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Title of the Study: "Efficacy and safety of Apalutamide in metastatic hormone sensitive prostate cancer patients in a real-world setting: a multicentric prospective cohort study."

Acronym: INTENT ApalutamIde iN metastatic prosTatE caNcer seTting

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Sponsor: ASST Spedali Civili di Brescia

Coordinating Center: ASST Spedali Civili di Brescia, Unit of Medical Oncology (prof Alfredo Berruti, dr Alberto Dalla Volta)

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11.1 Annex 1: Quality of Life questionnaires (FACT-P, BPI-SF)

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1. Introduction

Androgen deprivation therapy (ADT) with analogs of Luteinizing Hormone Releasing Hormone (LHRH-A) has long represented the mainstay of therapy for patients with metastatic hormone sensitive prostate cancer (mHSPC). In the last international guidelines (i.e. EAU, NCCN) [1,2] next generation hormonal agents (NGHA) have been recommended in association with ADT in the treatment algorithm for mHSPC.
Apalutamide is a potent nonsteroidal androgen receptor (AR) antagonist, proven to be effective in prolonging survival and delaying progression in mHSPC patients as compared to ADT plus placebo [3].
Apalutamide (Erleada®) + ADT is indicated in this setting.
Real-world data on recently approved drugs are of increasing interest in order to assess efficacy and safety in a more heterogeneous and broader population, especially for an expected long-term treatment [4].

1.1 Apalutamide: inner workings of action and clinical results

1.1.1 From preclinical development to phase II study

Metastatic prostate cancer is associated with a lethal phenotype. Besides ADT, NGHAs have emerged as viable therapeutic strategy for CRPC as well as for HSPC, prolonging survival in prostate cancer patients.
Among NGHAs, Apalutamide has been designed as an orally available competitive nonsteroidal AR antagonist, with inhibitory activity on AR nuclear translocation and binding to androgen response elements; moreover, it doesn't exhibit the agonist activity shown by bicalutamide in the context of AR overexpression [5]. Of note, Apalutamide antitumor activity on LNCaP/AR tumors in intact mice suggested its potential in the treatment of HSPC in combination with ADT [5].
Phase I study on 30 CRPC patients found a maximum efficacious dose of 240 mg once daily (OD), with a large therapeutic interval and a PSA response rate at 12 weeks of 46.7% [6].
Subsequent phase II study enrolled 51 patients with nonmetastatic castration resistant prostate cancer (nmCRPC) at high risk of progression to metastatic disease, defined as having a PSA doubling time (dt) ≤10 months or a PSA ≥8 ng/ml. Apalutamide was administered orally at the dose of 240 mg OD and was associated with an 89% PSA response rate at week 12 (primary endpoint) and a median time to PSA progression of 24 months [7]. Treatment discontinuation rate due to adverse events was of 18% and the most common reported adverse event was fatigue (61% any grade) while grade 3 adverse events were uncommon.
Notably, even though Apalutamide binds with low affinity $GABA_A$ receptor, seizure was not reported in either phase I or phase II study [5-7].

1.1.2 SPARTAN randomized phase III study

In SPARTAN trial [8] the efficacy of Apalutamide was tested, accordingly to previous phase II study, in a population of nmCRPC patients with high risk of progression to metastatic disease, defined as having no

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sign of metastatic disease at screening imaging (bone scan and total body CT scan) and a PSAdt ≤10 months. 1207 patients were randomly assigned with a 2:1 ratio to the Apalutamide arm (Apalutamide 240 mg daily, N=806) and to placebo arm (N=401). All patients in both arms continued ADT.

The prespecified primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the first detection of distant metastasis on imaging (as assessed by blinded independent central review) or death from any cause, whichever occurred first.

Secondary endpoints were time to metastases, progression-free survival (PFS), time to symptomatic progression, overall survival (OS) and time to initiation of cytotoxic chemotherapy.

Exploratory endpoints included time to PSA progression, PSA response rate, patient-reported outcomes and second PFS (PFS2).

The study followed the Prostate Cancer Working Group (PCWG) 2 guidelines [9].

The majority of patients received a primary treatment with radical intent on the prostate (76.6% prostatectomy or radiation to the prostate) and became castration resistant after a first biochemical relapse, with a median time from initial diagnosis to randomization of almost 8 years.

PSAdt was ≤6 months in over 70% of patients.

The primary endpoint of MFS was met, with a significant HR of 0.28 in favor of Apalutamide (MFS 40.5 vs 16.2 months), leading to study unblinding and allowing for crossover from placebo to Apalutamide arm.

Notably more than a half of patients relapsed on bone and this was independent from treatment arm.

All secondary endpoints were positive and favored Apalutamide. After 12 weeks PSA response rate was 89.7% in Apalutamide group.

Patient-reported outcomes indicated that patients in both arms maintained stable overall health-related quality of life over time.

The most common subsequent treatment was abiraterone plus prednisone (approximately 75% in both arms): PFS2 was significantly longer in Apalutamide arm (HR 0.49).

Adverse events (AEs) of any grade were reported at least once in 96.5% of patients in Apalutamide arm, with a 10.6% of treatment discontinuation rate due to AEs. Most reported AEs were fatigue (30.4%), hypertension (24.8%), rash (23.8%) and diarrhea (20.3%). Of these, most events were of low grade, while grade ≥3 events principally consisted in hypertension (14%) and rash (5.2%).

Treatment related AEs of special interest comprised fractures (11.7%), dizziness (9.3%), hypothyroidism (8.1%), mental-impairment disorders (5.1%) and 2 cases of seizures.

Data from the first interim analysis [8] were not already mature to show a clear OS benefit for Apalutamide in nmCRPC, however upon these results Apalutamide was approved for this setting in the US and EU.

The second interim analysis was conducted after a median follow-up of 41 months and showed a 25% reduction in the risk of death from any cause in favor of Apalutamide, despite 19% crossover rate from placebo to Apalutamide arm [10].

SPARTAN final analysis for OS was prespecified, event-driven and took place after a median follow-up of 52 months. Apalutamide reduced the risk of death of 22% (HR 0.78), with a median treatment duration of 32.9 months vs 11.5 months for placebo and a final OS of 73.9 months vs 59.9 months) [11].

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With additional follow-up, the safety profile of Apalutamide added to ADT remained unchanged with no evidence of cumulative toxicity.
The Authors discussed the role of early intensification of androgen signaling inhibition with a novel AR antagonist in patients with CRPC without metastases and at high risk to develop distant recurrence. SPARTAN results were corroborated with similar data from the PROSPER and ARAMIS trials, meeting their primary endpoint of MFS and showing benefit in OS for the addition of enzalutamide or darolutamide to ADT in the same setting.
Hence, patients with nmCRPC at high risk of progression based on PSAdt should receive a NGHA in addition to ADT.

1.1.3 TITAN randomized phase III study

The efficacy and safety of Apalutamide were also assessed in a randomized, multicenter, double-blind, placebo-controlled phase III trial in the hormone sensitive setting [12]. The TITAN study enrolled mHSPC patients, as documented on the basis of a positive bone scan (at least one lesion) with or without visceral or lymph-node involvement.
Eligible patients had an ECOG PS of 0 to 1 and could have received prior local treatments (if completed 1 year before randomization) as well as prior treatment with docetaxel (for a maximum of six cycles, without evidence of disease progression before randomization) and ADT (for no more than six months for mHSPC or three years for localized prostate cancer).
Patients were excluded from participation if they had a medical history of severe angina, myocardial infarction, congestive heart failure, thromboembolic events, predisposition to seizure or recent ventricular arrhythmias.
Among stratification criteria is worth mention previous docetaxel administration.
Patients were randomized according to a 1:1 ratio to receive Apalutamide 240 mg OD (N=525) or placebo (N=527). Coprimary endpoints were radiological progression-free survival (rPFS, defined as the time from randomization to first radiological evidence of progression or death from any cause, whichever occurred first) and OS. Patients were assessed for efficacy according to the PCWG-2 criteria.
Secondary endpoints were time to cytotoxic chemotherapy, time to pain deterioration by means of Brief Pain Inventory – Short Form (BPI-SF) questionnaire, time to chronic opioid use and time to skeletal-related event. A keynote secondary endpoint was evaluation of treatment efficacy in patients with low-volume vs high-volume disease as defined in CHAARTED study [13].
At first interim analysis (median follow-up of 22.7 months) TITAN study met the rPFS coprimary endpoint, with a two years rPFS rate of 68.2% for Apalutamide arm compared to 47.5% in the placebo arm (HR 0.48). The effect of Apalutamide on rPFS was consistent across subgroups, including previous docetaxel and both high and low volume disease.
A significant OS benefit in favor of Apalutamide arm was also evident at the 24 months landmark analysis (OS rate 82.4% vs 72.4%, HR 0.67).

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Formal analysis of secondary endpoints showed significant improvement in time to cytotoxic chemotherapy in favor of Apalutamide arm, while the hierarchical testing sequence failed to show statistically significant benefit in subsequently tested endpoints because of the paucity of the events.
The frequency of grade 3-4 AEs was similar between study arm (42.2% for Apalutamide vs 40.8% for placebo) and treatment discontinuation rate due to AEs was low (8% vs 5.3% in Apalutamide and placebo-treated patients). Most commonly reported AEs in Apalutamide arm were rash (27.1%), hot flushes (22.7%), fatigue (19.7%), hypertension (17.7%), back pain (17.4%) and arthralgia (17.4%). Grade 3-4 AEs reported in ≥5% of Apalutamide-treated patients were limited to hypertension (8.4%) and rash (6.3%).
Among AEs of special interest, falls were seen in 7.4% of Apalutamide-treated patients (vs 7.0% in placebo arm) and fracture rate was 6.3% (vs 4.6% in placebo arm); seizure was observed in 5 patients (3 in Apalutamide arm). Compared to SPARTAN trial, the differences in the incidence of falls and fractures between the apalutamide group and the placebo group were smaller.
The positive results from first preplanned interim analysis led to unblinding of treatment arms and subsequent crossover from placebo to apalutamide arm.
Final analysis was undertaken after a median follow-up of 44 months and confirmed a significant 35% reduction of the risk of death (OS not reached vs 52.2 months, HR 0.65) despite 39.5% crossover rate [14]. When adjusting for crossover the risk of death was reduced by 48%.
OS rates at 48 months were 65.1% vs 51.8% for Apalutamide and placebo treated patients respectively.
The benefit was consistent across high/low-volume and high/low risk (as per LATITUDE [15]) subgroups, while the interaction between treatment and any of the other subgroups (including previous docetaxel and visceral disease) was not statistically significant for OS.
The benefit observed across secondary endpoints was maintained at final analysis: of note the exploratory endpoint of PFS2 favored Apalutamide arm with PFS2 events occurring in 33% and 46.7% of Apalutamide- and placebo-treated patients respectively.
Analysis of patient-reported outcomes after 44 months of follow-up showed that baseline health-related quality of life (HRQoL) was maintained with the addition of Apalutamide to ADT.
Safety profile remained unchanged after additional follow-up.
The Author concluded that after a longer follow-up the data on OS and PFS2 emphasize the benefit of early institution of potent androgen signal inhibition with Apalutamide plus ADT in the hormone-sensitive phase and before progression to CRPC.

1.2 Safety of hormonal treatments: special considerations

Prostate cancer patients treated with ADT are exposed to chronic consequences of iatrogenic hypogonadism, which are more pronounced with the longer duration of treatments.
Observation and follow-up of metabolic toxicities related to combined androgen blockade with ADT and Apalutamide is of primary interest in the context of a real-world observational study.

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1.2.1 Bone fragility

Bone tissue apparently not involved by metastatic disease is frequently altered due to the effect of deranged bone metabolism on hormonal therapies, leading to increased risk of fragility fractures and disability [16]. This effect is even increased with the more recent introduction of NGHA as showed by data on fragility fractures in the experimental arms of CRPC studies [8; 17-20].
Bone loss is a rapid phenomenon under androgen deprivation, being observed by bone biomarkers after only 6 months and by BMD after 12 months of treatment [21].
Bone Mineral Density (BMD) by DXA scan is the standard approach to evaluate bone strength and its variation after therapies, being recommended by international guidelines for the assessment of secondary osteoporosis in cancer patients treated with hormonal deprivation [22].
In fact, after 12 months of ADT, median BMD loss is of 3.6% at lumbar spine, 3.11% at femoral neck and 1.59% for total hip [23].
This condition, named cancer treatment induced bone loss (CTIBL), is deemed responsible for the high fragility fracture rate seen in treated prostate cancer patients [16,24].
Recently, the description of a discrepancy between the estimated fracture risk by BMD and the observation of subclinical vertebral fractures [25] prompted investigators to incorporate into risk algorithms the so-called Trabecular Bone Score (TBS), a bone quality index [26]. TBS is a new tool that allows to evaluate bone microarchitecture, with special application in subjects at risk for fragility fracture in presence of normal BMD values [27].
Notably, both BMD and TBS can be simultaneously obtained through DXA scan.

1.2.2 Metabolic syndrome

Treatment with ADT is associated with increased risk of cardiovascular events, which is even more pronounced with NGHAs as seen in mCRPC clinical trials [28]. In TITAN study ischemic heart disease was reported in 3.3% vs 1.6% of patients of experimental and control arms, while hypertension was one of the most reported all-grade and high-grade adverse events [12,14].
One mechanism proposed for the increased cardiovascular risk under androgen deprivation is the development of a clinical picture that mimics many characteristics of metabolic syndrome.
In fact observational studies show a consistent increase in the incidence of type 2 diabetes, dyslipidemia, obesity and consequently of ischemic heart disease [29,30].
Obesity is a major risk factor for cardiovascular events and is commonly defined using the Body Mass Index (BMI), which however doesn't fully capture the increase of fat body mass (FBM) under ADT, being also influenced by changes in lean body mass (LBM), consistently decreasing in these patients [31].
DXA scan [32] is the main tool to assess body composition and its modifications upon therapies.

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In conclusion, prostate cancer patients treated with ADT and a NGHA should be advised to lead a healthy lifestyle (e.g. fat free diet, regular physical activity) and followed-up for metabolic alterations, in order to prevent major adverse events such as fractures or cardiovascular events.

2. Study purpose

This study is undertaken to describe the effectiveness of Apalutamide plus ADT in real world mHSPC patients treated according to reimbursement and clinical practice in Italy.

3. Study design, objectives and endpoints

This is a multicenter, observational, prospective clinical trial designed to explore efficacy and safety of Apalutamide plus ADT in a real-world population of patients, due to receive apalutamide treatment according to reimbursement rules in the metastatic hormone sensitive setting.
Effectiveness will be measured by estimated probability of rPFS at 24 months from treatment initiation.
Safety will be monitored through registration of adverse events (AEs) graded as per the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [33].
Furthermore, whole body DXA scan will be applied to observe and follow-up bone metabolism and body composition. The application of a whole body scan could cause the exposition to a slightly higher radiation dose with respect to lumbar spine and total hip DXA [34]. However, the absolute additional dose is negligible when compared with the naturally-occurring background radiation exposure [35], so that the cost-effectiveness of whole body DXA scan is unlikely to differ from a lumbar spine/total hip examination.
Patient-reported outcomes will be obtained through quality of life questionnaires.

3.1.1 Primary objective

Evaluation of the effectiveness of Apalutamide plus ADT in a real-world population of mHSPC patients.

3.1.2 Primary endpoint

The rate of radiological progression free survival (rPFS) at 2 years from treatment initiation will be measured as a primary endpoint. rPFS will be defined as the time from treatment beginning to the first imaging-based evidence of progressive disease or death, whichever occurs first.

3.2.1 Secondary objectives

- Reporting of real- world patient population characteristics.
- Effectiveness of Apalutamide plus ADT with follow-up longer than 24 months.
- Safety and quality of life changes during treatment with Apalutamide plus ADT.

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3.2.2 Secondary endpoints

Reporting of:

- Frequency of conventional or NG imaging at enrolment.
- Rate of dose modification or treatment discontinuation.
- Time to PSA progression (time from treatment initiation to PSA progression according to PCWG-3 criteria [36]) and PSA response rate (proportion of patients achieving at least 50% reduction from baseline).
- Time to pain progression (a 2-point minimal increase on BPI-SF item 3 “worst pain”).
- Overall survival (OS), defined as the time from treatment initiation to death from any cause.
- Effectiveness of Apalutamide plus ADT according to NGI based enrolment (defined as PSA response rate, rPFS and OS in patients whose metastatic disease was staged through a NGI at baseline) will be described for patient with available data.
- Occurrence rate of clinically relevant TEAEs (as per CTCAE v.5.0).
- Prevalence of clinical fractures and morphometric vertebral fractures assessed through DXA scan

Changes in:

- Bone pain assessed through BPI-SF questionnaire (pain relief is considered in case of score reduction to 4 or less, while a 2-point minimum decrease is considered significant [37].
- Quality of life evaluation through FACT-P questionnaire (clinically meaningful changes correspond to 6 points difference in total score) [38].
- BMD, TBS, FBM and LBM assessed through DXA scan.

4. Study Population

4.1 Inclusion criteria

1. Histological diagnosis of prostate carcinoma.
2. Age > 18 years.
3. Patients complying with Apalutamide reimbursed indication in mHSPC setting.
4. Subject capable to swallow the Study's medication and to comply with the Study's requirements.
5. Fertile patients and their partners must agree to use methods of contraception.
6. Signed informed consent.

4.2 Exclusion criteria

1. Patients with evidence of castration resistant disease (raising PSA despite castrate testosterone levels).
2. Patients previously treated with Apalutamide, another NGHT or an investigational product (before or in combination with Apalutamide) are excluded.

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3. Any condition or reason that, in the opinion of the Investigator, interferes with the ability of the patient to participate in the study, which places the patient at undue risk, or complicates the interpretation of safety data.

5. Study design

This is a prospective non-interventional multicentric study designed to explore effectiveness and safety of Apalutamide plus ADT in a real world setting of mHSPC patients.
Prostate cancer patients with metastatic hormone sensitive disease will receive Apalutamide at the standard dose of 240 mg OD; dose reductions to 180 mg or 120 mg OD, in case of toxicity, are allowed in accordance with the approved local labeling. Androgen deprivation therapy with LHRH analog will be maintained throughout treatment.

The total duration of study period will be of 48 months, comprehensive of 24 months for enrollment and at least 24 months of observation up to study completion.

The treatment will be continued until disease progression, withdrawal of consent or unacceptable toxicity throughout the study period. Upon completion of study period patients still responding to study treatment will continue treatment outside the study, as for clinical practice, and will be followed-up for OS.
Patients progressing during or after study period will be offered standard of care treatment.
Patients will be observed for effectiveness and safety of Apalutamide plus ADT treatment according to clinical practice. However, since a consensus on a standard follow-up schedule does not exist for mHSPC setting, participating Centers will be required to re-evaluate patients inside the following minimum prespecified time intervals:

Physical examination, vital signs, AEs, blood test (as for clinical practice):

- Baseline and at least every 2 months thereafter until study completion.

Routine blood test should include at least the following: blood cell count, glucose, creatinine, bilirubin (reflex), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), calcium, prostate specific antigen (PSA), testosterone total, follicle stimulating hormone (FSH).

- In case of a first increase in PSA value, next PSA test should be done within the next 4 weeks.

Imaging (as for clinical practice):

- Baseline and at least once per year (+/- 6 weeks) until study completion.
- In case of confirmed PSA progression and/or clinical progression, imaging should be reassessed within the next 4 weeks.

It is recommended that disease reassessment is done with the same imaging modality that was used for the definition of metastatic disease at baseline.

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DXA scan for changes in bone mineral density and body composition (as for clinical practice):

- Baseline
- Month 12
- Month 24

FACT-P and BPI-SF questionnaires:

- Baseline
- Month 6
- Month 12 and at least once per year until study completion.

6. Treatment evaluation

Disease response evaluation will be done as per clinical practice, through conventional imaging (CT scan of chest, abdomen and pelvis and bone scan) or NGI (choline PET, PSMA PET or WB-MRI), based on imaging modality used at baseline for disease staging.

- CT scan will assess response to treatment according to RECIST 1.1 criteria [39].
- Bone scan will assess response to treatment according to PCWG-3 criteria [36].
- Choline PET scan will assess disease response according to PERCIST criteria [40].
- PSMA PET scan will assess disease response according to PROMISE criteria [41].
- WB-MRI will assess disease response according to MET-P-RADS criteria [42].

Final results will be also analyzed by prespecified subgroups of conventional vs next-generation imaging.

7. Toxicity: monitoring and reference parameters

7.1 Apalutamide administration

Apalutamide tablets will be administered at the standard dose of 240 mg daily in single oral dose of four 60 mg capsules according to local labelling.

Medical castration with agonists or antagonists of LHRH must be continued in patients not previously submitted to surgical castration.

If a dose is missed, the missed dose should not be taken less than 12 h before the next dose.

7.2 Anticipated adverse events (AEs)

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The most frequent AEs experienced by ≥ 10% of subjects treated with Apalutamide in descending order of frequency were fatigue, skin rash, hypertension, hot flush, arthralgia, diarrhea, fall and weight decreased. Other important adverse reactions include fractures and hypothyroidism. For more details refer to current approved Summary of Product Characteristics (SmPC).

7.3 Dose modifications

Dose modification and/or treatment interruption will be proposed to patients experiencing high grade or intolerable AEs, according to Apalutamide SmPC

7.4 Potential drug interactions

Drug-drug interactions and relevant indications are reported in the SmCP.

8. Sample size and statistical methods

The descriptive analysis will consist of appropriate statistical methods (positional indices such as mean, median, standard deviation, minimum and maximum for continuous variables and tables of frequency for categorical variables).

PFS and OS will be computed through Kaplan-Meyer curves and rPFS after 2 years from treatment (primary endpoint) will be shown as proportion of progression-free and 95% C.I.

Secondary endpoints will be first evaluated with descriptive methods mentioned above, and then to investigate possible associations between factors of interest concerning the patient, the treatment and/or the disease (such as frequency of conventional or NG imaging at enrolment, rate of dose modification or treatment discontinuation, rate of clinically relevant TEAEs or prevalence of clinical fractures) we will use the chi square test (or the exact Fisher test, when required) on contingency tables concerning pairs of categorical variables, while we will use a Student t-test (or the corresponding non-parametric, when necessary) for the association between categorical and continuous variables and the correlation index of Pearson (or Spearman, when necessary) for continuous variables only.

The study will be planned as a multicentric observational, prospective study and based on the incidence of new patients with metastatic prostate cancer and the number of centers involved, we plan to enroll a total of 220 patients during the accrual time (2 years).

Considering the available information in literature [12] about the proportion, we can assume p=0.68 and from the formula $N = \frac{z^2_{\alpha/2} \cdot p(1-p)}{(MoE)^2}$ results that for a 95% confidence interval with that sample size we got a precision (Margin of Error) of about 6%.

9. Ethical aspects and good clinical practice

9.1 Ethical principles

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This study will be conducted in accordance with the present Protocol and under the Good Clinical Practice (GCP) principles defined by DM 15th July 1997, number 162 and in compliance with the Italian Ministerial Decree of 17/12/2004 (no-profit studies) and Guidelines for observational studies on medicinal products issued by the AIFA (Italian Medicines Agency) on 20th March 2008
The Protocol respects the principles established at 18th World Medical Assembly (Helsinki, 1964) and the last revision at 52nd (Edimburgh, 2000) World Medical Assemblies.

9.2 Informed consent

Each patient will provide written informed consent before any protocol-specific tests or evaluation are performed.
A properly executed, written informed consent, in compliance with Declaration of Helsinky, ICH GCP and local regulations will be obtained from each patient before entering the patient in the trial.
The informed consent document used will be evaluated and approved by the Ethics Committee.
The Investigator will provide copies of the signed informed consent form to each patient (or to the patient's legal representative) and will maintain the signed original document within the patient's record file per local requirements. The Investigator will also fully document the informed consent process in the patient's source record.

9.3 Maintaining Patient Confidentiality

All reports and patient samples will be identified only by a patient ID in order to maintain patient confidentiality.

9.4 Ethics Committee

The study will be submitted for approval to the local Ethics Committee that will approve the Study's identification (title, protocol number and version), the protocol documentations (protocol, informed consent) and their version's date.
All the data will be collected using the RedCap system, installed on a hardware platform managed by the Data Processing Center (CED) c/o the coordinating center (ASST Spedali Civili di Brescia).

9.5 Pharmacovigilance

DEFINITIONS
ADVERSE EVENT (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non investigational) product, whether or not related to that medicinal (investigational or non investigational) product. (Definition per International Conference on Harmonisation [ICH]). This includes any occurrence

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that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

ADVERSE REACTION (AR):
An adverse drug reaction (ADR) is defined as a response to a medicinal (investigational or non-investigational) product that is noxious and unintended. The phrase "response to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is possible, probable or very likely.
An ADR, in contrast to an adverse event, is characterized by the fact that a causal relationship between the medicinal product and the occurrence is suspected. All adverse events judged by either the reporting physician or the sponsor as having a reasonable causal relationship to a medicinal product qualify as ADRs.

SERIOUS ADVERSE EVENT (SAE):
A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening

(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

A SERIOUS ADVERSE REACTION is an ADR which meets seriousness criteria

UNEXPECTED ADVERSE REACTION (UAR): an adverse reaction, the nature or severity of which is not consistent with the applicable product information (investigator's brochure for an unauthorized investigational product or summary of product characteristics for an authorized product)

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR): any unexpected adverse reaction that is not consistent with the product information (unexpected) that at any dose: results in death; is life threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe); requires hospitalization or

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prolongation of existing hospitalization; results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect

Examples of adverse events include the following:

- A change, excluding minor fluctuations, in the nature, severity, frequency, or duration of a pre-existing condition
- Development of an intercurrent illness during the study
- Development of symptoms that may or may not be related to the use of a concomitant medication or investigational product
- Injury or accidents: if a medical condition is known to have caused the injury or accident, the medical condition and the accident should be reported as 2 separate medical events (for a fall secondary to dizziness, both “dizziness” and “fall” should be recorded separately)
- Investigational abnormalities (laboratory parameters, vital signs, ECG data) should be defined as adverse events only if the abnormality meets one of the following criteria:
    - · Induces clinical signs or symptoms
    - · Needs active intervention
    - · Needs interruption or discontinuation of study medication
    - · Abnormality or investigational value is clinically significant in the opinion of the investigator

An adverse event does not include the following:

- Medical or surgical procedures (surgery, endoscopy, tooth extraction, transfusion); the condition that leads to the procedure is an adverse event
- Pre-existing diseases or conditions present or detected prior to the start of study drug administration that do not worsen
- · Situations where an untoward medical event has not occurred (planned hospitalization for an elective procedure as known at the time of informed consent)

ASSESSMENT OF CAUSALITY

The causal relationship to treatment is determined by a physician and should be used to assess all adverse events.

The causal relationship can be one of the following:

Related

There is a reasonable causal relationship between administration of the medicinal product [or the product under study] and the adverse event.

Not Related

There is not a reasonable causal relationship between administration of the medicinal product [or the product under study] and the adverse event.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

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ASSESSMENT OF SEVERITY

The grade will be made using the following general categorical descriptors:
Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.
Moderate: Sufficient discomfort is present to cause interference with normal activity.
Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.
The participating physician should use clinical judgment in assessing the severity of events not directly experienced by the subject (eg, laboratory abnormalities).

SPECIAL SITUATIONS (SS)

Safety events that require reporting and/or safety evaluation include, but are not limited to:

a. Drug exposure during pregnancy (maternal and paternal)
b. Suspected transmission of any infectious agent via administration of the Product under study
c. Overdose of Product under study
d. Exposure to Product under study from breastfeeding
e. Suspected abuse/misuse of Product under study
f. Inadvertent or accidental exposure to Product under study
g. Any failure of expected pharmacological action (i.e., lack of effect) of Product under study
h. Medication error (includes potential, intercepted or actual) with or without patient exposure to the Janssen Product(s) under study, e.g., name confusion)
i. Unexpected therapeutic benefit

These safety events may not meet the definition of an adverse event; however, they are treated in the same manner as adverse events and reported in CRF

Special situations should be recorded in the CRF. The SSs a) and b) and any other that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and reported to the sponsor within 24 hours of them becoming aware of the event

If the clinician of the Coordination Research is in disagreement with the causality evaluation provided by the Investigator, both their viewpoints must be reported in SUSAR form.

REPORTING

All adverse events, whether or not related to the study drug, must be fully and completely documented on the adverse event case report form and in the patient's clinical record. Any adverse event resulting in

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discontinuation of study treatment must be recorded on the appropriate case report form as well as documented in the patient's clinical record.
All Serious Adverse events should be reported by the investigator within 24 hours of becoming aware to:

farmacia.sperimentazioni@asst-spedalicivili.it
Reporting of SAE should be done using the SAE/SUSAR FORM.

Notification will also be sent to the local Pharmacovigilance unit of Marketing Authorization Holder.

The AESI (Adverse Events of Special Interest) assessed as non-serious must be reported to Sponsor within one working day of the Investigator becoming aware of the event (with the same procedure for SAE/SUSAR) All serious adverse events should be reported immediately, anyway within 24 hours, since the investigator becomes aware of the event.
Any additional information, if collected, should be reported as a follow-up to the initial report: within 7 days of the initial report for the SUSAR that results in death/life threatening, within 15 days for all others.
For reported deaths of a subject, the investigator should supply the sponsor and the Ethics Committee with any additional information requested.
In addition, report of adverse events will be done, according to current local law, to local Health Authorities.

Once a year throughout the clinical trial, the Pharmacovigilance-Trial Responsible provides the Member States where the clinical trial is being conducted and the Ethics Committee with a listing of all suspected serious adverse reactions which have occurred over this period.

CONTRACEPTION

Male patients and their female partners of childbearing potential must use 2 acceptable methods of birth control (1 of which must include a condom as a barrier method) from the screening visit through 4 months after the last dose of study drug.
The 2 acceptable methods of birth control are as follows:

1. A condom (barrier method is required)
   AND
2. One of the following is required:

Established use of oral, injected, or implanted hormonal method;
Placement of an intrauterine device (IUD) or intrauterine system (IUS);
Additional barrier method including contraceptive sponge or occlusive cap (diaphragm or cervical/vaults caps) with spermicidal foam/ gel /film/ cream/suppository;
Tubal ligation performed at least 6 months before screening;
Vasectomy or other surgical castration at least 6 months before screening.
Patients must not donate sperm from first dose of study drug through 4 months after the last dose of study drug.

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If during the conduct of the clinical trial, a male subject impregnates his partner the subject should report the pregnancy to the Investigator. The Investigator will report the pregnancy to the farmacia.sperimentazioni@asst-spedalicivili.it as an SAE form within 24 hours, since the investigator becomes aware of the event.
The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information. The Investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome.
Notification will also be sent to the local Pharmacovigilance unit of Marketing Authorization Holder.

9.6 Data capture

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.
All the data will be collected using RedCap – ASST Spedali Civili platform, and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the investigator to allow direct access to his or her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection.

9.7 Financing

The Promoter asked for a financing to partially cover the cost of the Study, in full compliance with Italian law (decree December 11, 2014) on transparency and conflict of interest, and in accordance with the principal of scientific independence

9.8 Publication of the results

Final manuscript with study results will be submitted to international indexed peer-reviewed journals whose target is oncology and/or urologic oncology.
Data will also be submitted before publication as an abstract to international congresses.

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11.1 Annex 1: Quality of Life questionnaires (FACT-P, BPI-SF)

FACT-P (Versione 4)

Sotto abbiamo elencato delle affermazioni ritenute importanti da persone con la sua stessa malattia. **La preghiamo di cerchiare o contrassegnare un solo numero per riga per indicare la sua risposta in riferimento agli <u>ultimi 7 giorni</u>.**

	BENESSERE FISICO	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GP1	Mi manca l'energia	0	1	2	3	4
GP2	Ho nausea	0	1	2	3	4
GP3	Ho difficoltà ad occuparmi delle necessità della mia famiglia a causa delle mie condizioni fisiche	0	1	2	3	4
GP4	Ho dolori	0	1	2	3	4
GP5	Mi danno fastidio gli effetti collaterali della cura	0	1	2	3	4
GP6	Mi sento male	0	1	2	3	4
GP7	Sono costretto/a a trascorrere del tempo a letto	0	1	2	3	4

	BENESSERE SOCIALE/FAMILIARE	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GS1	Mi sento vicino/a ai miei amici	0	1	2	3	4
GS2	La mia famiglia mi sostiene moralmente	0	1	2	3	4
GS3	Ho appoggio morale dai miei amici	0	1	2	3	4
GS4	La mia famiglia ha accettato la mia malattia	0	1	2	3	4
GS5	Sono soddisfatto/a della comunicazione nella mia famiglia a proposito della mia malattia	0	1	2	3	4
GS6	Mi sento vicino/a al mio compagno/alla mia compagna (o alla persona che mi offre il maggiore appoggio)	0	1	2	3	4
Q1	*Indipendentemente dalla Sua attività sessuale, La preghiamo di rispondere alla seguente domanda. Se preferisce non rispondere, barri questa casella* ☐ *e passi alla prossima sezione.*					
GS7	Sono soddisfatto/a della mia attività sessuale	0	1	2	3	4

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FACT-P (Versione 4)

La preghiamo di cerchiare o contrassegnare un solo numero per riga per indicare la sua risposta in riferimento agli ultimi 7 giorni.

	BENESSERE EMOTIVO	Per niente	Un po'	Abba-stanza	Molto	Moltis-simo
GE1	Mi sento triste	0	1	2	3	4
GE2	Sono soddisfatto/a di come sto affrontando la mia malattia	0	1	2	3	4
GE3	Sto perdendo la speranza nella lotta contro la mia malattia	0	1	2	3	4
GE4	Sono nervoso/a	0	1	2	3	4
GE5	Mi preoccupo al pensiero della morte	0	1	2	3	4
GE6	Mi preoccupo che le mie condizioni possano peggiorare	0	1	2	3	4

	BENESSERE FUNZIONALE	Per niente	Un po'	Abba-stanza	Molto	Moltis-simo
GF1	Sono in grado di lavorare (si intende anche il lavoro a casa)	0	1	2	3	4
GF2	Il mio lavoro (si intende anche il lavoro a casa) mi gratifica	0	1	2	3	4
GF3	Riesco a godermi la vita	0	1	2	3	4
GF4	Ho accettato la mia malattia	0	1	2	3	4
GF5	Dormo bene	0	1	2	3	4
GF6	Provo ancora piacere nel dedicarmi ad attività di tempo libero	0	1	2	3	4
GF7	Al momento, sono soddisfatto/a della qualità della mia vita	0	1	2	3	4

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FACT-P (Versione 4)

La preghiamo di cerchiare o contrassegnare un solo numero per riga per indicare la sua risposta in riferimento agli <u>ultimi 7 giorni</u>.

	ULTERIORI PROBLEMI	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
C2	Sto dimagrendo	0	1	2	3	4
C6	Il mio appetito è buono	0	1	2	3	4
P1	Ho dolori che mi danno fastidio	0	1	2	3	4
P2	In certe zone del corpo sento dolore	0	1	2	3	4
P3	Il dolore mi impedisce di fare le cose che vorrei	0	1	2	3	4
P4	Sono soddisfatto del mio attuale livello di benessere	0	1	2	3	4
P5	Riesco a sentirmi uomo	0	1	2	3	4
P6	Ho difficoltà ad andare di corpo	0	1	2	3	4
P7	Ho difficoltà ad urinare	0	1	2	3	4
BL2	Urino più frequentemente del solito	0	1	2	3	4
P8	I miei problemi nell'urinare limitano le mie attività	0	1	2	3	4
BL5	Sono in grado di avere e mantenere un'erezione	0	1	2	3	4

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Breve questionario per la valutazione del dolore

Faccia un cerchio intorno al numero che meglio descrive quanto, nell' ultime 24 ore, il dolore ha influito negativamente sulle seguenti cose:

A. Attivita in genere

0 1 2 3 4 5 6 7 8 9 10

Non ha influito negativamente — Ha influito del tutto negativamente

B. Umore

0 1 2 3 4 5 6 7 8 9 10

Non ha influito negativamente — Ha influito del tutto negativamente

C. Possibilità di camminare

0 1 2 3 4 5 6 7 8 9 10

Non ha influito negativamente — Ha influito del tutto negativamente

D. Lavoro (sia in casa che fuori)

0 1 2 3 4 5 6 7 8 9 10

Non ha influito negativamente — Ha influito del tutto negativamente

E. Rapporti con le altre persone

0 1 2 3 4 5 6 7 8 9 10

Non ha influito negativamente — Ha influito del tutto negativamente

F. Sonno

0 1 2 3 4 5 6 7 8 9 10

Non ha influito negativamente — Ha influito del tutto negativamente

G. Godersi la vita

0 1 2 3 4 5 6 7 8 9 10

Non ha influito negativamente — Ha influito del tutto negativamente

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Regione Lombardia
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Breve questionario per la valutazione del dolore

Nella nostra vita, tutti abbiamo provato dolore in alcune occasioni (ad esempio mal di testa, contusioni, mal di denti). Ha mai avuto dolori diversi da questi nell'ultime 24 ore? ☐ Si ☐ No

Valuti il suo dolore facendo un cerchio intorno al numero che meglio descrive la **massima** intensità del suo dolore nell'ultime 24 ore.

0	1	2	3	4	5	6	7	8	9	10
Nessun Dolore										Peggior dolore immaginabile

Valuti il suo dolore facendo un cerchio intorno al numero che meglio descrive la **minima** intensità del dolore nell'ultime 24 ore

0	1	2	3	4	5	6	7	8	9	10
Nessun Dolore										Peggior dolore immaginabile

Valuti il suo dolore facendo un cerchio intorno al numero che meglio descrive l'intensità **media** del suo dolore.

0	1	2	3	4	5	6	7	8	9	10
Nessun Dolore										Peggior dolore immaginabile

Valuti il suo dolore facendo un cerchio intorno al numero meglio descrive l'intensità del suo dolore **attuale**.

0	1	2	3	4	5	6	7	8	9	10
Nessun Dolore										Peggior dolore immaginabile

Nell'ultime 24 ore, quanto sollievo ha avuto dalle cure o dalle medicine? Indichi con un cerchio la percentuate che meglio si adatta.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Nessun Giovamento										Scomparsa del dolore

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11.2 Annex 2: List of abbreviations.

ADT: androgen deprivation therapy

AE: adverse event

AR: adverse reaction

BMD: bone mineral density

BPI: Brief Pain Inventory

CRF: case report form

CT: computed tomography

CTCAE: common terminology criteria for adverse events

CYP: cytochrome P

DXA: dual energy x-ray absorptiometry

ECOG PS: eastern cooperative oncology group performance status

FBM: fat body mass

GCP: Good Clinical Practice

HR: hazard ratio

IUD: intrauterine device

IUS: intrauterine system

LBM: lean body mass

LHRH: luteinizing hormone releasing hormone

mCRPC: metastatic castration resistant prostate cancer

OD: once daily

OS: overall survival

PCWG: Prostate Cancer Working Group

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PFS: progression free survival

PSA: prostate specific antigen

RECIST: response evaluation criteria in solid tumors

rPFS: radiological progression free survival

SAE: serious adverse event

SmPC: summary of product characteristics

SUSAR: suspected unexpected adverse reaction

TBS: trabecular bone score

UAR: unexpected adverse reaction

ULN: upper limit of normal

WB-MRI: whole body magnetic resonance imaging