New horizons for prostate cancer: part 2

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This report is based on a seminar held during the 9th Annual Meeting of the British Uro-oncology Group in Bristol. The workshop reviewed emerging prostate cancer treatment strategies that are predicted to have a potential future impact on the management of prostate cancer.

...immunotherapy and developments in radiotherapy were discussed in part 1 of this article. In part 2, we will review inhibition of the androgen receptor and identification of novel targets.

IMPROVED INHIBITION OF THE ANDROGEN RECEPTOR

Castrate-resistant prostate cancer (CRPC) is understood to be largely driven through androgen-dependent signalling. As the use of conventional anti-androgen agents, such as bicalutamide, provides only a transient benefit in CRPC, considerable research attention has focused on the search for further anti-androgen strategies.

The enzyme cytochrome P450 17 (CYP17) is essential in the adrenal biosynthesis of androgens, and is therefore an obvious target in CRPC research. The CYP17 inhibitor, abiraterone, has demonstrated a survival benefit among patients with metastatic CRPC previously treated with chemotherapy. Enzalutamide (formerly MDV3100), a second-generation androgen receptor (AR) antagonist that emerged from a rational drug design programme, has recently gained FDA approval for metastatic CRPC after also showing a significant survival benefit in metastatic CRPC, while other CYP17 inhibitors are currently in early phase trials.

As well as significantly suppressing androgen activity, CYP17A1 inhibition with abiraterone is characterised by significant inhibition of cortisol synthesis. This effect is associated with a rise in adrenocorticotropic hormone (ACTH), which causes raised mineralocorticoid levels, leading to side-effects such as fluid retention, oedema, hypokalaemia and hypertension. Addition of concomitant exogenous glucocorticoids suppresses the ACTH drive, although the effect is sometimes incomplete.

As well as acting as a potent CYP17A1 inhibitor, abiraterone is also a weak AR antagonist. The relevance of this observation in clinical practice is still unclear, but it could explain some of the activity reported in preclinical models.

Although significant advances have been made in treatments for CRPC based on AR inhibition, the response rate to AR targeting following castration is currently only around 50–60 per cent, and even less in the post-chemotherapy setting. In order...
to understand the mechanisms causing resistance to abiraterone or enzalutamide therapy, a series of pertinent questions must be considered.

**Does CYP17A1 inhibition achieve a truly ligand-free state?**
Abiraterone achieves significant androgen suppression, but residual levels may be detected in both the urine and serum of patients.\(^5\) Furthermore, experiments in mouse xenografts have shown that CYP17A1 expression increases following abiraterone treatment, suggesting a possible mechanism of resistance to abiraterone.\(^6\)

**Can resistance occur through selection of AR mutations activated by exogenous glucocorticoids given with abiraterone?**
It has been known since the year 2000 that dual mutation of the AR is activated by cortisol and other steroids at levels of around 10nmol/l in vitro.\(^7\) Recent data have shown that prednisolone is present in patients treated with abiraterone/prednisolone at levels far greater than 10nmol/l,\(^4\) suggesting another possible source of resistance. However, it remains to be determined whether prednisolone actually activates the AR in patients.

**Does addition of an anti-androgen to CYP17A1 inhibition reverse resistance or increase response rate?**
Significant inhibition of AR activity by enzalutamide is observed in the presence of 0.1nM of the androgen R1881.\(^4\) However, when androgen levels are increased 10-fold, the level of inhibition is lost. This suggests that more potent inhibition of AR or concomitant inhibition of CYP17A1 may be required to reverse resistance.

**Does addition of an inhibitor of the PI3K/AKT pathway block of AR signalling reverse resistance?**
The two most frequently activated signalling pathways in prostate cancer are driven by AR and PI3K. Inhibitors of the PI3K pathway are in early clinical trials, and AR inhibitors confer clinical responses in most patients. Dual inhibition of the PI3K pathway and AR is a particularly interesting approach that is currently being actively pursued. The AR and PI3K pathways regulate each other through a reciprocal negative feedback system, such that inhibition of one activates the other. Therefore, tumour cells can adapt and survive when either single pathway is inhibited pharmacologically. Combined pathway inhibition in preclinical prostate tumour models provides a compelling rationale for combination therapy in patients.\(^8\)

**NOVEL TARGETS**
The pathophysiology of prostate cancer is complex, and provides multiple opportunities for intervention in the development of new treatment strategies. Key interactions identified to date are with the stroma (predominantly bone), the immune system and angiogenesis (Figure 1).

As more agents and newer approaches become available, it is increasingly important to devise methods of targeting patients by identifying prognostic and predictive factors for treatment success.

Clinical research in many solid tumours, such as breast cancer, is now almost always performed in a specific subgroup of patients, identified by genotype or phenotype. Some progress has been made in this regard with respect to prostate cancer, with the division of prostate cancer into different gene abnormalities\(^9\) raising the possibility of stratifying patients at the start of a trial. However, further research is needed.

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**Figure 1. Potential targets for treatment strategies in prostate cancer (reproduced with permission from Dayyani et al.)**

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required to provide a rationale for the molecular subclassification of the disease to allow true targeting of therapies. Furthermore, the source of the tissue used for analysis is an important consideration in this respect, with the molecular biology of primary tumour biopsy and metastatic disease showing notable differences. Therefore it will be impossible simply to use a sample from the pathology laboratory taken at the time of diagnosis to determine current prostate cancer type and therefore most appropriate treatment. Current biopsies or analysis of circulating tumour cells will be required for this purpose.

A number of novel non-hormonal therapies are currently being explored in CRPC, with examples described briefly below.

**Chemotherapy resistance**
Clusterin is a cytoprotective chaperone involved in cell survival. Expression of clusterin is correlated with Gleason score, castration resistance and chemotherapy resistance. Custirsen (OGX-011) potently inhibits clusterin expression and enhances the efficacy of anti-cancer therapies in vitro and in vivo. In a randomised phase 2 study, OGX-011 in combination with docetaxel and prednisone was well tolerated and was associated with increased overall survival compared with docetaxel and prednisone alone.\(^\text{19}\) This agent is therefore currently being investigated in two phase 3 studies, SYNERGY and SATURN.

Another target for chemotherapy resistance is endothelin A receptor inhibition. Endothelin-1 regulates osteoblastic bone remodelling via the endothelin A receptor and impacts invasion, metastasis, angiogenesis and apoptosis. The endothelin receptor antagonists, zibotentan and atrasentan, showed initial evidence of efficacy in phase 2 studies,\(^\text{16}\) although phase 3 studies have proved disappointing to date.\(^\text{13–16}\) The only phase 3 trial of zibotentan that is now continuing is ENTHUSE study 33, investigating zibotentan in combination with docetaxel and prednisone in men with metastatic CRPC.

**Angiogenesis**
Phase 3 studies of the anti-angiogenic agents bevacizumab\(^\text{17}\) and sunitinib\(^\text{18}\) in metastatic CRPC have also failed to meet their primary endpoints, although a benefit in terms of progression-free survival was observed. These phase 3 studies were initiated on the basis of positive results from phase 2 studies incorporating only a single arm.\(^\text{19–22}\) The failure of the subsequent phase 3 trials raises a question over the validity of using single-arm studies as a basis for initiating a large phase 3 study.

A number of other anti-angiogenic therapies are currently under investigation in phase 2 and 3 trials, including lenalidamide (phase 3), aflibercept (phase 3), tasquinimod (phase 3), combination therapy with lenalidamide/bevacizumab/prednisone (phase 2) and TKI258 (phase 2).

**Cabozantinib (XL184)**
Encouraging bone scan data have been acquired for the cMET and VEGFR2 inhibitor, cabozantinib, in metastatic CRPC,\(^\text{23}\) showing remarkable normalisation of bone scans within six weeks, as well as improvement in pain assessments. This agent is currently being further investigated in an ongoing phase 3 trial.

**Src**
Src is a member of the non-receptor tyrosine kinase family with established roles in prostate cancer growth, invasion and metastasis. When used as a single agent in metastatic CRPC in a pre-chemotherapy setting, the Src inhibitor, dasatinib, showed modest clinical activity,\(^\text{24}\) but a follow-up phase 3 trial failed to show survival benefit.

A more selective Src inhibitor, saracatinib, is currently undergoing phase 2 trials in the UK, and may be expected to offer greater benefit than dasatinib.

**SUMMARY**
A large number of new agents have become available over recent years for the management of prostate cancer. While this represents a triumph for research, it also raises the important question of how the different available agents should be sequenced for individual patients. This is a particularly important consideration when designing phase 3 trials in new agents in order to maximise the chances of positive trial outcomes. The other important consideration for future research is the development of suitable predictive biomarkers to allow individualisation of treatment and greater chances of treatment success.

**Declaration of interests**
The British Uro-oncology Group seminar 'New horizons for prostate cancer' was sponsored by Takeda. Takeda selected and briefed the speakers on the content of the session and they were paid an honorarium by Takeda. Takeda has had no editorial control over any publications arising from the meeting. David Dearnaley has attended and received honoraria for advisory boards and served as a consultant for Takeda, Amgen, Astellas Pharma and Succinct Healthcare. Abiraterone acetate was developed at the Institute of Cancer Research, which therefore has a commercial interest in the development of this agent. Christian Ottensmeier has attended and received honoraria for advisory boards, and has received an educational grant for a clinical trial from Bristol Myers Squibb. Gerhardt...
Attard has received consulting fees from Janssen-Cilag, Veriex and Millennium Pharmaceuticals, lecture fees from Janssen-Cilag, Ipsen, Takeda, Roche/Ventana and Sanofi-Aventis, and grant support from AstraZeneca and Roche/Genentech. He is on the ICR list of rewards to inventors of abiraterone acetate. Simon Crabb has received honoraria for advisory boards for Janssen and Sanofi.

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