately 30,000 men are diagnosed with prostate cancer each year in the UK. We are working on new treatments to improve outcome for patients with advanced prostate cancer.



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## Prostate cancer: Current treatment approaches

Prostate cancer is the most common malignancy in men, and the second most common cause of death in men from cancer. Comprising several different genetic forms of disease, some prostate cancers behave benignly and others much more aggressively. Differentiation of these various forms of disease, to minimise over-treatment and morbidity in more benign disease and maximise treatment and clinical benefit in patients with more aggressive disease, is key to the optimal management of prostate cancer.

To date, treatment for prostate cancer has primarily involved androgen deprivation therapy either by surgical castration or hormonal manipulation that ablates testicular male hormone (testosterone) synthesis. This form of treatment was the result of studies by Nobel Prize winner Professor Charles Huggins in Chicago as long ago as the 1940s. Since the development of treatments blocking testicular generation of testosterone, however, few advances in the treatment of advanced prostate cancer have been made. Recent studies have shown that docetaxel, a chemotherapy treatment used for a number of different cancers and derived from the needles of the yew tree, modestly increases average survival of these patients (by approximately three months).

▣ Treatment of advanced prostate cancer patients failing hormonal treatment remains an area of unmet medical need that requires urgent attention. ▣

## 'Hormone refractory prostate cancer': Is this still hormone dependent?

When treatment by androgen deprivation by surgical or chemical castration fails, the disease has been described as becoming hormone refractory. Hormone refractory prostate cancer is the cause of mortality from prostate cancer in nearly all patients. It had been assumed that prostate cancer cells become independent of the male androgen hormones at this stage. A number of recent studies, however, have suggested that prostate cancer may remain hormone dependent in patients that fail testicular androgen ablation. Evidence for this stems from the facts that:

- Prostate cancer biopsies continue to have high levels of testosterone despite ablation of testicular generation of male hormone by castration;
- All known genetic causes of hormone resistance result in increased signalling by the androgen receptor, which remains dependent on hormonal activation by the male steroid hormone;
- As prostate cancers fail androgen ablation by castration, the levels of key enzymes that can generate the male androgen hormone in the cancer increase in prostate cancer biopsies;
- There is increasing evidence that prostate cancer cells grown in a dish in the laboratory may generate male androgen hormones *de novo*.

Other evidence for the importance of male hormones in prostate cancer has been the recent discovery of a genetic aberration (similar to that observed in chronic myeloid leukaemia) that results in a powerful cancer-accelerating gene (oncogene), becoming driven by androgens (these are known as ETS gene translocations).

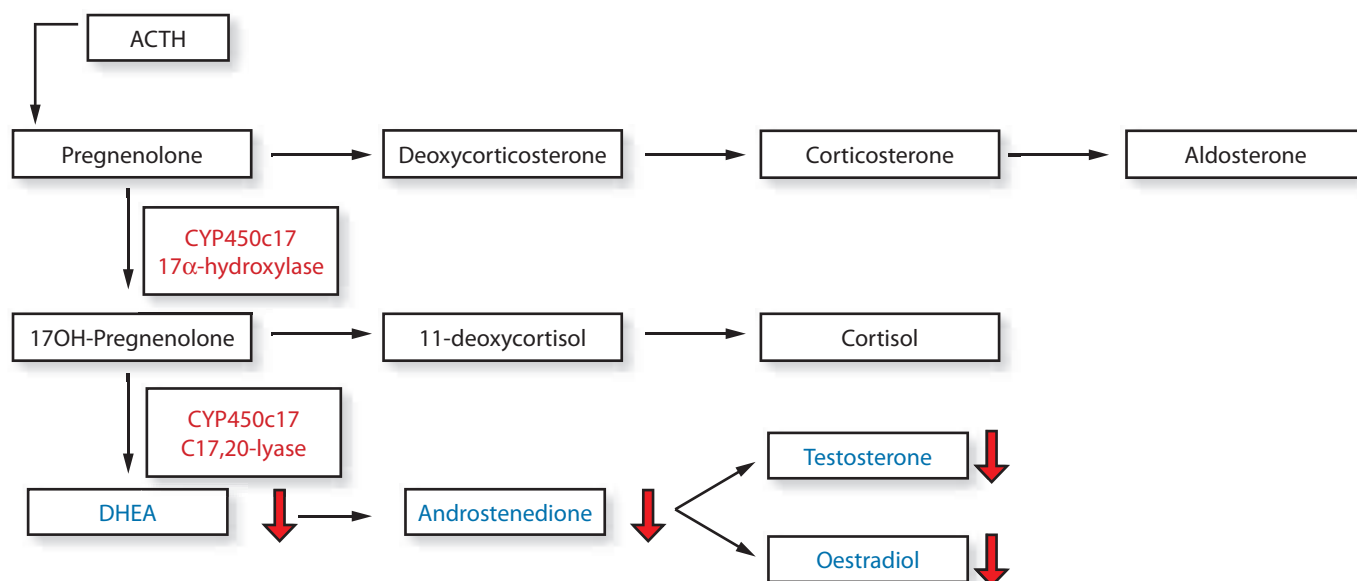
Overall, there is now robust evidence that continued hormone production and signalling remain critically important in so-called hormone refractory prostate cancer in men with advanced disease. ■

## Can we block this continued hormone dependence of prostate cancer?

There are many ways to block prostate cancer cell growth driven by male androgens. These include development of new agents that can block androgen hormone synthesis or that inhibit the activation of the downstream switch, the androgen receptor. Many research groups are working in this field but multiple attempts at developing potent and effective inhibitors of androgen receptor signalling have, to date, been disappointing. Nonetheless, it is envisioned that new drugs, that are better at blocking this genetic switch, will become available in the near future.

Professor Michael Jarman and his team of chemists at The Institute of Cancer Research took a different approach, focusing on generating a chemical inhibitor of a key enzyme implicated in steroid hormone synthesis called CYP17. This enzyme is vital for testosterone and oestrogen synthesis in humans. Loss of function of this enzyme occurs in a rare, hereditary and well-described condition known as congenital CYP17 (17 $\alpha$ -hydroxylase) deficiency. This rare genetic disorder allows a detailed understanding of the consequences of the inhibition of this enzyme in humans, predicting the impact and side

Figure 1: Daily abiraterone irreversibly inhibits the two enzymatic actions - 17 $\alpha$ -hydroxylase and C17,20-lyase - of the gene CYP450c17 (red), resulting in a decrease in downstream androgenic steroids (blue).



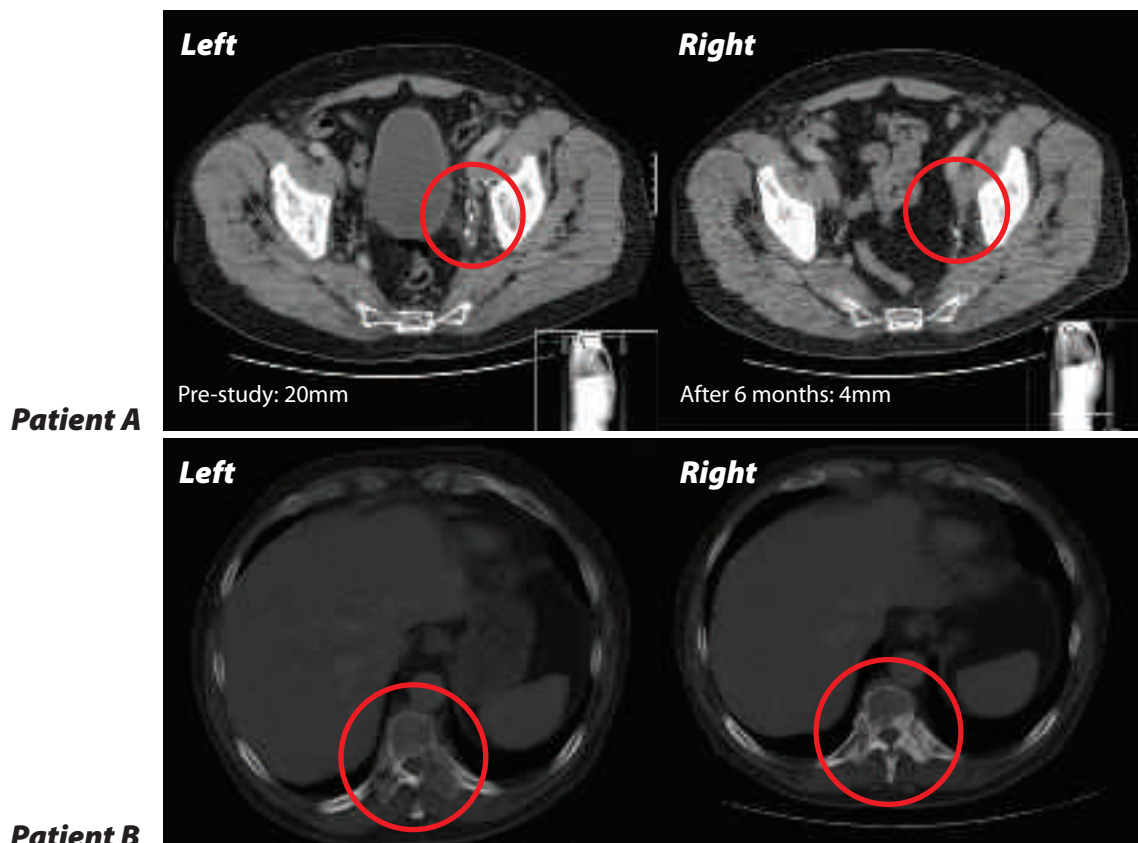


Figure 2: Prostate cancer responses to abiraterone.

Patient A. Left panel: Prior to treatment, pelvic lymph node disease was present. Right panel: Following abiraterone, this had regressed. The patient is still doing well on treatment after more than 12 months.

Patient B. Left panel: Prior to starting abiraterone the patient had back pain and destructive bone metastases (shown here on CT scan). Right panel: After 6 months his back pain had fully resolved with radiological evidence of restructuring bone disease. PSA fell from 76 to 5.5 ng/dl, with normalisation of alkaline phosphatase from 357 to 112 units/L, and a fall in circulating tumour cell numbers from 12 to 1.

effects of chemical drugs blocking its function including the loss of androgen and oestrogen generation. These observations alleviated concerns about the safety of blockade of this enzyme from an adrenal gland function perspective.

### Developing abiraterone: A potent inhibitor of male hormone synthesis

Abiraterone, a chemical inhibitor of the enzyme CYP17, which blocks male hormone synthesis was discovered by scientists at The Institute of Cancer Research under the leadership of Professor Michael Jarman (see Figure 1). Initial laboratory trials showed that this chemical had satisfactory drug-like properties, could be given safely as a tablet and induced prostate shrinkage in the laboratory unlike ketoconazole, a widely utilised, weak inhibitor of hormone synthesis that was initially developed as an antifungal drug. First in man trials, performed under the auspices of Cancer Research UK, confirmed that this agent can be safely administered to prostate cancer patients for up to 12 days with robust biochemical evidence of CYP17 blockade.

### Hormone refractory prostate cancer patients

In late 2005, the Drug Development Unit at The Royal Marsden commenced a Phase I trial in patients with advanced hormone refractory prostate cancer resistant to multiple hormone treatments. All patients had failed androgen hormone deprivation therapy with LHRH analogues such as Zoladex™ (goserelin) as well as androgen receptor antagonists such as Casodex™ (bicalutamide). Many patients had also failed treatment with the oestrogen-like drug diethylstilboestrol and the steroid dexamethasone. All patients on this initial trial had not previously received chemotherapy. The trial administered abiraterone once-daily as a capsule, and has shown that the drug is well tolerated and safe with a high degree of anticancer activity (see Figure 2). Many patients receiving abiraterone in this preliminary study have had documented anti-tumour activity, with tumour shrinkage on computed tomography (CT) scans, improving bone disease on bone scans and CT scans, as well as improved well-being, decreased pain and decreased use of pain killers (see Figure 2). Detailed endocrine studies, conducted by Professor Mitch Dowsett

and Dr Liz Folklerd in the Academic Department of Biochemistry, have also shown that abiraterone profoundly blocks testosterone and oestrogen synthesis (see Figure 3).

### Taxotere naïve and taxotere treated patients

Ongoing Phase II trials to evaluate the anti-tumour activity of abiraterone in patients with hormone refractory prostate cancer are now being conducted at The Royal Marsden. The first study, which was a seamless continuation of the Phase I trial, has so far shown 18 out of 30 patients to have more than a 50% fall in prostate specific antigen (PSA) levels, with more than half of the patients having a 90% PSA fall; decreases in PSA levels are associated with improved patient outcome. More than half of the patients with disease that can be measured on CT scan have had a partial response; that is measurable tumour shrinkage by standard (RECIST) criteria. Similar levels of anti-tumour activity have been demonstrated in early results of the first 20 patients on a separate Phase II trial in patients failing docetaxel.

■ This second study, which is currently based solely at The Royal Marsden, is to now start accrual at several sites including Memorial Sloan Kettering (New York), Dana Farber (Boston) and University of California at San Francisco. ■

### The future

The preliminary data acquired from The Royal Marsden clinical trial have now been confirmed by data from a separate ongoing Phase I trial at the University of California at San Francisco. Further evaluation of abiraterone, with American collaborators, is now planned with a view to pursuing Phase III, international, registration studies in the near future for regulatory approval. Overall and importantly, these data have shown that in patients with hormone refractory prostate cancer the disease commonly remains hormone driven. However, while these studies have identified a potentially valuable new anti-tumour drug for prostate cancer patients, much work still needs to be done. Not all patients respond to abiraterone, and it is likely that resistance to this drug will develop with time. Multiple other trials for patients with this disease, targeting tumour blood supply, programmed cell death and tumour cell replication, are ongoing in the Drug Development Unit and Academic Urology Unit. We envision that these studies will improve outcome for men with advanced prostate cancer, which currently kills more than one man per hour in the UK.

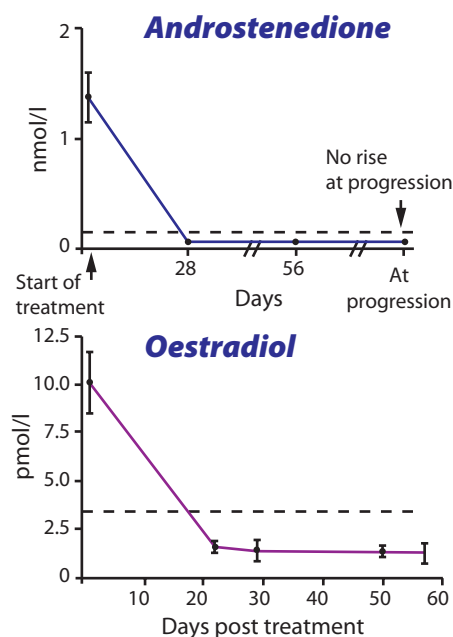
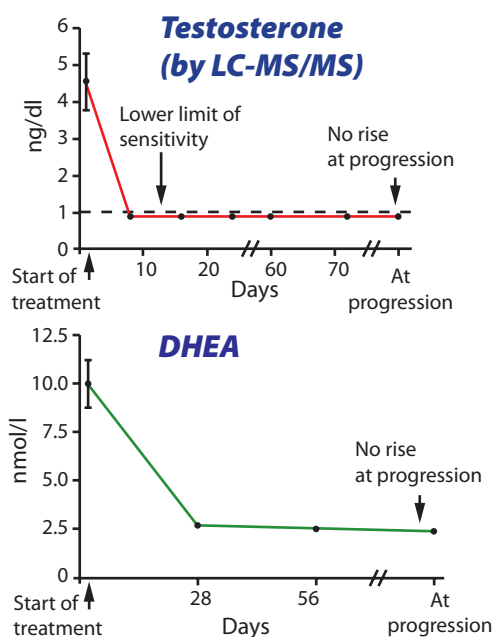


Figure 3: Abiraterone suppresses levels of testosterone, androgenic steroids and oestradiol to below the limit of sensitivity of super-sensitive assays.