Janssen EMEA *

Non-interventional Study Report

A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-resistant Prostate Cancer

Protocol 212082PCR4001

JNJ-212082-AAA (Abiraterone acetate)

*Janssen EMEA is a regional organization that operates through different legal entities in various countries. The legal entity acting as the sponsor for Janssen EMEA studies may vary, such as, but not limited to Janssen-Cilag International NV or Janssen Pharmaceutica NV. The term "sponsor" is used to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

PRINCIPAL INVESTIGATOR: Dr. Simon Chowdhury, MA, MBBS, MRCP, PhD

SPONSOR'S RESPONSIBLE MEDICAL OFFICER: Martin Lukac, MD

DATE REGISTRY INITIATED: 14 June 2013 (Date first patient signed informed consent)

DATE REGISTRY COMPLETED: 9 July 2018 (Date of last observation for last patient recorded as part of the database)

Status: Approved
Date: 24 October 2019
Prepared by: Janssen-Cilag Limited
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GCP Compliance: This study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

SYNOPSIS

Name of Sponsor/Company	Janssen EMEA*
Name of Investigational Product	JNJ-212082-AAA (Abiraterone acetate)

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Title of Registry: A Prospective Registry of Patients With a Confirmed Diagnosis of Adenocarcinoma of the Prostate Presenting With Metastatic Castrate-resistant Prostate Cancer

NCT No.: NCT02236637

Clinical Registry No.: CR100857

Principal Investigator: Dr. Simon Chowdhury

Study Center(s): Austria (2), Belgium (13), France (22), Germany (25), Israel (5), Italy (32), Luxembourg (2), Poland (8), Portugal (6), Russian Federation (7), Slovenia (3), Spain (14), Sweden (9), Switzerland (2), Turkey (7), United Kingdom (22)

Publication (Reference): None

Study Period: 14 June 2013 (Date first patient signed informed consent) to 9 July 2018 (Date of last observation for last patient recorded as part of the database)

Objectives: The objective of this prospective, observational registry was to document the characteristics and management of patients with metastatic castrate-resistant prostate cancer (mCRPC) in routine clinical practice, independent of treatment used. This was based on documentation and description of the following:

- Sequencing of treatment initiation, termination, and duration
- Relative effectiveness of treatments
- Defined medical resource utilization (MRU) and quality-of-life parameters
- Follow-up for survival

Research Methodology: This was a non-interventional, multicenter, prospective registry of patients with a confirmed diagnosis of adenocarcinoma of the prostate presenting with mCRPC, with documented metastatic disease and castration resistance. Patients were enrolled at the time of initiation of a new systemic mCRPC treatment or during surveillance within routine clinical practice. Observational methodology was used to capture data available from routine clinical practice. The decision of patients to take part in the registry did not influence their medical care. Treatment decisions were made at the sole discretion of the treating physician, per routine clinical practice. During the observational period, data were collected at the following time points of a patient's course of treatment in routine clinical practice:

- Initiation of a new systemic mCRPC treatment;
- Termination of a systemic mCRPC treatment;

- When the duration of a treatment or surveillance period was >3 months, data collection was performed at a minimum frequency of 3-monthly intervals during that period.

Number of Patients (planned and analyzed): Approximately 3,000 patients were planned to be included in this registry. To ensure a population representative of clinical practice and to reduce selection bias, all patients meeting the eligibility criteria at a participating site were consecutively enrolled, irrespective of their treatment. Unless otherwise specified per local regulations, all patients were required to give their informed consent to participate in this registry before any data collection.

Diagnosis and Main Criteria for Inclusion: Potential patients were male patients, aged at least 18 years, with a histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate, documented metastatic disease, and documented castration resistance. Patients must have been either initiating a new systemic mCRPC treatment (starting a new systemic mCRPC treatment within ±30 days from a baseline data collection) or considered to be in surveillance within clinical practice.

Test Product, Dose and Mode of Administration, Batch No.: Patients received their medication according to usual care in their treatment setting; no medication was provided by the sponsor. Dosing and administration of all treatments were at the sole discretion of the treating physician.

Duration of Treatment: The total duration of the registry was 5.5 years from the date that the first patient was enrolled, irrespective of the country or registry site. The duration of enrollment was 2.5 years. The maximum duration of follow-up for individual patients in the observational period of the registry was 3 years, regardless of when they were enrolled. The 3-year observation period documented the sequencing of systemic mCRPC treatments during routine clinical practice, considering the life expectancy of patients with mCRPC in the registry.

Criteria for Evaluation: The 3-year observation period documented the sequencing of systemic mCRPC treatments during routine clinical practice. Data on comorbidities, Eastern Cooperative Oncology Group (ECOG) performance status, patient-reported outcomes (EuroQol 5-Dimensions 5-Level [EQ-5D-5L] and Functional Assessment of Cancer Therapy-Prostate [FACT-P] questionnaires, where permitted per local regulations), medical resource use, biological parameters, and selected adverse events were also collected.

Survival data were collected for all patients until 3 years after their enrollment or the close of the registry, whichever occurred first, except for patients who withdrew their consent prior to completion of the observation period.

Statistical Methods: The goal of the targeted 3,000 patients was to collect data on a large population that was representative of a population with mCRPC in the Europe/Middle East/Africa region. The registry was designed to generate data for informative purposes; eg, for cost effectiveness calculations. As a result, it was descriptive rather than comparative and no formal hypotheses were tested in this registry. The sample size was, therefore, mainly determined by pragmatic considerations.

Analysis Sets: The evaluation set contained all patients enrolled who were not screen failures and not excluded from the analysis due to another reason (eg, inclusion criterion violation, other reason). The Zytiga exposed set consisted of all patients of the evaluation set for whom a treatment with abiraterone acetate was documented during the study. The following subgroups were defined and analyzed:

First-line mCRPC treatment: Patients who received abiraterone acetate [A], enzalutamide [E], docetaxel [D], cabazitaxel [C]. The number of previous mCRPC treatments were calculated. The first-line mCRPC treatment was determined by the number of patients receiving their first single treatments documented in the study, for patients who had received no previous treatments.

Subgroups of First-line mCRPC treatment:

- Patients with cardiovascular comorbidities, defined as a patient having at baseline any of the following comorbidities: hypertension, angina pectoris, history of myocardial infarction, arrhythmia,

thromboembolic disease, other cardiovascular, cerebrovascular accident and/or transient ischemic attack;

- Patients with diabetes (non-insulin dependent diabetes, insulin dependent diabetes);
- Subgroup of patients with visceral (liver and/or lung) metastasis;
- Sequence of second-line mCRPC treatment, defined by the sequences of 2 consecutive mCRPC treatments. All statistical analysis was performed on each treatment sequence.

For the evaluation set, the following information was summarized:

- Age, baseline and disease characteristics.
- Prostate cancer characteristics and tumor assessment data.
- Biological and clinical parameters.
- Treatment information for each patient.
- Time to progression (TTP): TTP was measured from the start date of the mCRPC treatment to the date of progression
- Progression-free survival (PFS): PFS was calculated as TTP, with the addition of death as an event.
- Time-to-next-therapy (TNT): TNT was measured from the start date of the mCRPC treatment to the start date of the next mCRPC therapy.
- Overall survival (OS): OS was measured from the start date of the mCRPC treatment to the date of death (regardless of cause).
- Quality-of-life scales: EQ-5D-5L (5 dimensions, Index Score and VAS) and FACT-P (5 subscales and global scale, plus a pain score).
- Medical resource utilization within one year before enrollment.
- Comorbidities of type other were summarized by preferred term and system-organ class (SOC).
- Prior and concomitant medication.

Adverse Events: All adverse events (AEs; whether serious or non-serious, related or not related) following exposure to at least one dose of abiraterone acetate were recorded in the case report form (CRF). A full serious adverse events (SAE) analysis was made only for patients receiving abiraterone acetate, not for other mCRPC treatments. Treatment-emergent was defined as onset of the (S)AE during abiraterone acetate treatment or within 30 days after a patient's last use of abiraterone acetate.

RESULTS:

First-Line mCRPC Treatment

STUDY POPULATION:

Overall, 1590 patients received first-line mCRPC treatment as part of routine care during the registry; among these, abiraterone acetate, enzalutamide and docetaxel were received by 754, 227 and 602 patients, respectively. A total of 247 (32.8%) patients in the abiraterone acetate group, 100 (44.1%) patients in the enzalutamide group and 166 (27.6%) patients in docetaxel group completed the registry. Death was the most frequently reported reason for withdrawal from the registry in all the groups (81.1%, 89.0% and 67.7% of patients who did not complete the registry in from the abiraterone acetate, enzalutamide and docetaxel groups, respectively). A follow-up period of >18 months was recorded for 63.3%, 68.3% and 59.1% of the patients receiving first-line abiraterone acetate, enzalutamide and docetaxel, respectively, during the registry.

Patients receiving docetaxel tended to be younger, with a median age of 69.0 years, compared with patients receiving abiraterone acetate and enzalutamide (median age of 76.0 years in both groups). Median prostate-specific antigen (PSA) levels at baseline tended to be higher in patients receiving first-line docetaxel (43.4 ng/ml) compared to patients receiving first-line abiraterone acetate (34.4 ng/ml) or enzalutamide (26.2 ng/ml). At diagnosis, a Gleason score of 8 to 10 was recorded for 51.0%, 60.6% and 58.4% of patients and distant metastases were observed in 35.0%, 42.3% and 50.1% of patients in the abiraterone acetate, enzalutamide and docetaxel groups respectively; bone lesions were the most commonly observed metastases in all the treatment groups.

In terms of prior treatment for prostate cancer, 10.5%, 7.9% and 8.6% of patients in the abiraterone acetate, enzalutamide and docetaxel groups, respectively, had undergone both radical prostatectomy and prostate-specific radiotherapy; 4.6%, 5.3% and 7.3% of patients in the abiraterone acetate, enzalutamide and docetaxel groups had undergone orchiectomy before study entry. At baseline, therapies for hypertension and simple analgesics were the most frequently reported concomitant medications in all 3 treatment groups; hypertension therapies were received by 52.3%, 55.1% and 46.2% of patients, and analgesics were received by 22.7%, 34.4% and 32.7% of patients in the abiraterone acetate, enzalutamide and docetaxel groups, respectively.

Radiological and PSA-only progression were the determining factors for the start of systemic mCRPC treatment in all the groups. Disease progression was the most frequently reported reason for first-line treatment discontinuation in the abiraterone acetate and enzalutamide groups (72.8% and 67.3% of patients, respectively); 50% of patients receiving docetaxel completed the course of treatment, and 27.0% discontinued due to disease progression; this could however be attributed to the shorter dosing regimen of docetaxel that is administered in prescribed number of cycles.

The Kaplan-Meier estimated median duration of treatment during the follow-up was 11.2 months, 13.0 months and 4.8 months in patients receiving abiraterone acetate, enzalutamide and docetaxel, respectively.

EFFECTIVENESS/OUTCOMES RESULTS:

The Kaplan-Meier estimated median TTP was 9.6 months, 10.3 months and 7.6 months in the abiraterone acetate, enzalutamide and docetaxel groups, respectively; unadjusted and propensity score adjusted analyses revealed significant differences between abiraterone acetate versus docetaxel, and enzalutamide versus docetaxel. The Kaplan-Meier estimated median OS was 27.1 months each in patients who received abiraterone acetate and enzalutamide, and 27.9 months in patients who received docetaxel.

At the end of first-line mCRPC treatment, patient-reported outcome (PRO) completion rates were generally low (<50%) in all the treatment groups. In all the groups, there were no clinically significant changes from baseline in the median EQ-5D-5L scores for any of the 5 dimensions in the scale: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression in the index score or VAS among patients receiving abiraterone acetate, enzalutamide and docetaxel. The proportion of patients reporting clinically meaningful improvements in the FACT-P and subscales were similar in the abiraterone acetate and enzalutamide groups; improvements in Global Scores, Prostate Cancer subscale and Pain subscale were reported by 34.3%, 47.9% and 44.6% of patients in the abiraterone acetate group, 38.1%, 48.3% and 50.6% of patients in the enzalutamide group and 25.0%, 39.3% and 46.5% of patients in the docetaxel group, respectively.

At the end of first-line mCRPC treatment, no significant changes from baseline were observed in the abiraterone acetate, enzalutamide and docetaxel groups in terms of the total days of hospitalization and emergency room visits due to prostate cancer or its treatment.

First-line mCRPC Treatment Comorbidities Subgroups (Cardiovascular Disease, Diabetes Mellitus and Visceral Metastases)

STUDY POPULATION:

Overall, among the patients receiving first-line mCRPC treatment, 1016 patients (504 patients in the abiraterone acetate group, 161 in the enzalutamide group and 351 in the docetaxel group) reported underlying cardiovascular disorders, 268 patients (121 in the abiraterone acetate group, 47 in the enzalutamide group and 100 in the docetaxel group) had diabetes mellitus, and 147 patients (59 in the abiraterone acetate group and 88 in the docetaxel group) had visceral metastases. The number of patients with visceral metastases who received first-line enzalutamide was too small to warrant a separate analysis. Among patients with cardiovascular disorders, 166 (32.9%), 66 (41.0%) and 87 (24.8%) patients in the abiraterone acetate, enzalutamide and docetaxel groups, respectively, completed the registry. In the diabetes mellitus subset, 42 (34.7%), 17 (36.2%) and 17 (17.0%) patients in the abiraterone acetate, enzalutamide and docetaxel groups, respectively, completed the registry. Among those with visceral metastases, the majority of the patients (49 [83.1%] in the abiraterone acetate group and 72 [81.8%] in the docetaxel group) did not complete the registry. Among patients with cardiovascular disease, the median duration of follow-up in the registry was 23.4 months [range=0, 41], 27.1 months [range=1, 39] and 22.1 months [range=0, 41] in the abiraterone acetate, enzalutamide and docetaxel groups, respectively. In the diabetes mellitus subgroup, median duration of follow-up was 24.5 months [range=1, 41], 24.0 months [range=1, 38] and 18.7 months [range=1, 39] in the abiraterone acetate, enzalutamide and docetaxel groups, respectively. Among patients with visceral metastases, the median duration of follow-up was 16.9 months [range=1, 38] and 18.0 months [range=2, 41] in patients receiving abiraterone acetate and docetaxel, respectively.

Among the subset of patients with cardiovascular disease, hypertension was the most commonly reported comorbidity in all the groups (81.5%, 80.1% and 82.3% of patients in the abiraterone acetate, enzalutamide and docetaxel groups, respectively). Among patients with diabetes mellitus, the majority of patients in each group (71.9%, 76.6% and 82.0% in the abiraterone acetate, enzalutamide and docetaxel groups, respectively) reported non-insulin dependent diabetes. Among patients with visceral metastases at baseline, bone lesions were reported for 76.3% of patients in the abiraterone acetate group and 65.9% of patients in the docetaxel group.

The majority of the patients (56.8% of patients with cardiovascular disease, 52.2% of patients with diabetes mellitus and 56.5% of patients with visceral metastases) had not received prior therapies such as radical prostatectomy or prostate-specific radiotherapy.

In all the subsets of patients with comorbidities, disease progression was the primary reason for treatment start; for the majority of patients in all the subsets (at least 79.5%), progression was determined by PSA and/or radiological assessment. In all the 3 subsets, disease progression was also the primary cause of discontinuation of first-line abiraterone acetate and enzalutamide, whereas completion of therapy was the main reason for stopping docetaxel treatment in all subgroups; this could however be attributed to the shorter dosing regimen of docetaxel which is administered in prescribed number of cycles, rather than a daily regimen.

EFFECTIVENESS/OUTCOMES RESULTS:

The Kaplan-Meier estimated median TTP for patients with cardiovascular disease was 9.7 months, 9.8 months and 7.4 in the abiraterone acetate, enzalutamide and docetaxel groups, respectively; in the diabetes mellitus subset, the median TTP was 12 months, 10.3 months and 7.7 months in the abiraterone acetate, enzalutamide and docetaxel groups, respectively. The median TTP in patients with visceral metastases was 6.2 months in the abiraterone group and 7.8 months in the docetaxel group.

The Kaplan-Meier estimated median OS in the cardiovascular disease subset was 27.4 months in the abiraterone acetate group and 26.1 months each in the enzalutamide and docetaxel groups. Median OS in

the subset of patients with diabetes mellitus was 30.8 months, 27.1 months and 24.3 months in patients who received abiraterone acetate, enzalutamide and docetaxel, respectively. Among patients with visceral metastases, median OS was 17.4 months in the abiraterone acetate group and 20.4 months in the docetaxel group

Analysis of Second-Line Treatment

STUDY POPULATION:

A total of 7 second-line sequence groups with at least 25 patients in each sequence were analyzed: abi-doce (178 patients), abi-enza (99 patients), abi-Ra223 (27 patients), doce-abi (191 patients), doce-caba (74 patients), doce-enza (116 patients) and enza-doce (42 patients).

There was a high degree of variation in demographic and disease characteristics among patients who received second-line treatment following completion or termination of first-line treatment; the median age in all second-line sequence groups ranged from 68.5 years (in the doce-caba group) to 78 years (in the abi-enza group). Gleason scores of 8-10 were recorded in 47.7% (abi-Ra223 group) to 61.1% (doce-caba group) of patients in all the sequence groups. The median time from initial diagnosis to inclusion in the registry ranged from 2.1 years (doce-caba group) to 5.4 years (abi-enza group). The median time from initial diagnosis to first detection of metastasis ranged from 0.1 years (in the doce-abi and doce-caba groups) to 3.4 years (in the abi-enza group). The median time from first metastatic diagnosis to inclusion in the registry ranged from 0.9 years (doce-caba group) to 1.6 years (abi-Ra223 group).

At initial prostate cancer diagnosis, non-metastatic tumors were observed in 31.9% (doce-enza group) to 58.2% (abi-enza group) of patients in all the sequence groups. Distant metastases (M1) were observed in 10.2% (abi-enza group) to 27.4% (doce-enza group) of patients in all the sequence groups. Locally advanced tumors were observed in 55.6% (abi-enza group) to 100% (abi-Ra223 group) of patients; metastatic lesions were most commonly observed in the bones [ranging from 67.6% (enza-doce group) to 100% (abi-Ra223 group) of patients in all the sequence groups].

The lowest and highest PSA levels at baseline were observed in the patients who switched from abiraterone acetate to Ra223 (21.90 ng/ml) and from docetaxel to cabazitaxel (46.22 ng/ml), respectively. At the start of second-line treatment, most patients in all the groups reported a worsening in the ECOG status from baseline except in the abi-enza and doce-abi sequence groups, in which a majority reported no change.

Disease progression, as assessed by PSA, radiological and clinical methods was the most frequent reason for initiating first- and second-line mCRPC treatment in all the sequence groups. The time difference between the end of first-line and initiation of second-line treatment tended to be higher in patients who received first-line docetaxel (median ranging from 3.0 to 3.8 months), compared to patients who received abiraterone acetate or enzalutamide (median ranging from 0.1 to 0.9 months); this could however be attributed to the short regimen of docetaxel which is administered in prescribed cycles, and progression is observed a few months after stopping treatment.

EFFECTIVENESS/OUTCOMES RESULTS:

The Kaplan-Meier estimated median OS ranged from 22.3 months (doce-caba group) to 31.5 months (doce-enza group) in all the sequence groups.

SAFETY RESULTS:

Overall, 899 (60.3%) of the 1490 patients who received at least one dose of abiraterone acetate within the registry reported at least 1 treatment-emergent adverse event (TEAE). Severe, moderate and mild TEAEs were reported by 43.9%, 33.8% and 22.2% of patients, respectively; the most commonly reported TEAEs were general disorders and administration site conditions (28.2%), musculoskeletal disorders (20.2%), and gastrointestinal disorders (16.0%).

Of all the TEAEs reported, 58.3% were considered by physicians to be unrelated to abiraterone acetate or doubtful, while 33.5% were considered at least possibly related to abiraterone acetate.

A total of 496 patients (33.3%) reported at least one serious TEAE. General disorders and administration site conditions and infections and infestations were the most frequently reported SOCs for serious TEAEs.

STUDY LIMITATIONS: This was an observational study and there was no randomization to allow direct treatment comparison. In addition, as treatment followed routine clinical practice, duration of exposure varied between treatments based on dosage regimens; the number of cycles of docetaxel treatment was limited and duration of and reason for stopping treatment cannot be compared between docetaxel and abiraterone or enzalutamide. Data were also collected at routine clinical visits, which may not have occurred at regular intervals for all patients. The staggered commercial availability of the treatments in participating countries, different treatment practices and settings, and timing of enrollment must be taken into consideration; the treatment options available in each country of the registry varied according to launch dates of different drugs that may have influenced findings.

CONCLUSIONS:

This prostate cancer registry presented effectiveness outcomes between the 3 most frequently used first-line treatment choices: abiraterone acetate, enzalutamide and docetaxel; comparable survival benefit was observed across all 3 treatments. The analysis of real-world characteristics, treatment patterns, and effectiveness outcomes of patients in the registry provides meaningful data to help physicians optimally manage all their patient groups with mCRPC. As the registry included many patients from a variety of countries, the results may be extrapolated to a wider population of men with mCRPC. No new safety signals were raised with respect to TEAEs reported following treatment with abiraterone acetate.