



Abiraterone acetate: redefining hormone treatment for advanced prostate cancer

Carmel J. Pezaro^{1,2}, Deborah Mukherji^{1,2} and Johann S. De Bono^{1,2}

¹ Drug Development Unit and Academic Urology Unit, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey SM2 5PT, UK

² The Institute of Cancer Research, Downs Road, Sutton, Surrey SM2 5PT, UK

Prostate cancer has long since been recognised as being hormonally driven via androgen receptor signalling. Abiraterone acetate (AA) is a rationally designed CYP17 inhibitor that blocks the conversion of androgens from non-gonadal precursors effectively, thus reducing testosterone to undetectable levels. AA has recently been proved to extend survival for men with metastatic castration-resistant prostate cancer who have progressive disease after first-line chemotherapy treatment. In addition, it is currently being tested in a Phase III trial in the pre-chemotherapy setting. This paper will review the preclinical discovery and clinical development of AA and will outline the strategy of parallel translational research.

Introduction

Despite the high prevalence of prostate cancer in Western society, effective new treatment options for advanced disease have only recently become available. Prostate cancer is the most commonly diagnosed cancer in males in Britain [1] and America [2] and is second only to lung cancer in causing cancer-related deaths in males [2,3]. In 1941 prostate cancer was recognised as being hormonally driven [4] and, for many years, the mainstay of treatment for men with metastatic disease was castration. In the 1980s it was found that achieving castrate levels of testosterone either surgically or medically using a luteinising hormone releasing hormone (LHRH) analogue resulted in an equivalent survival benefit [5]. Hormonal manipulation can result in prolonged periods of clinical and biochemical control, but most men eventually progress despite ongoing castrate levels of testosterone. This state was previously referred to as androgen- or hormone-insensitive prostate cancer and has also been described as castration-resistant prostate cancer (CRPC) or advanced prostate cancer (APC). In 2004 the TAX327 trial proved that first-line chemotherapy with docetaxel could prolong survival for men with metastatic CRPC [6]. Since 2010, five new treatments have been shown to prolong survival in CRPC in randomised studies: second-line chemotherapy with cabazitaxel [7]; autologous vaccine therapy [8]; administration of the novel radionucleotide radium²²³ [9,10]; and novel

hormonal therapy with abiraterone acetate (AA; ZytigaTM) [11] and also with the androgen receptor antagonist MDV3100 (de Bono and Scher, Press release 03 November 2011). The success of AA therapy has not only added an oral, well-tolerated treatment option but it has also challenged the previously held dogma about prostate cancer becoming 'hormone insensitive' or being 'maximally androgen-ablated'. The clinical development of AA has incorporated novel translational and biomarker-driven analyses that are likely to have an impact on future drug development for prostate cancer therapy. The purpose of this paper is to summarise the discovery and development of AA for the treatment of men with metastatic CRPC.

Preclinical development

In men who have undergone chemical castration with an LHRH analogue, 10% of circulating testosterone remains, due to the peripheral conversion of adrenal steroids to testosterone [12]. In the 1980s, it was observed that the antifungal agent ketoconazole could reduce testosterone and give symptom-relief to men with advanced prostate cancer [13]. This activity was largely caused by inhibition of cytochrome P450 (CYP) enzymes, including the CYP17A enzymes 17 α -hydroxylase and C17,20-lyase [14], which have key roles in the adrenal and gonadal synthesis of androgens. The use of ketoconazole was limited by concerns regarding toxicity [15], but the concept of therapeutic inhibition of this pathway encouraged scientists at the Institute for Cancer Research (ICR) in

Corresponding author: De Bono, J.S. (johann.de-bono@icr.ac.uk), (jdebono@icr.ac.uk)

London, supported by the Cancer Research Campaign, to use a mechanism-based approach to design a series of steroidal compounds incorporating a C16=17 double bond [16]. This led to the development of 17-(3-pyridyl)androsta-5,16-dien-3 β -ol (CB7598), which was identified as a potent inhibitor of CYP17 α -hydroxylase [17].

In vitro testing demonstrated the ability of CB7598 (AA; ZytigaTM) to inhibit ACTH (adrenocorticotrophic hormone)-mediated stimulation of adrenal cells [18]. In male WHT mice, administration of the acetylated pro-drug form of CB7598 caused a reduction in androgen-dependent organs including the prostate, seminal vesicles, testes and kidneys, and also led to a marked dose-dependent decrease in circulating testosterone levels [18]. Unlike ketoconazole, CB7598 did not appear to inhibit additional CYP enzymes and the animal model did not show any effect on the adrenal gland.

Clinical development

The clinical development of AA for men with advanced prostate cancer has been rapid and reflects well on the strong collaboration between the ICR and Cancer Research UK [19]. The initial repeat-dosing Phase I studies were published in 2008, followed rapidly by Phase II testing and publication in 2009 and 2010 and the landmark Phase III trial published early in 2011. Table 1 summarises the main efficacy endpoints of the published clinical trials of AA. In April 2011 the FDA approved AA for use after docetaxel treatment, with approval granted in the European Union in September 2011. In addition, AA continues to be tested in clinical trials.

Phase I studies

The first Phase I study was performed in castrate and non-castrate men with advanced prostate cancer [20]. Initially, single doses were administered at escalating dose levels in 16 men who were castrate on the basis of orchidectomy or LHRH analogue. It was found that a single dose of 500 mg was required to reduce circulating testosterone reliably to undetectable levels, an effect that lasted two to five days. In non-castrate men daily dosing of 800 mg for the 12-day duration of the study initially produced

complete testosterone suppression, but within three days a compensatory LH surge overcame the suppression. This clinical finding demonstrates the rationale for concomitant LHRH analogue during AA therapy.

A Phase I–II study published initially in 2008 [21] enrolled chemotherapy- and ketoconazole-naïve men. In the dose-finding study, participants received between 250 and 2000 mg AA daily. Although a maximum tolerated dose (MTD) was not reached, there appeared to be a plateau in the pharmacodynamic effect, as judged by increases in upstream steroid precursors, above 750 mg/day. A dose of 1000 mg/day was therefore selected for cohort expansion. The incidence of hypertension was similar in all dose cohorts and mineralocorticoid-associated side effects were managed with eplerenone, a mineralocorticoid receptor antagonist, or low-dose dexamethasone. Fed and fasted studies suggested that, although a high fat meal did not alter the maximum concentration of drug, absorption was extended. A convincing signal of efficacy was seen, with a $\geq 50\%$ prostate specific antigen (PSA) decline in 12 out of 21 men (57%), partial response (PR) by response evaluation criteria in solid tumours (RECIST) in five out of the eight men with radiologically evaluable disease and reports of clinical benefit including decreased pain and analgesic use.

The other Phase I study published in 2010 enrolled 33 men with chemotherapy-naïve metastatic CRPC, 19 of whom had previously been treated with ketoconazole [22]. Dose-finding was undertaken in parallel fed and fasted cohorts, using AA doses of 250–1000 mg daily. The MTD was not reached. Pharmacokinetic sampling revealed rapid metabolism of AA to the active metabolite, abiraterone. Administration resulted in a substantial reduction in circulating androgen (dehydroepiandrosterone sulfate; DHEA-S and testosterone) and an increase in upstream mineralocorticoids such as deoxycorticosterone. The fed cohort had substantially increased total drug exposure (AUC), but no additional significant toxicities were observed. From the 33 participants, 19 (58%) had a partial PSA response, including nine out of 19 (47%) men previously treated with ketoconazole. The median time to PSA progression was 234 days, with no significant difference between

TABLE 1

Summary of clinical trials with efficacy endpoints

Phase	Number and type of patients	Steroid use	Partial PSA response (%)	RECIST PR	Median TTP	Other
I	33, pre-chemo (19 post-K)	For adverse events	19 (58%) K: 9 (47%)	NA	234 days	
I–II	Ph I: 21 pre-chemo	For adverse events	12 (57%)	5 of 8 patients	NA	
I–II	Ph II: 42 pre-chemo	Dexa 0.5 mg OD at PD	28 (67%)	9 of 24 patients (37.5%)	225 days	
II	33, pre-chemo	Pred 5 mg BD	26 (79%)	9 of 13 patients (69%)	16.3 months	Bone flare in 11 of 23 patients
II	58, post-chemo (27 post-K)	Pred 5 mg BD	22 (36%) K: 7 (26%)	4 of 22 patients (18%)	169 days	
II	47, post-chemo	Optional	24 (51%)	8 of 30 (27%)	169 days	
III	1195, post-chemo (2:1 AA versus placebo)	Pred 5 mg BD	69% versus 6% ($P < 0.001$)	14% versus 2.8% ($P < 0.001$)	10.2 versus 6.6 months ($P < 0.001$)	Updated OS: 15.8 versus 11.2 months ($P < 0.0001$) PFS: 5.6 versus 3.6 months ($P < 0.001$)

Abbreviations: K, ketoconazole; OD, once daily; PD, progression of disease; BD, twice daily; AA, abiraterone acetate; PSA, prostate-specific antigen; RECIST, response evaluation criteria in solid tumours; PR, partial response; TTP, time to progression; OS, overall survival; PFS, progression-free survival; NA, not available.

ketoconazole-naïve or pre-treated patients. The observation that addition of a low-dose glucocorticoid was associated with normalisation of mineralocorticoid levels and improvement in blood pressure led the authors to suggest the inclusion of a low-dose steroid in future trials of AA.

Phase II clinical trials

In the Phase II component of the Phase I–II trial mentioned above, a total of 42 chemotherapy-naïve patients with good performance status [Eastern Cooperative Oncology Group (ECOG) PS 0–1] and progressive disease, as defined by PSA working group 1 (PSAWG1) criteria, were treated with AA 1000 mg/day [23]. The endpoint for the Phase II component was partial PSA response (as defined by $\geq 50\%$ PSA reduction) at or after 12 weeks. Partial PSA response was achieved in 28 patients (67%). In addition, nine (37.5%) of the 24 patients with RECIST-evaluable disease achieved a radiological PR. The main any-grade toxicities of hypokalaemia (37 patients, 88%), hypertension (19 patients, 40%) and fluid overload (13 patients, 31%) were recognised as being secondary to mineralocorticoid excess, and were managed with eplerenone at doses of 50–200 mg/day. The median time to progression (TTP) for those patients treated at 1000 mg was 225 days (95% CI 162–287 days). Of note, steroid treatment was not mandated at study entry but, instead, dexamethasone was added at first progression. The rationale for the ‘second step’ addition of dexamethasone was to suppress ACTH and steroid production upstream, thereby dampening possible non-specific activation of mutated, promiscuous androgen receptor (AR) by hormones upstream of CYP17. For 30 patients in whom dexamethasone was added and continued in combination for more than 12 weeks, 10 patients had a PSA response. Four of the ten patients had previously progressed on dexamethasone therapy, whereas six were dexamethasone naïve.

A further pre-chemotherapy single-arm Phase II trial published this year enrolled 33 men to receive AA 1000 mg/day and prednisone 5 mg twice daily [24]. Partial PSA response was observed in a total of 26 men (79%), with a median time to PSA progression of 16.3 months. This study specifically addressed the issue of ‘bone flare’, which has previously been reported in men with advanced prostate cancer as soon as two weeks after orchidectomy [25] and also after initiation of LHRH analogue therapy [26]. In this study, bone flare was defined as a discordance on disease assessments after three months of therapy, with a partial PSA response but bone scan assessment of disease progression (on the basis of an increase in either intensity or number of bone lesions) and followed by either improvement or stability on the six-month bone scan. From the 23 men with evaluable bone scans, 12 (52%) were reported as showing ‘progression’ at three months – eight because of new lesions and four owing to increased intensity in tracer uptake. Eleven of these cases met the criteria for bone flare in that the six-month bone scans showed improvement (four cases) or stability (seven cases). It is not yet known whether bone flare predicts subsequent durable response or whether bone scans should simply not be performed at the first time-point. It is certainly clear that bone scan changes after three months of AA should not be used to assess disease response in isolation. The second prostate cancer working group guidelines (PCWG2) aimed to avoid this issue by recommending that trials are not designed to include bone scans performed before three months on treatment and recommending

confirmation scans a minimum of six weeks after an initial scan suggestive of progression or response [27].

Two Phase II post-docetaxel trials were published in 2010. In one trial there were 58 participants, 27 of whom had previously been exposed to ketoconazole [28]. All participants were treated with AA 1000 mg/day continuously, combined with low-dose corticosteroid in the form of prednisone 10 mg/day. The primary endpoint was the rate of ≥ 50 PSA falls and this was observed in 22 (36%) individuals from the overall group, with a higher rate of falls in ketoconazole-naïve participants (45% versus 26%). The overall TTP was 169 days, but this was longer (198 days, 95% CI 82–393 days; compared with 99 days, 95% CI 57–169 days) in ketoconazole-naïve patients. Toxicity appeared mild, with 2% G3 fatigue being the most significant adverse event. No G4 toxicity events were noted.

The second post-docetaxel Phase II trial was the COU-AA-003 trial. Forty-seven men received AA 1000 mg/day [29]. Eight of the participants had previously received ketoconazole therapy. Of interest, this trial did not mandate corticosteroid treatment, however 18 men were on a low dose of corticosteroid at baseline. Twenty-seven men developed symptoms of secondary mineralocorticoid excess, managed either with low-dose glucocorticoids or with eplerenone. Partial PSA response was observed in 24 men (51%), with a median time to PSA-progression of 169 days. Out of a total of 30 men with RECIST-evaluable disease, PR was observed in eight individuals (27%).

Phase III clinical trials

The COU-AA-301 trial was published in early 2011 [11]. Positioned in the post-docetaxel setting, the trial randomised 1195 men with metastatic CRPC in a ratio of 2:1 to receive AA 100 mg/day with low-dose prednisone, or matching placebo with prednisone. At a planned interim analysis the trial was unblinded after meeting prespecified efficacy limits in the primary endpoint of overall survival. The median overall survival (OS) in patients receiving AA at the first interim analysis was 14.8 months, compared with 10.9 months in the placebo arm, giving a HR of 0.65 ($P < 0.001$). At the second and final preplanned analysis, the difference between the two arms increased to 4.6 months (15.8 months versus 11.2 months, $P < 0.0001$) [30]. Secondary efficacy endpoints, including TTP, radiological progression-free survival (PFS) and PSA response, also significantly favoured AA (Table 1). Notably, participants continued treatment until progression was confirmed by a combination of rising PSA, with radiographic progression and/or clinical deterioration. Reported toxicity appeared low, although there were higher mineralocorticoid side effects, such as fluid retention, hypokalaemia and hypertension, in patients who received AA. There was a non-statistical trend to higher all-grade liver abnormalities and cardiac dysfunction in the AA arm, but there was no difference in severe or fatal events in either category. Deaths within 30 days of treatment occurred more frequently in patients receiving placebo, as did adverse events resulting in death. The reported rates of G3–4 toxicity attributable to AA were low, with 3% hypokalaemia and 1% hypertension.

Results of the COU-AA-302 trial (NCT00887198) are awaited. This trial enrolled men with metastatic prostate cancer who had minimal or no symptoms from their disease but who had rising PSA despite surgical or chemical castration with LHRH analogue

therapy and a trial of additional anti-androgen (so-called but probably misnamed 'maximal androgen blockade'). COU-AA-302 rapidly recruited the required cohort of approximately 1000 participants. The primary outcome is a dual outcome of OS and PFS. Hopes for a new, well-tolerated oral treatment in the pre-chemotherapy setting are evident, but the recent increase in active post-chemotherapy treatments available at crossover means that improvement in OS could prove a difficult endpoint to achieve.

Translational/biomarker research

Circulating tumour cells

The AA trials have incorporated exploratory endpoints relating to changes in circulating tumour cells (CTCs). Assays to identify and collect tumour cells in peripheral blood samples from patients with advanced cancer have exploited the physical properties, biomarker expression or functional characteristics of malignant cells and have included nucleic-acid-based assays and capture of CTCs using antibodies against cell surface antigens [31]. The CellSearch[®] assay is an automated assay that quantifies CTCs per 7.5 ml blood sample. Epithelial cell adhesion molecule (EpCAM) magnetic beads are used to tag CTCs in the sample, which are then captured and labelled with fluorescent dyes. The accuracy of CellSearch[®] for CTC detection was at least 85% in spiking studies [32]. Our group reported a study of CTCs in men beginning a new line of chemotherapy and showed a statistically significant difference in survival for men with a favourable CTC count (defined as <5 CTCs per 7.5 ml blood) compared with an unfavourable count (≥5 CTCs per 7.5 ml blood; median OS 21.7 months compared with 11.5 months, $P < 0.0001$) [33]. In 2008 the FDA approved CellSearch[®] CTC enumeration for the monitoring of metastatic prostate cancer. Despite this, current expert guidelines do not recommend CTC analysis as part of treatment planning [34].

In the 42-patient Phase I–II study CTCs were collected as an exploratory endpoint and, out of 17 patients with a pre-treatment CTC count ≥5 (i.e. 'unfavourable'), 10 (59%) had a conversion on treatment to <5 (i.e. 'favourable') [23]. In COU-AA-003, CTCs were collected for 34 participants. In 27 of these men the baseline CTC count was unfavourable. On AA medication, 11 of the men displayed CTC count conversion and 18 had a ≥30% decline in CTC count [29].

In the COU-AA-301 study CTCs were collected for 972 patients at baseline and then at weeks four, eight and 12 (in 723 patients) on study. As early as week four, CTC conversion predicted OS [30].

The correlation between CTC count and OS was far greater than the currently applied surrogates of PSA and PFS. If CTC counts can be confirmed as a validated surrogate endpoint of overall survival, they could be widely used in future clinical trials and for judging therapy duration.

PTEN loss and ERG rearrangement

The pathogenesis of prostate cancer appears to involve key molecular events, including PTEN loss and rearrangement of the *ERG* gene, the combination of which has been shown to identify a group of men with particularly poor prognosis [35]. *ERG* rearrangement was examined by fluorescence in situ hybridization (FISH) in 18 patients in the earliest reported Phase I study and, of the six patients with *ERG* rearrangement, five had a partial PSA response on AA [21]. Following this, a larger dataset of 89 men was examined by multicolour FISH for *ERG* rearrangement in archival primary tumour tissue, biopsy samples of CRPC or CTCs [36]. Out of the 77 men with samples sufficient to assess *ERG* status, there was a significant association between the gene rearrangement and profound PSA-response to AA, with 12 of 15 (80%) patients with the rearrangement achieving a ≥90% PSA reduction on AA, compared with 20 of 62 (32%, $P = 0.001$) men without the rearrangement. There was a similar trend for partial (≥50%) PSA response, but this did not reach statistical significance.

The association between *TMPS2-ERG* and AA response remains a somewhat controversial issue, with a recently published report using an assay evaluating *ERG* mRNA expression showing different results [37]. In this study, CTCs from 42 patients treated in Phase II studies were examined for *ERG* expression. It was expressed in 15 cases, but did not appear to predict PSA-response to AA convincingly, with ≥50% and ≥90% PSA declines occurring, respectively, in seven (47%) and one (7%) of the 15 men with the rearrangement compared with ten (38%) and four (15%) of the 26 men without *ERG* expression. The low numbers of patients tested to date, and concerns about assay validity, means that firm conclusions cannot be drawn at this time, but further study is certainly warranted. The rearrangement was not prognostic in this small series.

Future directions

Clinical trials

The further development of AA is multifaceted (Table 2). AA is currently being tested in the early disease setting in castrate-sensitive men commencing LHRH analogues (ClinicalTrials.gov identifier NCT01088529 and NCT00924469) has been added as an

TABLE 2

Currently registered trials testing abiraterone acetate in advanced prostate cancer

Setting	Additional information	Phase	ClinicalTrials.gov number
Neoadjuvant with LHRHa	Before RP in high-risk men	II	NCT00924469
	Before RP in high-risk men	II	NCT01088529
	Before and during radical radiotherapy	II	NCT01023061
Hormone-sensitive APC with LHRHa	No evidence of metastatic disease	II	NCT01314118
	STAMPEDE: locally advanced or metastatic	II/III	NCT00268476
Second-line hormonal therapy	With dutasteride	II	NCT01393730
	With sunitinib or dasatinib	II	NCT01254864
	With every LHRHa	II	NCT01309672
Chemo-naïve APC	COU-AA-302	III	NCT00887198
Combination studies	With docetaxel chemotherapy	I	NCT01400555

Abbreviations: APC, advanced prostate cancer; LHRHa, LHRH analogue; RP, radical prostatectomy.

arm of the Phase II/III STAMPEDE trial for men with newly diagnosed APC (NCT00268476). It is also being evaluated alongside LHRH analogue and prednisone before and during radical radiotherapy (NCT01023061).

It seems probable that multiple combination trials will be proposed in view of the mild toxicity profile of AA therapy. Combination treatments with chemotherapy [38] and other active agents such as PI3K (phosphoinositide 3-kinase)/AKT (a serine/threonine protein kinase) inhibitors and PARP inhibitors [39] have been raised as logical strategies and trials are expected to commence in the near future.

In view of its action to prevent oestrogen conversion, AA is also being tested in post-menopausal women with advanced breast cancer (NCT00755885).

Other CYP17 inhibitors

Phase I results of TAK700 (orteronel) were presented at the 2010 ASCO-genitourinary symposium [40]. The Phase I study showed that doses of ≥ 300 mg twice daily resulted in mild toxicities and significant activity, as judged by 11 out of 14 patients achieving partial PSA responses. Following enrolment in the Phase I–II study, large Phase III studies have commenced in the pre- and post-chemotherapy settings (NCT01193244 and NCT01193257, respectively). Other Phase II studies are being carried out in men with rising PSA without radiological evidence of metastatic disease (NCT01046916), and in combination with docetaxel chemotherapy (NCT01084655).

Other drugs with a similar mode of action to AA are also in development, including the C(17,20) lyase inhibitor VT464 (Viamet Pharmaceuticals, NC, USA). TOK001 (Tokai Pharmaceuticals,

MA, USA) combines CYP17 inhibition with AR downregulation and AR antagonism and is currently in Phase I–II testing (NCT00959959). ARN509 (Aragon Pharmaceuticals, CA, USA) is

a selective androgen receptor degrader (SARD) agent and is in clinical development (NCT01171898).

Unanswered questions

The necessity for combined corticosteroid remains an unanswered question at present, but it is hoped that a trial might be able to help address this in the future. There is also the question as to whether AA should be continued beyond biochemical progression, extrapolating from previous thinking about controlling hormone-sensitive clones within the metastatic cancer and in-line with the stopping rules that were applied in COU-AA-301. Elegant preclinical and translational studies have described mechanisms underlying progression on AA, including upregulation of CYP17A1 and also the induction of androgen receptor splice variants that can function independently of ligand binding [41,42]. Clinical strategies to counteract these resistance mechanisms are now required. The sequencing of new treatments remains unclear, and finding markers to help select treatments for individual patients will be key for maximizing benefit and minimizing toxicity and costs.

Concluding remarks

AA is a rationally designed CYP17 inhibitor that has proved to be an effective and well-tolerated oral treatment for men with advanced CRPC. It has recently received FDA approval for use following docetaxel chemotherapy and there are ongoing clinical and translational studies that are exploring the best strategies for clinical use.

Conflicts of interest

All authors are ICR employees. The ICR has a commercial interest in Abiraterone and PI3K and AKT inhibitors. JS de Bono has served as a paid consultant for J&J, Sanofi-Aventis, Medivation, Astellas, AstraZeneca, Dendreon, Genentech, Pfizer, GSK.

References

- 1 Cancer Statistics Registrations: Registrations of Cancer Diagnosed in 2008, England. Office for National Statistics. National Statistics, London (MB1: no. 39)
- 2 Jemal, A. *et al.* (2010) Cancer statistics, 2010. *CA Cancer J. Clin.* 60, 277–300
- 3 Statistical Bulletin: Death Registrations by Cause in England and Wales, 2009. Office for National Statistics. National Statistics, London
- 4 Huggins, C. and Hodges, C.V. (2002) Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. *J. Urol.* 168, 9–12
- 5 Parmar, H. *et al.* (1987) Orchiectomy versus long-acting D-Trp-6-LHRH in advanced prostatic cancer. *Br. J. Urol.* 59, 248–254
- 6 Tannock, I.F. *et al.* (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N. Engl. J. Med.* 351, 1502–1512
- 7 de Bono, J.S. *et al.* (2010) Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet* 376, 1147–1154
- 8 Kantoff, P.W. *et al.* (2010) Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N. Engl. J. Med.* 363, 411–422
- 9 Nilsson, S. *et al.* (2010) Alpharadin, a novel, highly targeted alpha pharmaceutical with a good safety profile for patients with CRPC and bone metastases: combined analyses of phase I and II clinical trials. *ASCO Genitourinary Cancers Symposium* (Abstr. 103)
- 10 Parker, C. *et al.* (2011) Overall survival benefit of radium-223 chloride (Alpharadin) in the treatment of patients with symptomatic bone metastases in castration-resistant prostate cancer: a phase III randomised trial. *ECCO-ESMO Annual Congress 11*, Stockholm, Sweden (Abstr. LBA1)
- 11 de Bono, J.S. *et al.* (2011) Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* 364, 1995–2005
- 12 Hellerstedt, B.A. and Pienta, K.J. (2002) The current state of hormonal therapy for prostate cancer. *CA Cancer J. Clin.* 52, 154–179
- 13 Trachtenberg, J. (1984) Ketoconazole therapy in advanced prostatic cancer. *J. Urol.* 132, 61–63
- 14 Schuster, I. and Bernhardt, R. (2007) Inhibition of cytochromes p450: existing and new promising therapeutic targets. *Drug Metab. Rev.* 39, 481–499
- 15 Lake-Bakaar, G. *et al.* (1987) Hepatic reactions associated with ketoconazole in the United Kingdom. *Br. Med. J. (Clin. Res. Ed.)* 294, 419–422
- 16 Barrie, S.E. *et al.* (1993) Highly potent inhibitors of human cytochrome P-450 (17 α): activity in vitro and in vivo. *Br. J. Cancer* 67 (Abstr. P177)
- 17 Potter, G.A. *et al.* (1995) Novel steroidal inhibitors of human cytochrome P45017 α (17 α -hydroxylase-C17,20-lyase): potential agents for the treatment of prostatic cancer. *J. Med. Chem.* 38, 2463–2471
- 18 Barrie, S.E. *et al.* (1994) Pharmacology of novel steroidal inhibitors of cytochrome P450(17 α) (17 α -hydroxylase/C17-20 lyase). *J. Steroid Biochem. Mol. Biol.* 50, 267–273
- 19 Newell, D.R. *et al.* (2003) Professor Tom Connors and the development of novel cancer therapies by the Phase I/II Clinical Trials Committee of Cancer Research UK. *Br. J. Cancer* 89, 437–454
- 20 O'Donnell, A. *et al.* (2004) Hormonal impact of the 17 α -hydroxylase/C(17,20)-lyase inhibitor abiraterone acetate (CB7630) in patients with prostate cancer. *Br. J. Cancer* 90, 2317–2325
- 21 Attard, G. *et al.* (2008) Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J. Clin. Oncol.* 26, 4563–4571

- 22 Ryan, C.J. *et al.* (2010) Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J. Clin. Oncol.* 28, 1481–1488
- 23 Attard, G. *et al.* (2009) Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J. Clin. Oncol.* 27, 3742–3748
- 24 Ryan, C.J. *et al.* (2011) Phase II study of abiraterone acetate in chemotherapy-naïve metastatic castration-resistant prostate cancer displaying bone flare discordant with serologic response. *Clin. Cancer Res.* 17, 4854–4861
- 25 Sundkvist, G.M. *et al.* (1990) Dynamic quantitative bone scintigraphy in patients with prostatic carcinoma treated by orchiectomy. *Eur. J. Nucl. Med.* 16, 671–676
- 26 Johns, W.D. *et al.* (1990) Leuprolide therapy for prostate cancer. An association with scintigraphic “flare” on bone scan. *Clin. Nucl. Med.* 15, 485–487
- 27 Scher, H.I. *et al.* (2008) Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J. Clin. Oncol.* 26, 1148–1159
- 28 Danila, D.C. *et al.* (2010) Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J. Clin. Oncol.* 28, 1496–1501
- 29 Reid, A.H. *et al.* (2010) Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. *J. Clin. Oncol.* 28, 1489–1495
- 30 Scher, H.I. *et al.* (2011) Evaluation of circulating tumor cell (CTC) enumeration as an efficacy response biomarker of overall survival (OS) in metastatic castration-resistant prostate cancer (mCRPC): planned final analysis (FA) of COU-AA-301, a randomized double-blind, placebo-controlled phase III study of abiraterone acetate (AA) plus prednisone (P) post docetaxel. *J. Clin. Oncol.* 29 (Suppl. Abstr. LBA4517)
- 31 Yu, M. *et al.* (2011) Circulating tumor cells: approaches to isolation and characterization. *J. Cell Biol.* 192, 373–382
- 32 Allard, W.J. *et al.* (2004) Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases. *Clin. Cancer Res.* 10, 6897–6904
- 33 de Bono, J.S. *et al.* (2008) Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin. Cancer Res.* 14, 6302–6309
- 34 Horwich, A. *et al.* (2010) Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 21 (Suppl. 5), 129–133
- 35 Reid, A.H. *et al.* (2010) Molecular characterisation of ERG, ETV1 and PTEN gene loci identifies patients at low and high risk of death from prostate cancer. *Br. J. Cancer* 102, 678–684
- 36 Attard, G. *et al.* (2009) Characterization of ERG, AR and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer. *Cancer Res.* 69, 2912–2918
- 37 Danila, D.C. *et al.* (2011) TMPRSS2-ERG status in circulating tumor cells as a predictive biomarker of sensitivity in castration-resistant prostate cancer patients treated with abiraterone acetate. *Eur. Urol.* 60, 897–904
- 38 Ryan, C. (2010) Abiraterone in prostate cancer. *Clin. Adv. Hematol. Oncol.* 8, 761–762
- 39 Sartor, O. (2011) Combination therapy: abiraterone prolongs survival in metastatic prostate cancer. *Nat. Rev. Clin. Oncol.* 8, 515–516
- 40 Dreicer, R. *et al.* (2010) Safety, pharmacokinetics, and efficacy of TAK-700 in castration-resistant, metastatic prostate cancer: a phase I/II, open-label study. *2010 Genitourinary Cancers Symposium* (Abstr. 103)
- 41 Cai, C. *et al.* (2011) Intratumoral *de novo* steroid synthesis activates androgen receptor in castration-resistant prostate cancer & is upregulated by treatment with CYP17A1 inhibitors. *Cancer Res.* 71, 6503–6513
- 42 Mostaghel, E.A. *et al.* (2011) Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: induction of steroidogenesis & androgen receptor splice variants. *Clin. Cancer Res.* 17, 5913–5925