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ADIS DRUG EVALUATION

Abiraterone Acetate: A Review in Metastatic Castration-Resistant Prostrate Cancer

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Abstract Oral abiraterone acetate (Zytiga®) is a selective inhibitor of CYP17 and thereby inhibits androgen biosynthesis, with androgen signalling crucial in the progression from primary to metastatic prostate cancer (PC) and subsequently, in the development of metastatic castration-resistant PC (mCRPC). In large phase 3 trials and in the clinical practice setting, oral abiraterone acetate in combination with prednisone was an effective treatment and had an acceptable, manageable tolerability and safety profile in chemotherapy-naive and docetaxel-experienced men with mCRPC. In the pivotal global phase 3 trials, relative to placebo (+prednisone), abiraterone acetate (+prednisone) prolonged overall survival (OS) at data maturity (final analysis) and radiographic progression-free survival (rPFS) at all assessed timepoints. Given its efficacy in prolonging OS and its convenient once-daily oral regimen, in combination with prednisone, abiraterone acetate is an important first-line option for the treatment of mCRPC.

Abiraterone acetate: clinical considerations in metastatic castration-resistant prostate cancer

In combination with prednisone, significantly prolongs OS and rPFS in chemotherapy-naive and docetaxel-experienced patients

In combination with prednisone, provides efficacy in both the clinical trial and real-world clinical practice settings

Acceptable, manageable tolerability and safety profile

Associated with hypokalaemia, hypertension and fluid retention or oedema, secondary to its mechanism of action, and cardiac adverse events and hepatotoxicity

1 Introduction

Prostate cancer (PC) is the second most common cancer in men (accounts for 15% of all cancers), with more than 1 million new cases diagnosed in 2012 [1]. After PC has advanced to metastatic disease (affects 20–30% of patients), androgen ablation therapy is the standard first-line treatment, reflecting the crucial role that androgen receptor (AR) signalling axis plays in the development of both normal prostate and progression from primary to metastatic PC [2–4]. Despite initially responding to androgen ablation therapy, disease progression to metastatic castration-resistant PC (mCRPC) typically occurs

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within 2–3 years in the majority of patients, with these patients having a poor prognosis [2, 3]. Several mechanisms have been suggested for ongoing AR activation and PC growth, including upregulation of the AR, activation of the AR via other pathways, and ongoing androgen synthesis by adrenal glands and the prostatic tumour mediated by upregulation of CYP17 [4, 5]. CYP17 inhibition is one strategy for targeting mCRPC, with abiraterone acetate (Zytiga®) developed as a potent, selective, irreversible CYP17 inhibitor [4, 5]. This narrative review provides an update of the clinical profile of oral abiraterone acetate, in combination with oral prednisone, in the clinical trial and real-world clinical practice settings in men with mCRPC, and summarizes its pharmacological properties; some of these data were previously reviewed in *Drugs* [6].

2 Pharmacodynamic Properties

Abiraterone, the active metabolite of abiraterone acetate, irreversibly inhibits CYP17 (17α-hydroxylase/$C_{17,20}$-lyase), an essential enzyme in androgen biosynthesis that is expressed in testicular, adrenal and prostatic tumour tissues [7, 8]. CYP17 levels are significantly ($p = 0.0005$) higher (≈17-fold) in CRPC metastases than in primary prostate tumours [9]. As reviewed previously [6], pregnenolone and progesterone are converted to 17 α-hydroxy derivatives by 17α-hydroxylase and subsequently by $C_{17,20}$-lyase to dehydroepiandrosterone and androstenedione (precursors of androgens and testosterone).

In phase 1 or 2 trials (reviewed previously [6]), abiraterone acetate 250–2000 mg once daily was associated with antitumor effects, including reduced prostate-specific antigen (PSA) levels (a biomarker in patients with mCRPC) and circulating tumour cell (CTC) counts. Abiraterone acetate also suppressed serum testosterone levels to undetectable or near undetectable levels after ≤28 days' therapy in patients with progressive CRPC, and in combination with prednisone, suppressed blood and bone marrow aspirate testosterone levels to below pg/mL levels in patients with mCRPC, with this suppression maintained at disease progression [6]. In vivo, phenotypes that exhibited ultra, intermediate and minimal responses to abiraterone acetate treatment were identified in a mouse model utilizing patient-derived PC xenograft [10]. The ultraresponsive phenotype was characterized by reduced AR signalling with the development of abiraterone acetate resistance, suggesting an AR-independent pathway to sustain survival; whether this translates into a biomarker to predict sustainability of clinical responses remains to be fully elucidated [10]. The clinical efficacy of abiraterone acetate in combination with prednisone in phase 3 trials and the real-world clinical practice setting is discussed in Sect. 4.

Concomitant use of a corticosteroid with abiraterone acetate therapy ameliorated the adverse symptoms associated with abiraterone acetate-induced mineralocorticoid excess in phase 1 and 2 trials [6]; all participants in phase 3 trials (Sect. 4) received concomitant prednisone.

In patients with mCRPC, the QT/QTc interval does not appear to be affected by therapeutic dosages of abiraterone acetate (+prednisone) [11]. Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering abiraterone acetate with drugs known to prolong the QT interval or drugs that induce torsades de pointes (e.g class 1A and III antiarrhythmic drugs; methadone, moxifloxacin, antipsychotics) [7].

3 Pharmacokinetic Properties

Oral abiraterone acetate is rapidly absorbed and converted to its active metabolite abiraterone, with maximum plasma concentrations of abiraterone attained in a median time of 2 h in the fasted state [7, 8]. Systemic exposure of abiraterone is increased to a clinically relevant extent when abiraterone acetate is administered with food; thus, the drug should be taken 2 h after or at least 1 h before meals. At steady state, accumulation of abiraterone was observed, with exposure increasing twofold with multiple 1000 mg doses versus a single dose [7, 8, 12, 13]. Abiraterone is highly bound (>99%) to the human plasma proteins albumin and α-1 acid glycoprotein and appears to be extensively distributed into peripheral tissues (steady-state mean apparent volume of distribution 19,669 L [8]) [7, 8].

Metabolism of abiraterone predominantly occurs in the liver and involves hydroxylation, oxidation and sulphation [7], and is most likely mediated via esterase activity, with no involvement of CYP enzymes [8]. After a radiolabeled dose, ≈92% of circulating radioactivity is present as metabolites of abiraterone [7], with ≈88% of the radioactivity excreted in the faeces and ≈5% in urine [7, 8]. The major components in the faeces are unchanged abiraterone acetate (≈55%) and abiraterone (≈22%) [7, 8]. In patients with mCRPC, the mean terminal half-life of abiraterone in the plasma is 12 h [8].

There was no clinically relevant impact on the pharmacokinetics (PKs) of abiraterone acetate in patients with renal impairment or end-stage renal disease on haemodialysis [7, 8, 14]; in the EU, caution is advised in patients with severe renal impairment due to a lack of clinical data [7]. Mild hepatic impairment (Child-Pugh class A) had minimal effects on the PKs of abiraterone acetate [14], with no dosage adjustments required in these patients [7, 8]. Given that the drug is primarily metabolized in the liver and eliminated in the faeces, moderate or severe hepatic impairment (Child-Pugh class B and C) increased exposure to abiraterone and

prolonged elimination to a clinically relevant extent [7, 8, 14]; local prescribing information should be consulted for use in these patient populations.

In vitro, the major metabolites of abiraterone acetate inhibited the hepatic uptake transporter OAT1B1; no clinical data are available to confirm transporter based interaction [7]. In vitro, in addition to inhibiting CYP17, abiraterone is a strong inhibitor of CYP2D6 and CYP2C8 [7]. In men with mCRPC, the PKs of theophylline (a strong CYP1A2 substrate) were not altered when it was coadministered with abiraterone acetate [15]. Abiraterone acetate is potentially associated with clinically relevant drug-drug interactions when coadministered with strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, rifampicin, rifabutin), CYP2C6 substrates (e.g. dextromethorphan [15]) and drugs that are predominantly eliminated by CYP2C8 (.g. pioglitazone) [7, 8]. When coadministered with ketoconazole (strong CYP3A4 inhibitor), there was no clinically meaningful effect on the PKs of abiraterone in healthy volunteers [7, 8]. Local prescribing information should be consulted for comprehensive information on potential drug-drug interactions associated with abiraterone acetate use.

4 Therapeutic Efficacy

The efficacy of abiraterone acetate, in combination with prednisone, in men with histologically or cytologically confirmed mCRPC who were chemotherapy-naive (Sect. 4.1; COU-AA-302 trial) [16–18] or docetaxel-experienced (Sect. 4.2; COU-AA-301) [19, 20] was established in two pivotal, randomized, double-blind, global, phase 3 trials (extensively reviewed previously in *Drugs* [6]). Since then, overall survival (OS) data in chemotherapy-naive patients have matured [17] and randomized, double-blind, multicentre, phase 3 bridging trials in chemotherapy-naive [21] and -experienced [22] patients have evaluated abiraterone acetate (+prednisone) therapy in Asian patients (and in Russia [21]). Data from real-world clinical practice studies are also discussed (Sect. 4.3). In all phase 3 trials [16, 19, 21, 22], patients received oral abiraterone acetate 1000 mg or placebo once daily in combination with oral prednisone 5 mg twice daily. Efficacy analyses were conducted in the intent-to-treat population. Within each trial, patient demographics and characteristics were well balanced between treatment groups at baseline [16, 19, 21, 22].

4.1 In Chemotherapy-Naive Patients

In phase 3 trials, key eligibility criteria included confirmed disease progression, ongoing androgen deprivation with a serum testosterone level of <50 ng/dL, an ECOG performance status (PS) of <2, and no or mild symptoms according to the Brief Pain Inventory (BPI)-SF [16, 21]. In the overall population of COU-AA-302, 76 and 24% of patients had an ECOG PS of 0 or 1 [16]. In the bridging trial, 51 and 49% of patients had an ECOG PS of 0 and 1, with 92% having a Gleason score of ≥7 [21].

4.1.1 COU-AA-302

Coprimary endpoints were radiographic progression-free survival (rPFS) and OS assessed at specified timepoints (Table 1) [16]. The study was unblinded after the second interim analysis, with placebo (+prednisone) recipients switched to abiraterone acetate (+prednisone) therapy [16]. At the time of the final OS analysis (96% of 773 prespecified death events had occurred; median follow-up' 49.2 months), 238 patients in the placebo group had crossed over to abiraterone acetate (+prednisone); of whom, 93 patients crossed over as per protocol amendment [17].

For coprimary endpoints, median rPFS was significantly prolonged with abiraterone acetate (+prednisone) therapy compared with placebo (+prednisone) at the time of the first interim analysis, with OS significantly prolonged at the time of final analysis (Table 1) [16–18]. Median rPFS was also significantly prolonged at the time of second and third interim analyses in favour of abiraterone acetate (+prednisone) therapy, with a 57% reduction in the risk of disease progression or death at the time of first and second interim analyses and a 48% reduction in this risk at the time of the third interim analysis (Table 1) [16, 18]. At the time of the first interim analysis, hazard ratios (HRs) significantly favoured abiraterone acetate (+prednisone) over placebo (+prednisone) across all patient subgroups in terms of rPFS [16]. At the final analysis, 354 and 387 deaths had occurred in the abiraterone acetate (+prednisone) and placebo (+prednisone) groups, respectively, corresponding to a 19% reduction in the risk of death in the abiraterone acetate (+prednisone) group (Table 1) [17]. At the time of final analysis, median OS data in abiraterone acetate (+prednisone) recipients were consistent across all prespecified patient subgroups [17]. There was a significant correlation between rPFS and OS (estimated correlation coefficient of 0.72) [16, 23].

At all interim analysis timepoints, predefined secondary endpoints significantly ($p < 0.01$) favoured combination therapy with abiraterone acetate (+prednisone) over placebo (+prednisone) [16, 18]. For example, at the time of the third interim analysis, median times to PSA progression (TTPP) [11.1 vs. 5.6 months; HR 0.50; 95% CI 0.43–0.58; $p < 0.0001$], opiate utilization for PC-related pain (not yet reached vs. 23.7 months; HR 0.71; 95% CI 0.59–0.85; $p = 0.0002$), cytotoxic chemotherapy treatment (26.5 vs.

Table 1 Efficacy of oral abiraterone acetate plus oral prednisone in intent-to-treat analyses of the pivotal COU-AA-302 trial in chemotherapy-naive men with metastatic castration-resistant prostate cancer

Timepoint[a] (median follow-up; months)	Treatment group (no. of pts)	OS[b] (HR; 95% CI) [median value; months]	rPFS[b,c] (HR; 95% CI) [median value; months]
First interim analysis (NR) [16, 17]	ABI + PRE (546)	NYR	NYR (0.43; 0.35–0.52)**
	PL + PRE (542)	NYR	8.3
Second interim analysis (22.2) [16]	ABI + PRE (546)	NYR (0.75; 0.61–0.93)[d]	16.5 (0.43; 0.45–0.62)***
	PL + PRE (542)	27.2	8.3
Third interim analysis (27.1) [18]	ABI + PRE (546)	35.3 (0.79; 0.66–0.95)[d]	16.5 (0.52; 0.45–0.61)***
	PL + PRE (542)	30.1	8.2
Final analysis (49.2) [17]	ABI + PRE (546)	34.7	Not assessed
	PL + PRE (542)	30.3 (0.81; 0.70–0.93)*	Not assessed

ABI abiraterone acetate, *HR* hazard ratio, *NYR* not yet reached, *OS* overall survival, *PL* placebo, *PRE* prednisone, *pts* patients, *rPFS* radiographic progression-free-survival

* $p = 0.003$, ** $p < 0.001$, *** $p < 0.0001$ vs. PRE + PL

[a] 1st, 2nd, 3rd and final analyses conducted after occurrence of 209, 333, 434 and 741 deaths, respectively (i.e. 27, 43, 56 and 96% of prespecified 773 OS events). 1st analysis conducted after occurrence of 401 progression-free events

[b] Coprimary endpoint at all analyses (OS) and at the first interim analysis (rPFS)

[c] Assessed by an independent radiographer blinded to therapy; defined as freedom from death from any cause, freedom from progression in soft tissue lesions (MRI or CT scans; modified RECIST criteria) or on bone scans (Prostate Cancer Clinical Trials Working Group 2 criteria)

[d] As the HR did not cross the specified O'Brien-Fleming boundary, it was not considered statistically significant

16.8 months; HR 0.61; 95% CI 0.51–0.72; $p < 0.0001$) and ECOG PS decline of ≥1 point (12.3 vs. 10.9 months; HR 0.83; 95% CI 0.72–0.94; $p = 0.005$) were all significantly prolonged in the abiraterone acetate (+prednisone) group versus the placebo (+prednisone) group, with HRs favouring abiraterone acetate (+prednisone) for each of these outcomes [18]. At the time of the final OS analysis, the median time to opiate use for PC-related pain continued to favour abiraterone acetate (+prednisone) over placebo (+prednisone) therapy (33.4 vs. 23.4 months; HR 0.72; 95% CI 0.61–0.85; $p < 0.0001$) [17].

Relative to placebo (+prednisone), combination therapy with abiraterone acetate (+prednisone) improved the median time to rPFS, irrespective of *ERG* gene status [24]. The median time to rPFS favoured abiraterone acetate (+prednisone) in patients with more than one *ERG* gene fusion sequence (i.e. class 2+ Edel) secondary to deletion of 21q22 (22.0 vs. 5.4 months in the placebo group; HR 0.31; 95% CI 0.15–0.68; $p = 0.0033$; $n = 30$ and 21) and in those without *ERG* fusion (16.7 vs. 8.3 months; HR 0.53; 95% CI 0.38–0.74; $p = 0.0002$; $n = 112$ and 115). There was no significant between-group difference (BGD) in the risk of rPFS in those with one ERG fusion (i.e. class 1 Edel) secondary to deletion of 21q22 (13.8 vs. 10.9 months; HR 0.56; 95% CI 0.29–1.08; $n = 34$ and 30) [24].

Abiraterone acetate (+prednisone) significantly delayed the median time to deterioration in health-related quality of life (HR-QOL) at the time of second (12.7 vs. 8.3 months with placebo (+prednisone); HR 0.78; 95% CI 0.66–0.92; $p = 0.003$) [25] and third (12.7 vs. 8.3 months; HR 0.79; 95% CI 0.67–0.93; $p = 0.005$) [18] interim analyses, as assessed using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score (exploratory endpoints). A longitudinal analysis of HR-QOL data indicated that over the first year of treatment, abiraterone acetate (+prednisone) was associated with significant improvements in HR-QOL compared with placebo (+prednisone), as assessed by the FACT-P total scores and the PC subscale (PCS) scores and using the trial outcome index (a composite of the FACT-P scores for physical well-being, functional well-being and PCS) [26]. The ability to analyze these patient-reported outcomes after the first year was limited by the attrition of patients after this time [26].

In post hoc analyses of data from the third interim analysis, combination therapy with abiraterone acetate (+prednisone) provided better efficacy than placebo (+prednisone) in terms of primary and/or prespecified secondary outcomes, irrespective of age (<75 vs. ≥75 years) [27], prior endocrine therapy [28] or whether or not patients received concomitant bone-targeted therapies [29]. In a post hoc analysis evaluating first subsequent therapy (FST) post abiraterone acetate (+prednisone) treatment, 27 of 100 evaluable patients treated with docetaxel as FST achieved a confirmed decline of ≥50% in PSA, suggesting benefit with subsequent therapy [30]. In

abiraterone acetate (+prednisone) recipients, PSA kinetics (e.g. PSA ≥30, ≥50 and ≥90% response rate, PSA nadir, TTPP and PSA doubling time) were significantly ($p < 0.0001$) associated with OS at the third interim analysis, with abiraterone acetate (+prednisone) therapy having consistent effects on PSA kinetics (post hoc analysis) [31].

4.1.2 Asia and Russia Trial

Data from the pivotal COU-AA-302 trial are supported by a phase 3 bridging trial conducted in Asia and Russia ($n = 313$) [21]. The primary efficacy endpoint was the TTPP. An interim analysis was planned after ≈50% of TTPP events (i.e. 91 events) were observed to allow for early termination of the study if superiority was shown [21]. The interim analysis was conducted after 94 events had occurred [34 in the abiraterone acetate (+prednisone) group and 60 in the placebo (+prednisone) group; median follow-up' 3.9 months]. As the study passed the stopping criteria at this preplanned analysis, the study was unblinded and placebo patients were switched to abiraterone acetate (+prednisone) [21].

At the interim analysis, abiraterone acetate (+prednisone) therapy prolonged the median TTPP and reduced the risk of PSA progression by 58% compared with placebo (+prednisone) [median TTPP not yet reached vs. 3.8 months; HR 0.42; 95% CI 0.27–0.65; $p < 0.0001$] [21]. For secondary outcomes, a significantly higher proportion of patients in the abiraterone acetate (+prednisone) than in the placebo (+prednisone) group achieved a ≥50% decline in PSA level [50 vs. 21%; relative risk (RR) 2.4; $p < 0.0001$], with a higher objective response rate in the abiraterone acetate (+prednisone) group ($n = 35$ evaluable) than in the placebo (+prednisone) group ($n = 42$) [22.9 vs 4.8%; RR 4.8; $p = 0.0369$] [21].

4.2 In Docetaxel-Experienced Patients

In phase 3 trials, key eligibility criteria included confirmed PC previously treated with docetaxel, disease progression, ongoing androgen deprivation with a serum testosterone level of ≤50 [19] or <50 [22] ng/dL, and an ECOG PS of ≤2 [19, 22]. In COU-AA-301, 89% of patients had an ECOG PS of 0 or 1, 67% had radiographic evidence of disease progression before study entry, and 70 and 30% of patients had received one or two previous cytotoxic chemotherapy regimens [19]. In the Chinese trial, 92% of patients had an ECOG PS of 0 or 1, 7.5% of patients had radiographic evidence of disease progression and 92.5% of patients had only PSA evidence of disease progression at baseline [22].

4.2.1 COU-AA-301 Trial

The primary endpoint was OS, with an interim analysis planned after 534 deaths were observed (67% maturity) and a final analysis planned after 797 deaths had occurred [19]. The interim OS analysis was conducted after 552 death events (69% maturity; median follow-up of 12.8 months) [19], with the final OS analysis conducted after 775 death events (i.e. 97% maturity; median follow-up duration 20.2 months) [20]. The study was unblinded after analysis of the interim data, with placebo recipients switched to abiraterone acetate (+prednisone) therapy; for placebo recipients, final analysis data reported are from the study period prior to the switch in therapy [20]. Median treatment durations in the abiraterone acetate (+prednisone) and placebo (+prednisone) groups were 7.4 and 3.6 months [20].

Relative to placebo (+prednisone), abiraterone acetate (+prednisone) significantly prolonged the median duration of OS at the interim and final analysis, with a 35 and 26% reduction in the risk of death from any cause at these respective timepoints (Table 2) [19, 20]. In multivariate analyses, the OS benefit of abiraterone acetate (+prednisone) over placebo (+prednisone) was consistent after adjustment for baseline stratification factors at the interim (HR 0.66; 95% CI 0.55–0.78; $p < 0.001$) [19] and final analysis (HR 0.76; 95% CI 0.66–0.88; $p = 0.0003$) [20]. At the final analysis, the beneficial treatment effect of abiraterone acetate (+prednisone) on OS (i.e. all HRs <1) in prespecified subgroups of patients was consistent with that observed in the overall population, although some BGD differences were not statistically significant (reflecting low patient numbers in these subgroups) [20]. At the final analysis, abiraterone acetate (+prednisone) therapy also provided similar benefits over placebo (+prednisone) in terms of OS, irrespective of the presence or absence of visceral disease (with presence a negative prognostic factor) [exploratory analysis] [32], the timing of docetaxel administration and the reason for discontinuation of docetaxel (post hoc analysis) [20] or whether patients were aged <75 or ≥75 years (post hoc analysis) [33].

In post hoc analyses of final analysis data, abiraterone acetate (+prednisone) was more effective than placebo (+prednisone) for the median time to OS and rPFS and PSA response rates, irrespective of the type or duration of prior endocrine therapy [28]. At the time of the final analysis, PSA kinetics were significantly ($p < 0.0001$) associated with OS in abiraterone acetate (+prednisone) recipients, with abiraterone acetate (+prednisone) having consistent effects on PSA kinetics (post hoc analyses) [31]. In a retrospective analysis of final analysis data, abiraterone acetate (+prednisone) was associated with a significant prolongation of rPFS compared with placebo

Table 2 Efficacy of oral abiraterone acetate plus oral prednisone in intent-to-treat analyses of the pivotal COU-AA-301 trial in men with metastatic castration-resistant prostate cancer who had previously received docetaxel

Endpoint	Interim analysis [19]			Final analysis [20]		
	ABI + PRE ($n = 797$)	PL + PRE ($n = 398$)	HR (95% CI)	ABI + PRE ($n = 797$)	PL + PRE ($n = 398$)	HR (95% CI)
Median overall survival[a] (months)	14.8	10.9	0.65 (0.54–0.77)*	15.8	11.2	0.74 (0.64–0.86)**
Median TTPP (months)	10.2	6.6	0.58 (0.46–0.73)*	8.5	6.6	0.63 (0.52–0.78)**
Median rPFS (months)	5.6	53.6	0.67 (0.59–0.78)*	5.6	3.6	0.66 (0.58–0.76)**
PSA response[b] (% of pts)	29.1*	5.5		29.5**	5.5	

ABI abiraterone acetate, *HR* hazard ratio, *PL* placebo, *PRE* prednisone, *PSA* prostate-specific antigen, *pts* patients, *rPFS* radiographic progression-free survival, *TTPP* time to PSA progression

* $p < 0.001$, ** $p < 0.0001$ vs. PL + PRE

[a] Primary endpoint

[b] Reduction of ≥50% in baseline PSA level

(+prednisone), irrespective of whether the Gleason score at initial diagnosis was <8 (6.4 vs. 5.5 months; HR 0.70; 95% CI 0.56–0.86; $p = 0.0009$) or ≥8 (5.6 vs. 2.9 months; HR 0.58; 95% CI 0.48–0.72; $p = 0.0001$) [34].

Exploratory [35, 36] or retrospective [37] analyses have evaluated factors for predicting OS with abiraterone acetate (+prednisone) treatment, with a prognostic index model developed that utilized six risk factors that are individually associated with poor prognosis in men with mCRPC [38]. Based on 12-week data, CTC count and LDH level was shown to be a surrogate marker of OS, with respective 2-year OS rates in high-risk (i.e. CTC ≥5 cells/7.5 mL blood and LDH >250 U/mL) and low-risk (i.e. CTC <5 cells/7.5 mL blood and LDH ≤250 U/mL) patients of 2 and 46% [35]. The utilization of baseline corticosteroids did not impact on the beneficial effects of abiraterone acetate (+prednisone) therapy on OS, based on multivariate stepwise selective modeling [36]. In both univariate and multivariate analyses, baseline serum androgen (SA) level was significantly ($p < 0.0001$) associated with OS, with shorter OS seen in patients with SA levels below the median SA level than in those with SA levels above the median, irrespective of treatment group [37]. Of note, median OS was prolonged in the abiraterone acetate (+prednisone) group versus the placebo (+prednisone) group irrespective of baseline SA levels [37].

Specified secondary endpoints all favoured abiraterone acetate (+prednisone) treatment at the interim and final analyses (Table 2) [19, 20]. Objective response rates were also higher in the abiraterone acetate (+prednisone) than in the placebo (+prednisone) group at the interim (14.0 vs. 2.8% of patients; $p < 0.001$) [19] and final analysis (14.8 vs. 3.3% of patients; $p < 0.0001$) [20].

At the interim and/or final analysis, abiraterone acetate (+prednisone) recipients experienced significant benefits over placebo (+prednisone) recipients in terms of bone-related symptoms (patient-reported pain palliation and skeletal-related events) [7, 19, 39]. In patients with clinically significant pain at baseline, a significantly ($p \leq 0.0005$) higher proportion of patients in the abiraterone acetate (+prednisone) than placebo (+prednisone) group experienced pain-intensity palliation (assessed using the BPI-SF) at the interim (44 vs. 27%) [7, 19] and final analysis (45 vs. 29%) [39]. In the final analysis, the median time to pain intensity palliation (5.6 vs. 13.7 months) and the median duration of pain intensity palliation (4.2 vs. 2.1 months) were also significantly ($p < 0.002$) better in the abiraterone acetate (+prednisone) than placebo (+prednisone) group [39]. At the final analysis, abiraterone acetate (+prednisone) therapy delayed the development of skeletal-related events relative to placebo (+prednisone) [exploratory outcome], with patients in the abiraterone acetate (+prednisone) group having a significantly longer median time to occurrence of the first skeletal-related event (25.0 vs. 20.3 months; $p = 0.0001$) [39].

Abiraterone acetate (+prednisone) therapy was also associated with significant ($p < 0.05$) improvements in HR-QOL compared with placebo plus prednisone in terms of patient-reported fatigue (assessed by British Fatigue Inventory questionnaire) [40] and functional status (assessed by FACT-P) [41].

4.2.2 Chinese Trial

Data from the pivotal COU-AA-301 trial are supported by a Chinese phase 3 trial ($n = 214$ randomized) [22]. The primary efficacy endpoint was the median TTPP, with the final analysis planned after 163 PSA progression events. At the time of the final analysis, median treatment durations in the abiraterone acetate (+prednisone) [$n = 143$] and

placebo (+prednisone) [$n = 71$] groups were 32.3 and 16.9 weeks; 161 PSA progression events had occurred (median follow-up' 12.9 months) [22].

At the final analysis, abiraterone acetate (+prednisone) therapy prolonged TTPP compared with placebo (+prednisone), with a 49% reduction in the risk of PSA progression (5.55 vs. 2.76 months; HR 0.506; 95% CI 0.356–0.719; $p = 0.0001$) [22]. With exception of patients with a baseline ECOG PS of 2 (limited by low patient numbers), median TTPP significantly favoured (i.e. HRs <1) abiraterone acetate (+prednisone) therapy across all prespecified subgroups of patients [22]. In general, major secondary endpoints favoured abiraterone acetate (+prednisone) treatment over placebo (+prednisone) at the time of the final analysis [22]. There was a non-significant trend towards prolongation of OS in the abiraterone acetate (+prednisone) versus the placebo (+prednisone) group (HR 0.604; 95% CI 0.356–1.026), although the short follow-up period and low number of events (56 deaths had occurred) meant that median survival was not reached in either treatment group [22]. The PSA response rate was significantly higher in the abiraterone acetate (+prednisone) than placebo (+prednisone) group (54.5 vs. 18.3%; $p < 0.0001$), with no statistically significant BGD in the objective response rate (15.8 vs. 4.2%; $n = 57$ and 24 patients with measurable disease at baseline) [22].

4.3 Real-World Studies

Several large (n >300) studies have firmly established the efficacy of abiraterone acetate (+prednisone) treatment in men with mCRPC in the real-world clinical practice setting, including the open-label, global (23 countries), early access protocol (EAP) trial (primary outcome was safety; Sect. 5) [42], the French Temporary Authorization for Use (TAU) programme (retrospective) [43], the Belgian compassionate use programme (retrospective) [44] and other retrospective database/registry studies conducted in the USA [45] and Canada [46].

Overall, results from real-world studies [42–44, 46] reflected results observed in phase 3 trials discussed in Sects. 4.1 and 4.2. For example, in the EAP trial in taxane-experienced (98% had received docetaxel) men with mCRPC that had progressed ($n = 2314$), 30% of patients experienced PSA progression during abiraterone acetate (+prednisone) therapy (median follow-up of 5.7 months), with a median TTPP of 8.5 months [42]. At this time, clinical disease progression had occurred in 31% of patients, with a median time to clinical disease progression of 12.7 months [42].

The pivotal COU-AA-302 [19] and COU-AA-301 [16] trials enrolled patients with an ECOG PS of ≤2; hence, a retrospective, multicentre Canadian registry study was conducted in docetaxel-experienced or -naive patients with mCRPC to compare the efficacy of abiraterone acetate (+prednisone) therapy in patients with an ECOG PS of 0–1 ($n = 318$) with that in patients with an ECOG PS of ≥2 ($n = 201$) [46]. Albeit these data are limited by their retrospective nature, the median OS duration was prolonged in patients with an ECOG PS of 0–1 over that in patients with an ECOG of ≥2, irrespective of whether patients were docetaxel-naive (26.0 vs. 10.3 months) or docetaxel-experienced (19.2 vs. 8.7 months). In the overall group, patients with an ECOG PS of 0–1 were significantly more likely to achieve a PSA response (45 vs. 32% in those with an ECOG PS of ≥2; $p = 0.003$) and had a longer median TTPP (5.2 vs. 4.1 months; $p = 0.023$), median treatment duration (7.4 vs. 4.5 months; $p < 0.001$) and median OS (20.0 vs. 9.1 months; $p < 0.001$). Significantly fewer patients in the ECOG PS 0–1 group than in the ECOG PS ≥2 group experienced clinical progression (44 vs. 63%; $p < 0.001$). There was no statistically significant BGD in the respective rates of objective disease progression (31 vs. 25%) or PSA progression (77 vs. 72%) [46].

A large, retrospective, US database study compared the combined duration of PC treatment amongst patients initiated on abiraterone acetate (+prednisone) [$n = 2591$] versus that in patients initiated on enzalutamide ($n = 807$) [45]. Given that baseline characteristics were likely to differ between patients initiated on each of these treatments, between-treatment comparisons were adjusted using inverse probability of treatment weights [equivalent to 1718 patients in the abiraterone acetate (+prednisone) cohort and 1680 in the enzalutamide cohort], with results interpreted as the average treatment effect in the overall population. The mean durations of observation in the abiraterone acetate (+prednisone) and enzalutamide cohorts were 313.4 and 310.3 days, although abiraterone acetate (+prednisone) recipients had a longer mean duration of continuous mCRPC treatment (240.0 vs. 221.1 days; $p = 0.013$) and of PC treatment (270.7 vs. 249.6 days; $p = 0.009$). A significantly higher proportion of abiraterone acetate (+prednisone) than enzalutamide recipients were treated with chemotherapy (18.1 vs. 15.4%; $p = 0.035$) and corticosteroids (90.2 vs. 49.1%; $p < 0.001$). At 3, 6, 9, 12, 18 and 24 months, relative to enzalutamide recipients, abiraterone acetate (+prednisone) recipients were significantly less likely to discontinue mCRPC treatment (HRs 0.70–0.76; $p \leq 0.004$ at all timepoints) or discontinue any PC treatment (HRs 0.61–0.69; $p \leq 0.002$ at all timepoints). This study like other retrospective database studies had several limitations, including potential inaccuracies and omission in databases, assumption that a claim for drugs indicated their use and, although abiraterone acetate (+prednisone) resulted in a longer combined therapy duration, the reasons for stopping subsequent therapies may not be related to the initial therapy [45].

5 Tolerability and Safety

Given the nature of cancer therapy, abiraterone acetate (+prednisone) was generally well tolerated and had an acceptable safety profile in men with mCRPC participating in clinical trials and real-world studies discussed in Sect. 4. For the most part, discussion focuses on data from the pivotal phase 3 trials [16, 19, 20], a pooled integrated safety analysis of these trials reported in European Assessment Report ($n = 1333$ abiraterone acetate and 934 placebo recipients; both +prednisone) [47] and real-world data from the global EAP trial (primary outcome was safety) [42]. The overall tolerability profile of abiraterone acetate (+prednisone) in elderly patients appeared to be consistent with that in younger patients [8].

In the integrated safety analysis of the two pivotal clinical trials, although the majority (≥97%) of patients in the abiraterone acetate (+prednisone) and placebo (+prednisone) groups experienced at least one treatment-emergent adverse event (TEAE), relatively few patients discontinued study treatment because of an adverse event (10.9 vs. 10.7%) [47]. Treatment-related adverse events (TRAEs) occurred in ≈77% of patients in both treatment groups, with these events leading to study drug discontinuation in 5.4% of patients in both groups. Grade 3 or 4 TRAEs occurred in 22.8% of patients in the abiraterone acetate (+prednisone) group and 17.9% in the placebo (+prednisone) group, with serious TRAEs occurring in ≈10% of patients in both treatment groups. TRAEs leading to death occurred in 1.0% of patients in the abiraterone acetate (+prednisone) group and in 1.6% of patients in the placebo (+prednisone) group [47].

TEAEs of any grade occurring with an incidence of ≥20% in abiraterone acetate (+prednisone) recipients were infection and infestations (54 vs. 39% in the placebo group), fatigue (39 vs. 34%), back pain (32% in both groups), arthralgia (28 vs. 24%), peripheral oedema (25 vs. 20%), constipation (23 vs. 19%), nausea (22% in both groups), hot flush (22 vs. 18%), diarrhoea (22 vs. 18%), hypertension (22 vs. 13%) and bone pain (20 vs. 19%) [47]. Very common (incidence ≥10%) adverse reactions of any grade occurring in abiraterone acetate (+prednisone) recipients were hypertension, hypokalaemia and peripheral oedema (Sect. 5.1), and diarrhoea and urinary tract infection [7, 47].

There were no new safety concerns identified in the EAP trial of abiraterone acetate (+prednisone), with 41% of 2314 patients experiencing grade 3 or 4 TEAEs (16% experienced TRAEs) [42]. TEAEs resulted in 7% of patients discontinuing treatment (3% discontinued treatment because of TRAEs). Serious grade 3 or 4 TEAEs occurred in 25% of patients, with 7% of patients considered to have treatment-related serious grade 3 or 4 adverse events. Of the 86 deaths deemed unrelated to disease progression, <1% (18 deaths) were attributed to drug-related adverse events. As is typically the case for EAP trials, only data for adverse events considered by investigators to be serious or clinically important were collected during this study; these data are discussed in Sect. 5.1 [42].

5.1 Adverse Events of Special Interest

TRAEs occurring during abiraterone acetate (+prednisone) therapy that were considered of special interest included cardiac disorders (ischemic heart disease, myocardial infarction, supraventricular arrhythmias, supraventricular or ventricular tachyarrhythmia, cardiac failure and possible arrhythmia-related investigations, signs or symptoms), hepatotoxicity (liver function test abnormalities), hypokalaemia, hypertension and fluid retention or oedema [47].

Some adverse events (hypertension, hypokalaemia and fluid retention or oedema) appear to be related to the mechanism of action of abiraterone acetate (Sect. 2), with coadministration of a corticosteroid reducing the incidence and severity of these adverse events [7]. In the integrated safety analysis, 0.2–0.7% of patients in each treatment group experienced serious mineralocorticoid adverse events; in general, mineralocorticoid adverse events (of any grade) were able to be successfully managed medically [47].

The mechanism of abiraterone acetate-induced hepatotoxicity is not yet understood [7]. Serious hepatotoxicity occurred in 1.1% of patients in the abiraterone acetate (+prednisone) group and 0.6% in the placebo (+prednisone) group; no patients in either treatment group died of hepatotoxic events [47].

Grade 3 or 4 [16] or grade 3 [20] adverse events of special interest that occurred in ≥2% of patients in either of the pivotal trials were cardiac disorders (6% in the abiraterone acetate (+prednisone) group vs. 3% in the placebo (+prednisone) group [16]; 4 vs. 2% [20]), increased ALT levels (5 vs. <1% [16]), abnormalities in liver function tests (4 and <1%) [20], hypertension (4 vs. 3% [16]), increased AST levels (3 vs. <1% [16]), hypokalaemia (2 vs. 2% [16]; 4 vs. <1%) and fluid retention or oedema (<1 vs. 2% [16]; 2 vs. 1% [20]).

In the EAP trial, the respective overall incidence of grade 3 and 4 adverse events of special interest was 15 and 1% [42]. Those of grade 3 severity were hepatotoxicity (8% of patients), hypertension (4%), cardiac disorders (2%), osteoporosis (1%), hypokalaemia (1%) and fluid retention or oedema (1%). Relatively few patients experienced grade 4 adverse events of special interest; the most common of these were hepatotoxicity (1%) and hypertension (1%) [42].

In an integrated analysis of pivotal phase 3 trials, cardiovascular (CV) adverse reactions occurring in the

abiraterone acetate (+prednisone) and placebo (+prednisone) group were hypertension (14.5 vs. 10.5% of patients), atrial fibrillation (3.4 vs. 3.4%), tachycardia (2.8 vs. 1.7%), angina pectoris (1.9 vs. 0.9%), cardiac failure (1.9 vs. 0.6%) and arrhythmia (1.1 vs. 0.4%) [47]. Both of these trials excluded patients with uncontrolled hypertension or clinically significant heart disease; all patients were concomitantly treated with androgen deprivation therapy, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death [47].

Indirect evidence from meta-analyses of randomized controlled trials indicated that the safety profile of abiraterone acetate (+prednisone) differed from that with enzalutamide (abstracts; no heterogeneity values were reported) [48, 49]. Abiraterone acetate (+prednisone) therapy was associated with an increased risk of CV events of any grade (RR 1.28; 95% CI 1.06–1.55) or grade ≥3 (RR 1.76; 95% CI 1.12–2.75), whereas there was no increase in risk of these events in enzalutamide recipients [49]. Conversely, abiraterone acetate (+prednisone) therapy was not associated with an increased risk of fatigue of any grade, whereas enzalutamide treatment was associated with an increased risk of these events (RR 1.29; 95% CI 1.15–1.44) [49]. The risk of hypertension was also lower with abiraterone acetate (+prednisone) therapy than with enzalutamide for events of any grade (RR 1.61 vs. 2.26) or of grade ≥3 (RR 1.72 vs. 2.52), as was the risk of developing neurological disorders of any grade (RR 1.13 vs. 1.44) or psychiatric disorders of any grade (RR 1.04 vs. 1.43) [48].

6 Dosage and Administration

In the EU [7], abiraterone acetate is indicated in combination with prednisone or prednisolone for the treatment of mCRPC in men who are asymptomatic or mildly symptomatic after failure of androgen deprivation in whom chemotherapy is not yet clinically indicated, and in men whose disease has progressed on or after docetaxel-based chemotherapy. In the USA [8], abiraterone acetate is indicated in combination with prednisone for the treatment of patients with mCRPC. In Japan [50], the drug is indicated in combination with prednisolone for the treatment of patients with mCRPC. The recommended dosage of abiraterone acetate is 1000 mg once daily, with the drug to be taken on an empty stomach [7, 8, 50]. The recommended dosage of prednisone or prednisolone is 10 mg/day [7, 8]. Local prescribing information should be consulted for detailed information, including contraindications, dose adjustments, monitoring requirements, precautions and use in special patient populations.

7 Place of Abiraterone Acetate in the Management of Metastatic Castration-Resistant Cancer

PC continues to pose a significant burden on healthcare systems globally, especially mCRPC [3]. Albeit docetaxel remains a first-line option for the management of mCRPC, an improved understanding of the pathogenesis of PC over the last decade has resulted in the emergence of several new targeted therapies, of which the most widely used are abiraterone acetate (+prednisone), cabazitaxel (next generation taxane), enzalutamide (AR antagonist) and radium-223 (bone-targeted) [51, 52]. As first-line treatment options for mCRPC, 2017 NCCN [52] and 2016 EU/international (EAU-ESTRO-SIOG) [51] guidelines recommend various treatment options, including abiraterone acetate (+prednisone or prednisolone), docetaxel, enzalutamide and radium-223 (for symptomatic bone metastases), with no specific recommendation for one agent over another. The choice for second-line therapy will be affected by that for first-line treatment [51, 52].

Over recent years, there has been an apparent shift in the treatment of mCRPC from docetaxel as first-line therapy (91% of patients in 2010 vs. 15% in 2013) to newer non-cytotoxic drugs [in 2013, 67% received abiraterone acetate (+prednisone) for first-line therapy and 9% received enzalutamide], according to a retrospective US database analysis ($n = 3437$) [53]. Based on other US database analyses, compliance and adherence to abiraterone acetate (+prednisone) therapy was high in an observational study [54] and abiraterone acetate (+prednisone) appeared to be approximately three times more likely to be administered as first-line therapy than enzalutamide (both with concomitant corticosteroid) in retrospective analyses [55]. Of note, these studies have several limitations that should be considered carefully when interpreting results, including the inherent limitations of database studies, retrospective design, limited follow-up of patients and the specificity of ICD-9-CM coding [53, 54].

Oral abiraterone (+prednisone) was an effective treatment in chemotherapy-naive (Sect. 4.1) and docetaxel-experienced (Sect. 4.2) men with mCRPC in large, multicentre, phase 3 trials, including in Asian patients, and in the real-world clinical practice setting (Sect. 4.3). In pivotal global phase 3 trials in chemotherapy-naive (Sect. 4.1.1) and docetaxel-experienced (Sect. 4.2.1) patients, relative to placebo (+ prednisolone), abiraterone acetate (+prednisone) significantly prolonged OS at the time of final analyses and significantly prolonged rPFS at all assessed timepoints. In chemotherapy-naive patients, abiraterone acetate (+prednisone) therapy also provided better efficacy than placebo (+prednisone) in terms of

other key outcomes, including the median time to opiate utilization for cancer pain, time to cytotoxic chemotherapy initiation, time to ECOG performance status decline of ≥1 and TTPP (Sect. 4.1.1). Similarly, other key outcomes favoured abiraterone acetate (+prednisone) therapy in docetaxel-experienced patients, including TTPP and PSA response rate (Sect. 4.2.1).

To date there have been no head-to-head trials comparing the efficacy of abiraterone acetate (+prednisone) to that of enzalutamide or the optimal sequencing of these two agents; such trials would be of interest in determining the relative position of these two drugs in mCRPC.

Abiraterone acetate, in combination with prednisone, had an acceptable tolerability profile in the clinical trial and real-world setting, with relatively few patients [≈5% in the abiraterone acetate and placebo groups (both +prednisone)] discontinuing treatment because of a TRAE in pivotal phase 3 trials and most adverse events were medically manageable (Sect. 5). The tolerability profile of abiraterone acetate (+prednisone) was generally consistent between men with mCRPC who were chemotherapy-naive and those who had previously received docetaxel; no new safety signals were identified in the EAP trial conducted in the real-world setting. In general, the adverse events of special interest that occurred in clinical trials and the EAP trial were consistent with the known tolerability profile of abiraterone acetate (+prednisone) [Sect. 5.1]. Preliminary evidence from meta-analyses suggest that abiraterone acetate (+prednisone) therapy is associated with a higher risk of CV adverse events than enzalutamide (no risk), but a lower risk of hypertension, and unlike enzalutamide, abiraterone acetate (+prednisone) is not associated with an increased risk of fatigue, neurological disorders and psychiatric disorders (Sect. 5.1).

Pharmacoeconomic issues are an important consideration in contemporary healthcare systems; however, an in-depth discussion of these issues is beyond the scope of this review. The UK NICE appraisals considered abiraterone acetate (+prednisone) to be a cost-effective treatment option in men with mCRPC who have no or mild symptoms after androgen deprivation therapy has failed, and before chemotherapy is indicted [56] and in men with mCRPC previously treated with a docetaxel-containing regimen [57].

In conclusion, in large phase 3 trials and in the clinical practice setting, oral abiraterone acetate in combination with prednisone was an effective treatment and had an acceptable, manageable tolerability and safety profile in chemotherapy-naive and docetaxel-experienced men with mCRPC. In the pivotal global phase 3 trials, relative to placebo (+prednisone), abiraterone acetate (+prednisone) prolonged OS at data maturity and rPFS at all assessed timepoints. Given its efficacy in prolonging OS and its convenient once-daily oral regimen, in combination with prednisone, abiraterone acetate is an important first-line option for the treatment of mCRPC.

Data Selection Abiraterone: 212 records identified

Duplicates removed	13
Excluded at initial screening (e.g. press releases; news reports; not relevant drug/indication)	43
Excluded during initial selection (e.g. preclinical study; reviews; case reports; not randomized trial)	43
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	56
Cited efficacy/tolerability articles	33
Cited articles not efficacy/tolerability	24

Search Strategy: EMBASE, MEDLINE and PubMed from 2013 to present. Previous Adis Drug Evaluation published in 2013 was hand-searched for relevant data. Clinical trial registries/databases and websites were also searched for relevant data. Key words were Zytiga, CB-7598, CB-7630, JNJ-212082, abiraterone, prostate, prostatic, castration-resistant, androgen-independent, androgen insensitive. Records were limited to those in English language. Searches last updated 7 August 2017

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Compliance with Ethical Standards

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References

1. World Cancer Research Fund International. Cancer facts and figures: worldwide data. 2012. http://www.wcrf.org. Accessed 6 Apr 2017.
2. Chandrasekar T, Yang JC, Gao AC, et al. Mechanisms of resistance in castration-resistant prostate cancer (CRPC). Transl Androl Urol. 2015;4(3):365–80.
3. Kapoor A, Wu C, Shayegan B, et al. Contemporary agents in the management of metastatic castration-resistant prostate cancer. Can Urol Assoc J. 2016;10(11–12):E414–23.
4. Tsao CK, Galsky MD, Small AC, et al. Targeting the androgen receptor signalling axis in castration-resistant prostate cancer (CRPC). BJU Int. 2012;110(11):1580–8.
5. Schweizer MT, Antonarakis ES. Abiraterone and other novel androgen-directed strategies for the treatment of prostate cancer: a new era of hormonal therapies is born. Ther Adv Urol. 2012;4(4):167–78.
6. Hoy SM. Abiraterone acetate: a review of its use in patients with metastatic castration-resistant prostate cancer. Drugs. 2013;73(18):2077–91.
7. European Medicines Agency. Zytiga 250 mg tablets: summary of product characteristics. 2017. http://www.ema.europa.eu/. Accessed 14 Jul 2017.

8. Janssen Biotech Inc. Zytiga® (abiraterone acetate) tablets: US prescribing information. 2016. https://www.zytiga.com/. Accessed 20 Mar 2017.
9. Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. Cancer Res. 2008;68(11):4447–54.
10. Lam H-M, McMullin R, Nguyen HM, et al. Characterization of an abiraterone ultraresponsive phenotype in castration-resistant prostate cancer patient-derived xenografts. Clin Cancer Res. 2016. doi:10.1158/1078-0432.CCR-16-2054.
11. Tolcher AW, Chi KN, Shore ND, et al. Effect of abiraterone acetate plus prednisone on the QT interval in patients with metastatic castration-resistant prostate cancer. Cancer Chemother Pharmacol. 2012;70(2):305–13.
12. Chi KN, Spratlin J, Kollmannsberger C, et al. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. J Clin Pharmacol. 2015;55(12):1406–14.
13. Inoue K, Shishido A, Vaccaro N, et al. Pharmacokinetics of abiraterone in healthy Japanese men: dose-proportionality and effect of food timing. Cancer Chemother Pharmacol. 2015;75(1):49–58.
14. Marbury T, Lawitz E, Stonerock R, et al. Single-dose pharmacokinetic studies of abiraterone acetate in men with hepatic or renal impairment. J Clin Pharmacol. 2014;54(7):732–41.
15. Chi KN, Tolcher A, Lee P, et al. Effect of abiraterone acetate plus prednisone on the pharmacokinetics of dextromethorphan and theophylline in patients with metastatic castration-resistant prostate cancer. Cancer Chemother Pharmacol. 2013;71(1):237–44.
16. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138–48.
17. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152–60.
18. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). Eur Urol. 2014;66(5):815–25.
19. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995–2005.
20. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983–92.
21. Ye D, Huang Y, Zhou F, et al. A phase 3, double-blind, randomized placebo-controlled efficacy and safety study of abiraterone acetate in chemotherapy-naïve patients with mCRPC in China, Malaysia, Thailand and Russia. Asian J Urol. 2017. doi:10.1016/j.ajur.2017.01.002.
22. Sun Y, Zou Q, Sun Z, et al. Abiraterone acetate for metastatic castration-resistant prostate cancer after docetaxel failure: a randomized, double-blind, placebo-controlled phase 3 bridging study. Int J Urol. 2016;23(5):404–11.
23. Morris MJ, Molina A, Small EJ, et al. Radiographic progression-free survival as a response biomarker in metastatic castration-resistant prostate cancer: COU-AA-302 results. J Clin Oncol. 2015;33(12):1356–63.
24. Attard G, de Bono JS, Logothetis CJ, et al. Improvements in radiographic progression-free survival stratified by *ERG* gene status in metastatic castration-resistant prostate cancer patients treated with abiraterone acetate. Clin Cancer Res. 2015;21(7):1621–7.
25. Basch E, Autio K, Ryan CJ, et al. Abiraterone acetate plus prednisone versus prednisone alone in chemotherapy-naive men with metastatic castration-resistant prostate cancer: patient-reported outcome results of a randomised phase 3 trial. Lancet Oncol. 2013;14(12):1193–9.
26. Cella D, Li S, Li T, et al. Repeated measures analysis of patient-reported outcomes in prostate cancer after abiraterone acetate. J Community Support Oncol. 2016;14(4):148–54.
27. Smith MR, Rathkopf DE, Mulders PF, et al. Efficacy and safety of abiraterone acetate in elderly (75 years or older) chemotherapy naive patients with metastatic castration resistant prostate cancer. J Urol. 2015;194(5):1277–84.
28. Bellmunt J, Kheoh T, Yu MK, et al. Prior endocrine therapy impact on abiraterone acetate clinical efficacy in metastatic castration-resistant prostate cancer: post-hoc analysis of randomised phase 3 studies. Eur Urol. 2016;69(5):924–32.
29. Saad F, Shore N, Van Poppel H, et al. Impact of bone-targeted therapies in chemotherapy-naive metastatic castration-resistant prostate cancer patients treated with abiraterone acetate: post hoc analysis of study COU-AA-302. Eur Urol. 2015;68(4):570–7.
30. de Bono JS, Smith MR, Saad F, et al. Subsequent chemotherapy and treatment patterns after abiraterone acetate in patients with metastatic castration-resistant prostate cancer: post hoc analysis of COU-AA-302. Eur Urol. 2017;71(4):656–64.
31. Xu XS, Ryan CJ, Stuyckens K, et al. Correlation between prostate-specific antigen kinetics and overall survival in abiraterone acetate-treated castration-resistant prostate cancer patients. Clin Cancer Res. 2015;21(14):3170–7.
32. Goodman OB Jr, Flaig TW, Molina A, et al. Exploratory analysis of the visceral disease subgroup in a phase III study of abiraterone acetate in metastatic castration-resistant prostate cancer. Prostate Cancer Prostatic Dis. 2014;17(1):34–9.
33. Mulders PFA, Molina A, Marberger M, et al. Efficacy and safety of abiraterone acetate in an elderly patient subgroup (aged 75 and older) with metastatic castration-resistant prostate cancer after docetaxel-based chemotherapy. Eur Urol. 2014;65(5):875–83.
34. Fizazi K, Flaig TW, Stockle M, et al. Does Gleason score at initial diagnosis predict efficacy of abiraterone acetate therapy in patients with metastatic castration-resistant prostate cancer? An analysis of abiraterone acetate phase III trials. Ann Oncol. 2016;27(4):699–705.
35. Scher HI, Heller G, Molina A, et al. Circulating tumor cell biomarker panel as an individual-level surrogate for survival in metastatic castration-resistant prostate cancer. J Clin Oncol. 2015;33(12):1348–55.
36. Montgomery B, Kheoh T, Molina A, et al. Impact of baseline corticosteroids on survival and steroid androgens in metastatic castration-resistant prostate cancer: exploratory analysis from COU-AA-301. Eur Urol. 2015;67(5):866–73.
37. Ryan CJ, Molina A, Li J, et al. Serum androgens as prognostic biomarkers in castration-resistant prostate cancer: results from an analysis of a randomized phase III trial. J Clin Oncol. 2013;31(22):2791–8.
38. Chi KN, Kheoh T, Ryan CJ, et al. A prognostic index model for predicting overall survival in patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate after docetaxel. Ann Oncol. 2016;27(3):454–60.
39. Logothetis CJ, Basch E, Molina A, et al. Effect of abiraterone acetate and prednisone compared with placebo and prednisone on pain control and skeletal-related events in patients with metastatic castration-resistant prostate cancer: exploratory analysis of data

from the COU-AA-301 randomised trial. Lancet Oncol. 2012;13(12):1210–7.
40. Sternberg CN, Molina A, North S, et al. Effect of abiraterone acetate on fatigue in patients with metastatic castration-resistant prostate cancer after docetaxel chemotherapy. Ann Oncol. 2013;24(4):1017–25.
41. Harland S, Staffurth J, Molina A, et al. Effect of abiraterone acetate treatment on the quality of life of patients with metastatic castration-resistant prostate cancer after failure of docetaxel chemotherapy. Eur J Cancer. 2013;49(17):3648–57.
42. Sternberg CN, Castellano D, Daugaard G, et al. Abiraterone acetate for patients with metastatic castration-resistant prostate cancer progressing after chemotherapy: final analysis of a multicentre, open-label, early-access protocol trial. Lancet Oncol. 2014;15(11):1263–8.
43. Houede N, Beuzeboc P, Gourgou S, et al. Abiraterone acetate in patients with metastatic castration-resistant prostate cancer: long term outcome of the Temporary Authorization for Use programme in France. BMC Cancer. 2015;15:222.
44. Van Praet C, Rottey S, Van Hende F, et al. Abiraterone acetate post-docetaxel for metastatic castration-resistant prostate cancer in the Belgian compassionate use program. Urol Oncol. 2016;34(6):254.e7–13.
45. Pilon D, Behl AS, Ellis LA, et al. Duration of treatment in prostate cancer patients treated with abiraterone acetate or enzalutamide. J Manag Care Spec Pharm. 2017;23(2):225–35.
46. Azad AA, Eigl BJ, Leibowitz-Amit R, et al. Outcomes with abiraterone acetate in metastatic castration-resistant prostate cancer patients who have poor performance status. Eur Urol. 2015;67(3):441–7.
47. European Medicines Agency. Zytiga-H-C-2321-II-0004-G: EPAR assessment report variation. 2013. http://www.ema.europa.eu. Accessed 14 Jul 2017.
48. Ruiz Gracia P, Dearden L, Antoni L, et al. Meta-analysis of randomized clinical trials in metastatic castration resistant prostate cancer: comparison of hypertension, neurological and psychiatric adverse events on enzalutamide and abiraterone acetate plus prednisone treatment [abstract no. 738P]. Ann Oncol. 2016;27(Suppl. 6).
49. Moreira RB, Debiasi M, Maluf F, et al. Differential side effects profile in mCRPC patients treated with abiraterone or enzalutamide: a meta-analysis of randomized controlled trials [abstract no. 73]. J Clin Oncol. 2016;34(2 Suppl.).
50. Janssen Pharma Co. Abiraterone acetate (Zaitiga®) 250 mg tablet: Japanese prescribing information. 2015. http://www.pmda.go.jp/. Accessed 21 May 2017.
51. Cornford P, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part II: treatment of relapsing, metastatic, and castration-resistant prostate cancer. Eur Urol. 2017;71(4):630–42.
52. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: prostate cancer. 2017. https://www.nccn.org. Accessed 20 Mar 2017.
53. Flaig TW, Potluri RC, Ng Y, et al. Treatment evolution for metastatic castration-resistant prostate cancer with recent introduction of novel agents: retrospective analysis of real-world data. Cancer Med. 2016;5(2):182–91.
54. Lafeuille MH, Grittner AM, Lefebvre P, et al. Adherence patterns for abiraterone acetate and concomitant prednisone use in patients with prostate cancer. J Manag Care Pharm. 2014;20(5):477–84.
55. Ellis LA, Lafeuille MH, Gozalo L, et al. Treatment sequences and pharmacy costs of 2 new therapies for metastatic castration-resistant prostate cancer. Am Health Drug Benefits. 2015;8(4):185–95.
56. Ramaekers BL, Riemsma R, Tomini F, et al. Abiraterone acetate for the treatment of chemotherapy-naive metastatic castration-resistant prostate cancer: an evidence Review Group Perspective of an NICE Single Technology Appraisal. Pharmacoeconomics. 2017;35(2):191–202.
57. National Institute for Health and Clinical Excellence. Abiraterone for castration-resistant metastatic prostate cancer previously treated with a docetaxel-containing regimen (NICE technology appraisal guidance 259). 2016. http://guidance.nice.org.uk/. Accessed 17 Jul 2017.