Abiraterone for the treatment of metastatic castration-resistant prostate cancer that has progressed on or after a docetaxel-based chemotherapy regimen

Prepared September 2011

Disease background (1-4)

Prostate cancer is the most common cancer in men in England and Wales, with over 32,000 new diagnoses and over 9,000 deaths due to prostate cancer recorded in 2007. Its incidence increases with age, with around 80% of cases occurring in men over the age of 65 years.

It is estimated that around 55-60% of men with prostate cancer will develop metastatic disease, most commonly involving bone. The initial treatment for metastatic disease is hormonal ablation, either with surgery (bilateral orchidectomy) or medically with gonadotrophin releasing hormone analogues such as goserelin, leuprorelin or triptorelin. A luteinising hormone-releasing hormone (LHRH) antagonist is also now available (degarelix) – this avoids the initial testosterone flare that is seen with the agonists. Although most patients will initially respond to this type of therapy, the disease usually progresses in the presence of castrate levels of testosterone after around 12-18 months and alternative treatment strategies are then required. The cancer may respond to additional hormonal strategies, but ultimately the cancer becomes unresponsive to further conventional hormonal manipulation.

Docetaxel was approved in 2004 for use in combination with prednisone for the treatment of hormone-refractory metastatic prostate cancer and was approved by NICE for this indication in 2006, for those with a Karnofsky performance status of ≥60%. It has become the standard first-line chemotherapy in this setting, on the basis of an improvement in survival compared with mitoxantrone plus prednisone. The standard treatment for those who progress following first-line therapy with docetaxel is evolving and many studies have investigated the role of salvage chemotherapy (e.g. mitoxantrone; vinorelbine). The first agent to demonstrate a survival advantage in this setting is the taxane derivative cabazitaxel, which was associated with a 2.4 month median improvement in overall survival, compared to mitoxantrone (both in addition to prednisolone/prednisone), in a Phase III study.

Various different terms have been used to describe prostate cancers that have relapsed after initial hormone ablation therapy – hormone-refractory prostate cancer (HRPC), androgen-independent cancers, and hormone-independent cancers. The castrate-resistant but still hormone sensitive cancer (CRPC) has been clearly characterised and it is important to differentiate this from true HRPC – although CRPC responds to secondary hormone manipulations, true HRPC resists all hormonal measures. The prognosis is poor for patients with HRPC, with survival not expected to exceed 9-12 months.

Abiraterone

Abiraterone acetate (Zytiga®), a prodrug of abiraterone, is a potent inhibitor of the cytochrome P450 c17 (CYP17) enzyme, a critical enzyme in testosterone synthesis, which blocks androgen synthesis by the adrenal glands and testes and within the prostate tumour itself (5, 6).
The European Medicines Agency approved marketing authorisation for abiraterone acetate in September 2011, for use in combination with prednisone/prednisolone for the treatment of metastatic CRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen (7).

**Estimated cost**

The company supplied a budgetary impact assessment for the provision of abiraterone acetate within the London SHA through the CDF which uses the population assumptions detailed below.

<table>
<thead>
<tr>
<th>Population estimates for the London SHA</th>
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<tbody>
<tr>
<td>Total London SHA population</td>
<td>7,753,600</td>
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<tr>
<td>0.052% incidence of prostate cancer</td>
<td>4,027</td>
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<tr>
<td>22% of patients diagnosed at the metastatic stage (stage IV)</td>
<td>886</td>
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<tr>
<td>17% of patients diagnosed at an earlier stage will go on to develop metastases</td>
<td>886</td>
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<tr>
<td>All patients with stage IV disease will go on to develop CRPC</td>
<td>1,570</td>
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<tr>
<td>50% of patients with CRPC will receive treatment with docetaxel plus prednisolone</td>
<td>785</td>
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<tr>
<td>75% of patients who have received docetaxel will be alive following treatment</td>
<td>589</td>
</tr>
<tr>
<td>90% of patients who are alive following docetaxel will be eligible for treatment with abiraterone acetate</td>
<td>530</td>
</tr>
<tr>
<td>Number of eligible patients per 100,000 population</td>
<td>7</td>
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**Drug cost estimates**

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<tr>
<td>Cost per 30 days (120 x 250mg tablets)*</td>
<td>£2,930</td>
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<tr>
<td>Average cost per patient (based on an average of 8 cycles)</td>
<td>£23,440</td>
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* based on basic NHS price (excluding VAT)

Based on the current list price, and using the above assumptions, the estimated cost (assuming a 50% uptake) would be around £82,000 per 100,000 population.

**Evidence for abiraterone within its proposed licensed indication**

The main study supporting the approval of abiraterone acetate within its proposed indication is a Phase III trial (COU-AA-301) that was stopped early, as a positive effect on overall survival was observed at the first pre-planned interim analysis (6). [Phase II studies have not been reported here due to the availability of a Phase III trial.]

Previous studies have shown that disease progression following initial medical or surgical castration may be in part due to synthesis of androgens within the tumour, with castration-resistant prostate cancer cells over-expressing the enzymes required for biosynthesis. Abiraterone acetate, an inhibitor of CYP17 and thus androgen biosynthesis, has demonstrated activity in Phase II studies; this Phase III study was therefore conducted to further evaluate its activity in mCRPC.

**Study design**: Randomised, double-blind, placebo-controlled, multinational study (147 sites in 13 countries), evaluating whether abiraterone acetate prolongs overall survival in patients with metastatic CRPC who have previously received either one or two prior chemotherapy regimens, at least one of which was docetaxel-based.
**Participants:** Men with prostate cancer that had previously been treated with docetaxel and who had disease progression, ongoing androgen deprivation (serum testosterone $\leq 2.0$ nmol/L), and an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of $\leq 2$.

**Treatments:** 1195 eligible men were randomised to abiraterone acetate (1g [four 250mg tablets] orally once daily; n=797) or placebo (n=398), both in combination with prednisone (5mg orally twice daily), to continue until documented disease progression. Randomisation was stratified according to baseline ECOG PS, level of worst pain over the previous 24 hours recorded on the Brief Pain Inventory-Short Form (BSI-SF; scale of 0-10), number of previous chemotherapy regimens (1 or 2), and type of evidence of disease progression (increase in prostate-specific antigen [PSA] concentration only versus radiographical evidence of progression ± increased PSA).

**Endpoints:** The primary endpoint was overall survival (OS); secondary endpoints included PSA response rate (proportion of patients with $\geq 50\%$ decrease from pre-treatment baseline, confirmed on two occasions $\geq 4$ weeks apart); time to PSA progression (defined for PSA responders as an increase of $\geq 50\%$ over nadir and absolute increase by $\geq 5$ng/ml, and for PSA non-responders as $\geq 25\%$ increase over nadir or baseline and absolute increase by $\geq 5$ng/mL); and radiographical evidence of progression-free survival (PFS according to RECIST and bone scan).

**Patient characteristics:** The median age was 69 years (range 39-95 years), with around one quarter aged 75 years or above, and 90% with an ECOG PS of 0 or 1. The majority had metastatic disease of the bone (89-90%) and just under half (41-45%) had nodal involvement; 8-11% had liver metastases. Patients could have had up to 2 prior lines of chemotherapy, with at least one being docetaxel based (approximately 70% of patients had previously received one line of cytotoxic chemotherapy and the remainder had received two; no further details of past therapy are given).

**Main efficacy results:** At the first pre-planned interim analysis, after a median follow-up of 12.8 months (median duration of treatment of 8 months in the abiraterone acetate group and 4 months in the placebo group), the main results were as follows:

- A total of 333 patients in the abiraterone acetate group (42%) and 219 in the placebo group (55%) died during the study. The median overall survival (OS) was 14.8 months in the abiraterone acetate group and 10.9 months in the placebo group (HR 0.65; 95% CI 0.54-0.77; p<0.001). Abiraterone was therefore associated with a median overall survival advantage of 3.9 months compared with placebo.

- The effect of abiraterone acetate on overall survival was seen to be consistent across virtually all subgroups tested and the statistical significance of the result was robust after adjustment for stratification factors in a multivariate analysis (HR 0.66; 95% CI 0.55-0.78; p<0.001). There was no significant improvement in OS in patients with ECOG PS 2, possibly due to patient numbers (10% of patients in the study).

On the basis of these overall survival data, the independent data and safety monitoring committee recommended unblinding of the study, and patients in the placebo group were able to crossover to abiraterone acetate in an extension study. [Note: As the study power calculation was based on a total of 797 survival events, its early termination meant that the required number of events had not been met (552 events occurred) and the study was therefore underpowered.]
Secondary endpoints reported include the following:

- Confirmed PSA response rates were 29% with abiraterone acetate and 6% with placebo (p<0.001)
- Objective response rates (according to RECIST) were 14% versus 3%, respectively (p<0.001)
- Time to PSA progression was 10.2 months versus 6.6 months, respectively (HR 0.58; 0.46-0.73; p<0.001)
- Median PFS (on the basis of radiographical evidence) was 5.6 months versus 3.6 months, respectively (HR 0.67; 95% CI 0.59-0.78; p<0.001)

Following guidance from regulatory authorities, Janssen conducted the second and final analysis of the data after a median follow-up of 20.2 months (775 events). At this time the median OS was 15.8 months for the abiraterone acetate arm and 11.2 months in the control arm (difference of 4.6 months; HR 0.74; 95% CI 0.64-0.86; p<0.0001) (8).

The authors comment that their results show that continued androgen-receptor signalling contributes to disease progression in this setting, and that other endocrine therapies should be evaluated in this stage of disease.

They note that the study validates the hypothesis that biosynthesis of steroids downstream of CYP17 contributes to disease progression in a subgroup of men who have disease that remains driven by steroid ligands. As this subgroup cannot be identified a priori, they say that continuing to call this disease ‘hormone refractory’ is imprecise.

Another Phase III study is evaluating abiraterone acetate in patients with metastatic CRPC who have not received previous treatment with a docetaxel-based chemotherapy. The authors of an editorial accompanying the COU-AA-301 study comment that its results provide sufficient evidence to justify trialling its use in all patients with metastatic CRPC (9).

Main toxicity results:

Blockade of CYP17 leads to elevated mineralocorticoid levels, and adverse events related to this phenomenon were more common in the abiraterone acetate group (Grade 1-4, overall 55% versus 43%; p=0.001). These included fluid retention and oedema (31% versus 22%; p=0.04), hypokalaemia (17% versus 8%; p<0.001), and hypertension (10% versus 8%; p=NS); the majority were grade 1/2 events. Although cardiac events occurred in a numerically higher number of patients randomised to abiraterone acetate, these were primarily grade 1 or 2 and there was no statistically significant difference in the rate seen with abiraterone versus placebo (13% versus 11%, respectively). There were no increases in levels of fatal cardiac events between the two groups (1.1% versus 1.3%, respectively).

Although abiraterone acetate has been associated with elevated aminotransferase levels (one grade 4 event occurred early in the study, after which monitoring was increased), liver function test abnormalities occurred in a similar proportion of patients (overall 10% of patients in the abiraterone acetate group and 8% of those in the placebo group; grade 3/4 changes in 3.5% and 3.0%, respectively).

Other common adverse events seen in the study (rate in abiraterone acetate versus placebo) included fatigue (44% versus 43%), back pain (30% versus 33%), nausea (30% versus 32%), constipation (26% versus 31%), bone pain (25% versus 28%), arthralgia (27% versus 23%), and urinary tract infections (12% versus 7%, p=0.02).
Overall, adverse events led to discontinuation in 19% of the abiraterone acetate group and 23% of the placebo group (p=0.09) (10). The authors comment that treatment with abiraterone acetate did not appear to increase the risk of metabolic changes or symptoms associated with chronic androgen deprivation, but that longer follow-up is required to evaluate any late toxic effects.

Summary

Although there is currently no standard treatment for patients with metastatic CRPC who progress following docetaxel, palliative options currently used include mitoxantrone with or without steroids, and best supportive care. Newer agents are being trialled in this setting and the taxane derivative cabazitaxel was recently licensed, a Phase III study demonstrating that it increased median overall survival by 2.4 months compared to mitoxantrone (both in combination with prednisone/prednisolone).

Abiraterone acetate has been approved by the European Medicines Agency for use in combination with prednisone/prednisolone for the treatment of metastatic CRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

The main Phase III study published to date (n=1195) compared abiraterone acetate (1g daily) plus prednisone to prednisone alone; at the time of the study design no drugs had been associated with any survival advantage in this patient group. The abiraterone acetate group had a median overall survival advantage of 3.9 months at the time of the first interim analysis, and the study was terminated early based on these results (at which time it was underpowered, as only 552 of the 797 survival events the power calculation was based on had occurred). The second and final analysis (at which time 775 events had taken place), showed that the median OS advantage had increased to 4.6 months (HR 0.74; p<0.0001). Patients randomised to placebo are able to cross over to abiraterone and will be evaluated in the extension study. Abiraterone acetate was associated with manageable toxicity distinct from that associated with cytotoxics (which would give it an advantage over cabazitaxel and palliative chemotherapy regimens in this setting).

The authors of the Phase III study note that it is not possible to identify patients who have disease that remains driven by steroids before treatment is started. At the present time therefore if would not be possible to identify particular patients who are more likely to respond to abiraterone acetate (i.e. those with CRPC rather than HRPC). If this could be done it would allow more effective targeting of treatment so that those with true hormone-resistant disease could receive other therapies.

References

1) NICE: Abiraterone for the treatment of metastatic, castrate-resistant prostate cancer following previous cytotoxic chemotherapy. Final scope (July 2011) http://guidance.nice.org.uk/TA/Wave26/4
7) Zytiga Prostate Cancer Drug Approved in EU. BioSpace report, 7th September 2011

8) Fizazi K et al (2011) Final overall survival analysis of COU-AA-301, a phase 3 study of abiraterone acetate plus prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) pretreated with docetaxel. 2011 European Multidisciplinary Cancer Congress; abstract 7000
