Protocol

A multicenter randomized Phase III trial of enzalutamide versus abiraterone as a first-line endocrine therapy for castration-resistant prostate cancer

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Abstract

Background: Recent large-scale randomized studies have demonstrated that two new hormone preparations (abiraterone and enzalutamide) prolong survival in docetaxel-treated or -naive castration-resistant prostate cancer (CRPC) patients. Nonetheless, no reports have directly compared antitumor effects between these two agents, and no clear guidelines are available for choosing between the agents.

Objective: The present clinical study is aimed at comparing antitumor effects and adverse events between abiraterone and enzalutamide by allocating CRPC patients deemed not indicated for docetaxel treatment to receive either of the two agents.

Methods: This study is an open-label, comparative study allocating CRPC patients to abiraterone- or enzalutamide-treatment arms (allocation factors: age <70 versus ≥70 years and presence/absence of metastases) and assessing the treatment results. Each arm will contain 25 patients. Upon confirmation of prostate-specific antigen (PSA) failure or progression on imaging, patients undergo cross-over to receive the alternative study drug. The primary endpoint is PSA response rate (percentage of patients with a decrease in PSA level by ≥50%) in the abiraterone- and enzalutamide-treatment arms.

Results: Patient recruitment is ongoing as of May 2018.

Conclusions: Recently, cross-resistance between abiraterone and enzalutamide has been an issue of focus. Urologists thus tend to prefer docetaxel rather than sequential therapies using two hormonal preparations after the progression of a first hormonal preparation. From that perspective, our clinical trial is rather out of fashion. Nevertheless, we assume that many patients are forced to receive hormonal sequential therapy in the actual clinical setting, since most such patients cannot receive chemotherapeutic agents due to old age or poor performance status. This is why we are attempting this randomized clinical trial comparing abiraterone and enzalutamide. We will try to identify which drug is suitable for initial hormonal therapy among CRPC
patients who do not meet the indications for docetaxel therapy in terms of not only anti-
tumor effect, but also adverse events and quality of life.

**Trial Registration:** University Hospital Medical Information Network (UMIN) ID:

UMIN000022102

Keywords: Castration resistant prostate cancer (CRPC), Abiraterone, Enzalutamide
Introduction
Hormone therapies have considered beneficial for the treatment of advanced prostate cancer (1). In fact, hormone therapies are known to be safe and highly effective, but the biggest drawback is the lack of sustained antitumor effects. Scientists have long been frustrated in attempts to find pharmacotherapies, including anticancer agents, that would prolong survival among patients with prostate cancer that has acquired resistance to hormone therapies (castration-resistant prostate cancer, CRPC). In 2004, docetaxel became the first anticancer agent confirmed to prolong survival in CRPC patients in two large-scale clinical trials (2, 3), and was also adopted as the first-line treatment for CRPC in Japan. In addition, recent large-scale randomized studies have demonstrated that two new hormone preparations (abiraterone and enzalutamide) prolong survival in docetaxel-treated (4, 5) or -naïve CRPC patients (6, 7). Clinical use of the two agents in Japan began in 2014. While these two hormone preparations (abiraterone and enzalutamide) have different mechanisms of action, both exhibit strong inhibitory effects on remaining androgen after androgen-deprivation therapy (ADT), leading to antitumor effects. Nonetheless, no reports have directly compared antitumor effects between these two agents, and clear guidelines remain lacking for choosing between the two agents. The present clinical study is aimed at comparing antitumor effects and adverse events between abiraterone and enzalutamide by allocating CRPC patients deemed to not meet the indications for docetaxel treatment to receive either of the two agents.
Methods
1. STUDY PATIENTS

1.1 Inclusion Criteria

1) Subjects in the study are CRPC patients after concomitant anti-androgen therapy with at least a single agent who are docetaxel-naïve and deemed to not meet the indications for docetaxel treatment (regardless of the presence or absence of metastasis).

- CRPC is defined as an increase in prostate-specific antigen (PSA) that is \( \geq 25\% \) and \( \geq 2 \) ng/ml over the nadir PSA level obtained on measurements taken at least 4 weeks apart, with the day of CRPC confirmation defined as the day of relapse (day of disease progression). Testosterone level is measured at the same time to confirm that the level is no higher than the castration level (i.e., <50 ng/dl).

- Indication for docetaxel: The first-line therapy shall be a docetaxel-prednisolone (DP) therapy for patients with a Gleason score \( \geq 8 \) and multiple bone metastases for whom the duration of response to a hormone therapy is short (approx. standard, within 2 years) and whose systemic conditions can more than withstand DP therapy.

2) Absolute PSA level \( \geq 5 \) ng/ml
3) Age <85 years
4) Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 to 2 and expectation of survival \( \geq 3 \) months
5) Proper organ function
   - White blood cell count \( \geq 3,000/\text{mm}^3 \) or neutrophil count \( \geq 1,500/\text{mm}^3 \)
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations \( \leq 1.5 \) times the institutional upper limit of reference
6) Personal provision of written informed consent to participate in the study

1.2 Discontinuation Criteria
If discontinuation of the study drug administration is deemed justified due to a serious adverse event or when any of the following criteria are met, the investigator shall discontinue study drug administration at their discretion and record in the case report form the reasons thereof and the findings available at discontinuation.

1) Study continuation is deemed difficult due to disease progression (PSA recurrence or clinical recurrence)
2) Study continuation is deemed difficult due to an adverse event
3) Occurrence of Grade 4 toxicities as assessed by Japanese Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by Japan Clinical Oncology Group (JCOG)/Japan Society of Clinical Oncology (JSCO)
4) Withdrawal of consent or a request to discontinue study treatment by the subject or a family member
5) Study continuation is deemed difficult due to an unforeseen incident
6) Study continuation is deemed difficult by the investigator due to any other reason

1.3 Dose-Reduction Criterion
In cases of mild adverse events, the dose of the study drug may be halved and then gradually increased or decreased depending on the condition of the subject.

2. STUDY DESIGN
An open-label, randomized comparative study
The study is an open-label, comparative study that allocates CRPC patients to an abiraterone-treatment arm or an enzalutamide-treatment arm (allocation factors: age [<70 versus ≥70 years] and presence/absence of metastases) and will assess the treatment results.

3. PATIENT ENROLLMENT
3.1 Enrollment Procedure
The investigator checks that candidate patients conform with the inclusion criteria and enrolls patients according to the procedure below.
1) Acquire written consent from the patient, complete the required information on a
patient enrollment sheet, and transmit the sheet by facsimile to the patient enrollment center.

2) The patient enrollment center checks the information provided on the patient enrollment sheet for eligibility and performs patient enrollment and allocation to treatment arm. The patient enrollment center sends the investigator a patient enrollment notification that provides information on the allocated treatment.

3) The investigator checks the patient enrollment notification sent by the patient enrollment center and initiates administration of the allocated treatment drug.

3.2 Patient Enrollment Center
The address of the Patient Enrollment Center is as follows:

Clinical Research Center, Wakayama Medical University
811-1 Kimiidera, Wakayama City, Wakayama 641-0012, Japan
Tel: 073-441-0867; Fax: 073-441-0868
E-mail: dc_csc@wakayama-med.ac.jp

3.3 Random Allocation and Stratification Factors Used for Allocation
The patient enrollment center randomly allocates patients to either the abiraterone-treatment arm or the enzalutamide-treatment arm in a 1:1 ratio. The factors of 1) age (<70 versus ≥70 years) and 2) presence/absence of metastases are used as stratification factors for random allocation.

4. TREATMENTS

4.1 Hormone Therapy
Allow surgical castration or continuous treatment with a luteinizing hormone-releasing hormone (LHRH) agonist (Leuplin or Zoladex).

4.2 Study Drugs
4.2.1 Abiraterone
Product name: Zytiga 250 mg
Therapeutic category: Prostate cancer therapeutic agent (cytochrome P450 [CYP] 17 inhibitor)
Trade name: Zytiga tablets 250 mg
Dosage and administration: Usually for adults, administer 1,000 mg orally as abiraterone acetate, once daily under fasting conditions concomitantly with prednisolone.

Precautions related to dosage and administration
1. The effect of food causes an increase in the maximum concentration (Cmax) and area under the curve (AUC) for abiraterone. As a result, avoid taking abiraterone from 1 h before to 2 h after a meal (refer to the Pharmacokinetics section)
2. Become familiar with the information in the Clinical Results section before administering prednisolone.
3. In cases of elevated values for liver function tests while a patient is undergoing abiraterone treatment, temporarily interrupt, reduce the dose of, or discontinue abiraterone treatment with the following guidelines as a reference.

Adverse Drug Reactions (ADRs)
Summary of incidences of ADRs
Until the time of approval, ADRs (including laboratory abnormalities) occurred in 46 of 95 patients (48.4%) evaluated for safety in the Japanese phase II clinical study. Major ADRs were increased AST (GOT) in 13 patients (13.7%), increased ALT (GPT) in 12 patients (12.6%), hypokalemia in 8 patients (8.4%), hyperlipidemia in 7 patients (7.4%), and hypertension in 4 patients (4.2%). In phase III clinical studies conducted overseas, ADRs (including laboratory abnormalities) occurred in 991 of 1,333 patients (74.3%) evaluated for safety. The major ADRs were: fatigue, 328 patients (24.6%); hot flush, 202 patients (15.2%); hypokalemia, 188 (14.1%); nausea, 179 patients (13.4%); peripheral edema, 160 patients (12.0%); hypertension, 125 patients (9.4%); constipation, 108 patients (8.1%); diarrhea, 101 patients (7.6%); vomiting, 92 patients (6.9%); dizziness, 81 patients (6.1%); increased AST (GOT), 69 patients
(5.2%); and increased ALT (GPT), 68 patients (5.1%).

**Clinically Significant ADRs**

1. **Cardiac disorder**  
   Frequency unknown<sup>Note</sup>  
   As cardiac failure and other serious cardiac disorders may occur, patients are closely monitored. In the event of any abnormality, take appropriate actions including discontinuation of treatment.

2. **Fulminant hepatitis, hepatic failure, and hepatic function disorder**  
   Fulminant hepatitis may occur (frequency unknown)<sup>Note</sup>. Moreover, hepatic function disorder accompanied by increased AST (GOT) (13.7%), increased ALT (GPT) (12.6%), or increased bilirubin (2.1%) may occur and may result in hepatic failure. Thus, monitor patients closely using periodic liver function tests. In the event of any abnormality, take appropriate actions such as dose reduction or treatment interruption or discontinuation.

3. **Hypokalemia**  
   Hypokalemia accompanied by symptoms such as convulsion or muscular weakness may occur, with some cases reportedly resulting in arrhythmia. Monitor patients closely by periodic measurements of serum electrolyte concentrations, including serum potassium. In the event of any abnormality, take appropriate actions such as potassium supplementation or interruption of abiraterone treatment.

4. **Thrombocytopenia**  
   Frequency unknown<sup>Note</sup>  
   As thrombocytopenia may occur, monitor patients closely. In the event of any abnormality, take appropriate actions including interruption of abiraterone treatment.

5. **Rhabdomyolysis**  
   As rhabdomyolysis may occur, pay attention to any muscular weakness, myalgia, increased creatine kinase (CK) (or creatine phosphokinase [CPK]), and increased myoglobin in blood/urine. In the event of any such symptoms,
take appropriate actions including discontinuation of abiraterone treatment.

4.2.2 Enzalutamide
Product name: Xtandi 40 mg
Therapeutic category: Prostate cancer therapeutic agent
Trade name: Xtandi capsules 40 mg
Dosage and administration: Usually for adults, administer 160 mg orally as
enzalutamide, once daily.
Precautions related to dosage and administration: The efficacy and safety of
enzalutamide have not been established in patients without concomitant
surgical or medical castration.

Precautions
** Careful administration
(Administer with care to the following patients)
1. Patients with a current or past history of epilepsy or other convulsive
disease (convulsive seizure may occur.)
2. Patients predisposed to convulsive seizure (e.g., patients complicated with
cerebral injuries or stroke, who have such a history, or who are undergoing
treatment with an agent that lowers the convulsive seizure threshold)

Important Precautions
1. As an agent for endocrine therapy, enzalutamide should be used only in
patients deemed indicated for enzalutamide treatment by a physician who is
well versed and experienced in pharmacotherapies for cancer.
2. As convulsive seizure may occur, patients undergoing treatment with
enzalutamide should exercise cautions when operating a motor vehicle or
other machines associated with potential hazards.

Drug Interactions
Summary of drug interactions
Enzalutamide is metabolized mainly by the drug-metabolizing enzyme
CYP2C8. Moreover, enzalutamide exhibits induction effects on CYP3A4,
CYP2C9, CYP2C19, CYP2B6*, uridine diphosphate (UDP)-
glucuronyltransferase (UGT)*, and P-glycoprotein (P-gp),* and inhibitory
activity against P-gp*, breast cancer-resistance protein (BCRP)*, organic
cation transporter 1 (OCT1)*, and organic anion transporter 3 (OAT3)* (*: *in
vitro* data). Due to the long elimination half-life (4.7-8.4 days), enzalutamide
may still induce or inhibit metabolic enzymes and transporters after completion
of treatment.

*Summary of Incidences of ADRs*

*<Japanese clinical studies>*
In Japanese phase I/II clinical studies in CRPC patients, 31 of 47 patients who
received enzalutamide (66.0%) developed ADRs. Major ADRs included
hypertension (14.9%), constipation (14.9%), fatigue (12.8%), decreased
appetite (12.8%), decreased weight (10.6%), and prolonged QT on
electrocardiograms (10.6%). (As of the time of approval, March 2014)

*<Overseas clinical studies>*
In phase III studies conducted overseas in CRPC patients with prior docetaxel
treatment, 554 of 800 patients who received enzalutamide (69.3%) developed
ADRs. Major ADRs included fatigue (21.5%), nausea (20.1%), hot flush
(15.0%), decreased appetite (12.6%), and asthenia (10.0%). (As of the time of
approval, March 2014)

*<International clinical trial>*
In an international phase III clinical trial in chemotherapy-naïve CRPC
patients, 556 of 871 patients (including 28 Japanese) who received
enzalutamide (65.0%) developed ADRs. Major ADRs included fatigue
(25.3%), hot flush (13.4%), and nausea (13.3%). (As of the time of amendment
of precautions related to indications, October 2014)

Frequencies of the following ADRs are based on the tabulation of patients who
received enzalutamide in the Japanese phase I/II clinical studies, overseas
phase III clinical studies, and international phase III clinical trial.
**Clinically Significant ADRs**
1. Convulsive seizure (0.2%)
   As convulsive seizure such as convulsion and status epilepticus may occur,
   monitor patients closely. In the event of any abnormality, discontinue treatment
   and take appropriate actions.
2. Thrombocytopenia (frequency unknown)
   As decreased platelets may occur, monitor patients closely. In the event of any
   abnormality, discontinue treatment and take other appropriate actions.

4.2.3 **Definition of protocol treatment period**
The protocol treatment period is defined as the period of study drug (abiraterone or
enzalutamide) administration as primary or secondary treatment.

4.2.4 **Definition of study period**
The study period is defined as the period from the day of consent until the day of
confirmation of the final outcome.
The investigator shall survey the outcome in patients after the protocol treatment is
stopped until outcome confirmation or loss to follow-up.

4.3 **Allocation to Study Drug**
Enroll patients after obtaining written informed consent from each patient by providing
information on details of the study using written information for the patient.
Allocate patients to a treatment arm (abiraterone- or enzalutamide-treatment arm) in
such a way that both arms are comparable in terms of: 1) age (≤70 versus ≥70 years);
and 2) presence/absence of metastases.

4.4 **Study Schedule**
Study schedule

<table>
<thead>
<tr>
<th>Test</th>
<th>Screening</th>
<th>Every 3 Months</th>
<th>Every 6 Months</th>
<th>At Crossover or Suspected Disease Progression</th>
<th>At Study Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject characteristics/underlying disease information</td>
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Perform the above tests on each patient before enrollment to assess whether the patient meets the inclusion criteria. Perform blood tests, including PSA, monthly. Conduct a QOL survey (FACT-P) every 3 months. *Refer to the attachment for FACT-P.

Perform CT bone scintigraphy every 6 months. Perform blood tests, including PS and PSA, CT (chest and abdomen, plain), bone scintigraphy, and other tests at crossover to the alternative treatment or when symptoms lead to suspicion of disease progression.

**4.5 Crossover of Study Drugs**
Upon confirmation of PSA failure (deemed to have occurred when the PSA level
reaches double the baseline level on three occasions (not necessarily consecutive) or progression is evident on imaging or a patient is considered to have trouble taking the study drug due to adverse events), have the patient cross-over to receive the alternative study drug. Subjects in the present clinical study are those for whom docetaxel is not considered to be indicated. Nevertheless, before a patient crosses-over to receive the alternative study drug, explain to the patient again about the propriety of docetaxel treatment and evaluate the propriety. Patients who are deemed indicated for docetaxel treatment at this point in time shall be considered a dropout and given docetaxel treatment.

5. OBSERVATIONS, TESTS, AND ENDPOINTS

5.1 Before Treatment Initiation
Check patient consent, PS, PSA, hematology tests, biochemical tests, CT (chest and abdomen, plain), bone scintigraphy, presence/absence of prior treatment, and QOL.

5.2 Efficacy Evaluation

5.2.1 PSA
Check PSA monthly.

5.2.2 Plain CT of chest and abdomen and bone scintigraphy
Perform plain CT of chest and abdomen and bone scintigraphy every 6 months. At treatment crossover (enzalutamide → abiraterone, abiraterone → enzalutamide, or a switch to another therapy including best supportive care or when symptoms indicate suspected progression of disease stage, perform plain CT of the chest and abdomen and bone scintigraphy as well, so as to assess the effects of the prior treatment and to check for any new lesions.

5.2.3 Definition of initial date of reckoning in endpoint evaluations
The measurement of PSA or imaging progression-free survival with respect to the primary treatment begins on the first day of the primary treatment. The measurement of overall PSA or imaging progression-free survival after cross-over from the primary to secondary treatment also begins on the first day of primary treatment. The
measurement of time to use of chemotherapy or BSC, or the overall survival also
begins on the first day of the primary treatment.

5.3 Safety Evaluation
5.3.1 Adverse events
An adverse event is any event (abnormal clinical finding, subjective or objective
symptom, or abnormal change in laboratory test value) occurring during the study
after initiation of the study drug treatment, regardless of the relationship to the study
drug.
Evaluate adverse events based on abnormal finding, symptom, laboratory test value,
and/or severity according to the Japanese Common Terminology Criteria for Adverse
Events (CTCAE) version 4.0 by JCOG/JSCO.

5.3.2 Serious adverse events
An adverse event is serious if the event is observed any time after initiation of the
study drug treatment up to 30 days following treatment completion (or
discontinuation) and:

1) results in death;
2) is life-threatening;
3) requires hospitalization or prolongation of hospitalization for treatment;
4) results in persistent or significant disability/incapacity; or
5) results in a congenital anomaly.

Upon the occurrence of a serious adverse event for which a causal relationship to the
protocol treatment cannot be excluded, the investigator shall provide appropriate
interventions/treatments, promptly (within 24 h of awareness) complete the required
information on a Serious Adverse Event Report in accordance with the procedure at
the medical institution the investigator is affiliated with, and communicate the event to
the study secretariat by facsimile.

5.3.3 Laboratory tests
5.3.3.1 Hematology tests
Tests: White blood cell count, differential white blood cell counts, hemoglobin, and
platelet count
Test schedule: Baseline and once-monthly thereafter
5.3.3.2 Clinical chemistry tests
Tests: AST, ALT, ALP, total bilirubin, creatinine, albumin, Na, K, Cl, P, and Ca
Test schedule: Baseline and once-monthly thereafter

5.4 Primary Endpoint
PSA response rates (percentages of patients with PSA level decreasing by \( \geq 50\% \)) to the
primary treatment in the abiraterone- and enzalutamide-treatment arms.

5.5 Secondary Endpoints
1) PSA or imaging progression-free survival with the primary treatment in the
   abiraterone- and enzalutamide-treatment arms
2) PSA response rate (percentage of patients with PSA level decreasing by \( \geq 50\% \)) with
   secondary treatment in the abiraterone- and enzalutamide-treatment arms
3) Overall PSA or imaging progression-free survival after cross-over treatment with
   both abiraterone and enzalutamide
4) Time to use of chemotherapy or best supportive care (BSC)
5) Overall survival
6) Comparison of quality of life (QOL) as assessed by the Functional Assessment of
   Cancer Therapy-Prostate (FACT-P)
7) Adverse events

6. ETHICAL CONSIDERATIONS
6.1 Regulations to be Complied with
All researchers involved in this research (study) shall comply with the Declaration of
Helsinki (Version Fortaleza, October 2013) (as translated by the Japan Medical
Association) and the Ethical Guidelines for Medical and Health Research Involving
Human Subjects (enforced on April 1, 2015 and partially revised on February 28, 2017)
in the conduct of this research.

6.2 Informed Consent
The principal investigator or investigator shall fully inform each subject using written
information to allow them to decide whether to participate in the study and obtain from
each subject written informed consent to participate in the study based on their own free
will.
Upon obtaining written informed consent, the principal investigator or investigator who
informed the subject shall confirm whether the subject fully understood the contents of
the written information before consenting. The principal investigator or investigator shall fill in the date on which the information was provided and the date of confirmation of the subject’s intent on the written informed consent form and affix their seal or signature to the form. Each subject shall provide consent after gaining a full understanding of the contents of the written information, and shall then affix their seal or signature to, and date the form.

The principal investigator or investigator shall provide a copy of the sealed or signed written informed consent along with the written information to the subject who provided consent and shall properly retain the original of the written consent at their medical institution.

When a matter arises that concerns the subject’s intent to participate in the study, the principal investigator or investigator shall amend the written information, inform the participating subjects again using the revised written information, and obtain written informed consent from the subjects to continue participation in the study based on their own free will.

In the event a subject participating in the study requests withdrawal of consent, document the request in a study participation withdrawal form. If possible, prepare a Consent Withdrawal Form. The subject shall fill in the date of withdrawal of consent and affix their seal or signature to the Consent Withdrawal Form, and the principal investigator or investigator shall fill in the date of verification and affix his/her seal or signature to the form. The principal investigator or investigator shall provide a copy of the sealed or signed consent withdrawal form to the subject who withdraws consent and shall retain the original at their medical institution.

6.3 Approval by Institutional Review Board/Ethics Committee

Before the study is underway, the protocol, written information for the patient, written informed consent form, and the justification to conduct the study must be submitted for
review by a committee at each study site (such as an institutional review board or ethics committee pursuant to the regulations of the study site) and receive its approval.

6.4 Safeguard of Personal Information

All parties involved in this study shall strictly safeguard the personal information of subjects pursuant to the *Personal Information Protection Act*. When providing case report forms or information on adverse events and other relevant data to a party outside of his/her own medical institution, the investigator shall pay due attention to safeguarding personal information by actions such as replacing the identities of the subjects concerned with subject identification codes or enrollment numbers so that no third party can identify the individuals. Prepare a reference table that links the enrollment numbers issued to each subject at the time of acquisition of consent to each of their fields of personal information (name and medical record number), to allow identification or collation, as necessary, of enrolled subjects whose information has been anonymized. Retain the reference table under strict safeguard at each study site. When identifying or collating enrolled a subject, use the enrollment number issued at enrollment. Take similar measures to safeguard the personal information of subjects when publishing results of this research.

6.5. Important Findings on Genetic Characteristics, etc.

This research is expected to yield no important findings on the genetic characteristics of subjects that may be relevant to health or inherited by their offspring.

6.6. Compensation

In the event the conduct of this study causes any adverse events that result in health hazards to a subject, the investigator shall administer appropriate treatments and take the best possible actions, including other necessary measures. Furthermore, as the conduct of this study is covered by insurance, any health hazards will be handled within
the scope of the Adverse Drug Reaction Relief System.

6.7. Remuneration or Financial Burden to Study Subjects
This research does not provide any remuneration to or impose any financial burden on
the study subjects.

6.8. Disclosure of Subject Information and Handling of Inquiries from Subjects
   6.8.1. Responses to requests for disclosure of subject information, etc.
   In the event of a subject personally requesting the disclosure of information that
   involves privacy issues, in principle, the researchers (the principal investigator,
   coordinator, and investigator) at the study site that enrolled the subject shall handle
   such a request.
   6.8.2. Reception of inquiries, etc., from subjects
   Subjects may submit general inquiries or file complaints related to privacy by postal
   mail or e-mail to the address below or by facsimile to the facsimile number below.

7. STATISTICS
7.1 Analysis Sets
   7.1.1 Full analysis set (FAS)
   The FAS includes all enrolled patients, excluding those with any major protocol
   violations (failure to provide consent or any major procedural violations).
   7.1.2 Per-protocol set (PPS)
   The PPS includes those subjects in the FAS who receive the study treatment allocated
   according to the protocol, excluding those who fail to meet any eligibility criteria,
   meet any exclusion criteria, or take any prohibited concomitant drugs, etc.
   7.1.3 Statistical analyses and analytical plans
   In all efficacy evaluations, use the FAS as the primary analysis set, with analyses of
   the PPS performed for reference purposes. Perform safety evaluations using the PPS.

7.2 Efficacy Evaluation
   7.2.1 Primary endpoint (PSA response rates with primary treatment in the
   abiraterone- and enzalutamide-treatment arms)
   Calculate the point estimate and Clopper-Pearson exact 80% confidence interval (CI)
   of the PSA response rate with primary treatment among FAS population in the
   abiraterone- and enzalutamide-treatment arms, respectively. Determine the 95%CI and
perform Fisher’s exact test for reference purposes. Furthermore, calculate the odds ratio and 95%CI for PSA response. In addition, estimate the impacts of prognostic factors and treatment effects by multiple logistic regression analysis. Meanwhile, determine estimated odds ratios adjusted based on the regression coefficient of a multiple logistic regression analysis and its 95%CI. Use adjustment factors for allocation and any patient characteristics distributed unevenly between arms (with a value $P \leq 0.2$ as a guide) as influencing factors.

7.2.2 Secondary endpoints

PSA or imaging progression-free survivals with primary treatment in the abiraterone- and enzalutamide-treatment arms

Determine the estimated survival curve among the FAS population in each arm by the Kaplan-Meier method. Moreover, under certain circumstances, perform a similar analysis on the PPS population. In such cases, use Greenwood’s formula to calculate the 95%CI and determine median survival, 1-year survival rate, and respective CIs. In addition, use the Cox proportional hazard model to estimate the impacts of prognostic factors and treatment effects. Meanwhile, determine the estimated hazard ratio and its 95%CI based on the regression coefficient of the Cox proportional hazard model. Use adjustment factors for allocation and any subject characteristics that were distributed unevenly between arms (with a value of $P \leq 0.2$ as a guide) as prognostic factors.

PSA response rates with secondary treatment in the abiraterone- and enzalutamide-treatment arms

Determine rates by performing an analysis similar to that used to determine PSA response rates with the primary treatment among the FAS population in the abiraterone- and enzalutamide-treatment arms.

Overall PSA or imaging progression-free survival after crossover of the two treatments (abiraterone and enzalutamide)

Determine survival by performing an analysis similar to that used to determine the
PSA or imaging progression-free survivals with the primary treatment among the FAS population in the abiraterone- and enzalutamide-treatment arms.  

**Time to initiation of chemotherapy or BSC**  
Calculate medians and interquartile ranges among the FAS population in the abiraterone- and enzalutamide-treatment arms and perform comparative analysis by the Wilcoxon test.  

**Overall survival**  
Determine overall survival by performing an analysis similar to that used to determine the PSA or imaging progression-free survivals with the primary treatment among the FAS population in the abiraterone- and enzalutamide-treatment arms.  

**Comparison of QOLs as measured by FACT-P**  
Calculate medians and interquartile ranges among the FAS population in the abiraterone- and enzalutamide-treatment arms and perform a comparative analysis by the Wilcoxon test.  

**Adverse events**  
Tabulate adverse events in each arm and compare the severity and frequency of adverse events between arms.  

8. **TARGET SAMPLE SIZE**  
N = 50 (n=25 per arm)  

*Sample size rationale*  
With no crossover treatment regimen consisting of abiraterone (AA) and enzalutamide (Enza), as “1st line + 2nd line,” available in Japan, we plan to conduct a pilot parallel arm study in the present research. As such, the primary endpoint selected is the proportion of subjects with a PSA response (PSAR) ≥50% with first-line treatment. In studies to date, the PSAR with AA as prior treatment was 78% in the PREVAIL study (2014) investigating “AA → Enza,” while the PSAR was 62% in the COUAA302 study investigating “Enza → AA.” Given its nature as a pilot study, the research must necessarily evaluate PSARs in both arms in Japan, assuming that patient characteristics are evenly distributed. A CI of 80% (confidence coefficient, 0.80) by the Clopper-
Pearson exact method is thus considered for the PSAR in each arm. With the expected PSAR of 70% in both arms and assuming a one-sided interval width of 0.15%, the minimum sample size required is 21. Allowing the potential that a few subjects would become ineligible, we selected a sample size of 25 per arm, or a total of 50. The confidence coefficient of 0.80 is considered to correspond to a significance level of 0.10 on the one-sided alternative hypothesis in a single arm. PSAR with second-line treatment was 17.6% for “Enza → AA” and 22.9% for “AA → Enza” (Nadal et al., 2015). With the expected PSAR with second-line treatment at 20% and assuming a sample size of 25%, the one-sided width of the 80% CI is 12.8%, which allows estimation based on a CI width equivalent to that for the PSAR with first-line treatment.

9. PROTOCOL CHANGES AND STUDY DISCONTINUATION/COMPLETION

9.1. Protocol Changes
In the event of protocol changes becoming necessary during the study, the principal investigator shall decide what changes to make and promptly inform the investigator at each study site in writing about the changes and the reasons thereof. In cases of significant change to the protocol, the investigator shall report the change to the head of medical institution and obtain an approval for the change, along with approval from the institutional review board/ethics committee.

9.2. Completion of Protocol
Once data lock is confirmed, consider the study complete. Upon receiving communication of the data lock from the data center, the principal investigator shall report on completion of the study to the investigator at each study site, who shall report the completion to the head of medical institution and the ethics committee.

9.3. Discontinuation of Protocol
9.3.1. Rules to discontinue the entire study
1) When the principal investigator determined after evaluating reports of study progress and study monitoring that completing the study is difficult due to reasons
such as patient enrollment delays or frequent protocol deviations
2) When serious safety or efficacy issues are judged to be associated with the study
to justify its discontinuation based on new information that has become available
after initiation of the study
3) When it is determined that safety issues are associated with the study or that
continuation of the study is not meaningful based on an evaluation of relevant
information obtained from sources outside of this study, such as literature articles
or conference presentations

9.3.2. Procedure for making decisions to discontinue the entire study
The principal investigator must request the ethics committee conduct a review and
accept its recommendations. Based on the recommendations, the principal investigator
shall make a determination on the necessity to discontinue the entire study according
to the rules provided in the preceding subsection. If the principal investigator
disagrees with the recommendations, then the principal investigator shall report the
reasons to the ethics committee.
After making a decision to discontinue the entire study, the principal investigator shall
communicate with the investigators immediately about the reasons thereof and what
actions to take. Upon receiving such a communication, investigators shall inform
subjects about discontinuation of the entire study and the reasons thereof, and shall
immediately take appropriate actions.

10. STUDY CONTROL
10.1. Monitoring
Monitors shall make sure that the human rights, safety, and welfare of subjects are
protected and that this study is conducted in compliance with the most up-to-date
protocol and standard operating procedures, etc. In addition, monitors shall access
source documents and other study-related records directly to confirm that the data and
other information reported by the principal investigator or investigators are accurate and
10.2. Monitoring Methods
The data center shall perform monitoring centrally and periodically. In central monitoring, the case report forms collected and other data reported are checked to make sure that the study is conducted in a safe manner and in accordance with the protocol. Monitoring results are to be submitted to the principal investigator and ethics committees.

10.3. Deviations from Per-Protocol Treatments
The principal investigator or investigator may deviate from the protocol for this study if such deviation is medically unavoidable so as to avoid immediate hazard to a subject. In such a case, the principal investigator or investigator shall report the deviation and the reasons thereof to the ethics committee through the head of his/her institution as soon as possible. Moreover, the principal investigator or investigator shall document all deviations from the protocol for this study, regardless of the reasons.

10.4. Audits
No audits are planned in this study.

11. RETENTION OF SOURCE DOCUMENTS AND OTHER RECORDS

11.1. Scope of Source Documents
The term “source document” in the study refers to any of the following:
   (1) Records pertaining to subject consent and information provision
   (2) Medical records, laboratory test data, imaging study films, and other records on which case report form data are based; data saved in electronic medical records

   are also considered source documents.

11.2. Retention of Records by Participating Medical Institutions
The principal investigator shall retain the following study-related records for 5 years from the date of the final report or 3 years from the date of the final publication of the study results, whichever is later.
   (1) Source documents
   (2) Informed consent forms and other documents related to this study or copies
thereof that have been prepared by the personnel of a participating medical
institution
(3) Protocol (the latest version), documents pertaining to study review obtained from
the institutional review board, and other documents obtained during the conduct
of the study
(4) Other documents generated in the work related to the study

11.3. Disposal of Records
Dispose records according to the methods and procedures for retention and disposal
established by the institution one is affiliated to, with consideration given to methods
such as anonymization.

12. INFORMATION ENTRIES IN CASE REPORT FORMS AND THEIR
SUBMISSION
The investigators, etc., in this study shall prepare case report forms in accordance with
the Guide on Filling Out Case Report Forms and submit the prepared case report forms
to the data center by postal mail or in person. Investigators, etc., shall prepare and retain
a copy of each case report form before its submission.

13. STUDY PERIOD
From December 2014 to December 2022
Patient enrollment period: September 2014 to December 2019

14. DATA PUBLICATION
The principal investigator shall register this study with the University Hospital Medical
Information Network Clinical Trials Registry (UMIN-CTR) before the conduct of the
study and shall register the end-of-study results on the same registry after study
completion. Furthermore, the principal investigator shall publish the results in a
conference presentation or a thesis promptly after completion of the study. Author
names and their order shall be approved by the principal investigator and the protocol
author before publication of the results in any conference presentation or journal
15. PARTY RESPONSIBLE FOR COSTS OF STUDY (SOURCE OF FUNDING)
As this study is supported by the research fund of the Department of Urology, Wakayama Medical University, there are no conflicts of interest.

Results
Patient recruitment is ongoing as of May 2018.

Discussion
In terms of sequential therapy of novel hormonal preparations (abiraterone and enzalutamide), clinical outcomes of enzalutamide following abiraterone (8, 9) or abiraterone following enzalutamide (10, 11) have been reported. However, these studies were rather small-scale retrospective studies, and no randomized trials comparing these sequential therapies appear to have been reported to date. Recently, cross-resistance between abiraterone and enzalutamide has been an issue of some focus. The most well-known mechanism of resistance is AR-V7, which is an androgen receptor splicing variant (12). Patients expressing AR-V7 showed lower response rates and poor prognosis when treated with abiraterone as well as enzalutamide. In fact, the response rate to the second drug is reportedly lower than that to first therapy in sequential therapies (8-11). Urologists thus tend to prefer docetaxel over sequential therapies using two hormonal preparations after the progression of first hormonal preparation. From that perspective, our clinical trial is rather out of fashion. Nevertheless, we assume that many patients are forced by necessity to undergo sequential hormonal therapy in the actual clinical setting, since most such patients cannot receive chemotherapeutic agents due to old age or poor performance status. This is why we are undertaking this randomized clinical trial comparing abiraterone and enzalutamide. We are trying to identify which drug is most suitable for initial hormonal therapy (in terms of not only anti-tumor effects, but also adverse event and QOL)
among CRPC patients who do not meet the indications for docetaxel therapy.

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Conflicts of Interest
None declared.
References

Patients with castration-resistant prostate cancer after concomitant anti-androgen therapy with at least a single agent who are docetaxel-naïve and deemed not indicated for docetaxel treatment (age ≤85 years; absolute PSA level ≥5 ng/ml)

Informed consent acquisition and patient enrollment

Randomization
Allocation factors: age (<70 vs. ≥70 years) and presence/absence of metastases

Abiraterone-treatment arm

Continuous treatment with LHRH agonist
Abiraterone
Daily oral administration of 1,000 mg/day
Concomitant Predonine 5-10 mg/day

PSA failure or progressive disease (PD) on imaging; trouble taking medication due to adverse events

Transition to docetaxel treatment or best supportive care (BSC)

Enzalutamide-treatment arm

Continuous treatment with LHRH agonist
Enzalutamide
Daily oral administration of 160 mg/day

PSA failure: defined as PSA level reaching ≥2-fold baseline level on three occasions (not necessarily consecutive)

Abiraterone-treatment arm

Continuous treatment with LHRH agonist
Abiraterone
Daily oral administration of 1,000 mg/day
Concomitant Predonine 5-10 mg/day

Enzalutamide-treatment arm

Continuous treatment with LHRH agonist
Enzalutamide
Daily oral administration of 160 mg/day

PSA failure or PD on imaging

Transition to docetaxel treatment or best supportive care (BSC)

Concomitant Predonine 5-10 mg/day