PRODUCT NAME

ZYTIGA® (abiraterone acetate) 250 mg tablets

DOSAGE FORMS AND STRENGTHS

Tablet

ZYTIGA tablets contain 250 mg of abiraterone acetate

White to off-white, oval tablets, debossed with AA250 on one side.

For excipients, see *PHARMACEUTICAL INFORMATION – List of Excipients*.

CLINICAL INFORMATION

Indications

ZYTIGA is indicated in combination with prednisone or prednisolone for the treatment of patients with metastatic castration resistant prostate cancer.

Dosage and Administration

Dosage

The recommended dosage of ZYTIGA is 1000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food. ZYTIGA should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ZYTIGA. The tablets should be swallowed whole with water (see *Pharmacokinetic Properties – Absorption*).

ZYTIGA is used with low-dose prednisone or prednisolone. The recommended dosage of prednisone or prednisolone is 10 mg daily.

Serum transaminases and bilirubin should be measured prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly (see *Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess and Hepatotoxicity and Hepatic impairment*).

Hepatic impairment

No dosage adjustment is necessary for patients with pre-existing mild hepatic impairment. There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. ZYTIGA should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk (see *Warnings and Precautions – Hepatotoxicity and Hepatic impairment* and *Pharmacokinetic Properties – Special Populations*). ZYTIGA should not be used in patients with severe hepatic impairment (see *Warnings and Precautions – Hepatotoxicity and Hepatic impairment* and *Pharmacokinetic Properties – Special Populations*).

For patients who develop hepatotoxicity during treatment with ZYTIGA (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases above 5 times the upper limit of normal or bilirubin increases above 3 times the upper limit of normal) treatment should be withheld immediately until liver function tests normalize (see *Warnings and Precautions – Hepatotoxicity and Hepatic impairment*). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablets) once daily. For patients being re-treated, serum transaminases and bilirubin should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, discontinue treatment with ZYTIGA. Reduced doses should not be taken with food (see *Dosage and Administration – Dosage*).

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, ZYTIGA should be discontinued and patients should not be re-treated with ZYTIGA.

Renal impairment

No dosage adjustment is necessary for patients with renal impairment (see *Pharmacokinetic Properties – Special Populations*).

Contraindications

Pregnancy

ZYTIGA is contraindicated in women who are or may potentially be pregnant (see *Pregnancy, Breast feeding and Fertility – Pregnancy*).

Warnings and Precautions

Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess

ZYTIGA may cause hypertension, hypokalemia and fluid retention (see *Adverse Reactions*) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see *PHARMACOLOGICAL PROPERTIES — Mechanism of action*). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia.

ZYTIGA should be used with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction (LVEF) <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 301) or NYHA Class II to IV heart failure (in Study 302) was not established (see *Adverse Reactions* and *PHARMACOLOGICAL PROPERTIES — Clinical Studies*). Before treatment with ZYTIGA, hypertension must be controlled and hypokalemia must be corrected. Blood pressure, serum potassium and fluid retention should be monitored at least monthly.

Hepatotoxicity and Hepatic impairment

Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies (see *Adverse Reactions*). Serum transaminase and bilirubin levels should be measured prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. If at any time the ALT or AST rises above 5 times the upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment with ZYTIGA should be interrupted immediately and liver function closely monitored.

Re-treatment with ZYTIGA may only take place after the return of liver function tests to the patient's baseline and at a reduced dose level (see *Dosage and Administration — Hepatic impairment*).

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, ZYTIGA should be discontinued and patients should not be re-treated with ZYTIGA.

There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. ZYTIGA should be used with caution in patients with moderate hepatic impairment only if the benefit clearly outweighs the possible risk (see *Dosage and Administration – Hepatic impairment* and *Pharmacokinetic Properties – Special Populations*). ZYTIGA should not be used in patients with severe hepatic impairment (see *Dosage and Administration – Hepatic impairment* and *Pharmacokinetic Properties – Special Populations*).

There have been rare post-marketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome (see *Adverse Reactions*).

Corticosteroid withdrawal and coverage of stress situations

Caution is advised and monitoring for adrenocortical insufficiency should occur if patients need to be withdrawn from prednisone or prednisolone. If ZYTIGA is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see *Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess*).

In patients on prednisone or prednisolone who are subjected to unusual stress, increased dosage of a corticosteroid may be indicated before, during and after the stressful situation.

Use with chemotherapy

The safety and efficacy of concomitant use of ZYTIGA with cytotoxic chemotherapy has not been established (see *PHARMACOLOGICAL PROPERTIES – Clinical studies*).

Interactions

Effect of food on abiraterone acetate

Administration of ZYTIGA with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of ZYTIGA given with food has not been established. **ZYTIGA must not be taken with food** (see *Dosage* and *Administration and Pharmacokinetic Properties – Absorption*).

Interactions with other drugs

Potential for other drugs to affect abiraterone exposures

In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampicin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC_∞ of abiraterone was decreased by 55%.

Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital) during treatment with ZYTIGA are to be avoided, or used with careful evaluation of clinical efficacy.

In a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Potential for ZYTIGA to affect exposures to other drugs

Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. In a clinical study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased by approximately 200%. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when ZYTIGA is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.

In the same study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10%, when pioglitazone was given together with a single dose of 1000 mg abiraterone acetate. Although these results indicate that no clinically meaningful increases in exposure are expected when ZYTIGA is combined with drugs that are predominantly eliminated by CYP2C8, patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA.

Pregnancy, Breast-feeding and Fertility

Pregnancy

ZYTIGA is contraindicated in women who are or may potentially be pregnant (see *Contraindications*).

There are no human data on the use of ZYTIGA in pregnancy and ZYTIGA is not for use in women of child-bearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the fetus (see

PHARMACOLOGICAL PROPERTIES – Mechanism of action and NON–CLINICAL INFORMATION – Reproductive Toxicology).

It is not known if abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of child-bearing potential, a condom is required along with another effective contraceptive method.

To avoid inadvertent exposure, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves.

Breast-feeding

ZYTIGA is not for use in women.

It is not known if either abiraterone acetate or its metabolites are excreted in human breast milk.

Effects on Ability to Drive and Use Machines

No studies on the effects of ZYTIGA on the ability to drive or use machines have been performed. It is not anticipated that ZYTIGA will affect the ability to drive and use machines.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of abiraterone acetate based on the comprehensive assessment of the available adverse event information. A causal relationship with abiraterone acetate cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common adverse reactions seen with ZYTIGA are peripheral edema, hypokalemia, hypertension, urinary tract infection, hematuria, aspartate aminotransferase increased, alanine aminotransferase increased, dyspepsia, and fractures.

ZYTIGA may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In clinical studies anticipated mineralocorticoid effects were seen more commonly in patients treated with ZYTIGA, versus patients treated with placebo: hypokalemia 21% versus 11%, hypertension 16% versus 11%, and fluid retention (peripheral edema) 26% versus 20%, respectively. In patients treated with ZYTIGA, grades 3 and 4 hypokalemia and grades 3 and 4 hypertension were observed in 4% and 2% of patients, respectively. Mineralocorticoid effects generally were able to be successfully managed

medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions (see *Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess*).

In studies of patients with metastatic advanced prostate cancer who were using a LHRH agonist, or were previously treated with orchiectomy, ZYTIGA was administered at a dose of 1000 mg daily in combination with low dose prednisone or prednisolone (10 mg daily).

Adverse reactions due to ZYTIGA that occurred at a rate of ≥ 1% (all grades) are shown in Table 1:

Table 1: Adverse Reactions Due to ZYTIGA in ≥ 1% of Patients in Clinical Studies[a]

	ZYTIGA 1000 mg daily with prednisone or prednisolone n=1680[b]		
System Organ Class Adverse Reaction	All grades %	Grade 3 %	Grade 4 %
General Disorders and Administration Site Conditions			
Edema peripheral	26	1	<1
Metabolism and Nutrition Disorders			
Hypokalemia	21	3	<1
Hypertriglyceridemia	2	<1	0
Infections and Infestations			
Urinary tract infection	12	2	<1
Hepatobiliary Disorders			
Alanine aminotransferase increased	7	2	<1
Aspartate aminotransferase increased	9	2	<1
Vascular Disorders			
Hypertension	16	2	0
Injury, poisoning and procedural complications			
Fractures[c]	7	2	<1
Cardiac Disorders			
Cardiac failure[d]	2	1	<1
Angina pectoris	2	<1	0
Arrhythmia	1	0	0
Atrial fibrillation	3	1	<1
Tachycardia	2	<1	0
Renal and urinary disorders			
Hematuria	9	1	0
Gastrointestinal Disorders			

Dyspepsia	7	0	0

[a] All patients were using an LHRH agonist or had undergone orchiectomy.
[b] n=patients assessed for safety.
[c] Fractures includes all fractures with the exception of pathological fracture.
[d] Cardiac failure includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased.

The adverse reaction, adrenal insufficiency, occurred in Phase 3 clinical studies at a rate of 0.5% in patients taking ZYTIGA and at a rate of 0.2% in patients taking placebo.

Cardiovascular effects

Both Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, NYHA Class III or IV heart failure (Study 301) or Class II to IV heart failure (Study 302) or cardiac ejection fraction measurement of < 50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominantly with the use of LHRH agonists, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the Phase 3 studies in patients taking ZYTIGA versus patients taking placebo were as follows: 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%.

Hepatotoxicity

Drug-associated hepatotoxicity with elevated ALT, aspartate transaminase (AST) and total bilirubin has been reported in patients treated with ZYTIGA. Across all clinical studies, liver function test elevations (ALT or AST increases of > 5X ULN or bilirubin increases > 1.5X ULN) were reported in approximately 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. In the 301 clinical study patients whose baseline ALT or AST was elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, ZYTIGA was withheld or discontinued. In two instances marked increases in liver function tests occurred (see *Warnings and Precautions – Hepatotoxicity and Hepatic impairment*). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6X ULN. Upon discontinuation of ZYTIGA, both patients had normalization of their liver function tests and one patient was re-treated with ZYTIGA without recurrence of the elevations. In Study 302, grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patients treated with ZYTIGA. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases and 1 with AST elevation approximately 3 weeks after the last dose of ZYTIGA). Treatment discontinuations due to ALT and AST increases were reported in 1.7% and 1.3% of patients treated with ZYTIGA and 0.2% and 0% of patients treated with placebo, respectively; no deaths were reported due to hepatotoxicity events.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests. In the 301 trial patients with baseline ALT and AST ≥ 2.5X ULN in the absence of liver metastases and > 5X ULN in the presence of liver metastases were excluded. In the 302 trial patients with liver metastases were not eligible and patients with baseline ALT and AST ≥ 2.5 X ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see *Dosage and Administration – Hepatic impairment*). Patients with elevations of ALT or AST > 20X ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity associated with ZYTIGA is not understood.

Post-marketing experience

Adverse reactions identified during the post-marketing experience based on spontaneous reports with ZYTIGA are described below. The frequencies are provided according to the following convention:

Uncommon ≥ 1/1000 and < 1/100, Rare ≥ 1/10000 and < 1/1000

System Organ Class: Respiratory, thoracic and mediastinal disorders

Rare: Allergic alveolitis

System Organ Class: Musculoskeletal and connective tissue disorders
Uncommon: Rhabdomyolysis, Myopathy
System Organ Class: Hepatobiliary disorders
Rare: Hepatitis fulminant, Acute hepatic failure

Overdose

Human experience of overdose with ZYTIGA is limited.

There is no specific antidote. In the event of an overdose, administration of ZYTIGA should be stopped and general supportive measures undertaken, including monitoring for arrhythmias. Liver function also should be assessed.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Other hormone antagonists and related agents, **ATC code**: L02BX03

Mechanism of action

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumor tissues. It catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals (see *Warnings and Precautions – Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess*).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with LHRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Treatment with ZYTIGA decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects

ZYTIGA decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH agonists alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. In a Phase 3 clinical study of patients who failed

prior chemotherapy with taxanes, 38% of patients treated with ZYTIGA, versus 10% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Use of Spironolactone

Patients in pivotal clinical trials with ZYTIGA were not allowed to use spironolactone as spironolactone binds to the androgen receptor and may increase PSA levels.

Clinical studies

The efficacy of ZYTIGA was established in two randomized placebo controlled multicenter Phase 3 clinical studies (Studies 301 and 302) of patients with metastatic castration resistant prostate cancer.

Study 302 enrolled patients who were asymptomatic or mildly symptomatic and had not received prior chemotherapy, whereas Study 301 enrolled patients who received prior chemotherapy containing a taxane. In both studies patients were using an LHRH agonist or were previously treated with orchiectomy. In the active treatment arms, ZYTIGA was administered at a dose of 1000 mg daily in combination with low dose prednisone or prednisolone 5 mg twice daily. Control patients received placebo and low dose prednisone or prednisolone 5 mg twice daily.

Because changes in PSA serum concentration do not always predict clinical benefit, in both studies patients were maintained on ZYTIGA until discontinuation criteria were met as specified for each study below.

Study 302 (asymptomatic or mildly symptomatic patients who did not receive prior chemotherapy)

In Study 302, (n=1088) the median age of enrolled patients was 71 years for patients treated with ZYTIGA plus prednisone or prednisolone and 70 years for patients treated with placebo plus prednisone or prednisolone. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients in both arms. Patients with visceral metastases were excluded. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours. In addition to the co-primary endpoint measures, benefit was also assessed using time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG performance score by ≥ 1 point and time to PSA progression based on Prostate Cancer Working Group-2 (PCWG2) criteria.

In the 302 study treatments were discontinued at the time of unequivocal clinical progression. Treatments could also be discontinued at the time of confirmed radiographic progression at the discretion of the investigator.

Radiographic progression free survival was assessed with the use of sequential imaging studies as defined by PCWG2 criteria (for bone lesions) and modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria (for soft tissue lesions). Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

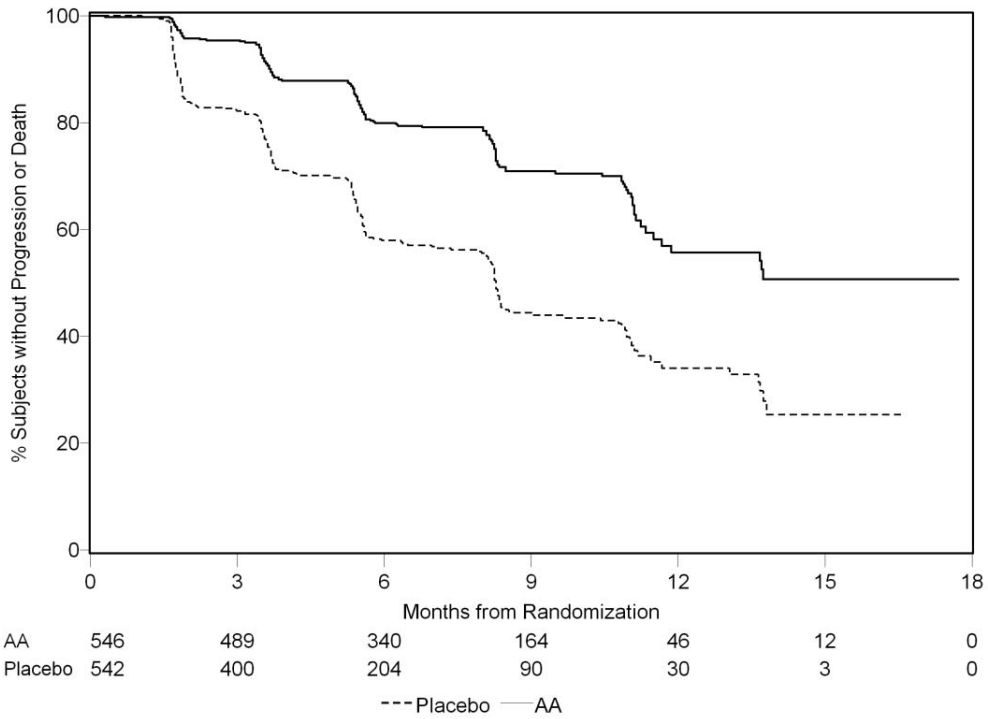
At the planned rPFS analysis there were 401 events; 150 (28%) of patients treated with ZYTIGA and 251 (46%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed (see Table 3 and Figure 1).

Table 1: Study 302: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone or Prednisolone Plus LHRH Agonists or Prior Orchiectomy

	ZYTIGA (N=546)	PLACEBO (N=542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median rPFS in months (95% CI)	Not reached (11.66, NE)	8.3 (8.12, 8.54)
p-value*	< 0.0001	
Hazard ratio** (95% CI)	0.425 (0.347, 0.522)	

NE = Not Estimated.
* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
**Hazard ratio (HR) < 1 favors ZYTIGA.

Figure 1: Kaplan Meier Curves of Radiographic Progression-free Survival in Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone or Prednisolone plus LHRH Agonists or Prior Orchiectomy



AA = ZYTIGA

However, subject data continued to be collected through the date of the second interim analysis of Overall survival (OS). The investigator radiographic review of rPFS performed as a follow up sensitivity analysis is presented in Table 4 and Figure 2.

Six hundred and seven (607) subjects had radiographic progression or died: 271 (50%) in the abiraterone acetate group and 336 (62%) in the placebo group. Treatment with abiraterone acetate decreased the risk of radiographic progression or death by 47% compared with placebo (HR = 0.530; 95% CI: [0.451, 0.623], p < 0.0001). The median rPFS was 16.5 months in the abiraterone acetate group and 8.3 months in the placebo group.

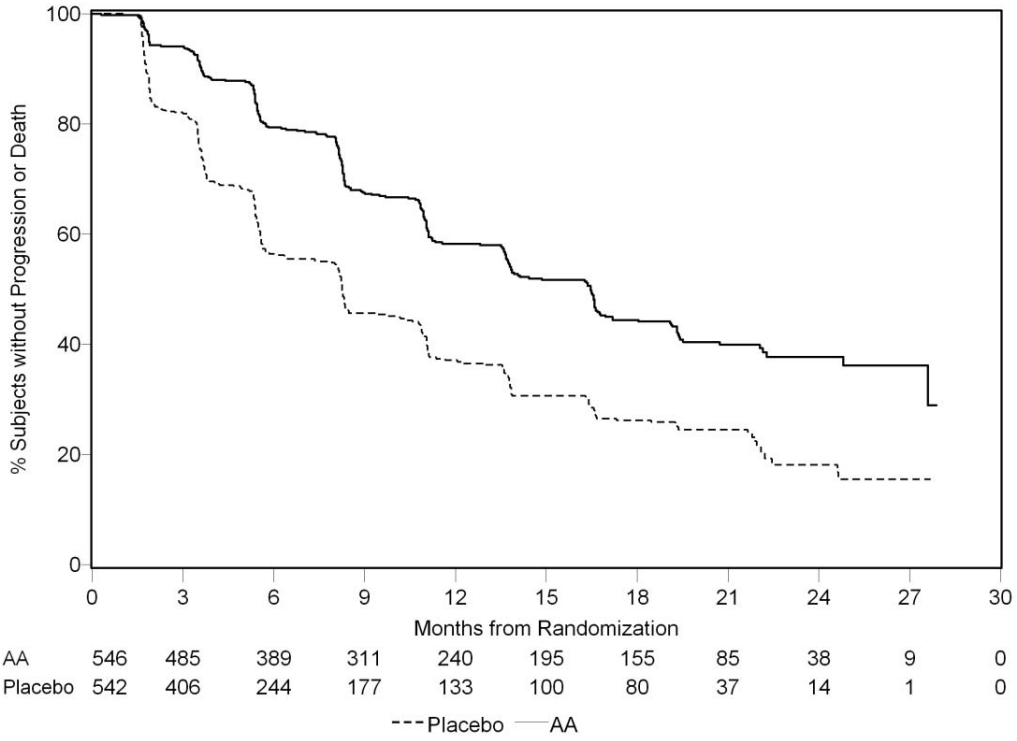
Table 2: Study 302: Radiographic progression-free survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS-Investigator Review)

	ZYTIGA (N=546)	PLACEBO (N=542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	271 (50%)	336 (62%)
Median rPFS in months (95% CI)	16.5 (13.80, 16.79)	8.3 (8.05, 9.43)

p-value*	< 0.0001
Hazard ratio** (95% CI)	0.530 (0.451, 0.623)

* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
**Hazard ratio < 1 favours ZYTIGA.

Figure 2: Kaplan Meier curves of radiographic progression free survival in patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH analogues or prior orchiectomy (At second interim analysis of OS Investigator Review)



AA = ZYTIGA

A planned interim analysis (IA) for overall survival was conducted after 333 deaths were observed. The study was unblinded based on the magnitude of clinical benefit observed and patients in the placebo group were offered treatment with ZYTIGA. Overall survival was longer for ZYTIGA than placebo with a 25% reduction in risk of death (HR = 0.752; 95% CI: [0.606, 0.934], p = 0.0097), but OS was not mature and interim results did not meet the pre-specified stopping boundary for statistical significance (see Table 5). Survival continued to be followed after this IA.

The planned final analysis for OS was conducted after 741 deaths were observed (median follow-up of 49 months). Sixty five percent (354 of 546) of patients treated with ZYTIGA, compared with 71% (387 of 542) of patients treated with placebo, had died. A statistically significant OS benefit in favor of the ZYTIGA-treated group was demonstrated with a 19.4% reduction in risk of death (HR = 0.806; 95% CI: [0.697, 0.931], p = 0.0033) and an improvement

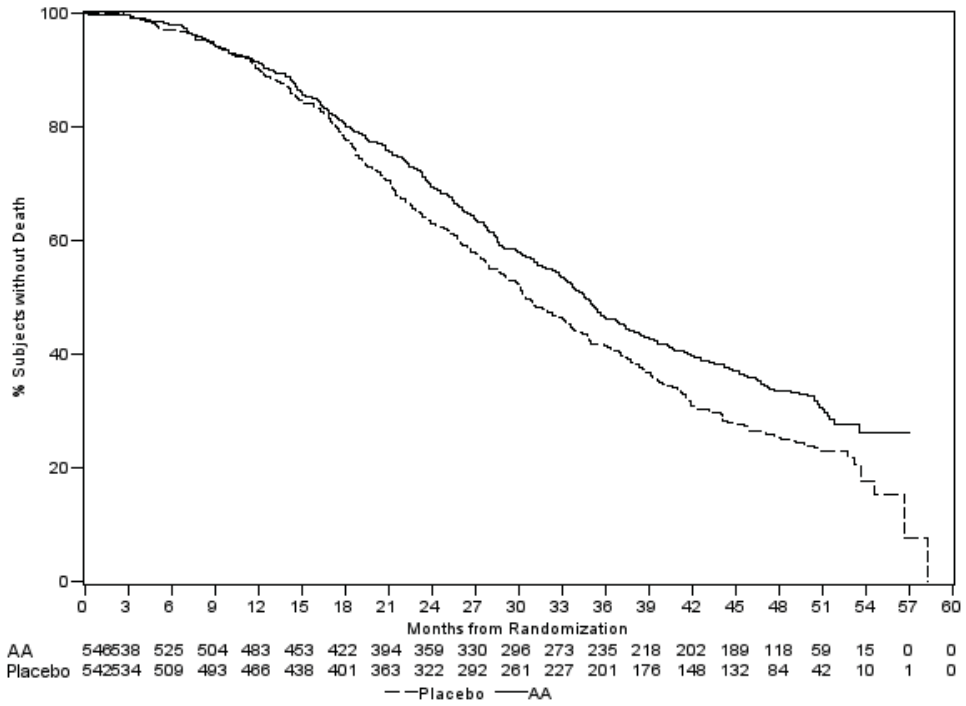
in median OS of 4.4 months (ZYTIGA 34.7 months, placebo 30.3 months) (see Table 5 and Figure 3). This improvement was demonstrated despite subsequent therapy being common, irrespective of whether patients initially received abiraterone acetate or placebo. Subsequent therapies in the abiraterone acetate and placebo patient groups included abiraterone acetate, 69 (13%) and 238 (44%); docetaxel, 311 (57%) and 331 (61%); cabazitaxel, 100 (18%) and 105 (19%); and enzalutamide 87 (16%) and 54 (10%) patients respectively.

Table 3: Study 302: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone or Prednisolone Plus LHRH Agonists or Prior Orchiectomy

	ZYTIGA (N=546)	PLACEBO (N=542)
Interim Survival Analysis		
Deaths	147 (27%)	186 (34%)
Median overall survival in months (95% CI)	Not reached (NE, NE)	27.2 (25.95, NE)
p-value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606, 0.934)	
Final Survival Analysis		
Deaths	354 (65%)	387 (71%)
Median overall survival in months (95% CI)	34.7 (32.7, 36.8)	30.3 (28.7, 33.3)
p-value*	0.0033	
Hazard ratio** (95% CI)	0.806 (0.697, 0.931)	

NE=Not Estimated.
* p-value is derived from a log-rank test stratified by baseline ECOG score (0 or 1).
**Hazard ratio < 1 favors ZYTIGA.

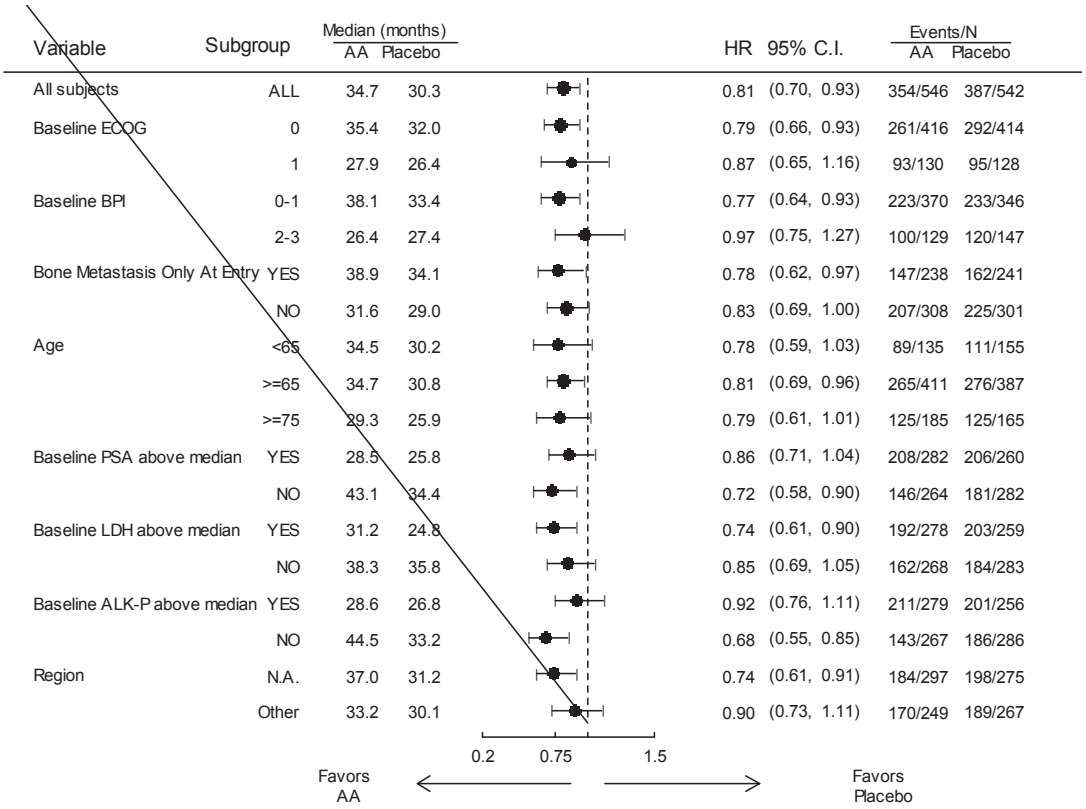
Figure 3: Kaplan Meier Survival Curves of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone or Prednisolone plus LHRH Agonists or Prior Orchiectomy, Final analysis



AA = ZYTIGA

Subgroup analyses consistently favor treatment with ZYTIGA (see Figure 4).

361 **Figure 4: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval**



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363 AA=ZYTIGA; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern
364 Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North
365 America; NE=not evaluable

366 In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated
367 for ZYTIGA vs. placebo treatment in all prospectively defined secondary endpoint measures as
368 follows:

369 **Time to PSA progression based on PCWG2 criteria:** The median time to PSA progression
370 was 11.1 months for patients receiving ZYTIGA and 5.6 months for patients receiving placebo
371 (HR = 0.488; 95% CI: [0.420, 0.568], $p < 0.0001$). The time to PSA progression was
372 approximately doubled with ZYTIGA treatment (HR = 0.488). The proportion of subjects with a
373 confirmed PSA response was greater in the ZYTIGA group than in the placebo group (62%
374 versus 24%; $p < 0.0001$).

375 **Time to opiate use for cancer pain:** The median time to opiate use for prostate cancer pain at
376 the time of final analysis was 33.4 months for patients receiving ZYTIGA and was 23.4 months
377 for patients receiving placebo (HR = 0.721; 95% CI: [0.614, 0.846], $p < 0.0001$).

Time to initiation of cytotoxic chemotherapy: The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving ZYTIGA and 16.8 months for patients receiving placebo (HR = 0.580; 95% CI: [0.487, 0.691], p < 0.0001).

Time to deterioration in ECOG performance score by ≥1 point: The median time to deterioration in ECOG performance score by ≥ 1 point was 12.3 months for patients receiving ZYTIGA and 10.9 months for patients receiving placebo (HR = 0.821; 95% CI: [0.714, 0.943], p = 0.0053).

The following study endpoints demonstrated a statistically significant advantage in favor of ZYTIGA treatment:

Objective response: Objective response was defined as the proportion of subjects with measurable disease achieving a complete or partial response according to RECIST criteria (baseline lymph node size was required to be ≥ 2 cm to be considered a target lesion). The proportion of subjects with measurable disease at baseline who had an objective response was 36% in the ZYTIGA group and 16% in the placebo group (p < 0.0001).

Pain: Treatment with ZYTIGA significantly reduced the risk of average pain intensity progression by 18% compared with placebo (p = 0.0490). The median time to progression was 26.7 months in the ZYTIGA group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score): Treatment with ZYTIGA decreased the risk of FACT-P (Total Score) degradation by 22% compared with placebo (p = 0.0028). The median time to degradation in FACT-P (Total Score) was 12.7 months in the ZYTIGA group and 8.3 months in the placebo group.

Study 301 (patients who had received prior chemotherapy)

Eleven percent of patients enrolled in Study 301 had an ECOG performance score of 2; 70% had radiographic evidence of disease progression with or without PSA progression; 70% had received one prior cytotoxic chemotherapy and 30% received two. Liver metastasis was present in 11% of patients treated with ZYTIGA.

It was recommended that patients be maintained on their study drugs until there was PSA progression (confirmed 25% increase over the patient's baseline/nadir) together with protocol-defined radiographic progression and symptomatic or clinical progression. The primary efficacy endpoint was overall survival.

In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with ZYTIGA, compared with 55% (219 of 398) of patients treated with placebo, had died. A statistically significant improvement in median overall survival was seen in patients

411 treated with ZYTIGA (see Table 6 and Figure 5). An updated survival analysis was conducted
412 when 775 deaths (97% of the planned number of deaths for the final analysis) were observed.
413 Results from this updated survival analysis were consistent with those in the primary survival
414 analysis (see Table 6).

Table 4: Study 301: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone or Prednisolone Plus LHRH Agonists or Prior Orchiectomy

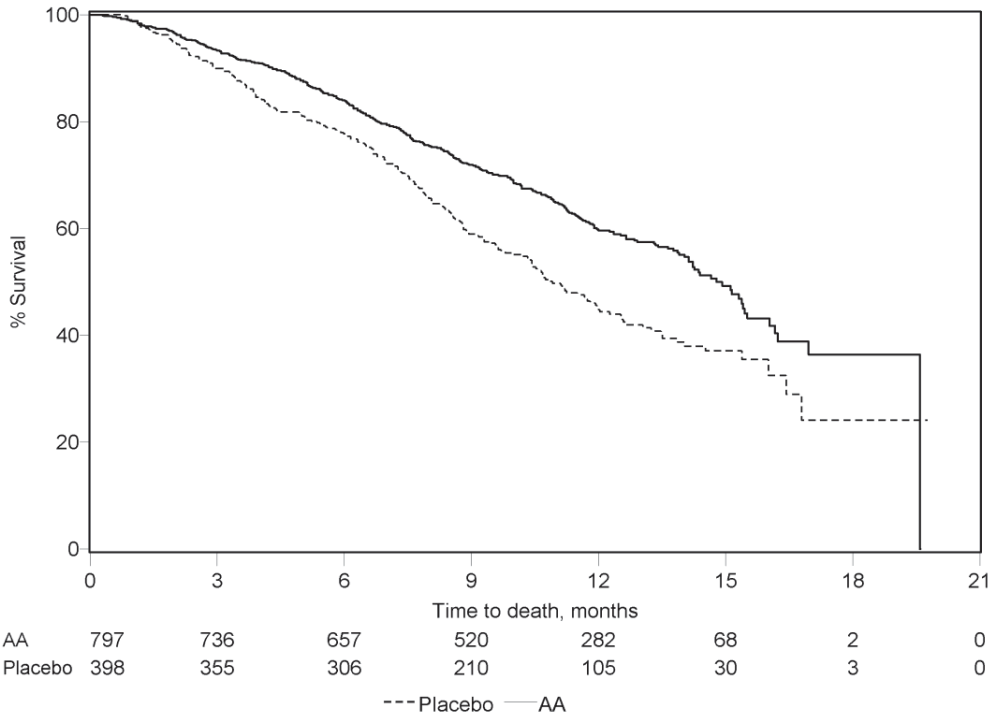
	ZYTIGA (N=797)	PLACEBO (N=398)
Primary Survival Analysis		
Deaths	333 (42%)	219 (55%)
Median overall survival in months (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p-value	< 0.0001	
Hazard ratio* (95% CI)	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths	501 (63%)	274 (69%)
Median overall survival in months (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio* (95% CI)	0.740 (0.638, 0.859)	

* Hazard ratio < 1 favors ZYTIGA.

415
416 At all evaluation time points after the initial few months of treatment, a higher proportion of
417 patients treated with ZYTIGA remained alive, compared with the proportion of patients treated
418 with placebo (see Figure 5).

419

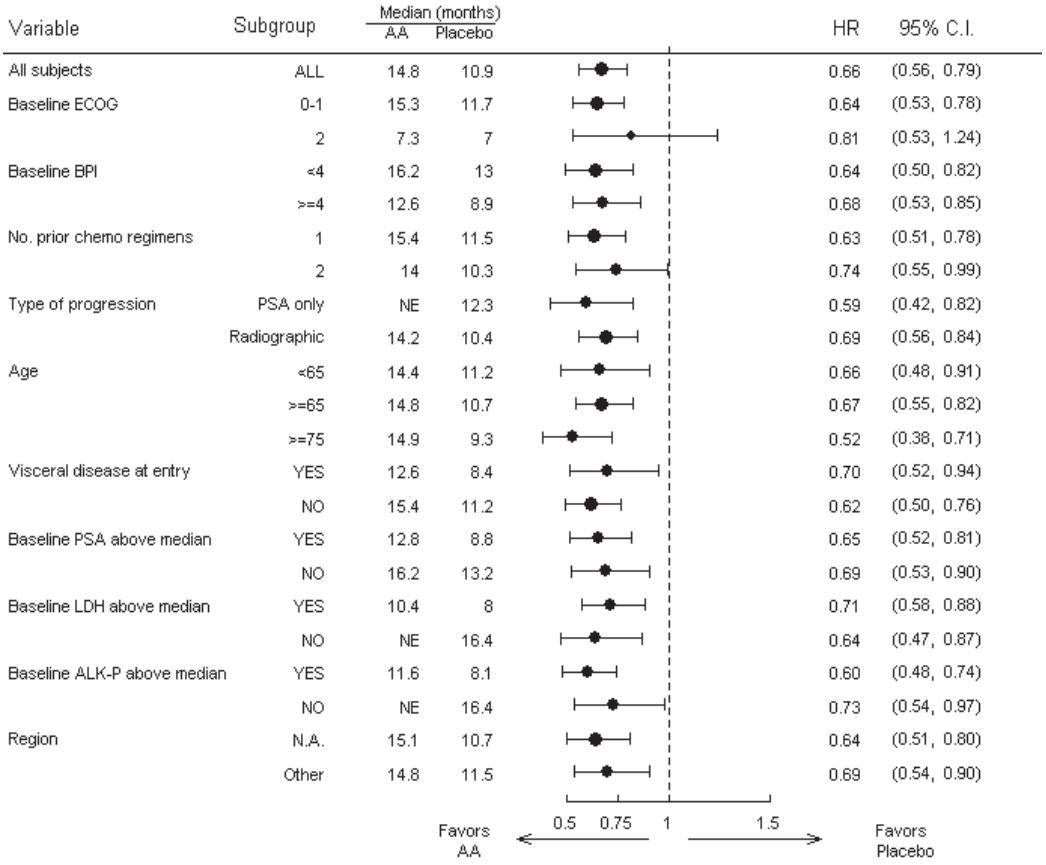
Figure 5: Kaplan Meier Survival Curves of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone or Prednisolone plus LHRH Agonists or Prior Orchiectomy



AA = ZYTIGA

Subgroup survival analyses showed a consistent survival benefit for treatment with ZYTIGA (see Figure 6).

Figure 6: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval



AA=ZYTIGA; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable

In addition to the observed improvement in overall survival, all secondary study endpoints favored ZYTIGA and were statistically significant after adjusting for multiple testing as follows:

Patients receiving ZYTIGA demonstrated a significantly higher total PSA response rate (defined as a $\geq$ 50% reduction from baseline), compared with patients receiving placebo: 38% versus 10%, $p < 0.0001$.

The median time to PSA progression was 10.2 months for patients treated with ZYTIGA and 6.6 months for patients treated with placebo (HR = 0.580; 95% CI: [0.462, 0.728], $p < 0.0001$).

The median radiographic progression-free survival was 5.6 months for patients treated with ZYTIGA and 3.6 months for patients who received placebo (HR = 0.673; 95% CI: [0.585, 0.776], $p < 0.0001$).

Pain

The proportion of patients with pain palliation was statistically significantly higher in the ZYTIGA group than in the placebo group (44% versus 27%, p = 0.0002). A responder for pain palliation was defined as a patient who experienced at least a 30% reduction from baseline in the BPI-SF worst pain intensity score over the last 24 hours without any increase in analgesic usage score observed at two consecutive evaluations four weeks apart. Only patients with a baseline pain score of ≥ 4 and at least one post-baseline pain score were analyzed (n=512) for pain palliation.

A lower proportion of patients treated with ZYTIGA had pain progression compared to patients taking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 46%). Pain progression was defined as an increase from baseline of ≥ 30% in the BPI-SF worst pain intensity score over the previous 24 hours without a decrease in analgesic usage score observed at two consecutive visits, or an increase of ≥ 30% in analgesic usage score observed at two consecutive visits. The time to pain progression at the 25th percentile was 7.4 months in the ZYTIGA group, versus 4.7 months in the placebo group.

Skeletal-Related Events

A lower proportion of patients in the ZYTIGA group had skeletal-related events compared with the placebo group at 6 months (18% vs. 28%), 12 months (30% vs. 40%), and 18 months (35% vs. 40%). The time to first skeletal-related event at the 25th percentile in the ZYTIGA group was twice that of the control group at 9.9 months vs. 4.9 months. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

Pharmacokinetic Properties

General Introduction

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor (see *PHARMACOLOGICAL PROPERTIES – Mechanism of action*).

Absorption

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 17-fold increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in highly variable exposures. Therefore, **ZYTIGA must not be taken with food.** ZYTIGA should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ZYTIGA. The tablets should be swallowed whole with water (see *Dosage and Administration*).

Distribution and protein binding

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Metabolism

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represent approximately 43% of total radioactivity.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Special populations

Renal impairment

The pharmacokinetics of abiraterone was compared in patients with end-stage renal disease on a stable hemodialysis schedule, versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1000 mg dose did not increase in patients with end-stage renal disease on dialysis.

Administration of ZYTIGA in patients with renal impairment including severe renal impairment does not require dose reduction (see *Dosage and Administration*).

Hepatic impairment

The pharmacokinetics of abiraterone was examined in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral 1000 mg dose increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. No dosage adjustment is necessary for patients with pre-existing mild hepatic impairment. There are no data on the clinical safety and efficacy of multiple doses of abiraterone acetate when administered to patients with moderate or severe hepatic impairment (Child Pugh Class B or C). No dose adjustment can be predicted. ZYTIGA should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk (see *Dosage and Administration – Hepatic impairment and Warnings and Precautions – Hepatotoxicity and Hepatic impairment*). ZYTIGA should not be used in patients with severe hepatic impairment. For patients who develop hepatotoxicity during treatment with ZYTIGA suspension of treatment and dosage adjustment may be required (see *Dosage and Administration – Hepatic impairment and Warnings and Precautions – Hepatotoxicity and Hepatic impairment*).

Effects on the QT interval

In a cardiovascular safety study in patients with metastatic advanced prostate cancer there were no significant effects of abiraterone acetate on the cardiac QT/QTc interval.

NON-CLINICAL INFORMATION

Carcinogenicity and Mutagenicity

Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone and rat specific. Abiraterone acetate was not carcinogenic in female rats.

Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of genotoxicity tests, including an *in vitro* bacterial reverse mutation assay (the Ames test), an *in vitro* mammalian chromosome aberration test (using human lymphocytes) and an *in vivo* rat micronucleus assay.

Reproductive Toxicology

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced fetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate was not teratogenic.

In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone.

ZYTIGA is contraindicated in pregnancy (see *Contraindications – Pregnancy* and *Pregnancy, Breast-feeding and Fertility – Pregnancy*).

Animal Toxicology

In all animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period.

After chronic treatment from 13 weeks onward, bile duct/oval cell hyperplasia, associated with increased serum alkaline phosphatase and/or total bilirubin levels, was seen in rat and monkey livers. After a 4-week recovery period, serum parameters reversed, whereas bile duct/oval cell hyperplasia persisted.

Cataracts were seen in rats after 26 weeks of treatment. These changes were still present after a 4-week recovery period. Cataracts were not seen in monkeys after 39 weeks of treatment.

PHARMACEUTICAL INFORMATION

List of Excipients

ZYTIGA tablets contain the following excipients:

colloidal silicon dioxide

croscarmellose sodium

lactose monohydrate

magnesium stearate

microcrystalline cellulose

povidone

sodium lauryl sulfate

Incompatibilities

Not applicable

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Keep out of the sight and reach of children.

Nature and Contents of Container

ZYTIGA is available in high-density polyethylene round white bottles fitted with a polypropylene cap. Package size is 120 tablets.

Instructions for Use and Handling and Disposal

Based on its mechanism of action, ZYTIGA may harm a developing fetus; therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves (see *Pregnancy, Breast-feeding and Fertility – Pregnancy*).

Any unused product or waste material should be disposed of in accordance with local requirements.