Cost-effectiveness analysis of enzalutamide for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer in Japan

Hiroyuki Okumura1,†,*, Sachie Inoue2, Shevani Naidoo3,†, Stefan Holmstrom4,† and Hideyuki Akaza5

1Astellas Pharma Inc., Chuo-Ku, Tokyo, Japan, 2CRECON Medical Assessment Inc., Shibuya-ku, Tokyo, Japan, 3Astellas Pharma Inc., Chertsey, UK, 4Astellas Pharma Inc., Leiden, The Netherlands and 5Strategic Investigation on Comprehensive Cancer Network, The University of Tokyo, Tokyo, Japan

*For reprints and all correspondence: Hiroyuki Okumura, Astellas Pharma Inc., 2-5-1, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan. E-mail: hm-okmra@zc4.so-net.ne.jp

†Employee of Astellas Pharma Inc. at the time of the study.

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Abstract

Background: We aimed to evaluate cost-effectiveness of enzalutamide in chemotherapy-naïve metastatic castration-resistant prostate cancer patients in Japan.

Methods: A Markov model was developed to capture time spent by patients in various health states: stable, progression and death. Abiraterone acetate and docetaxel were set as active comparators. Clinical outcomes were obtained from the PREVAIL, COU-AA-302 and TAX327 trials. Treatment sequence, concomitant drugs and therapies for adverse events were estimated from responses to a survey by 14 Japanese prostate cancer experts. The analytic perspective was public healthcare payer, with a 10-year time horizon. The incremental cost-effectiveness ratio was estimated from quality-adjusted life-years and Japanese public healthcare costs. Probabilistic sensitivity analysis was performed to assess the robustness of the findings.

Results: According to the survey, the most common treatment sequences were (i) enzalutamide → docetaxel → cabazitaxel (enzalutamide-first sequencing), (ii) abiraterone → enzalutamide → docetaxel (abiraterone-first sequencing) and (iii) docetaxel → enzalutamide → cabazitaxel (docetaxel-first sequencing). In the base-case analysis, enzalutamide-first sequencing saved 1.74 million Japanese Yen versus abiraterone-first sequencing, with a 0.129 quality-adjusted life-year gain (dominant). Enzalutamide-first sequencing had a cost increase of 4.44 million Japanese Yen over docetaxel-first sequencing, with a 0.371 quality-adjusted life-years gain. The incremental cost-effectiveness ratio of enzalutamide-first sequencing versus docetaxel-first sequencing was estimated as 11.94 million Japanese Yen/quality-adjusted life-years. Probabilistic sensitivity analyses demonstrated that, compared with abiraterone-first sequencing, enzalutamide-first sequencing had an 87.4% probability of being dominant.

Conclusions: Results modeled herein suggest that the enzalutamide-first sequencing is more cost-effective than the abiraterone-first sequencing, but less cost-effective than docetaxel-first sequencing for chemotherapy-naïve patients with metastatic castration-resistant prostate cancer.
Introduction

Prostate cancer (PCa) is one of the most common cancers in men worldwide (1). In Japan, PCa was the fourth most prevalent cancer in 2012 (2). The mortality rate for men with PCa has continued to increase in Japan (3), despite PCa mortality rates per 100,000 people remaining unchanged in the latest 2013–2015 report from Japan’s National Cancer Center (2). Hence, this disease is expected to be associated with significant burden on the healthcare system in terms of cost and reduced patient quality of life (QoL) in Japan.

Development of PCa is dependent on androgen; therefore, depleting or blocking androgen action has been the standard of care for PCa patients (4). Enzalutamide is a potent androgen receptor signaling inhibitor that blocks androgen binding, nuclear translocation and androgen receptor DNA binding and activation (5). Clinical efficacy and safety of enzalutamide in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients was investigated in the phase 3, randomized, double-blind, placebo-controlled PREVAIL trial (6). Compared with placebo, enzalutamide significantly increased overall survival (OS) and radiographic progression-free survival (rPFS), and reduced the risk of a first skeletal-related event (SRE) [hazard ratio (HR) 0.72; 95% confidence interval (CI) 0.61, 0.84]. Enzalutamide was well-tolerated and the incidence of treatment discontinuation due to adverse events (AEs) was similar to placebo.

The use of enzalutamide for treating patients with PCa is well defined in various national treatment guidelines. For example, the National Comprehensive Cancer Network recommends treatment with enzalutamide, abiraterone acetate plus prednisone (referred to from here on as ‘abiraterone’), docetaxel plus prednisone, and second-line hormone therapy for patients with mCRPC (7). Additionally, the National Institute for Health and Care Excellence (NICE) recommends enzalutamide treatment for patients with hormone-relapsed metastatic PCa who are chemotherapy-naïve or who have been previously treated with a docetaxel-containing regimen (8).

Several studies have evaluated treatment cost-effectiveness for chemotherapy-naïve or chemotherapy-treated patients with mCRPC. Massoudi et al. evaluated the relative value of enzalutamide versus abiraterone treatment from a US third-party-payer perspective (9) based on efficacy results from the PREVAIL (6) and COU-AA-302 (10) trials. The study found that enzalutamide could potentially improve survival and decrease progression at lower costs within a 1-year time horizon compared with abiraterone, concluding that enzalutamide was cost-effective compared with abiraterone for treating chemotherapy-naive mCRPC patients. Kearns et al. reviewed the single technology appraisal process of cabazitaxel for patients with hormone-relapsed metastatic PCa previously treated with a docetaxel-containing regimen (11). Following review, the UK Independent Evidence Review Group updated its cost-effectiveness analysis to estimate an incremental cost-effectiveness ratio (ICER) of £212 038 per quality-adjusted life-year (QALY) gained for enzalutamide compared with cabazitaxel, although highlighting the uncertainty of methodological issues arising from a network meta-analysis comparing cabazitaxel, enzalutamide and other treatment options (8).

Like many countries, Japan is facing an increased burden on healthcare finances due to its aging population and high cost of medical technology (2). In response, the pilot introduction of cost-effectiveness evaluation (the Japanese health technology assessments) began in April 2016, selecting anti-cancer drugs nivolumab and trastuzumab emtansine as target technologies (2). As such, interest in cost-effectiveness evaluation of technologies is expected to increase in Japan.

This study aimed to evaluate the cost-effectiveness of enzalutamide in line with analysis guidelines published by the Ministry of Health, Labour and Welfare (12,13) for chemotherapy-naïve mCRPC patients in the Japanese healthcare setting, utilizing results of the PREVAIL trial as the main clinical evidence. We defined several conditions such as analytical perspective, comparator(s), analytical method, time horizon, outcome measure, discount rate and so on (13). In addition, the modeling methodology conforms to best practice as outlined by the International Society of Pharmacoeconomics and Outcomes Research (14).

Materials and methods

Clinical evidence

Table 1 shows the clinical evidence, including some baseline patient characteristics. The efficacy and safety of enzalutamide in chemotherapy-naïve patients with mCRPC was investigated in the PREVAIL trial (6), which was designed to determine the benefit of enzalutamide versus placebo as assessed by OS and rPFS.

Although the PREVAIL study was unblinded after the planned interim analysis on 16 September 2013 to minimize the uncertainty in estimation of lifetime outcomes, data were retrieved until 30 June 2014 and used in the final pre-planned analysis (Table 1).

Treatment sequence and costs in Japan

Treatment sequence and medical resource consumption relating to each treatment, palliative care and AEs for patients with mCRPC in Japan were estimated from a questionnaire completed by 14 Japanese PCa medical experts from 14 typical healthcare centers in the field of PCa from across the country. Clinicians were selected based on their affiliation (at the time of study) with regional hospitals that served many patients with PCa and their availability to participate in the survey. In this survey, each drug for the first-line therapy was assumed to be used for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer, who had tumor progression, and the second-line therapy followed by the third-line therapy was assumed to be used after progression of the first-line therapy. The survey was conducted in May and June 2016.

Treatment sequence (i.e. percentage of patients receiving a treatment as second- and third-line after progressing on first-line regimens [enzalutamide, abiraterone or docetaxel]) was surveyed, and cabazitaxel was added as one of the options for second- and third-line regimens. The percentage of patients not taking second- and third-line regimens was also surveyed. Each of the second- and third-line treatment options with the highest implementation rate in the survey
### Table 1. Summary of baseline patient characteristics and trial results (efficacy data)

|                           | PREVAIL (6) | COU-AA-302 (100) | TAX327 (18) |
|---------------------------|-------------|------------------|-------------|
|                           | Enzalutamide | Abiraterone + P  | Docetaxel + P |
|                           | Placebo + P  | Placebo + P      | Placebo + P  |
| **Baseline patient characteristics** |             |                  |             |
| Median age, years          | 72.0        | 71.0             | 68.0        |
| Median PSA, ng/ml          | 54.1        | 44.2             | 37.7        |
| Gleason score ≥ 8, %       | 50.6        | 52.4             | 50.6        |
| OS, Median                 | 33.5        | 35.3             | 45.0        |
| HR 95% CI                  | 0.74 (0.66, 0.87) | 0.59 (0.46, 0.76) | 0.52 (0.45, 0.61) |
| P-value                    | <0.0001     | 0.031            | <0.0001     |
| **TTD/rPFS**               |             |                  |             |
| Median                    | 17.71       | 4.55             | N/A         |
| HR 95% CI                 | 0.24 (0.21, 0.28) | 0.52 (0.45, 0.61) | N/A         |
| P-value                   | <0.0001     | N/A              | N/A         |

N/A, not applicable; P, prednisone/prednisolone; PSA, prostate-specific antigen.

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**Figure 1. Analysis model.**

**Figure 2. Relationship between total costs and QALY gained.**

was incorporated in the base-case treatment sequence for first-line regimens.

Related costs, including costs of active drugs, concomitant drugs, hospitalization associated with docetaxel and cabazitaxel, routine visit and monitoring, palliative care, and AEs, were calculated by multiplying the volume of medical resource consumptions with corresponding unit costs for the fiscal year 2016, as defined by the Ministry of Health, Labour and Welfare (12). Each SRE treatment cost was estimated from articles published in Japanese or respective guidelines (15,16).

**Model design**

The study population was defined as chemotherapy-naïve patients with mCRPC based on the PREVAIL study. The target treatment was enzalutamide and the active comparators were abiraterone and docetaxel.

A three-state Markov model was developed by Vicente et al. (17) and was based on an analysis model submitted to NICE (8), which comprised: stable disease, three different facets of progressed disease and death (Fig. 1). The progressed disease state comprises three sub-states: post-progression 1 (second-line treatment), post-progression 2 (third-line treatment) and palliative therapy. In the clinical setting, patients tend to receive active treatments once they progress from the...
stable disease state. Thus, the combined post-progression 1 and post-progression 2 states were modeled to compose a progressed disease state. The model also considered transition to a palliative therapy state from stable and progressed disease states before death. Costs and utility value of each state, with its decrease due to AEs and SREs associated with each treatment, were also considered.

Cycle length was set at 3 weeks, with a 10-year time horizon. Analysis was conducted from the public healthcare payer perspective, with a discount rate of 2% set for both cost and effectiveness parameters according to guidelines (13).

**Transition probabilities**

Treatment efficacy of abiraterone was derived from the results of the COU-AA-302 trial (10). An indirect comparison of the efficacies of enzalutamide versus abiraterone was performed by assuming that the control arms in the PREVAIL and COU-AA-302 trials provided the same efficacy.

Treatment efficacy of docetaxel was derived from the TAX327 trial results (18). As there were no studies comparing docetaxel with placebo or prednisone, or enzalutamide with docetaxel directly, an indirect comparison of enzalutamide versus docetaxel was conducted by comparing their efficacies with the GALGB 9182 study (mitoxantrone plus corticosteroid vs. corticosteroid alone) (19).

Efficacy data on OS, rPFS, and time to treatment discontinuation (TTD) were available in the PREVAIL and COU-AA-302 trials, while only OS was reported in the TAX 327 trial. Therefore, the Weibull distribution was used to model OS for the enzalutamide, abiraterone and placebo arms of the PREVAIL and COU-AA-302 trials. For docetaxel, OS was modeled by applying the HR to a reference curve (i.e. PREVAIL placebo arm). Time to progression for the enzalutamide, abiraterone and placebo arms of the PREVAIL

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### Table 2. Utility values

| Item                          | Value  | References      |
|-------------------------------|--------|-----------------|
| Stable disease                | 0.844  | PREVAIL (21)    |
| QoL gain                      |        |                 |
| Enzalutamide                  | 0.022  | PREVAIL (21)    |
| Abiraterone                   | 0.022  | Assumed equal to enzalutamide |
| Post-progression 1            | 0.64   | Wolff et al. (20) |
| Post-progression 2            | 0.66   | Wolff et al. (20) |
| Palliative therapy            | 0.5    | Sandblom (27)   |
| QoL reduction at AE           | −0.153 to −0.069 | Swinburn (28) Wolff et al. (20) |
| QoL reduction at SRE          | −0.237 to −0.036 | PREVAIL (29) |

### Table 3. Resource consumption survey (treatment sequence)

| First line   | Second line | Treatment rate, % | Third line | Treatment rate, % |
|--------------|-------------|-------------------|------------|-------------------|
|              |             | Mean | Standard deviation | Range | Mean | Standard deviation | Range |
| Enzalutamide | Abiraterone | 43.6 | ±29.05 | 0–90 | Docetaxel | 85.4 | ±16.64 | 50–100 |
|              |             | 55.0 | ±30.13 | 10–100 | Others | 14.6 | ±16.64 | 0–50 |
|              |             | 52.9 | ±27.65 | 10–90 | Docetaxel | 41.1 | ±32.47 | 0–100 |
|              |             | 45.7 | ±28.27 | 10–90 | Abiraterone | 30.7 | ±33.39 | 0–100 |
|              |             | 1.4  | ±3.63  | 0–10 | Cabazitaxel | 8.2  | ±9.92  | 0–30  |
| Abiraterone  | Enzalutamide| 52.9 | ±27.65 | 10–90 | Others | 14.3 | ±17.85 | 50–100 |
|              |             | 55.0 | ±27.65 | 10–90 | Cabazitaxel | 52.1 | ±34.01 | 0–100 |
|              |             | 45.7 | ±28.27 | 10–90 | Others | 42.1 | ±31.42 | 0–100 |
|              |             | 1.4  | ±3.63  | 0–10 | Others | 5.7  | ±11.58 | 0–40  |
| Docetaxel    |              | 53.6 | ±20.52 | 25–90 | Docetaxel | 38.2 | ±29.97 | 0–85  |
|              |             |      |        |       | Others | 55.0 | ±34.14 | 0–100 |
|              |             |      |        |       | Others | 6.8  | ±8.68  | 0–20  |
|              |             |      |        |       | Abiraterone | 48.2 | ±29.85 | 0–85  |
|              |             |      |        |       | Others | 46.4 | ±32.49 | 0–100 |
|              |             |      |        |       | Others | 5.4  | ±7.96  | 0–20  |
|              |             |      |        |       | Abiraterone | 47.8 | ±17.87 | 10–80 |
|              |             |      |        |       | Others | 41.1 | ±18.33 | 10–60 |
|              |             |      |        |       | Others | 11.1 | ±26.19 | 0–80  |
| Cabazitaxel  |              | 13.6 | ±16.92 | 0–50 | Others | 2.1  | ±5.79  | 0–20  |
|              |             |      |        |       | Others | 2.1  | ±5.79  | 0–20  |

*n = 14.

*Percentage of ‘Others’ was assumed the rate of not taking second- or third-line treatment.
| Item                                      | Prices (JPY) | References                                      |
|-------------------------------------------|--------------|------------------------------------------------|
| **Enzalutamide**                          |              |                                                |
| price: JPY 2354.1/40 mg                   |              |                                                |
| Dose: 160 mg/day                          |              |                                                |
| Enzalutamide: price per day               | 9638         | Medical resource consumption survey            |
| Concomitant drugs: price per week         | 5145         | Reimbursement point tables (12)                |
| Prices for outpatient and testing per week| 2762         |                                                |
| Up to 3 months                            | 2890         |                                                |
| On and after fourth month                 | 3089         |                                                |
| After chemotherapy                        | 14978        |                                                |
| **Abiraterone**                           |              |                                                |
| price: JPY 3690.9/250 mg                  |              |                                                |
| Dose: 1000 mg/day                         |              |                                                |
| Abiraterone: price per day                | 14978        |                                                |
| Concomitant drugs: price per week         | 4464         |                                                |
| Prices for outpatient and testing per week| 2726         |                                                |
| Up to 3 months                            | 2773         |                                                |
| On and after fourth month                 | 2960         |                                                |
| After chemotherapy                        |              |                                                |
| **Docetaxel**                             |              |                                                |
| price: JPY 15 471/20 mg, 52 835/80 mg     |              |                                                |
| Dose: 129.75 mg/3 weeks                   |              |                                                |
| Cabahtaxel                                |              |                                                |
| price: JPY 593 069/60 mg                  |              |                                                |
| Dose: 43.25 mg/3 weeks                    |              |                                                |
| End-of-life care per 3 months             |              |                                                |
| Hospitalization for chemotherapy per 3 weeks|            |                                                |
| Adverse event treatment costs per event   |              |                                                |
| Abdominal pain                            | 116 904      | Medical resource consumption survey (12)       |
| Anemia                                    | 107 880      |                                                |
| Anorexia                                  | 110 905      |                                                |
| Asthenia                                  | 75 849       |                                                |
| Back pain                                 | 147 710      |                                                |
| Bone pain                                 | 195 907      |                                                |
| Diarrhea                                  | 88 266       |                                                |
| Fatigue                                   | 53 415       |                                                |
| Febrile neutropenia                       | 256 381      |                                                |
| Hematuria                                 | 139 379      |                                                |
| Hypertension                              | 25 990       |                                                |
| Hypokalemia                               | 76 269       |                                                |
| Leukopenia                                | 128 754      |                                                |
| Nausea                                    | 104 686      |                                                |
| Neutropenia                               | 129 348      |                                                |
| Thrombocytopenia                          | 147 776      |                                                |
| Vomiting                                  | 119 758      |                                                |

(Continued)
Skeletal-related events and adverse events

The model included the following SREs: spinal cord compression, pathological bone fractures, and radiation and surgery therapies for bone. The number of patients with an SRE was extracted from PREVAIL trial data (6). As there was no information in the public domain on SREs in patients treated with abiraterone or docetaxel, it was assumed that the rates of SREs in the patients treated with abiraterone or docetaxel were the same as those in the patients treated with enzalutamide.

The model incorporated commonly occurring AEs with a severity grade \( \geq 3 \) and an incidence rate of \( \geq 2\% \) for any treatment group.

Utility

Utility for each of the states was based on systematic literature review results reported by Wolff et al. (20) or the PREVAIL study (21). The PREVAIL study included Japanese patients and post hoc analysis on a Japanese cohort demonstrate consistency of efficacy and safety results with the overall PREVAIL population (22). The decrements of utility for patients experiencing SREs or AEs were set by referring to published articles and the PREVAIL study, or were based on assumptions. The utility values are summarized in Table 2.

Analysis

The cost-effectiveness of the treatment sequence with enzalutamide as first-line treatment (enzalutamide-first sequencing) compared with abiraterone or docetaxel as the first-line treatment (abiraterone or docetaxel-first sequencing) was measured by the ICER and calculated using the following equation:

\[
\text{ICER} = \frac{\text{expected costs for target treatment} - \text{expected costs for comparator treatment}}{\text{QALY gained for target treatment} - \text{QALY gained for comparator treatment}}.
\]

In Japan, the ICER threshold value (i.e. the threshold to be judged as cost-effective) has not been clearly established. Therefore, we considered several ICER thresholds that were deemed cost-effective in other countries: £20 000/QALY as established by NICE in the UK (23), US$50 000/QALY (24) and the Japanese reports describing the expected range of willingness-to-pay thresholds of JPY 7.5 million/QALY (primary threshold), JPY11.25 million/QALY and JPY 15 million/QALY in previous reports (25).

Scenario analyses

Several scenario analyses were conducted with other treatment sequence options and altered drug costs to their previous costs immediately before the repricing for the market expansion of enzalutamide (as of March 2016).

Sensitivity analyses

One-way sensitivity analyses and probabilistic sensitivity analyses were performed to evaluate the uncertainty in the results of the base-case analysis. The range of input parameters in the one-way
sensitivity analyses were set based on the 95% CIs of each parameter. The values applied to parameter distribution for probabilistic sensitivity analyses were calculated from mean values and standard errors. The analysis was conducted using a 1000-iteration Monte Carlo simulation. Parameter distribution types are summarized in the Online Supplementary Table S1.

Results

Resource consumption survey

From the survey, the most common treatment sequence (first → second → third) was enzalutamide → docetaxel → cabazitaxel as target regimen, with abiraterone → enzalutamide → docetaxel and abiraterone → cabazitaxel as active comparators. Those treatment sequences were set as the base-case condition. However, the implementation rates of each regimen in the second-line treatment on enzalutamide-first sequencing and abiraterone-first sequencing were comparable; thus, the impact of those treatment sequences was evaluated in the scenario analysis. Related costs were also estimated from the survey responses. Survey results regarding treatment sequences and estimated costs are summarized in Tables 3 and 4.

Base-case analysis

Results of the base-case analysis showed that enzalutamide-first sequencing saved JPY 1.74 million versus abiraterone-first sequencing with a 0.129 QALY gain. Thus, enzalutamide-first sequencing was determined to be the dominant strategy compared with abiraterone-first sequencing (Table 5).

Compared with docetaxel-first sequencing, enzalutamide-first sequencing had a cost increase of JPY 4.44 million and a 0.371 QALY gain. The ICER of enzalutamide-first sequencing with docetaxel-first sequencing was estimated as JPY 11.94 million/QALY gained.

The relationship between total costs and QALY gained is shown in Fig. 2.

Scenario analysis

Two scenarios regarding the setting of treatment regimens were implemented according to the survey results:

- Scenario 1. Enzalutamide-first sequencing was changed from enzalutamide → docetaxel → cabazitaxel to enzalutamide → abiraterone → docetaxel.
- Scenario 2. Abiraterone-first sequencing was changed from abiraterone → enzalutamide → docetaxel to abiraterone → docetaxel → cabazitaxel.

In both cases, similar results were obtained by comparing enzalutamide-first sequencing with the abiraterone-first and docetaxel-first sequencing described in the base-case analysis (Table 5).

The scenario analyses alternating drug costs of enzalutamide (JPY 9638/day in the base-case to JPY 12 778/day), abiraterone (no alteration from JPY 14 978/day in the base-case), docetaxel (JPY 4495/day in the base-case to JPY 5035/day) and cabazitaxel (no alteration from JPY 20 425/day in the base-case) to the previous costs immediately before the repricing for the market expansion of enzalutamide (as of March 2016) were implemented (scenario 3). Compared with abiraterone-first sequencing, enzalutamide-first sequencing had a cost increase of JPY 12 767 with a 0.129 QALY gain. The ICER of enzalutamide-first sequencing with abiraterone-first sequencing had an estimated JPY 99 339/QALY gained. In the comparison of enzalutamide-first sequencing with docetaxel-first

### Table 5. Analysis results

| Groups                        | Total costs, JPY | Difference | QALY | Difference | ICER, JPY/QALY |
|-------------------------------|-----------------|------------|------|------------|----------------|
| Base-case analysis             |                 |            |      |            |                |
| Enzalutamide-first sequence    | 13 777 531      | −1 713 996 | 2.340| 0.136      | Dominant       |
| Abiraterone-first sequence     | 15 491 527      | −2 205     | 2.371| 0.159      | Dominant       |
| Docetaxel-first sequence       | 10 386 685      | −1 969     | 2.340| 0.371      | 11 944 636     |

Sequences: enzalutamide → docetaxel → cabazitaxel, abiraterone → enzalutamide → docetaxel, docetaxel → enzalutamide → cabazitaxel

Scenario analysis 1

| Enzalutamide-first sequence    | 13 495 511      | −2 017 776 | 2.371| 0.159      | Dominant       |
| Abiraterone-first sequence     | 15 313 287      | −2 212     | 2.371| 0.402      | 10 334 885     |
| Docetaxel-first sequence       | 9 340 946       | −1 969     | 2.340| 0.371      | 15 366 070     |

Sequences: enzalutamide → abiraterone → docetaxel, abiraterone → enzalutamide → docetaxel, docetaxel → enzalutamide → cabazitaxel

Scenario analysis 2

| Enzalutamide-first sequence    | 13 777 531      | −1 713 996 | 2.340| 0.136      | Dominant       |
| Abiraterone-first sequence     | 15 491 527      | −2 205     | 2.371| 0.159      | Dominant       |

Sequences: enzalutamide → docetaxel → cabazitaxel, abiraterone → docetaxel → enzalutamide

Scenario analysis 3 (alterations of drug costs to the previous costs immediately before repricing for market expansion of enzalutamide, as of March 2016)

| Enzalutamide-first sequence    | 16 094 090      | 12 767     | 2.340| 0.129      | 99 339         |
| Abiraterone-first sequence     | 16 081 323      |            | 2.212|            |                |
| Docetaxel-first sequence       | 16 094 090      | 5 707 405  | 2.340| 0.371      | 15 366 070     |

Sequences: enzalutamide → docetaxel → cabazitaxel, abiraterone → enzalutamide → docetaxel, docetaxel → enzalutamide → cabazitaxel

| Enzalutamide-first sequence    | 13 777 531      | −1 713 996 | 2.340| 0.136      | Dominant       |
| Abiraterone-first sequence     | 15 491 527      | −2 205     | 2.371| 0.159      | Dominant       |

Sequences: enzalutamide → docetaxel → cabazitaxel, abiraterone → docetaxel → enzalutamide

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sequencing, the ICER had an estimated JPY 15.37 million/QALY gained (Table 5).

Sensitivity analyses
Results of the one-way sensitivity analyses in the base-case setting are summarized in tornado diagrams of the ICERs for abiraterone-first and docetaxel-first sequencing (Fig. 3). The result that enzalutamide-first sequencing was more cost-effective than abiraterone-first sequencing was generally secured within the range of each parameter. Compared with docetaxel-first sequencing, the ICER range exceeded the threshold value sets in this analysis.

Results of probabilistic sensitivity analyses are shown in a cost-effectiveness plane with the incremental QALY on the horizontal axis and the incremental cost on the vertical axis (Fig. 4). When compared to abiraterone, the probability of enzalutamide-first sequencing being dominant was 87.4% and the probability being below JPY 7.5 million/QALY, JPY 11.25 million/QALY and JPY 15.00 million/QALY was 100% (Fig. 4A–C). There was a 4.8% probability of enzalutamide being cost-effective compared with docetaxel at a primary threshold of JPY 7.5 million (Fig. 4D), but at a secondary threshold of JPY 11.25 million, there was a 44.4% probability of enzalutamide being cost-effective (Fig. 4E).

Discussion
The present study, based on the most common treatment sequences identified in a survey conducted with 14 Japanese PCa experts, showed that enzalutamide-first sequencing (enzalutamide → docetaxel → cabazitaxel) was the dominant strategy compared with abiraterone-first sequencing (abiraterone → enzalutamide → docetaxel) for chemotherapy-naïve patients with mCRPC. This study is a model simulation incorporating evidence from various studies. Therefore, the robustness of our results was ascertained by using one-way sensitivity analyses and probabilistic sensitivity analyses.

| Parameter                                                                 | Low    | High   |
|---------------------------------------------------------------------------|--------|--------|
| OS intercept of enzalutamide                                             | 3.71–3.85 |        |
| Rate of receiving second-line treatment among patients with first-line enzalutamide | 0.00–1.00 |        |
| OS intercept of abiraterone                                               | 3.61–3.80 |        |
| Drug cost per day of abiraterone                                          | 11,234–18,723 |        |
| rPFS intercept of abiraterone                                             | 2.44–2.89 |        |
| rPFS shape of abiraterone                                                 | −0.63–0.28 |        |
| Drug cost per day of enzalutamide                                         | 72,29–12,048 |        |
| Rate of receiving second-line treatment among patients with first-line abiraterone | 0.00–1.00 |        |

**Figure 3.** Tornado diagram (base-case): (A) enzalutamide versus abiraterone and (B) enzalutamide versus docetaxel.
from this study. As a result, the cost-effectiveness of enzalutamide-first sequencing versus abiraterone-first sequencing was ensured, and the probability of enzalutamide-first sequencing being dominant was 87.4%.

Although treatment sequence was determined from survey results, abiraterone-first sequencing as an active comparator contained enzalutamide, while enzalutamide-first sequencing did not contain abiraterone. This setting might work favorably for enzalutamide-first sequencing. In order to eliminate uncertainty from the result of enzalutamide-first sequencing without abiraterone, an additional analysis was conducted changing enzalutamide-first sequencing to enzalutamide → abiraterone → docetaxel. Enzalutamide-first sequencing with enzalutamide → abiraterone → docetaxel did not change the result of enzalutamide-first being dominant over abiraterone-first sequencing (abiraterone → enzalutamide → docetaxel).

Comparison of enzalutamide-first sequencing (enzalutamide → docetaxel → cabazitaxel) with docetaxel-first sequencing (docetaxel → enzalutamide → cabazitaxel) showed that enzalutamide-first sequencing was less cost-effective (ICER = JPY 11.94 million/QALY gained). Paulden et al. described that treatments fulfilling two conditions—treatment for patients with a short life expectancy (normally less than 24 months) and sufficient evidence that the treatment offers an extension of life (normally of at least an additional 3 months)—are permitted a higher threshold of up to £50 000 per QALY according to the NICE’s ‘end of life’ amendment (26). This is regarded as equivalent to applying a maximum weight of 2.5 from a defined ICER threshold (£20 000 per QALY in NICE). In Japan, androgen deprivation therapy with bicalutamide and flutamide is often carried out before castration-resistant PCa diagnosis and there is a possibility that typical treatment history of PCa may differ between Western and Japanese patients. In addition, since the time of the completion of this study, treatment sequence may have changed from when the questionnaires were administered to the Japanese experts. This may have the potential to impact selection of the sequence of treatment used in this study. However, high-quality Japanese evidence regarding rPFS and OS for the drugs targeted in this analysis could not be collected, since there were no studies to date that specifically addressed efficacy and safety of PCa treatments in the Japanese population. Secondly, since the clinical evidence for each drug used in this analysis was not obtained from direct comparison, such as head-to-head clinical trials, the heterogeneity of each study might influence the analysis results. The implementation of indirect comparisons was considered; however, the treatment of control arms in each clinical trial was not limited to placebo and, therefore, we assumed that placebo, best supportive care, and prednisone had the same OS and rPFS. Finally, generalizability of estimated costs might not be established. In the present study, however, cost parameters were estimated from a medical resource consumption survey of 14 Japanese PCa experts and answers did not deviate substantially.

Enzalutamide-first sequencing meets the conditions of NICE’s definition for ‘end of life’ due to the expected poor prognosis for mCRPC patients and expected QALY increase of 0.371 compared with docetaxel-first sequencing. From this perspective, the ICER of JPY 11.94 million/QALY gained might be an acceptable level of cost-effectiveness.

The present study has several limitations. Firstly, not all clinical evidence was derived from Japanese patients with PCa and there is the possibility that race differences may have affected clinical outcomes. In Japan, androgen deprivation therapy with bicalutamide and flutamide is often carried out before castration-resistant PCa diagnosis and there is a possibility that typical treatment history of PCa may differ between Western and Japanese patients. In addition, since the time of the completion of this study, treatment sequence may have changed from when the questionnaires were administered to the Japanese experts. This may have the potential to impact selection of the sequence of treatment used in this study. However, high-quality Japanese evidence regarding rPFS and OS for the drugs targeted in this analysis could not be collected, since there were no studies to date that specifically addressed efficacy and safety of PCa treatments in the Japanese population. Secondly, since the clinical evidence for each drug used in this analysis was not obtained from direct comparison, such as head-to-head clinical trials, the heterogeneity of each study might influence the analysis results. The implementation of indirect comparisons was considered; however, the treatment of control arms in each clinical trial was not limited to placebo and, therefore, we assumed that placebo, best supportive care, and prednisone had the same OS and rPFS. Finally, generalizability of estimated costs might not be established. In the present study, however, cost parameters were estimated from a medical resource consumption survey of 14 Japanese PCa experts and answers did not deviate substantially.
Furthermore, the impact of the uncertainty of those cost parameters on the analysis results was evaluated by sensitivity analyses and the result showed those parameters had relatively small impact on the overall results.

In conclusion, results obtained in the present study, using a Markov model developed as per Japanese guidelines for economic evaluation, suggest that for chemotherapy-naive patients with mCRPC in the Japanese clinical settings, enzalutamide-first sequencing is more cost-effective than abiraterone-first sequencing, while it might be less cost-effective than docetaxel-first sequencing.

Supplementary Material
Supplementary material can be found at Japanese Journal of Clinical Oncology online.

Access to study data
Access to anonymized, individual, participant-level data will not be provided for this trial as it meets one or more of the exceptions described on www.clinicalstudydatarequest.com under ‘Sponsor Specific Details for Astellas’.

Author contributions
H.O. and S.N. developed the concept for the study and, together with S.I., were responsible for the study design and its conduct. Data acquisition was performed by H.O. and S.I. The data were analyzed and interpreted by H.O., S.I., S.N., S.H. and H.A. H.O. and S.I. were involved in drafting the article. All authors critically reviewed the manuscript and approved the final version.

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Conflict of interest statement
H.O., S.N. and S.H. were employees of Astellas Pharma Inc. at the time of the study. S.I. is an employee of CRECON Medical Assessment Inc. CRECON Medical Assessment Inc. was paid to conduct analyses for this study. H.A. reports serving as a study investigator for Astellas Pharma Inc. and grants from Takeda Pharmaceutical Company Limited and Astellas Pharma Singapore Pte Ltd.

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