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BMJ Open Efficacy and safety of apalutamide in patients with metastatic castration-resistant prostate cancer (GENESIS): protocol for a multicentre, open-label, single-arm clinical trial

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ABSTRACT

Introduction This is a multicentre, open-label, single-arm clinical trial to evaluate the efficacy and safety of apalutamide in patients with metastatic castration-resistant prostate cancer.

Methods and analysis The trial will be performed at 4 university hospitals and 14 city hospitals in Japan. The target number of patients will be 110. The patients will be orally administered 240 mg apalutamide once daily during the treatment period. The primary outcome is the prostate-specific antigen (PSA) response rate. PSA response is defined as $\geq 50\%$ decline from baseline at 12 weeks. Secondary outcomes are time to PSA progression, progression-free survival, overall survival, progression-free survival during second therapy, $\geq 50\%$ decline in PSA from baseline at 24 and 48 weeks, $\geq 90\%$ decline in PSA from baseline or lower PSA detection sensitivity after the initial dose at 12, 24 and 48 weeks, PSA maximal changes, accumulated PSA response from screening to 24 and 48 weeks, and grade 3 or 4 adverse events according to the Common Terminology Criteria for Adverse Events version 4.0.

Ethics and dissemination This study has been approved by the Certified Research Review Board of Kobe University (No. CRB5180009). All participants will be required to provide written informed consent. Findings will be disseminated through scientific and professional conferences and peer-reviewed journal publications. The datasets generated during the study will be available from the corresponding author on reasonable request.

Trial registration number jRCTs051220077.

INTRODUCTION

Since approximately 10 years ago, many new drugs with different mechanisms of action have become available for the treatment of advanced prostate cancer, and the sequential drug treatment strategy for advanced prostate cancer has changed significantly.¹ Although traditional hormone therapy, known as vintage hormone therapy, is still used for advanced prostate cancer cases in Japan,²

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This trial is a prospective, multicentre, investigator-initiated study assessing apalutamide in patients with metastatic castration-resistant prostate cancer.
- ⇒ The study setting, criteria, inclusion, interventions and outcomes are based on a pragmatic approach to ensure external validity.
- ⇒ The data will be used to inform a possible future large, multicentre, double-blind, randomised phase III trial.
- ⇒ The results from this study should be considered hypothesis generating because of the single-arm uncontrolled design.

newer agents are gradually becoming more widely available and many favourable results have been reported.^{3–11}

Apalutamide is an orally available nonsteroidal antiandrogenic and potent inhibitor of androgen receptor (AR) signalling that binds directly to the ligand-binding domain of AR, inhibiting AR nuclear transfer and its binding to DNA or transcription cofactors. From the results of two large randomised controlled clinical trials, SPARTAN (a phase 3 double-blind, randomized study of apalutamide versus placebo in patients with nonmetastatic castration-resistant prostate cancer) and TITAN, overseas guidelines recommend apalutamide as one of the standard treatments for castration-resistant prostate cancer (CRPC) without metastasis from conventional imaging (CT/MRI, bone scintigraphy) results, as well as for castration-sensitive prostate cancer with metastasis.^{12 13} In particular, the SPARTAN trial demonstrated a benefit for non-metastatic CRPC (mCRPC) with a prostate-specific antigen (PSA) doubling time < 10 months. In Japan, apalutamide has been approved and introduced into clinical

practice, and the package insert indicates its use for the treatment of CRPC without distant metastasis and prostate cancer with distant metastasis.

Chemotherapeutic agents such as docetaxel, anti-AR agent enzalutamide and testosterone synthesis inhibitor abiraterone acetate, as well as taxane-based cabazitaxel recommended for docetaxel-resistant patients, are recommended for mCRPC in Japan (Prostate Cancer Treatment Guidelines 2016).¹⁴ The efficacy and safety of apalutamide have been shown in an international phase II trial in patients with mCRPC.¹⁴ However, there have been few phase III and other trials conducted in Japan, and evidence specifically in the Japanese population is currently limited.

There is a need to further investigate the usefulness of apalutamide in Japanese patients with mCRPC. Therefore, the current study aims to comprehensively evaluate the efficacy of apalutamide in Japanese patients with mCRPC who failed initial hormonal therapy (vintage hormonal therapy alone, androgen deprivation therapy plus abiraterone acetate or androgen deprivation therapy plus docetaxel). The following data will be evaluated: PSA response, time to PSA progression, progression-free survival (PFS), overall survival (OS), disease status and PFS after second-line therapy (PFS2).

METHODS AND ANALYSIS

Study design and setting

This study is a non-randomised, prospective, open-label, multicentre, single-arm clinical trial of patients with mCRPC that commenced on 16 August 2022. The expected date of completion (final visit of the last patient) is the end of July 2027. A summary of the study is presented in figure 1. This study will be performed at 4 university hospitals and 14 city hospitals in Japan, namely Kobe University Hospital, Hamamatsu University Hospital, Tottori University Hospital, Hiroshima University Hospital, Kakogawa City Hospital, Sanda City Hospital, Akashi City Hospital, Kansai Rosai Hospital,

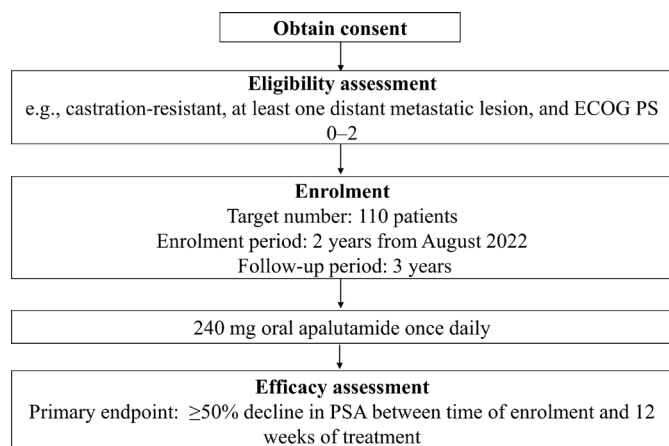


Figure 1 Summary of the study protocol. ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen.

Kobe City Medical Center West Hospital, Japanese Red Cross Society Himeji Hospital, Hyogo Prefectural Amagasaki General Medical Center, Hyogo Prefectural Awaji Medical Center, Hyogo Prefectural Kakogawa Medical Center, Kita-Harima Medical Center, Seirei Mikatahara General Hospital, Hamamatsu Medical Center, Iwata City Hospital and Chutoen General Medical Center. The data analysis period will continue for 1 year after the date of registration. This study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement. All study data will be stored and archived in the data centre of the Kobe Clinical and Translational Research Center.

Study population

Inclusion criteria

Patients will be included in the study if they satisfy all the following criteria:

1. Patients with histologically significant adenocarcinoma.
2. Patients with one or more distant metastases.
3. Patients who received any one of the following treatments for hormone-sensitive cancer: androgen ablativ therapy including combined androgen blockade therapy; combination therapy with androgen ablativ therapy and abiraterone acetate; or combination therapy with androgen ablativ therapy and docetaxel.
4. Patients diagnosed with mCRPC from at least one of the following criteria: castration level of blood testosterone <50 ng/dL after androgen ablativ therapy; PSA level ≥ 1 ng/mL that has increased on two successive occasions at least 1 week apart; appearance of ≥ 2 new bone lesions; or nodal or visceral metastases as defined by Response Evaluation Criteria in Solid Tumours 1.1 with Prostate Cancer Working Group 3 modifications.¹⁵
5. Laboratory requirements within 2 months before enrolment: aspartate transaminase ≤ 100 U/L, alanine transaminase ≤ 100 U/L and serum creatinine ≤ 2.0 mg/dL.
6. Eastern Cooperative Oncology Group performance status 0–2.
7. Age ≥ 20 years.
8. Patients who decline treatment with one of the commonly accepted first-line treatments for mCRPC (abiraterone, enzalutamide, docetaxel, radium-223 and olaparib).
9. Patients provide informed consent for participation in this study.

Exclusion criteria

Patients will be excluded from the study if any of the following criteria apply:

1. Patients who have histologically neuroendocrine differentiation or small cell.
2. Patients who have received apalutamide, enzalutamide or darolutamide for metastatic prostate cancer or non-mCRPC.

3. Patients who received local therapy (total prostatectomy or definitive radiotherapy) within 1 year before enrolment.
4. Patients with a serious active viral infection.
5. Patients with a history of malignant tumours that are considered not cured, other than prostate cancer.
6. Patients with other severe acute or chronic diseases.
7. Patients with psychiatric disorders or symptoms that are considered to create difficulties for participation in this study.
8. Patients found to be intolerant of components of the test drug (or excipients).
9. Patients who are considered inappropriate for participation in this study for other reasons at the physicians' discretion.

Intervention

After screening for eligibility registration, the patients will be treated orally with 240 mg apalutamide once daily. A summary of other study outcomes, assessments and procedures is presented in online supplemental table 1. Anti-cancer drugs, radiation therapy (including radium-223 dichloride), hyperthermia, immunotherapy, nirmatrelvir tablets and copacked ritonavir tablets will be prohibited during this clinical trial.

Outcomes

Primary outcome

PSA response rate: PSA response is defined as $\geq 50\%$ decline from baseline at 12 weeks.

Secondary outcomes

1. Time to PSA progression.
2. PFS.
3. OS.
4. PFS2.
5. $\geq 50\%$ decline in PSA from baseline at 24 and 48 weeks.
6. $\geq 90\%$ decline in PSA from baseline at 12, 24 and 48 weeks, or below detection limit after the initial dose.
7. PSA maximal changes.
8. Accumulated PSA response from screening to 24 and 48 weeks.
9. Grade 3 or 4 adverse events according to Common Terminology Criteria for Adverse Events version 4.

Patient enrolment and data management

Patients will be recruited from 16 August 2022 to 31 July 2024 at 4 university hospitals and 14 city hospitals in Japan, namely, Kobe University Hospital, Hamamatsu University Hospital, Tottori University Hospital, Hiroshima University Hospital, Kakogawa City Hospital, Sanda City Hospital, Akashi City Hospital, Kansai Rosai Hospital, Kobe City Medical Center West Hospital, Japanese Red Cross Society Himeji Hospital, Hyogo Prefectural Amagasaki General Medical Center, Hyogo Prefectural Awaji Medical Center, Hyogo Prefectural Kakogawa Medical Center, Kita-Harima Medical Center, Seirei Mikatahara General Hospital, Hamamatsu Medical Center, Iwata City Hospital and Chutoen General Medical Center. All

patients who provide consent to participate, fulfil the inclusion criteria, and do not meet any of the exclusion criteria will be enrolled. The data centre will issue the patient enrolment confirmation form that contains the eligibility judgement after the data centre confirms the patient's eligibility. The primary investigator or subinvestigator will enter the case report form (CRF) data for each patient into the electronic data capture system. The principal investigator will confirm that the entered CRF data are complete and correct, electronically sign the CRF on the electronic data capture system, and print a copy of the signed CRF for filing. The primary investigator will retain the CRF printout. If there are any queries about the CRF data that are entered by the staff at the data centre, the primary investigator or subinvestigator should promptly respond to the queries.

Prior treatment

Because the efficacy of apalutamide varies greatly depending on prior treatment,¹⁴ we will consider two cohorts. The main cohort will be cases without prior abiraterone acetate or docetaxel treatment. The subcohort will be cases with prior abiraterone acetate or docetaxel treatment.

Analysis population

The analysis populations for efficacy are the full analysis set (FAS) and the per-protocol set (PPS). The FAS will also serve as the analysis population for safety. The FAS is defined as all patients enrolled in this study and administered at least one dose of apalutamide. The PPS is defined as patients in the FAS, excluding those with any of the following significant protocol violations regarding study method and concomitant therapy: violation of the inclusion or exclusion criteria, and critical violation of the protocol that could affect efficacy evaluation. All analyses will be carried out with the FAS; however, the primary and secondary endpoints will be analysed with the FAS and PPS.

Data analysis

The handling of the enrolled patients for analysis will be determined by discussion among the coordinating investigators, committee and chief of statistical analysis before data lock. If data are missing, they will not be imputed for analysis of the primary endpoint. All cases will be analysed after data are fixed. The analysis will be conducted in two cohorts: a cohort of patients who have not received prior abiraterone or docetaxel and a cohort of patients who have received prior abiraterone or docetaxel. For all efficacy assessments, the FAS analysis will be the primary analysis and the PPS analysis will be used as a reference.

Analysis of the primary outcome

We will estimate the PSA response rate and its 95% CI. A binomial test will be performed only for the case cohort without prior abiraterone acetate or docetaxel treatment, with the null hypothesis being 'PSA response rate

is <70%'. The significance level for the test will be 0.025 (one sided).

Analysis of the secondary outcomes

1. For time to PSA progression, Kaplan-Meier (KM) plots will be generated, and we will estimate the percentage of non-PSA progression and its 95% CI at 12, 24 and 48 weeks after treatment as estimated by the KM method.
2. For PFS, we will generate KM plots and estimate the PFS rate and its 95% CI at 12, 24 and 48 weeks after treatment as estimated by the KM method.
3. For OS, we will generate KM plots and estimate the OS rate and its 95% CI at 12, 24 and 48 weeks after treatment as estimated by the KM method.
4. We will generate KM plots for PFS2 and estimate the PFS rate and its 95% CI at 12, 24 and 48 weeks after treatment as estimated by the KM method.
5. Estimate the PSA response rate and its 95% CI, defined as the percentage of PSA responses at 24 and 48 weeks after the start of treatment.
6. Estimate the proportion of patients with a $\geq 90\%$ decrease in PSA or a post-treatment PSA level below the detection limit (<0.1 ng/mL) and their 95% CIs, compared with the pretreatment level at 12, 24 and 48 weeks after the start of treatment.
7. Calculate the summary statistics of the maximum PSA decline.
8. Estimate the percentage of PSA cumulative response and its 95% CI at 24 and 48 weeks after the start of treatment.

Analysis of safety endpoints

For the safety endpoints, the frequency and rate of disease and other events will be tabulated. The frequency and rate of disease will also be calculated for safety endpoints for the combined cohorts of patients who have not received prior abiraterone acetate or docetaxel, and for patients who have received prior abiraterone acetate or docetaxel.

Exploratory analysis

For each case, the duration of apalutamide treatment, apalutamide withdrawal period, adverse events, PSA progression and imaging progression will be illustrated on swimmer's plots.

Monitoring and auditing

Periodic monitoring of the study will be performed to ensure that the human rights and welfare of patients are protected. The study will be safely conducted in accordance with the protocol and the applicable regulatory requirements under the Clinical Trials Act, and data collection will be properly executed. The coordinating investigator will appoint monitors for the study. The items to be checked at monitoring are specified in the 'Written procedure for implementation of study monitoring'.

For quality assurance, an audit will be performed in the study.

Sample size calculation

The target number of patients is 110. There has been a limited number of previous clinical trials in patients with mCRPC. In an overseas phase II trial in patients with mCRPC treated with or without abiraterone acetate, the response rate of PSA after 12 weeks of apalutamide induction was 22% (4/18) and 88% (22/25) in the treated and untreated groups, respectively, with significant differences depending on previous treatment.¹⁵ The results of apalutamide treatment in Japan are limited in mCRPC, and the actual treatment status of the patients in this clinical study is not yet clear.¹⁵ In particular, the number of patients refractory to abiraterone acetate and docetaxel is expected to be small, at 20%–30% of the total number of patients in the study.

For abiraterone acetate-naïve and docetaxel-naïve cases, the threshold response rate was set at 70% based on clinician opinion, and the expected response rate was estimated more conservatively than the 85% reported in the literature.¹⁵ Under these settings, the minimum number of cases will be 78, calculated using an exact binomial test with a type I error probability alpha of 0.025 (one sided) and a power of 1-beta of $\geq 85\%$. We will need 86 cases to account for the 10% drop-out rate and other factors.

We estimate that 20% of the eligible patients will be previously treated with abiraterone acetate or docetaxel and therefore set the target number of patients for the entire study at 110, with the restriction that at least 86 abiraterone acetate-naïve or docetaxel-naïve patients must be enrolled. These statistics reveal that the above-targeted sample size will be sufficient for detection of the primary endpoint in this study.

Study period

The study period of this trial began the day that it was released by the Japan Registry of Clinical Trials (jRCT) on 16 August 2022; the participant entry period will begin the day it was released by jRCT and continue to 31 July 2024. The study follow-up will be completed by 31 July 2027.

Patient and public involvement

None.

Ethics and dissemination

The study will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the Clinical Trials Act and all of the applicable regulatory requirements. Ethics approval will be overseen by Kobe University Clinical Research Ethical Committee (reference number: C220001). This study has been approved by the Certified Research Review Board of Kobe University (No. CRB5180009). This study was registered at the jRCT on 16 August 2022 (jRCTs0 51220077). Details are available at the following address: https://jrct.niph.go.jp/latest-detail/jRCTs0_51220077. Written informed consent will be obtained from all participants before any study procedure is performed (online supplemental material

1). The participants will be informed that apalutamide is not a proven drug for patients with mCRPC and will be offered the opportunity to first be treated with one of the well-studied drug regimen (abiraterone, enzalutamide, docetaxel, radium-223 and olaparib). All patients will review the consent form and agree that they fully understand the details of the study procedures. Informed consent will be administered by a suitably qualified and experienced individual who will be delegated this duty by the principal investigator.

Any protocol changes that could have an impact on study conduct and/or participant risk–benefit profile, including changes in objectives, design, sample size, participant characteristics, staff changes or significant administrative aspects, will require approval from the relevant Certified Review Board. Minor protocol corrections and/or clarifications that could affect study conduct or the participant risk–benefit profile will be viewed as administrative changes and documented internally. Deidentified data will be made available to other interested investigators for additional analyses, on reasonable request, following reports of primary outcomes and with appropriate data use agreement. The findings of this study will be disseminated through scientific and professional conferences and a peer-reviewed journal.

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