NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Abiraterone Devatis 500 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Abiraterone Devatis tablets contain 500 mg of abiraterone acetate.

Excipients with known effects:

Sugars as lactose monohydrate.
Each 500 mg film-coated tablet contains 253.2 mg of lactose monohydrate and 11.76 mg of sodium.

For the full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

Abiraterone Devatis 500 mg film coated tablets are purple coloured, oval, biconvex film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Abiraterone Devatis is indicated in combination with prednisone or prednisolone and androgen deprivation therapy (ADT) for the treatment of high-risk metastatic hormone naïve prostate cancer (mHNPC) or newly diagnosed high-risk metastatic hormone sensitive prostate cancer (mHSPC)

Abiraterone Devatis is also indicated with prednisone or prednisolone for:

- the treatment of patients with metastatic castration resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated (see **Clinical Trials** section).
- the treatment of patients with metastatic advanced prostate cancer (castration resistant prostate cancer, mCRPC) who have received prior chemotherapy containing a taxane.

4.2 Dose and method of administration

The recommended dosage of Abiraterone Devatis is 1000 mg (two 500 mg tablets) as a single daily dose that **must not be taken with food**. Abiraterone Devatis tablets must be taken as a single dose once daily on an empty stomach. Abiraterone Devatis must be taken at least two hours after eating and food must not be eaten for at least one hour after taking Abiraterone Devatis. The tablets must be swallowed whole with water (see **section 5.2 – Absorption).**

Dosage of prednisone or prednisolone

For metastatic hormone naïve prostate cancer (mHNPC) or hormone sensitive prostate cancer (mHSPC), Abiraterone Devatis is used with 5 mg prednisone or prednisolone daily. (see **section 4.4 - Corticosteroid withdrawal and coverage of stress situations**)

For metastatic castration-resistant prostate cancer (mCRPC), Abiraterone Devatis is used with 10 mg prednisone or prednisolone daily. (see **section 4.4 - Corticosteroid withdrawal and coverage of stress situations**)
Recommended monitoring

Serum transaminases and bilirubin should be measured prior to starting treatment with Abiraterone Devatis, 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 **section 4.4**).

Patients started on Abiraterone Devatis who were receiving a LHRH agonist should continue to receive a LHRH agonist.

Special populations

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 when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. Abiraterone Devatis should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk (see **section 4.4 – Hepatotoxicity and Hepatic Impairment** and **section 5.2 – Hepatic Impairment**). Abiraterone Devatis should not be used in patients with pre-existing moderate or severe hepatic impairment. For patients who develop hepatotoxicity during treatment with abiraterone (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 normalise (see **section 4.4**). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (one 500 mg tablet) 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 Abiraterone Devatis. Reduced doses should not be taken with food.

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

Renal impairment

No dosage adjustment is necessary for patients with renal impairment.

4.3 Contraindications

Abiraterone Devatis is contraindicated in women who are or may potentially be pregnant.

4.4 Special warnings and precautions for use

Hypertension, hypokalaemia and fluid retention due to mineralocorticoid excess

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The safety of abiraterone 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 studies 3011 and 302) was not established. Before treatment with abiraterone, hypertension must be controlled and hypokalaemia must be corrected.

Abiraterone may cause hypertension, hypokalaemia and fluid retention (see **section 4.8**) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see **section 5.1**). 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, hypokalaemia or fluid retention, e.g. those with heart failure, recent myocardial infarction

or ventricular arrhythmia. In postmarketing experience, QT prolongation and Torsades de Pointes have been observed in patients who develop hypokalaemia or have underlying cardiovascular conditions while taking abiraterone.

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 **section 4.8**). Very rarely hepatitis fulminant and hepatic failure has been seen. Serum transaminase and bilirubin levels should be measured prior to starting treatment with abiraterone, 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 abiraterone should be interrupted immediately and liver function closely monitored.

Re-treatment with Abiraterone Devatis may only take place after the return of liver function tests to the patient's baseline and at a reduced dose level (see **section 4.2**).

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

There are no data on the clinical safety and efficacy of multiple doses of abiraterone when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. Abiraterone Devatis should be used with caution in patients with moderate hepatic impairment only if the benefit clearly outweighs the possible risk. Abiraterone Devatis should not be used in patients with severe hepatic impairment (see sections **section 4.2 – Hepatic impairment** and **5.2 – Special Populations**).

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 abiraterone is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of 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. 17α hydroxylase inhibition by abiraterone decreases glucocorticoid production.

Hypoglycaemia

Isolated cases of hypoglycaemia have been reported when abiraterone plus prednisone/ prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see **INTERACTIONS – Interactions with other drugs – Potential for abiraterone to affect exposures to other drugs**). Blood glucose should be monitored in patients with diabetes.

Use with chemotherapy

The safety and efficacy of concomitant use of abiraterone with cytotoxic chemotherapy has not been established.

Use in combination with radium 223 dichloride

In a randomised clinical trial in patients with asymptomatic or mildly symptomatic bone-predominant

metastatic castration resistant prostate cancer, at the time of unblinding, the addition of radium 223 dichloride to abirateroneplus prednisone/prednisolone showed an increase in mortality and an increased rate of fracture. Radium 223 dichloride is not recommended for use in combination with abiraterone plus prednisone/prednisolone outside of clinical trials.

4.5 Interaction with other medicines and other forms of interaction

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. In a clinical study to determine the effects of abiraterone (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

In the same study to determine the effects of abiraterone (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 200%. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when abiraterone is administered with drugs activated by or metabolised by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolised by CYP2D6 should be considered. There are no clinical data on the use of abiraterone with drugs that are substrates of CYP2C8.

Abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been investigated. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution.

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 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 abiraterone are to be avoided, or used with careful evaluation of clinical efficacy.

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

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. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with abiraterone Examples of medicinal products metabolized by CYP2C8 include pioglitazone and repaglinide (see **WARNINGS AND PRECAUTIONS – Hypoglycaemia**).

4.6 Fertility, pregnancy and lactation

Pregnancy

Category D

Abiraterone Devatis is contraindicated in women who are or may potentially be pregnant (see **section 4.3**).

There are no human or animal data on the use of abiraterone in pregnancy and abiraterone 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 foetus.

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 Abiraterone Devatis without protection, e.g. gloves.

Breast-feeding

Abiraterone Devatis is not for use in women.
It is not known if either abiraterone or its metabolites are excreted in human breast milk.

Fertility

See **section 5.3**.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Adverse Drug Reactions from Clinical Trials

In an analysis of adverse reactions of composite Phase 3 studies with abiraterone, adverse reactions that were observed in ≥ 10% of patients were peripheral oedema, hypokalaemia, urinary tract infection and alanine aminotransferase increased and/or aspartate aminotransferase increased.

Abiraterone may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In Phase 3 studies anticipated mineralocorticoid effects were seen more commonly in patients treated with abiraterone versus patients treated with placebo; hypokalaemia 18% versus 8%, hypertension 22% versus 16% and fluid retention (peripheral oedema) 23% versus 17%, respectively. In patients treated with abiraterone versus patients treated with placebo, grades 3 and 4 hypokalaemia were observed in 6% and 1% of patients, grades 3 and 4 hypertension were observed in 7% and 5%, and grades 3 and 4 fluid retention oedema were observed in 1% and 1% 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 drug reactions (see **section 4.4**).

In a Phase 3 study of patients with newly diagnosed high-risk mHNPC or mHSPC (Study 3011) who were receiving and remained on ADT (a luteinising hormone-releasing hormone [LHRH] agonist or orchiectomy), abiraterone was administered at a dose of 1000 mg daily in combination with low dose prednisone (5 mg daily) and ADT in the active treatment arm; ADT and placebo were given to control patients. The median duration of treatment with abiraterone was 24 months.

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

Table 1: Adverse Reactions in ≥ 1% of Patients in Study 3011a

	Abiraterone 1000 mg daily with prednisone and ADT n=597[b]			Placebos and ADT n=602[b]		
System Organ Class Adverse Reaction	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Metabolism and Nutrition Disorders						
Hypokalaemia	20.4%	9.5%	0.8%	3.7%	1.2%	0.2%
Vascular Disorders						
Hypertension	36.7%	20.3%	0%	22.1%	9.8%	0.2%

[a] All patients were receiving an LHRH agonist or had undergone orchiectomy.
[b] n=patients assessed for safety.

In a Phase 3 study of patients with metastatic castrate resistant prostate cancer who had received prior chemotherapy (study 301) who were using a LHRH agonist, or were previously treated with orchiectomy, abiraterone was administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone (10 mg daily) in the active treatment arm; placebo plus low dose prednisone or prednisolone (10 mg daily) was given to control patients. Patients were intolerant to or had failed up to two prior chemotherapy regimens, one of which contained a taxane. The average duration of treatment with abiraterone was 8 months.

Adverse drug reactions that occurred at a rate of ≥1% (all grades) are shown in **Table 2**.

Table 2: Adverse drug reactions due to abiraterone in ≥1% of patients in a phase three study (Study 301)[a]

	Abiraterone 1000 mg daily with prednisone or prednisolone (10 mg) n=791[b]			Placebo with prednisone or prednisolone (10 mg) n=394[b]		
System Organ Class Adverse Drug Reaction	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
General Disorders and Administration Site Conditions						
Oedema peripheral	25	1	<1	17	1	0
Metabolism and Nutrition Disorders						
Hypokalaemia	17	3	<1	8	1	0
Hypertriglyceridaemia	1	<1	0	0	0	0
Infections and Infestations						
Urinary tract infection	12	2	0	7	1	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	3	1	0	1	<1	<1
Vascular Disorders						
Hypertension	9	1	0	7	<1	0
Injury, poisoning and procedural complications						
Fractures	6	1	<1	2	0	0
Cardiac Disorders						

Cardiac failure[c]	2	2	<1	1	0	<1
Angina pectoris	1	<1	0	1	0	0
Arrhythmia	1	0	0	0	0	0
Atrial fibrillation	2	1	0	1	1	0
Tachycardia	3	0	0	2	0	0

[a] All patients were receiving an LHRH agonist or had undergone orchiectomy.
[b] n = patients assessed for safety
[c] Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased

In a second placebo-controlled, multicenter phase 3 clinical study (study 302), in asymptomatic or mildly symptomatic, chemotherapy naïve patients with metastatic advanced prostate cancer who were using a LHRH agonist or were previously treated with orchiectomy, abiraterone was also administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone 10 mg daily in the active treatment arm. Placebo plus low dose prednisone or prednisolone 10 mg daily was given to control patients. The average duration of treatment with abiraterone in study 302 was 13.8 months.

Adverse drug reactions that occurred at a rate of ≥1% (all grades) are shown in **Table 3**.

Table 3: Adverse drug reactions due to abiraterone in ≥1% of patients in a phase three study (Study 302)[a]

	Abiraterone 1000 mg daily with prednisone or prednisolone (10 mg) n=542[b]			Placebo with prednisone or prednisolone (10 mg) n=540[b]		
System Organ Class Adverse Drug Reaction	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
Gastrointestinal Disorders						
Dyspepsia	11	0	0	5	<1	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	12	5	1	5	1	<1
Aspartate aminotransferase increased	11	3	0	5	1	0
Renal and Urinary Disorders						
Haematuria	10	1	0	6	1	0

[a] All patients were using an LHRH agonist or had undergone orchiectomy.
[b] n = patients assessed for safety

The most common adverse drug reactions that resulted in drug discontinuation in combined data from Phase 3 studies were alanine aminotransferase increased, aspartate aminotransferase increased and hypokalaemia (each in <1% of patients taking abiraterone).

The adverse drug reaction, adrenal insufficiency, occurred in the Phase 3 clinical studies at a rate 0.3% in patients taking abiraterone and at a rate of 0.1% inpatients taking placebo.

In the Phase 3 studies, 70% of patients were 65 years and over, and 27% were 75 years and over for patients taking abiraterone. No overall differences in safety were observed between these elderly patients and younger patients.

Cardiovascular effects

The three 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, or NYHA Class III or IV heart failure (study 301) or Class II to IV heart failure (studies 3011 and 302) or cardiac ejection fraction measurement of <50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominately 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 abiraterone versus patients taking placebo were as follows: atrial fibrillation 2.6% vs. 2.0%, tachycardia 1.9% vs. 1.0%, angina pectoris 1.7% vs. 0.8%, cardiac failure 0.7% vs. 0.2% and arrhythmia 0.7% vs. 0.5%.

Hepatotoxicity

Drug-associated hepatotoxicity with elevated ALT, AST and total bilirubin has been reported in patients treated with abiraterone. Across Phase 3 clinical studies, hepatotoxicity grades 3 and 4 (e.g. ALT or AST increases of > 5 X ULN or bilirubin increases > 1.5 X ULN) were reported in approximately 6% of patients who received abiraterone, typically during the first 3 months after starting treatment. In Study 3011, grade 3 or 4 hepatotoxicity was observed in 8.4% of patients treated with abiraterone. Ten patients who received abiraterone were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011. In the 301 clinical study, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5 X ULN, or elevations in bilirubin > 3 X ULN were observed, abiraterone was withheld or discontinued. Hepatic metastases and baseline elevations in alkaline phosphatase associated with prostate cancer were present in a few of these patients. In two instances marked increases in liver function tests occurred (see **section 4.4**). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of abiraterone, both patients had normalisation of their liver function tests and one patient was re-treated with abiraterone 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 abiraterone. 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 abiraterone). In Phase 3 clinical studies, treatment discontinuations due to ALT and AST increases or abnormal hepatic function were reported in 1.1% of patients treated with abiraterone and 0.6% of patients treated with placebo. 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 3011 trial, patients with baseline ALT and AST > 2.5 X ULN, bilirubin > 1.5 X ULN or those with active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction were excluded. 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 **section 4.2**). 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 abiraterone is not understood.

Post-marketing experience

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

Very common ≥ 1/10; 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 Gastrointestinal Disorders

Very common: Diarrhoea

System Organ Class: Hepatobiliary Disorders

Very rare: Hepatitis fulminant, hepatic failure

System Organ Class: Cardiac disorders

Very rare: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalaemia or had underlying cardiovascular conditions).

System Organ Class: Immune System Disorders – Hypersensitivity

Very rare: Anaphylactic reaction (severe allergic reactions that include, but are not limited to difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash (urticaria))

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https//nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Human experience of overdose with abiraterone is limited.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: endocrine therapy, other hormone antagonists and related agents,
ATC code: L02BX03

Mechanism of action

Abiraterone acetate (Abiraterone Devatis) 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 in prostatic tumour tissues. It catalyses 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 **section 4.4**).

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

Use of Spironolactone

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

Pharmacodynamic effects

Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH agonists alone or by orchiectomy. 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, 29% of patients treated with abiraterone, versus 6% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Effects on the QT interval

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

Clinical trials

The efficacy of abiraterone was established in three randomised placebo controlled multicenter Phase 3 clinical studies (studies 3001, 301 and 302) of patients with hormone naïve metastatic prostate cancer and metastatic castration resistant prostate cancer.

Study 3011 enrolled patients who were newly diagnosed (within 3 months of randomisation) mHNPC who had high-risk prognostic factors. High-risk prognosis was defined as having at least 2 of the following 3 risk factors: (1) Gleason score of ≥8; (2) presence of 3 or more lesions on bone scan; (3) presence of measurable visceral (excluding lymph node disease) metastasis. In the active arm, abiraterone was administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone 5 mg once daily in addition to ADT (LHRH agonist or orchiectomy), which was the standard of care treatment. Patients in the control arm received ADT and placebos for both abiraterone and prednisone.

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 a LHRH agonist or were previously treated with orchiectomy. In the active treatment arms, abiraterone 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 all studies patients were maintained on abiraterone until specific discontinuation criteria were met for each study below.

Study 3011 (patients with newly diagnosed high-risk metastatic hormone naïve prostate cancer (mHNPC) or hormone sensitive prostate cancer (mHSPC)

In Study 3011, (n=1199) the median age of enrolled patients was 67 years. The ECOG performance status was 0 or 1 for 97% of patients. Patients with uncontrolled hypertension, significant heart disease, or NYHA Class II or worse heart failure were excluded. Co-primary efficacy endpoints were overall survival (OS) and radiographic progression-free survival (rPFS). The median baseline pain score, as measured by the Brief Pain Inventory Short Form (BPI-SF) was 2.0 in both the treatment and placebo groups. In addition to the co-primary endpoint measures, benefit was also assessed using time to skeletal-related event (SRE), time to subsequent therapy for prostate cancer, time to initiation of chemotherapy, time to pain progression and time to PSA progression.

In the 3011 study, treatment continued until disease progression, withdrawal of consent, the occurrence of unacceptable toxicity, or death.

Radiographic progression-free survival was defined as the time from randomisation to the occurrence of radiographic progression or death from any cause. Radiographic progression included progression by bone scan (according to modified PCWG2) or progression of soft tissue lesions by CT or MRI (according to RECIST 1.1).

At the planned rPFS analysis there were 593 events; 239 (40.0%) of patients treated with abiraterone and 354 (58.8%) 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 4** and **Figure 1**).

Table 4: Radiographic Progression-Free Survival - Stratified Analysis; Intent-to-treat Population (Study PCR3011)

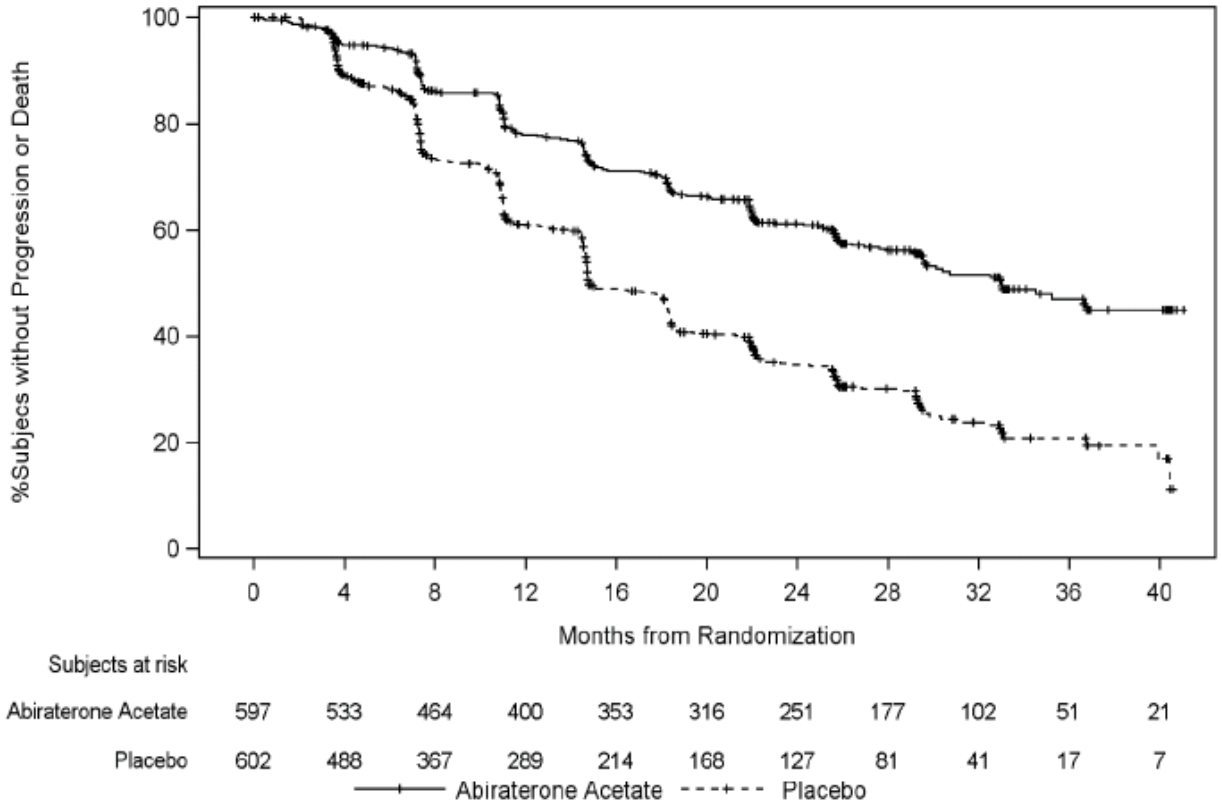
	AA-P	Placebo
Subjects randomised	597	602
Event	239 (40.0%)	354 (58.8%)
Censored	358 (60.0%)	248 (41.2%)
Time to Event (months)		
25th percentile (95% CI)	14.59 (11.47, 15.61)	7.43 (7.29, 10.58)
Median (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
75th percentile (95% CI)	NE (NE, NE)	30.36 (29.24, 39.95)
Range	(0.0+, 41.0+)	(0.0+, 40.6+)
6-month event-free rate (95% CI)	0.941 (0.918, 0.957)	0.867 (0.836, 0.892)
12-month event-free rate (95% CI)	0.779 (0.742, 0.812)	0.611 (0.567, 0.652)
18-month event-free rate (95% CI)	0.702 (0.661, 0.739)	0.476 (0.431, 0.520)
24-month event-free rate (95% CI)	0.611 (0.568, 0.652)	0.347 (0.303, 0.391)
30-month event-free rate (95% CI)	0.532 (0.483, 0.579)	0.250 (0.206, 0.296)
36-month event-free rate (95% CI)	0.471 (0.414, 0.526)	0.209 (0.162, 0.260)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.466 (0.394, 0.550)	

Note: += censored observation, NE=not estimable. The radiographic progression and death are considered in defining the rPFS event. AA-P= subjects who received abiraterone and prednisone.

[a] p value is from a log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or present).

[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours AA-P.

Figure 1: Kaplan-Meier Plot of Radiographic Progression-free Survival; Intent-to-treat Population (Study PCR3011)



At the planned first interim analysis (IA-1) for overall survival, four hundred and six (406; 47.7% of the total number of deaths required at the final analysis) deaths had occurred (169 subjects in the AA-P group and 237 subjects in the Placebo group). A statistically significant improvement in OS in favour of AA-P plus ADT was observed with a 38% reduction in the risk of death (HR=0.621; 95% CI: 0.509, 0.756) compared to Placebo plus ADT. Median survival was not reached in the AA-P group versus 34.7 months in the Placebo group (p<0.0001, crossing the pre-specified boundary for OS at Interim Analysis 1 of 0.010) (see **Table 5** and **Figure 2**). The study was un-blinded based on the magnitude of clinical benefit observed and patients in the placebo group were offered treatment with abiraterone. Survival continued to be followed after this IA.

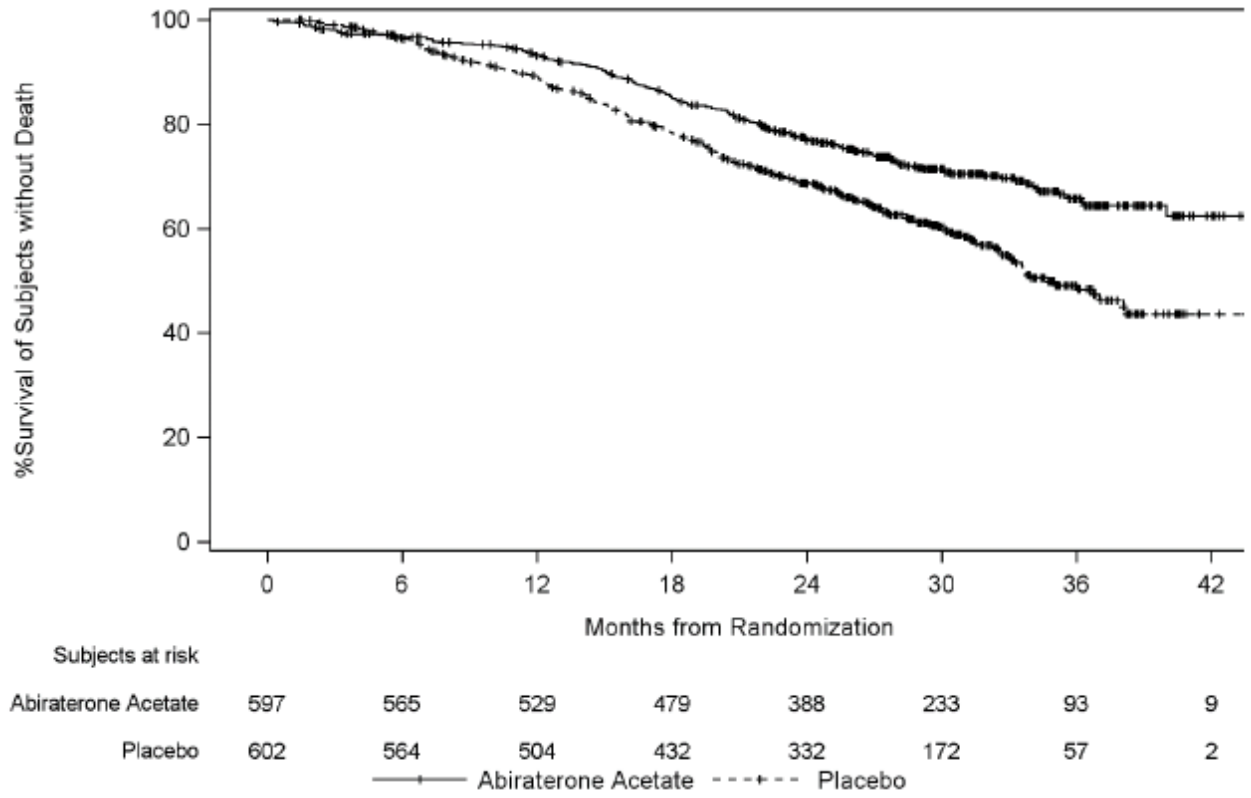
Table 5: Overall Survival, Stratified Analysis; Intent-to-treat Population (Study PCR3011)

	AA-P	Placebo
Subjects randomised	597	602
Event	169 (28.3%)	237 (39.4%)
Censored	428 (71.7%)	365 (60.6%)
Overall Survival (months)		
25th percentile (95% CI)	26.12 (22.74, 30.13)	19.75 (17.91, 21.82)
Median (95% CI)	NE (NE, NE)	34.73 (33.05, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.1, 43.5+)	(1.4+, 43.5+)
12-month event-free rate (95% CI)	0.931 (0.908, 0.949)	0.892 (0.863, 0.914)

24-month event-free rate (95% CI)	0.769 (0.732, 0.802)	0.686 (0.646, 0.723)
36-month event-free rate (95% CI)	0.658 (0.608, 0.704)	0.492 (0.436, 0.546)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.621 (0.509, 0.756)	

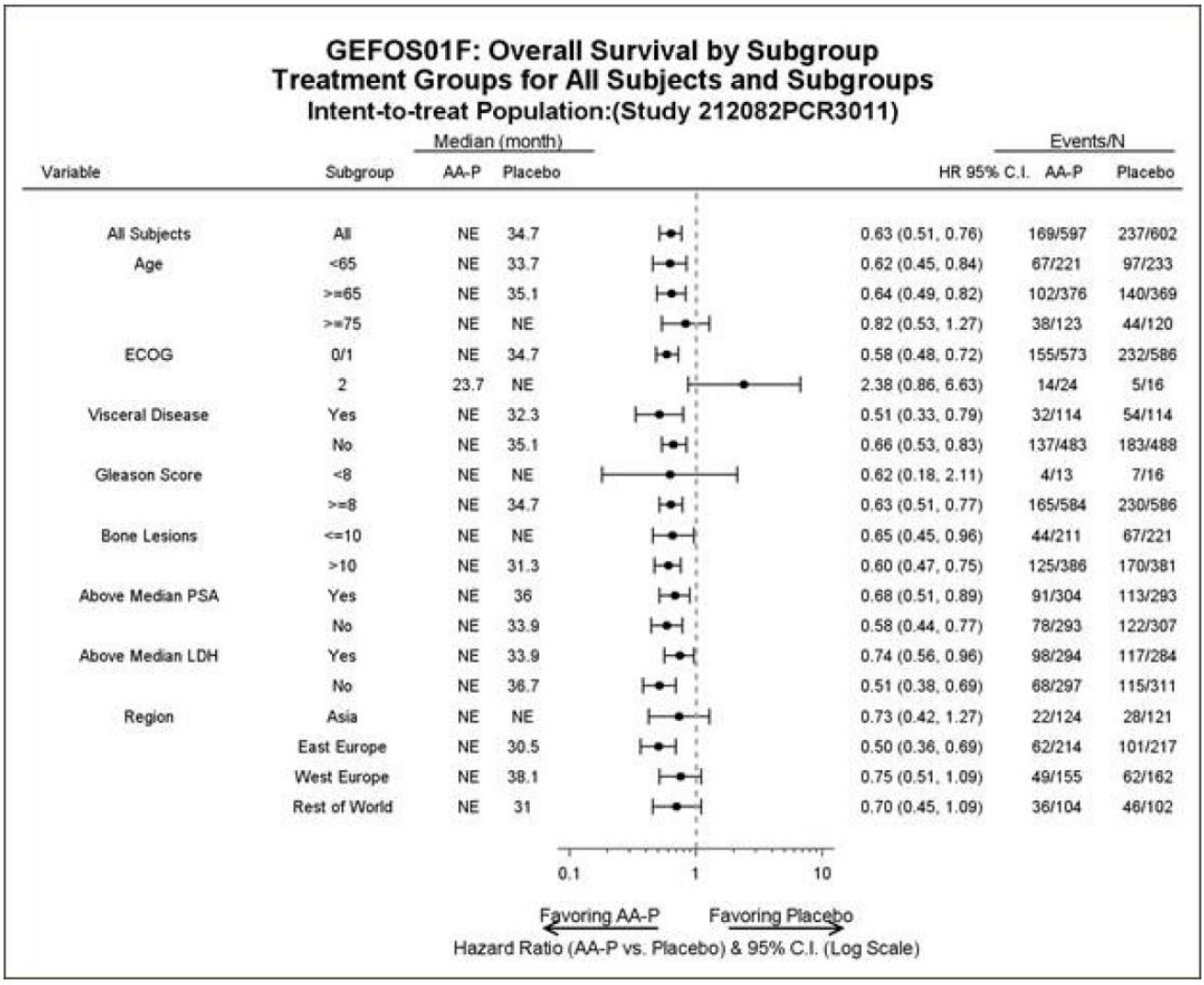
Note:+= censored observation, NE = not estimable. AA-P= subjects who received abiraterone and prednisone.
[a] p value is from log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or present).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours AA-P.

Figure 2: Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study PCR3011)



Subgroup analyses consistently favour treatment with abiraterone (see **Figure 3**).

Figure 3: Overall Survival by Subgroup; Intent-to-treat population (Study PCR3011)



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

Time to skeletal-related event (SRE)

There was a 30% reduction in the risk of skeletal-related events (HR = 0.703; 95% CI: [0.539, 0.916] p < 0.0086). The median time to SRE has not been reached for the abiraterone or placebo study arm.

Time to PSA progression based on PCWG2 criteria

The median time to PSA progression was 33.2 months for patients receiving abiraterone and 7.4 months for patients receiving placebo (HR = 0.299; 95% CI: [0.255, 0.352], p <0.0001).

Time to subsequent therapy

The median time to subsequent therapy at the time of interim analysis was not reached for patients receiving abiraterone and was 21.6 months for patients receiving placebo (HR = 0.415; 95% CI: [0.346, 0.497], p <0.0001).

Time to initiation of chemotherapy

The median time to initiation of chemotherapy was not reached for patients receiving abiraterone and

was 38.9 months for patients receiving placebo (HR = 0.443; 95% CI: [0.349, 0.561], p < 0.0001).

Time to pain progression

The median time to pain progression was not reached for patients receiving abiraterone and was 16.6 months for patients receiving placebo (HR = 0.695; 95% CI: [0.583, 0.829], p = <0.0001).

The majority of exploratory endpoints favored treatment with abiraterone and prednisone (AA-P) over Placebo. A statistically significant improvement in prostate cancer-specific OS was observed for AA-P treatment compared with Placebo (HR=0.547, p<0.0001). A confirmed PSA response was observed in 91.0% of subjects in the AA-P group and 66.8% of subjects in the Placebo group (relative risk=1.362; p<0.0001). The overall response rate (complete plus partial response) in subjects with measurable disease at baseline was significantly higher in the AA-P group compared with those in the Placebo group (p=0.0002).

The time to degradation analyses of patient reported outcome (PRO) measures consistently demonstrated that treatment with AA-P delayed degradation and progression of pain, functional status, fatigue and health-related quality of life. Based on the change from baseline using repeated measures mixed-effect model statistically significant differences were observed between AA-P and Placebo as early as Cycle 2 and maintained throughout the study.

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

This study enrolled chemotherapy näive patients who were asymptomatic or mildly symptomatic and for whom androgen deprivation therapy has failed and in whom chemotherapy is not yet clinically indicated. A score of 0-1 on Brief Pain Inventory Short Form (BPI SF) worst pain in last 24 hours was considered asymptomatic, and a score of 2-3 was considered mildly symptomatic. Failure of androgen deprivation therapy in the protocol was defined as Prostate cancer progression documented by PSA according to PCWG2 (e.g. two values taken at least one week apart increasing over the nadir) or radiographic progression according to modified RECIST criteria, with previous anti-androgen therapy and progression after withdrawal. Patients who received combined androgen blockade with an anti-androgen must have shown PSA progression after discontinuing the anti-androgen prior to enrollment (≥ 4 weeks since last flutamide, ≥ 6 weeks since last bicalutamide or nilutamide).

In study 302, (n=1088) the median age of enrolled patients was 71 years for patients treated with abiraterone 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. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). 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 study 302, 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. Patients should not be discontinued based on PSA progression alone and should remain on treatment until fully confirmed clinical progression utilising multiple assessment criteria.

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). PCWG2 criteria require a confirmatory bone scan to document progression. PCWG2 criteria require a confirmatory bone scan to document progression. Analysis of rPFS utilised centrally-reviewed radiographic assessment of progression.

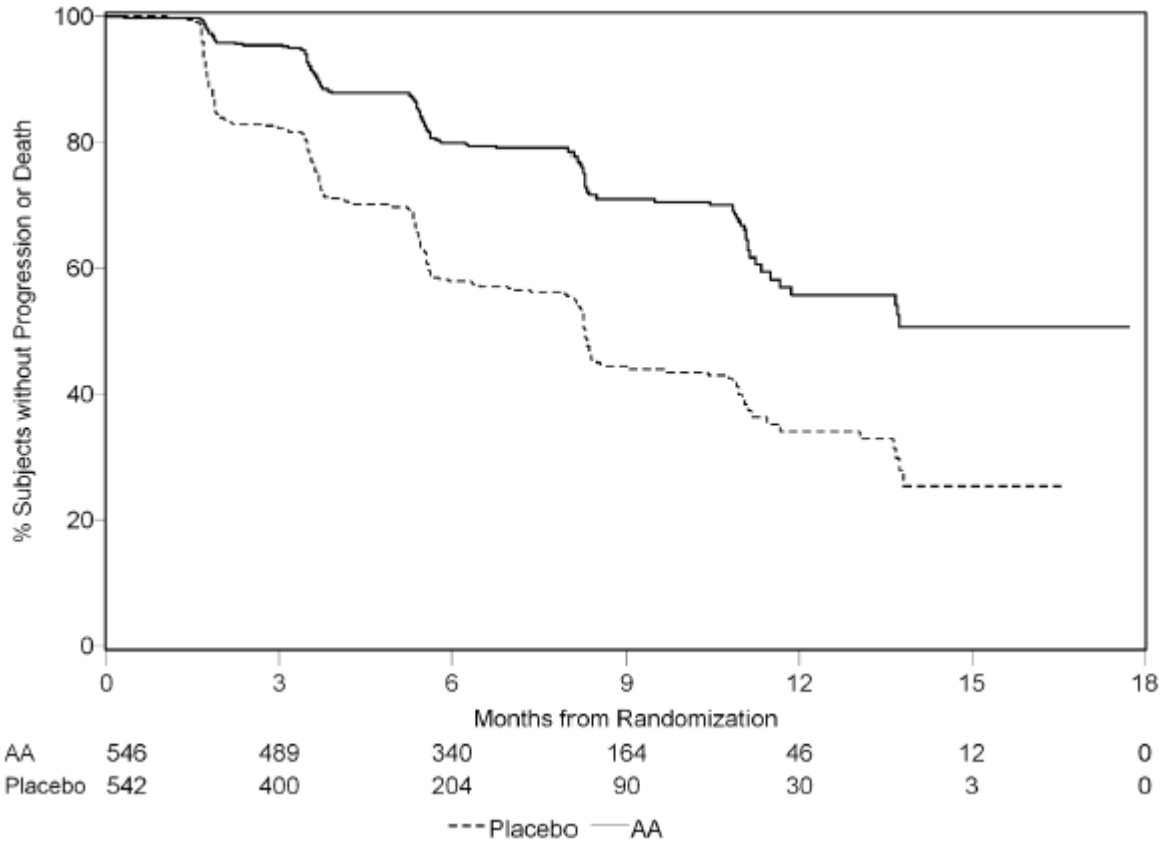
At the planned rPFS analysis there were 401 radiographic progression events; 150 (28%) of patients treated with abiraterone and 251 (46%) of patients treated with placebo had radiographic evidence of progression. A significant difference in rPFS between treatment groups was observed (see **Table 6** and **Figure 4**).

Table 6: Study 302: Radiographic Progression-free Survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy

	ABIRATERONE (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 (11.6, 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 <1 favours abiraterone

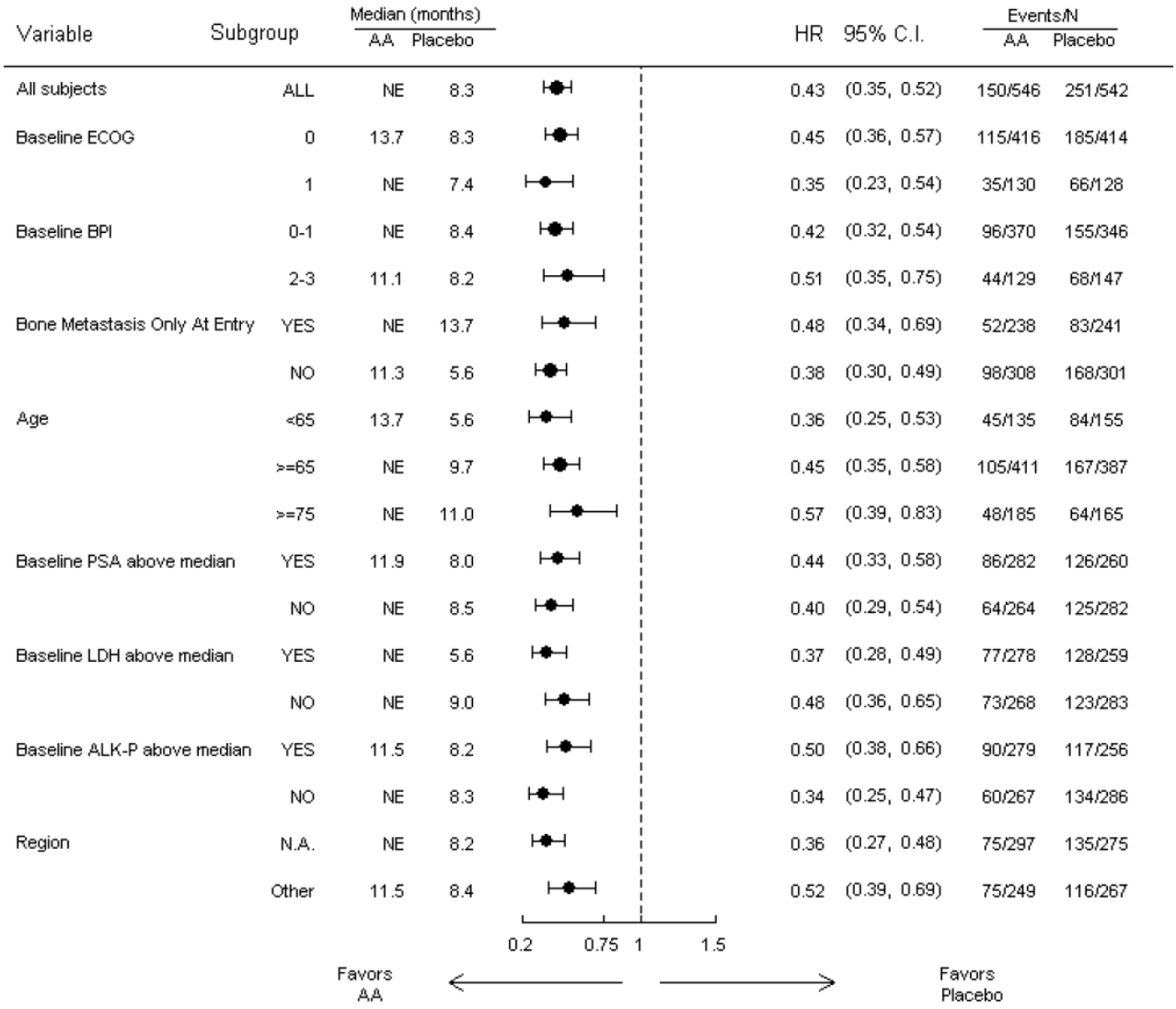
Figure 4: Kaplan Meier curves of radiographic Progression-free Survival in patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH Agonists or prior orchiectomy



Subgroup analyses of rPFS are presented in **Figure 5**. The treatment effect of abiraterone on the co-

primary endpoint of the independent review of rPFS was consistently favorable and highly robust across all subgroups.

Figure 5: Radiographic Progression-Free Survival by subgroup cut-off date of 20 December 2010



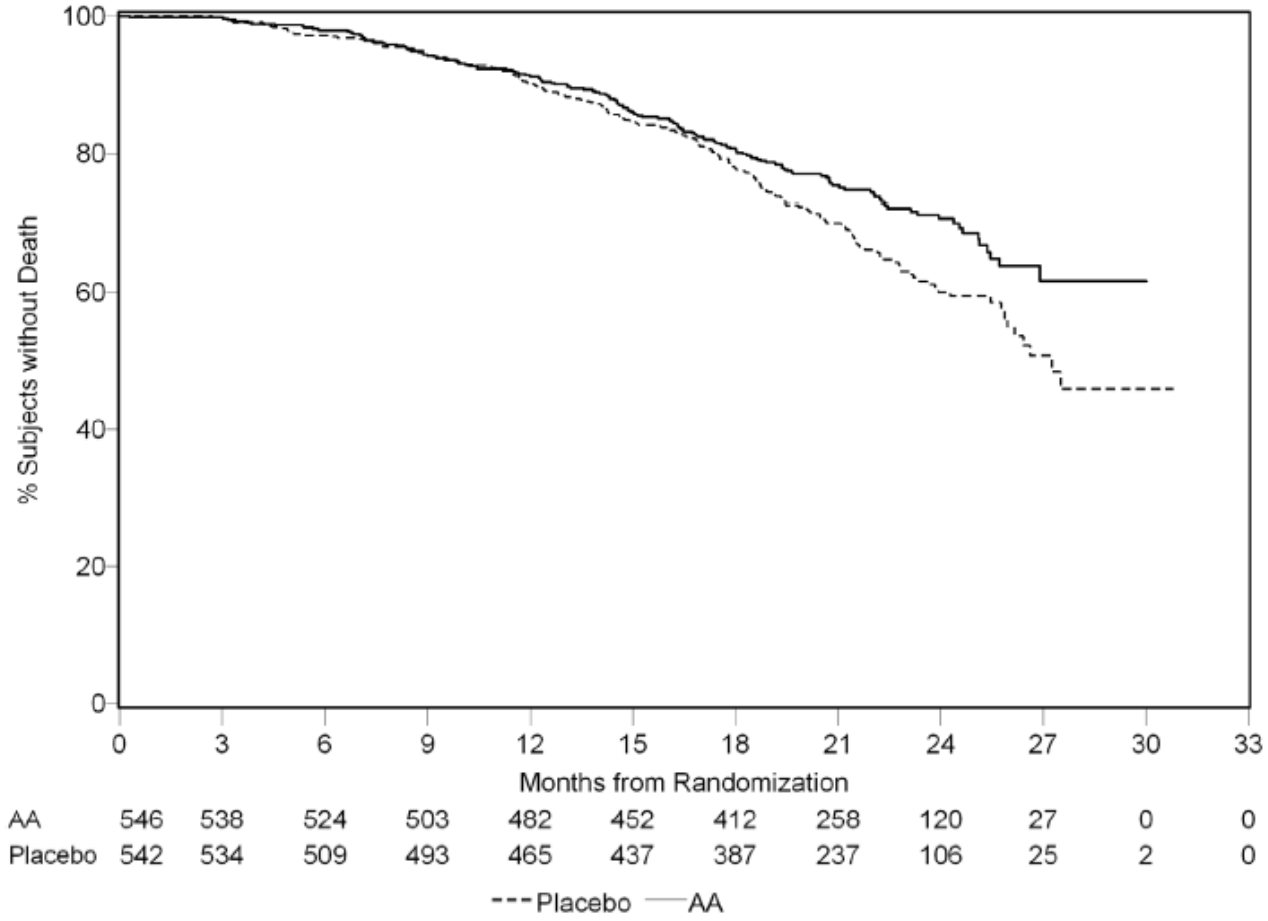
The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.
AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not estimable; No.=number; PSA=prostate-specific antigen

A planned analysis for overall survival was conducted after 333 deaths were observed. The study was unblinded, following the recommendation of the Independent Data Monitoring Committee (IDMC), based on the magnitude of clinical benefit observed. Twenty seven percent (147 of 546) of patients treated with abiraterone, compared with 34% (186 of 542) of patients treated with placebo, had died. Overall survival was longer for abiraterone than placebo with a 25% reduction in risk of death (Hazard Ratio = 0.752; 95% CI: 0.606 - 0.934). The p value was 0.0097 which did not meet the pre-specified level (0.0008) to claim statistical significance (see **Table 7** and **Figure 6**).

Table 7: Study 302: Overall Survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy		
	ABIRATERONE (N=546)	**PLACEBO (N=542)**
Overall Survival		
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)	

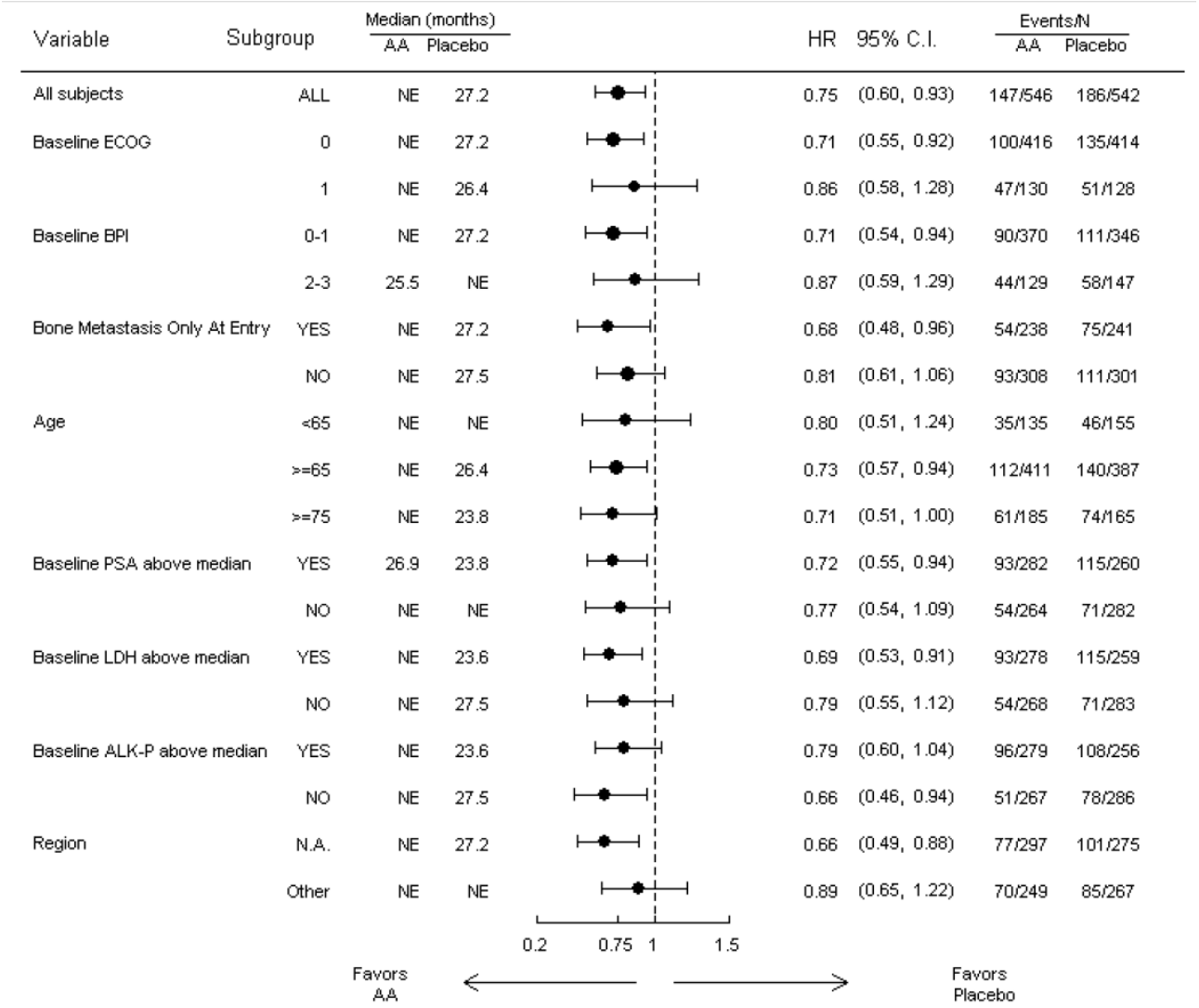
NE = Not estimated
*P value is derived from a log-rank test stratified by baseline ECOG score (0 or 1)
**Hazard ratio <1 favours abiraterone

Figure 6: Kaplan Meier Survival curves of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy



Subgroup analyses of overall survival are presented in **Figure 7**. The treatment effect of abiraterone on overall survival was favorable across all subgroups (all HR<1.0).

Figure 7: Overall Survival by subgroup (Study COU-AA-302: ITT Population)



The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.
AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not estimable; No.=number; PSA=prostate-specific antigen

In addition to the observed improvements in overall survival and rPFS, benefit was demonstrated for abiraterone versus placebo treatment in all the secondary endpoint measures as follows.

Time to PSA progression based on PCWG2 criteria:

Median time to PSA progression was 11.1 months for patients receiving abiraterone and 5.6 months for patients receiving placebo (HR=0.488; 95%CI: [0.420, 0.568], p<0.0001). Time to PSA progression was approximately doubled with abiraterone treatment. The proportion of subjects with a confirmed PSA response was greater in the abiraterone group than in the placebo group (62% versus 24%; p<0.0001).

Time to opiate use for cancer pain:

The median time to opiate use for prostate cancer pain was not reached for patients receiving

abiraterone and was 23.7 months for patients receiving placebo (HR=0.686; 95%CI: [0.566, 0.833], p=0.0001).

Time to initiation of cytotoxic chemotherapy:

The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving abiraterone 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 abiraterone 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 abiraterone 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 abiraterone group and 16% in the placebo group (p<0.0001).

Pain:

Treatment with abiraterone 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 abiraterone group and 18.4 months in the placebo group.

Time to degradation in the FACT-P (Total Score):

Treatment with abiraterone 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 abiraterone 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 abiraterone.

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.

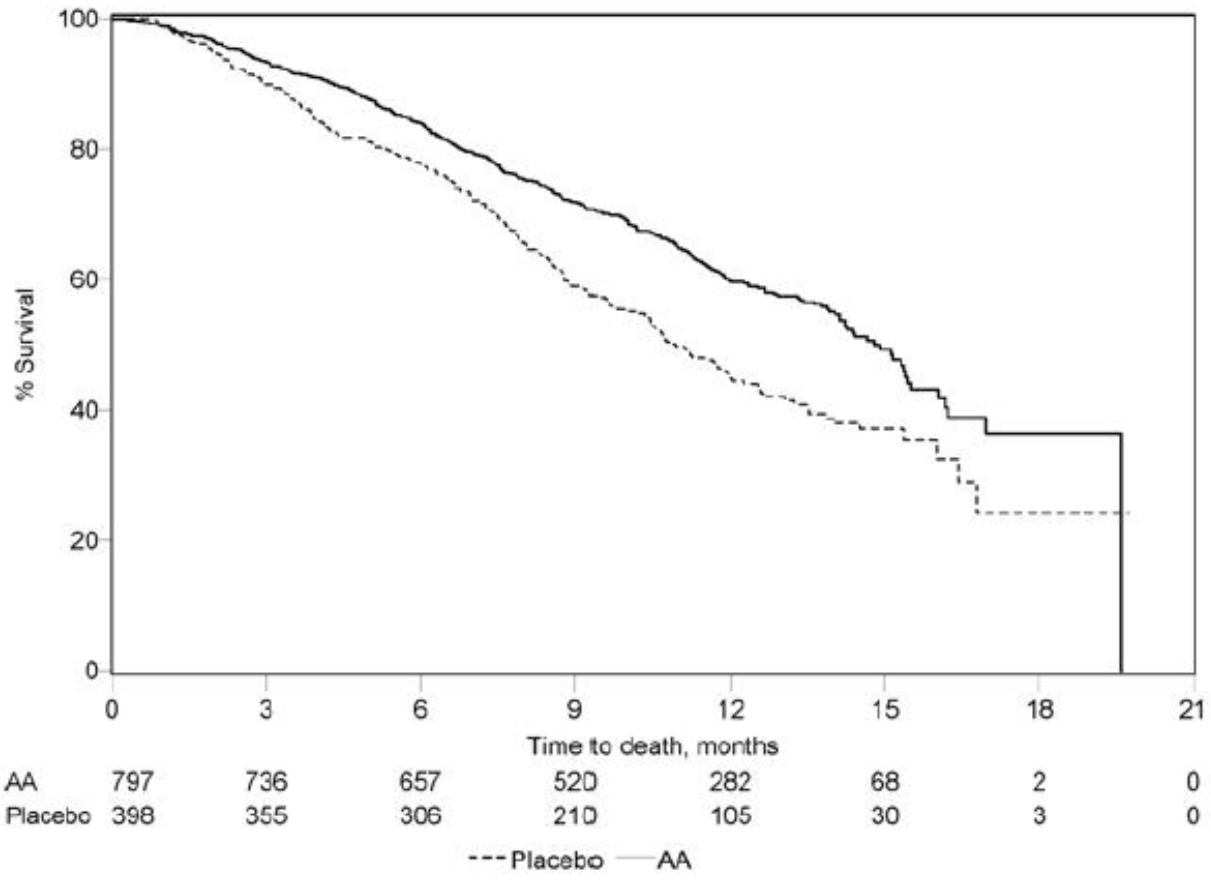
In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with abiraterone compared with 55% (219 of 398) of patients treated with placebo had died. A statistically significant improvement in median overall survival was seen in patients treated with abiraterone (see **Table 8**).

Table 8: Study 301: Overall Survival of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy		
	ABIRATERONE (N=797)	**PLACEBO (N=398)**
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)	

Hazard ratio <1 favours abiraterone

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with abiraterone remained alive compared with the proportion of patients treated with placebo (see **Figure 8**).

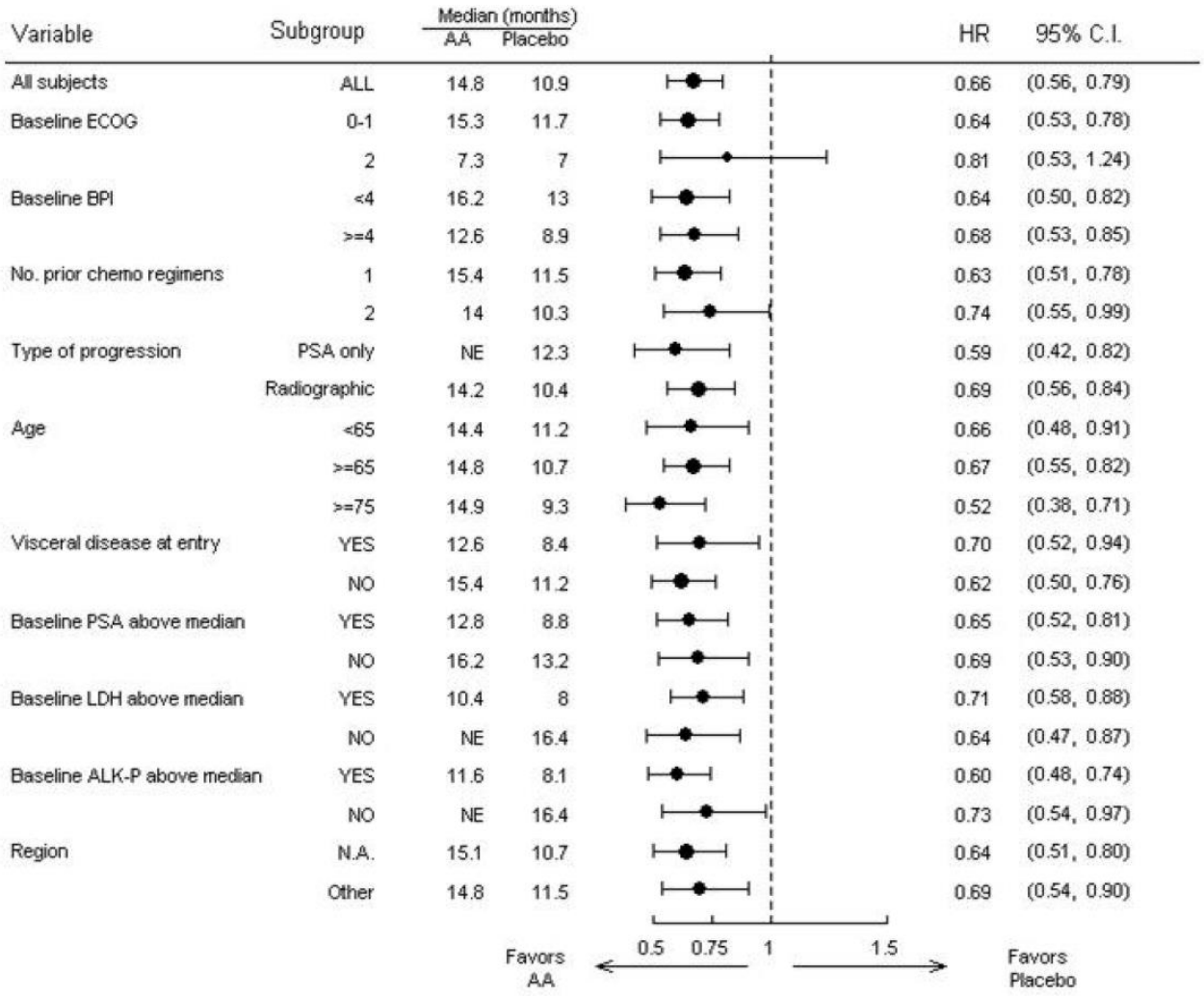
Figure 8: Kaplan Meier survival curves of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy



AA = abiraterone acetate

Subgroup survival analyses showed a consistent survival benefit for treatment with abiraterone (see **Figure 9**).

Figure 9: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval



AA=abiraterone acetate; 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; No.=number

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

Patients receiving abiraterone demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo: 29% versus 6%, p<0.0001.

The median time to PSA progression was 10.2 months for patients treated with abiraterone 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 abiraterone 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 abiraterone group than in the placebo group (44% versus 27%, p=0.0002).

A lower proportion of patients treated with abiraterone had pain progression compared to patients taking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 46%). The time to pain progression at the 25th percentile was 7.4 months in the abiraterone group, versus 4.7 months in the placebo group.

Skeletal-Related Events

A lower proportion of patients in the abiraterone 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 abiraterone group was twice that of the control group at 9.9 months vs 4.9 months.

5.2 Pharmacokinetic Properties

Following administration of abiraterone, the pharmacokinetics of abiraterone has 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 (see **section 5.1**).

Absorption

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

Effect of food on absorption

Administration of abiraterone 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 abiraterone with meals has the potential to result in highly variable exposures. Therefore, **Abiraterone Devatis must not be taken with food**. Abiraterone Devatis tablets must be taken as a single dose once daily on an empty stomach. Abiraterone Devatis must be taken at least two hours after eating and food must not be eaten for at least one hour after taking Abiraterone Devatis. The tablets must be swallowed whole with water (see **section 4.2**).

Distribution

The plasma protein binding of 14C-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 hydrolysed 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.

The major enzymes involved in the metabolism of abiraterone are CYP3A4 for phase I (oxidative) metabolites, the sulfotransferase (SULT) isozyme SULT2A1, and UDP-glucuronosyl transferase

(UGT) UGT1A4. No studies have been conducted to determine if drugs that induce or inhibit these enzymes affect the metabolism of abiraterone.

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 faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22 % of the administered dose, respectively).

Additional information on special populations

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 when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. Abiraterone Devatis should be used with caution in patients with moderate hepatic impairment, only if the benefit clearly outweighs the possible risk (see **sections 4.2 – Hepatic impairment** and **4.4 – Hepatotoxicity and Hepatic impairment**). Abiraterone should not be used in patients with severe hepatic impairment.

For patients who develop hepatotoxicity during treatment with abiraterone suspension of treatment and dosage adjustment may be required (see **sections 4.4** and **4.2**).

Renal impairment

The pharmacokinetics of abiraterone was compared in patients with end-stage renal disease on a stable haemodialysis 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 abiraterone in patients with renal impairment including severe renal impairment does not require dose reduction (see **section 4.2**).

5.3 Preclinical safety data

Carcinogenicity

Carcinogenicity studies were not conducted with abiraterone.

Genotoxicity

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. Genotoxicity studies have not been conducted with the main human metabolites of abiraterone.

Effects on fertility

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

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

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

In studies in rats (13-and 26-weeks) and monkeys (up to 39-weeks), decreases in testosterone levels, atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone. These effects were observed at exposure levels similar to or lower than the human clinical exposure, based on abiraterone AUC. Abiraterone is contraindicated in pregnancy (see **sections 4.3** and **4.6**).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Sodium lauryl sulfate
Hypromellose
Colloidal silicon dioxide
Magnesium stearate

The tablet coating contains:

Polyvinyl alcohol
Titanium dioxide
Macrogol/PEG
Talc
Iron oxide red
Ferrosoferric oxide / Black iron oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

Abiraterone Devatis is available as 60 film coated tablets in blister packs of PVC/PE/PVDC sealed with aluminium foil.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

Based on its mechanism of action, Abiraterone Devatis may harm a developing foetus; therefore, women who are pregnant or women who may be pregnant should not handle Abiraterone Devatis without protection, e.g. gloves (see **section 4.6**).

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Devatis Limited
45 Yarrow Street, Invercargill, 9810
New Zealand
Tel: +64 3 211 0080
Fax: +64 3 211 0079
www.devatis.nz

9. DATE OF FIRST APPROVAL

10. DATE OF REVISION OF THE TEXT

17.01.2024