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Unmet needs in non-metastatic castration-resistant prostate cancer from the Japanese patient perspective: a discrete choice experiment

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ABSTRACT

Objectives With novel antiandrogen treatments of varying clinical benefits and risks becoming available, this study investigates how patients with castration-resistant prostate cancer (CRPC) value differences in treatment characteristics.

Design Cross-sectional observational study.

Setting A discrete choice experiment was conducted. Patients chose between two hypothetical non-metastatic CRPC (nmCRPC) treatments defined by six attributes: risk of fatigue, falls or fracture, cognitive impairment, hypertension, rashes as side effects to treatment and extension of time until cancer-related pain occurs.

Participants A total of 137 adult male patients with CRPC with no prior experience with chemotherapy and with Eastern Cooperative Oncology Group status 0–1 were recruited. Patients were excluded if they participated in an investigational programme outside of routine clinical practice, had a clinically relevant medical or psychiatric condition, or diagnosis of visceral/other metastases not related to the prostate, or were otherwise deemed ineligible by the referring physician.

Primary outcome measures Relative preference weights and relative importance of the attributes was estimated by hierarchical Bayesian logistic regression.

Results Among the treatment attributes, 'risk of cognitive impairment as a side effect of treatment' was the most important attribute (relative importance (RI) (95% CI): 27.47% (24.80% to 30.14%)), followed by 'extension of time until cancer-related pain occurs' (RI (95% CI): 17.87% (15.49% to 20.25%)) and the 'risk of falls or fracture' (RI (95% CI): 15.99% (14.73% to 17.25%)). The 'risk of hypertension as a side effect of treatment' (RI (95% CI): 13.77% (12.73% to 14.81%)) had similar RI as 'risk of rashes as a side effect of treatment' (RI (95% CI): 13.17% (12.15% to 14.19%)), followed by the 'risk of fatigue as a side effect of treatment' (RI (95% CI): 11.74% (10.75% to 12.73%)).

Conclusions Patients consider the risk of cognitive impairment as a side effect of treatment as the most important attribute in nmCRPC, followed by the extension of time until cancer-related pain occurs, and the risk of falls and fracture. These features should be considered in treatment decision making for nmCRPC in Japan.

Strengths and limitations of this study

- A major strength of this study is the application of the discrete choice experiment (DCE) methodology to determine the relative value that patients place on different attributes of their non-metastatic castration-resistant prostate cancer (CRPC) treatment.
- Another strength lies in the development of the final DCE survey, which encompassed a series of systematic steps including literature review, qualitative exploratory interviews and cognitive interviews with patients with CRPC.
- A limitation is the representativeness of the patients with CRPC included in this study, who were a convenient sample recruited from a few selected facilities in Japan.
- Another limitation is that the DCE design may not have the same clinical meaning or emotional consequence of an actual treatment decision.

INTRODUCTION

Castration-resistant prostate cancer (CRPC), defined as rising prostate-specific antigen levels despite castrate levels of testosterone and ongoing androgen deprivation therapy (ADT), represents 10%–20% of patients with prostate cancer (PC).[1] One-third of the patients with CRPC progress to bone metastasis within 2 years. Bone metastases can cause significant pain and skeletal-related events and increase the risk of mortality, hence there is a need to delay or prevent progression to the metastatic state for patients with non-metastatic CRPC (nmCRPC) and possibly prolong overall survival (OS) while maintaining the patient's quality of life.[2]

Treatment options for nmCRPC traditionally include ADT in the form of luteinising hormone-releasing hormone and first-generation non-steroidal antiandrogens (flutamide and bicalutamide), as well as

novel hormones enzalutamide and abiraterone acetate (approved CRPC treatments in Japan). The recent approval of second-generation androgen receptor inhibitors apalutamide and darolutamide as new treatment options for nmCRPC in Japan could affect the treatment landscape.

Enzalutamide and apalutamide reported extension of metastasis-free survival (MFS) (36.6 months enzalutamide vs 14.7 months placebo; 40.5 months apalutamide vs 16.2 months placebo) in the primary analyses of their respective clinical trials in nmCRPC, and reported efficacy in extending OS (67.0 months for enzalutamide vs 56.3 months placebo; 73.9 months for apalutamide vs 59.9 months placebo), based on final analyses.[3–6] They also reported adverse effects during treatment such as fatigue (enzalutamide: 46%; apalutamide: 33%, all grades), falls (enzalutamide: 18%; apalutamide: 22%) and seizures (enzalutamide: <1%; apalutamide: 0.2%, in subjects which excluded previous history of seizures).[3 4 6] More recently, darolutamide demonstrated extension of MFS (40.4 months vs 18.4 months placebo) with rates of adverse events reported as falls (5.2%), fatigue (13.2%), rash (3.1%) and seizures (0.2% in subjects that included patients with previous history of seizures) and extension of OS (31% reduction in death compared with placebo; HR (95% CI): 0.69 (0.53 to 0.88); two-sided p=0.003).[7]

With these novel antiandrogen treatments of different clinical benefits and risks becoming available, it is important to understand how patients with CRPC value differences in treatment characteristics. Patients' health-related preferences simply go beyond cure and are particularly cogent in situations in which several choices of optimal therapy are available and treatment decisions have to be made.[8] This is underlined by a study in Japan which reported that patients with PC preferred shared decision making with physicians and were interested to be involved in the decision making on their disease management.[9] Overall, increased patient involvement is an important part of quality improvement since it has been associated with improved health outcomes.[10]

Previous studies elucidating patient preferences in CRPC treatment revealed that patients valued attributes affecting their daily quality of life (such as treatment side effects or bone pain) over extension of survival.[11–15] However, most of these studies were related to metastatic CRPC (mCRPC) treatment, with limited information on patient preferences towards nmCRPC treatment. Therefore, this study aimed to investigate how Japanese patients with CRPC would value the differences in the attributes of treatment options in nmCRPC.

METHODS

Study design

A discrete choice experiment (DCE) was conducted to measure patients with nmCRPC's treatment preferences in Japan. It was conducted in three phases (1) phase 1, the concept elicitation phase, to elicit concepts for the development of attributes list for DCE, (2) phase 2, cognitive pre-testing phase, to solicit feedback and determine the content validity of the draft DCE questionnaire and (3) phase 3, final DCE paper-based survey. Survey development took place in accordance with good research practices.[16] The participating institutions were selected to ensure representativeness in terms of geographical distribution in Japan. Informed consent was obtained from all the participants prior to any activities related to the study.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research. Part of the data used in this study were obtained from patients who provided self-reported information through the survey.

Study population

Patients recruited in all phases of this study fulfilled the following inclusion criteria: (1) aged 20 and above, (2) male, diagnosed with either nmCRPC or mCRPC, (3) no prior experience with chemotherapy, (4) Eastern Cooperative Oncology Group performance status 0–1 and (5) able to read and understand Japanese, and can provide informed consent and complete the survey instrument. Patients were excluded if they were participating in an investigational programme with interventions outside of routine clinical practice, had a clinically-relevant medical or psychiatric condition which, in the opinion of the investigator would interfere with completing the study, a diagnosis of visceral metastasis/other metastasis not related to the prostate, or were otherwise deemed ineligible by the referring physician. Patients recruited in the qualitative phases (phase 1 and 2) were excluded as participants for the main DCE survey. For the quantitative phase, a consecutive, convenience sample of patients were recruited from each participating institution, to account for potential variations in treatment patterns, scheduling of hospital visits and the size and general health of the population of interest.

A target sample size of 150 patients was planned to complete the main DCE survey. Each respondent would answer 10 preference-elicitation questions choosing between two hypothetical treatments defined by six attributes, which followed the common guidelines and rule-of-thumb for the sample size in DCE studies,[17] similar to majority of previously published studies.[16] The sample size fulfilled the recommendation of maximum SE of 0.05[18] based on simulation and was deemed feasible to recruit in Japan.

Survey development

Survey development encompassed a series of systematic steps including literature review, qualitative exploratory interviews and cognitive interviews with patients with CRPC (patients with nmCRPC and mCRPC). Literature review was conducted to identify and characterise relevant treatment attributes for nmCRPC treatments using

Figure 1 Example of preference-elicitation task.

PubMed and Embase. Attributes relating to impact on health-related quality of life (HRQoL) and efficacy were identified. Qualitative face-to-face, 60-min interviews were conducted in the concept elicitation phase with four patients with nmCRPC and four patients with mCRPC. Findings from this phase together with literature review were used to elicit concepts and attributes for inclusion in the draft DCE survey. The draft survey was tested in cognitive face-to-face interviews on another group of patients (four patients with nmCRPC and four patients with mCRPC), and feedback from the interviews were used to finalise the DCE survey.

DCE survey

The DCE task included a series of preference-elicitation questions, each asking respondents to choose between hypothetical treatments for nmCRPC. An example of a single preference-elicitation question presented to respondents is shown in figure 1.

The DCE was designed to collect data to estimate relative preference weights, relative importance of the attributes and the trade-offs patients were willing to make in one attribute for changes in another attribute. In addition to the DCE choice tasks, demographic and clinical patient characteristics, as well as HRQoL measurement (EORTC QLQ-PR25)[19] were collected from patients. Patients' PC related clinical characteristics and screening information was reported by the physicians. The experimental design of the DCE was a balanced overlap design using Sawtooth Software (Lighthouse Studio, V.9.5.3) targeting only the main effect of the attributes. This method guaranteed that sufficient patients saw different combinations of attributes and levels, with all attribute levels varying independently according to the experimental design. The design of the DCE in this study featured eight blocks of 10 preference-elicitation questions and each patient was given one block of questions. In addition, each patient was also given a hold-out question containing two treatment profiles with the absolute best-case scenario and the absolute worst-case scenario to assess and assure comprehension of the DCE.

Statistical analysis

The study sample was described with respect to demographics, disease history, comorbidity and HRQoL variables using frequencies and percentages for categorical variables and counts, means and SDs for continuous variables.

The choice data were analysed using hierarchical Bayesian logistic regression models with effects coding parameterisation (the third level being the base level) and non-informative priors for the parameters, using *rjags* package in R.[20] The outcome variable of this model was choice, and the predictor variables were the levels within each attribute. Point estimates of model coefficients represent mean preference weights at the aggregate level, defined as the marginal utility of a change in that attribute. With these estimates, the magnitude of the trade-offs for patients choosing among the attribute levels can be assessed. The relative importance estimates were calculated at the respondent level by dividing the range of each attribute (utility of most favourable level minus utility of least favourable level) by the sum of the ranges of all attributes. The resulting estimates are percentages, reflecting the importance of each attribute relative to the others.

The preference weights matching to each attribute level were summed for treatment profiles at the individual level. The summed preference weights of different treatment profiles were compared to determine which treatment profile would be most preferred.

The relative preference weights for each attribute level were also compared across two subgroups: nmCRPC and mCRPC, to determine whether preferences vary by patient disease status.

Further exploratory analysis was conducted to examine whether preferences vary by patient demographics, disease and medical history, as well as HRQoL using one-way analysis of variance. For all analyses, p values <0.05 were considered statistically significant. Analyses were performed using R V.3.5.1[21] and SPSS V.22.0.[22]

RESULTS

Participants

A total of 137 patients with CRPC, recruited from six participating institutions and correctly answered the hold-out question, were included in the analyses, with 60 patients with nmCRPC and 77 patients with mCRPC. The mean age was 75.8 (SD=7.5), 83.9% were married,

Table 1 Physician-reported patient clinical characteristics

		Total (N=137)	
		N	%
Prostate cancer stage at diagnosis	Stage I	2	1.46
	Stage IIA	14	10.22
	Stage IIB	21	15.33
	Stage III	28	20.44
	Stage IV M0 (no evidence of metastasis)	13	9.49
	Stage IV M1 (metastatic)	56	40.88
	I do not have this information	3	2.19
Experienced since prostate cancer diagnosis	Symptomatic skeletal-related events	7	5.11
	Seizure	0	0
	Cognitive impairment	0	0
	Patient-reported fatigue	1	0.73
	None of the above	129	94.16
Metastatic status of prostate cancer	Yes	77	56.20
	No	60	43.80
ECOG grade at study enrolment	Grade 0	106	77.37
	Grade 1	31	22.63
Symptomatic status at study enrolment	Symptomatic	3	2.19
	Asymptomatic	134	97.81
First type of prostate cancer related treatment (ADT)	LHRH agonist, LHRH antagonist	86	62.77
	Surgery (orchiectomy)	7	5.11
	Vintage antiandrogens (e.g., bicalutamide, flutamide)	86	62.77
	Oestrogen	1	0.73
	Unknown	2	1.46
Treatment currently prescribed for prostate cancer	Abiraterone	30	21.90
	Enzalutamide	43	31.39
	Vintage antiandrogens (e.g., bicalutamide, flutamide)	15	10.95
	LHRH agonist, LHRH antagonist	126	91.97
	Ra-233 (Xofigo)	1	0.73
	External beam radiotherapy (EBRT)	3	2.19
	Bisphosphonate	5	3.65
	Denosumab	29	21.17
	Opioid	1	0.73
	Steroid	35	25.55
	NSAID / paracetamol / COX-2 inhibitors	4	2.92
	Other	11	8.03
	No treatment / watch and wait	2	1.46

Continued

Table 1 Continued

		Total (N=137)	
		N	%
Treatment prescribed prior to current treatment	Abiraterone	13	9.49
	Enzalutamide	15	10.95
	Vintage antiandrogens (e.g., bicalutamide, flutamide)	71	51.82
	LHRH agonist, LHRH antagonist	49	35.77
	Strontium-89	1	0.73
	Ra-233 (Xofigo)	13	9.49
	EBRT	34	24.82
	Bisphosphonate	9	6.57
	Denosumab	20	14.60
	Surgery	11	8.03
	Opioid	1	0.73
	Steroid	10	7.30
	NSAID / paracetamol / COX-2 inhibitors	2	1.46
	Other (nmCRPC clinical trial participant)	6	4.38
	Other (other prostate cancer clinical trial participant)	4	2.92
	Other	23	16.79
	No other treatment other than first ADT	18	13.14
		Mean	SD
Duration of disease (years)		6.8	5.2
Duration of metastasis (months)		50.6	41.4
Duration of CRPC (months)		24.5	17.6

ADT, androgen deprivation therapy; CRPC, castration-resistant prostate cancer; ECOG, Eastern Cooperative Oncology Group; LHRH, luteinising hormone-releasing hormone; nmCRPC, non-metastatic CRPC; NSAID, non-steroidal anti-inflammatory drug.

45.3% had at least 2-year college education and 30.0% were still employed. Only seven patients (5.1%) reported being currently cared for by a primary caregiver for their PC; 42.3% of patients suffered from hypertension. The details are shown in online supplemental table 1. Patients had been diagnosed with PC for an average of 6.8 years (SD=5.2) with 56 of them (40.9%) in Stage IV M1 (metastatic) at diagnosis. Seven patients (5.1%) had experienced symptomatic skeletal-related events (SSE) since diagnosis. None of the patients were diagnosed with having seizures or cognitive impairment at the time of enrolment in the study. The details are shown in table 1.

Attributes and levels in the DCE

The final specific attributes included in the DCE were: (1) risk of fatigue as a side effect of treatment, (2) risk of falls or fractures as a side effect of treatment, (3) risk of cognitive impairment as a side effect of treatment, (4) risk of hypertension as a side effect of treatment, (5) extension of time until cancer-related pain occurs and (6) risk of rashes as a side effect of treatment (online supplemental table 2).

Patient preferences estimates

The hierarchical Bayesian logistic regression model results are reported in figure 2 and online supplemental table 3. All levels of all attributes were significantly associated with choice (all p<0.05). The greater the range of preference weights within an attribute, the stronger the relationship between that attribute and treatment choice.

Among the 137 patients with CRPC, the 'risk of cognitive impairment as a side effect of treatment' was the most important attribute, with a relative importance (RI) of 27.47% (95% CI 24.80% to 30.14%); followed by 'extension of time until cancer-related pain occurs' (RI (95% CI): 17.87% (15.49% to 20.25%)) and the 'risk of falls or fracture' (RI (95% CI): 15.99% (14.73% to 17.25%)). The 'risk of hypertension as a side effect of treatment' (RI

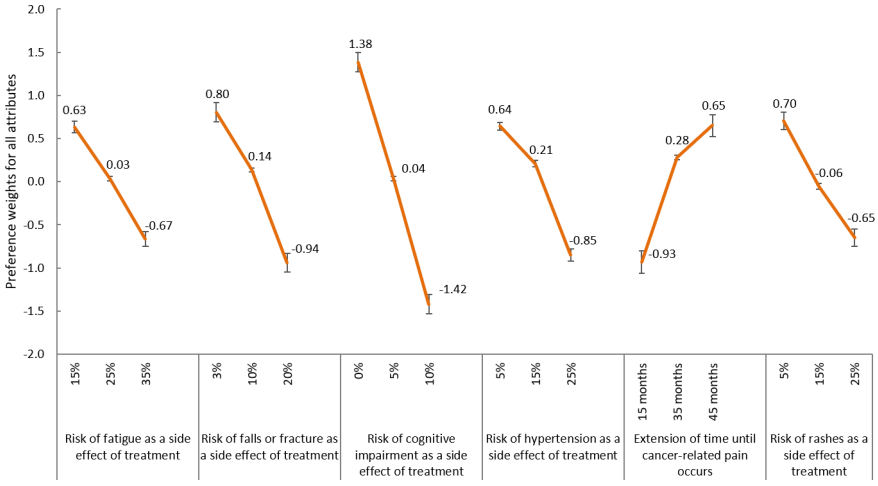

Figure 2 Attribute-level preference weights: overall sample (N=137).

(95% CI): 13.77% (12.73% to 14.81%)) had similar RI as 'risk of rashes as a side effect of treatment' (RI (95% CI): 13.17% (12.15% to 14.19%)), followed by the 'risk of fatigue as a side effect of treatment' (RI (95% CI): 11.74% (10.75% to 12.73%)) (figure 3).

The RI for patients with nmCRPC and mCRPC is further illustrated in figure 4. Compared with patients with mCRPC, patients with nmCRPC placed more importance to risk of cognitive impairment as a side effect of treatment (RI: 31.53% vs 24.30%).

Based on the preference weights for attributes, summed preference weights were derived for three hypothetical treatment profiles with varying attribute levels in table 2. Among patients with CRPC, treatment profile I, with the lowest risk of side effects, had significantly higher summed preference weights mean (mean (95% CI): 3.23 (2.91 to 3.56) vs −2.09 (−2.30 to −1.88) vs −0.062 (−0.15 to 0.026)), compared with the other two treatment profiles. The results were similar for both nmCRPC and mCRPC subgroups, in that majority of patients would prefer the profile with the lowest risk of side effects.

Patient preferences by demographic, health history and HRQoL

No significant differences in preferences weights were observed when comparing across demographic and health history variables (online supplemental table 4), nor was there any significant association between patient HRQoL and treatment preference (online supplemental table 5).

DISCUSSION

Dedicated qualitative interviews and DCEs play an important role in understanding and assessing patient's priorities in selecting available treatment options. DCEs have been used to elicit patient preferences in many other therapeutic fields as well as for PC.[23–28] This study also applied DCE methodology to determine the relative value that patients place on different attributes of their nmCRPC treatment. Our results suggest that patients with CRPC (both nmCRPC and mCRPC) preferred safer treatment profiles with lesser risk of adverse events, given that most chose a hypothetical treatment profile with the least risk of side effects. This is consistent with previous studies reporting that avoiding side effects is relatively important to patients with CRPC when considering treatment options.[11 12] In our study, patients with CRPC considered the risk of cognitive impairment as a side effect of treatment as the most important treatment attribute in nmCRPC,

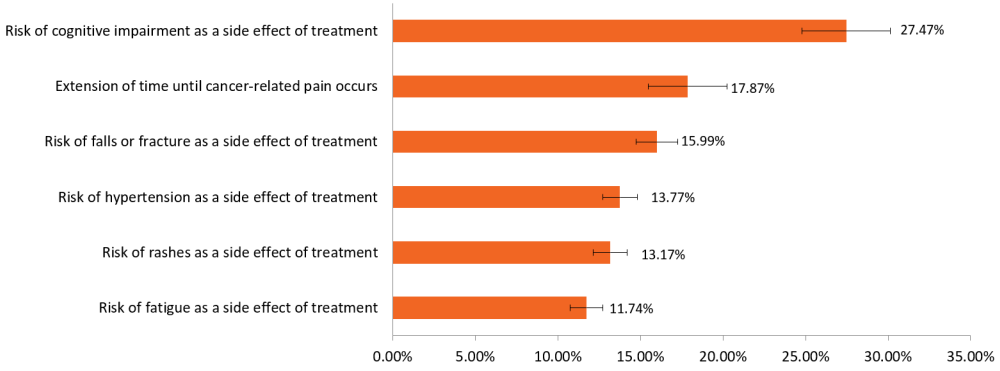

Figure 3 Relative importance of treatment attributes: overall sample (N=137).

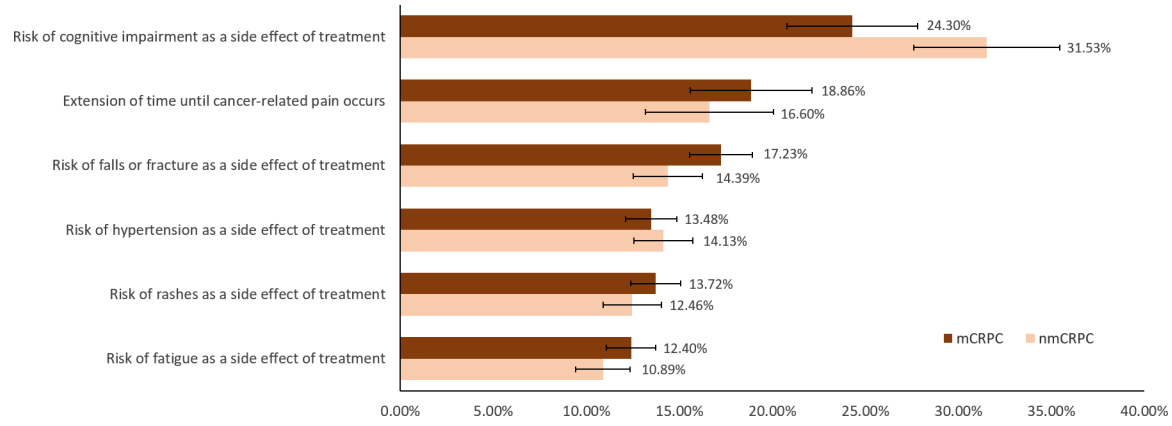

Figure 4 Relative importance of treatment attributes: nmCRPC versus mCRPC. mCRPC, metastatic castration-resistant prostate cancer; nmCRPC, non-metastatic CRPC.

followed by extension of time until cancer-related pain occurs. Furthermore, patients were willing to trade-off effectiveness such as time until pain occurs for lower risk of side effects such as cognitive impairment. Our results are also consistent with recent patient preference studies on CRPC treatment which reported cognition and memory problems as being relatively more important than other treatment attributes.[12 29]

The impact on cognition and cognitive impairment in older adults with cancer has been reported, and it is thought that the triple conditions of ageing, cancer and cancer treatment can negatively affect cognition.[30] In PC, a meta-analysis by McGinty *et al* showed that patients who received ADT performed significantly worse on visuomotor tasks compared with non-cancer control groups, and they noted that these findings are consistent with the known effects of testosterone on cognitive functioning in healthy men.[31] Any factor influencing cognition, therefore, is of great importance for patients with nmCRPC due to the possibly relatively long period of ADT treatment even prior to CRPC. Furthermore, in the nmCRPC state, patients are largely asymptomatic,[32] and having cognitive impairment may greatly affect their ability to function independently, hence compromising their quality of life. Indeed, a study on Japanese community-dwelling older adults showed that even mild cognitive impairment may be related to an increased risk for the development of disability in the future.[33]

Looking at the degree of relative importance that patients with mCRPC and patients with nmCRPC separately placed on these two attributes, patients with nmCRPC weighed more on risk of cognitive impairment

Table 2 Summary of patient preference for different treatment profiles

		Treatment profile I	Treatment profile II	Treatment profile III
Attribute levels	Risk of fatigue as a side effect of treatment	15%	25%	35%
	Risk of falls or fracture as a side effect of treatment	3%	20%	10%
	Risk of cognitive impairment as a side effect of treatment	0%	5%	5%
	Risk of hypertension as a side effect of treatment	5%	25%	15%
	Extension of time until cancer-related pain occurs	15 months	35 months	35 months
	Risk of rashes as a side effect of treatment	5%	25%	15%
CRPC	Summed preference weights: mean (95% CI)	3.234 (2.905 to 3.563)	−2.088 (−2.296 to −1.880)	−0.062 (−0.149 to 0.026)
	Patients in favour of the profile: N (%)	128 (93.4%)	2 (1.5%)	7 (5.1%)
mCRPC	Summed preference weights: mean (95% CI)	3.226 (2.776 to 3.675)	−2.141 (−2.420 to −1.861)	−0.151 (−0.268 to −0.034)
	Patients in favour of the profile: N (%)	72 (93.5%)	1 (1.3%)	4 (5.2%)
nmCRPC	Summed preference weights: mean (95% CI)	3.245 (2.758 to 3.732)	−2.020 (−2.334 to −1.706)	0.053 (−0.073 to 0.179)
	Patients in favour of the profile: N (%)	56 (93.3%)	1 (1.7%)	3 (5%)

CRPC, castration-resistant prostate cancer; mCRPC, metastatic CRPC ; nmCRPC, non-metastatic CRPC.

while patients with mCRPC weighed more on extension of time until cancer-related pain occurs. The difference in the degree of importance could be associated with most patients with nmCRPC being asymptomatic, hence, accordingly, with a long duration of hormonal therapy, patients would want to spend their daily lives with a well-maintained HRQoL that precludes an increased risk of cognitive impairment while on treatment. Similarly, for patients with mCRPC, due to increased age, advanced disease stage and having experienced more bone metastasis-related pain, the importance of pain management to maintain HRQoL in the time they have left is understandable. In a qualitative study on pain in CRPC with bone metastasis, patients reported that bone pain was the most prominent and debilitating symptom associated with their condition, while another study found that bone pain was found to be the strongest predictor of SSE, which are linked with a reduced quality of life and worse outcomes.[34 35]

These results are also congruent to a study by Nakayama *et al*, which showed the differences in the patients' treatment preferences across different PC stages wherein patients with more advanced PC would prefer efficacy, whereas patients in less advanced PC would prefer maintenance of HRQoL.[27] Our study reflects a similar trend where the patients' preference reflected a mixture of putting more emphasis on efficacy (mCRPC) as well as on safety and tolerability (nmCRPC), with patients wanting to protect their HRQoL via an implied need to delay cognitive side effects, as well as delaying cancer-related pain.

The need of Japanese patients for minimal side effects while receiving effective nmCRPC therapy, as reflected in their preferences for safer treatment features, should be considered in treatment decision making. Novel antiandrogen treatments have their own reported central nervous system related treatment features relating to cognitive impairment and efficacy in delaying pain progression, among others. A better awareness of attributes that influence patients' treatment decision may enable clinicians to communicate with patients more effectively when making shared decisions on CRPC treatment strategies.

Finally, we attempted to put together the results here and from a physician preference study done in parallel with this study, and physicians were also asked about their preferences for the same set of attributes. From the physician perspective, 'extension of time until cancer-related pain occurs' were the most important, followed by 'risk of falls or fracture as a side effect of treatment'. However, 'risk of cognitive impairment as a side effect of treatment' ranked only fourth in terms of attribute relative importance, showing a gap in how patients and physicians perceive treatment attributes in nmCRPC (online supplemental figure 1). Although no formal statistical comparison was conducted, the observed gap in patients' and physicians' perception of nmCRPC treatment attributes emphasises the need for open communication of treatment benefits and risks between patients and their physicians. In previous studies on gaps between patients and physicians' preferences in PC, different reasons for such gaps have been put forward, such as the structure of patient–physician encounters being typically physician-driven, or that physicians may judge patients' health using different reference points from their clinical practice experience.[36 37] Clinical decision making could be balanced by asking patients' regarding their personal preferences about treatment risks and benefits to establish patient-centred care.

A few limitations of this study should be noted. Due to sample selection during recruitment, respondents who were healthy enough to participate and were interested in research may be over-represented, hence could potentially introduce selection bias. Patient recruitment limited to the five institutions and the use of convenience sample may raise concerns about the external validity of the findings, however, descriptive data on the sample demographic and health characteristics reported would help put our sample within the context of the total CRPC population. In addition, responses in the DCE were centred around hypothetical treatment profiles. One of the key aspects of this design was to stimulate possible clinical decisions, but this does not mean it has the same clinical meaning or emotional consequence of an actual decision. Hence, differences could arise between stated and actual response. Potential hypothetical bias can be limited by constructing choice questions that mimic realistic clinical choices as closely as possible and map clearly into clinical evidence. Although not central to the research question, a few of our potential covariates (eg, comorbidities) were reported directly from the patient without clinical verification. This decision was made to ease the burden on the physician investigators though it does introduce possible additional measurement error in the assessment of these variables. Lastly, the study failed to reach the target sample size of 150 patients and the sample sizes for the subgroups were limited in this study, therefore, caution should be taken in interpreting and generalising the results in terms of subgroup comparisons.

CONCLUSION

Patients value safety and prioritise features such as lower risk of cognitive impairment, and extension of time until pain occurs when choosing among nmCRPC treatment options with similar efficacy but different safety profiles. Such an assessment provides insights into the patients' nmCRPC treatment preferences and taking them into consideration will help physicians when developing their treatment strategies for their patients in Japan.

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Contributors HU contributed input to the study design as expert opinion leader, as well as to data collection and interpretation of the results. HM, AY, KK, GA and TS were responsible for data collection and interpretation of study results. VG, SS and YC were responsible for study design, data aggregation and analysis, study coordination and medical writing. DAL was responsible for creating the study design, data interpretation and overall coordination of the study. All authors read and approved the final manuscript.

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Competing interests DAL is an employee of Bayer Yakuhin. VG, SS and YC are employees of Kantar, Health Division.

Patient consent for publication Not required.

Ethics approval The protocol was approved by the respective Institutional Review Boards (IRBs) of each participating institution: Yokohama City University Ethical Committee (Approval No. B181004003 for Yokohama City University Medical Center), Tokyo Metropolitan Hospital Clinical Research Evaluation Committee (Approval No. 19-a08 for Tokyo Metropolitan Hospital), Harasanshin Hospital Ethical Committee (Approval No. 2019-03 for Harasanshin Hospital), Dokkyo Medical University Saitama Medical Center Clinical Research Ethical Review Committee (Approval No. 1915 for Dokkyo Medical University Saitama Medical Center), Yokosuka Kyosai Hospital Clinical Research Ethical Review Committee (Approval No. 19-7 for Yokosuka Kyosai Hospital); and by a Central IRB (NPO Clinical Research Support Network Japan, Approval No. 20131) for Satoh Takefumi Prostate Clinic which did not have an in-house IRB.

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Data availability statement Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA 'Principles for responsible clinical trial data sharing'. This pertains to scope, time point and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the Study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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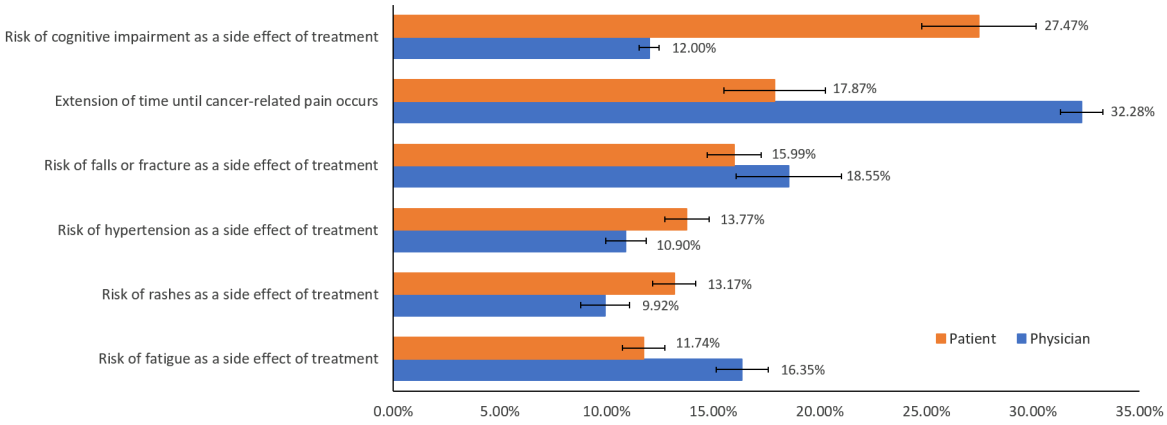
Supplementary material

Supplementary figure 1 Relative importance of treatment attributes: patients vs. physicians.



Supplementary table 1 Patient-reported demographics and other baseline characteristics.

		Total (N = 137)	
		N	**%**
Age [year] Category	<60	5	3.65%
	60-<70	20	14.60%
	70-<80	65	47.45%
	80-<90	43	31.39%
	≥90	3	2.19%
Marital status	Single	6	4.38%
	Married	115	83.94%
	Divorced	2	1.46%
	Separated	1	0.73%
	Widowed	10	7.30%
	Living with partner	2	1.46%
Level of education	Elementary school	0	0.00%
	Junior high school	23	16.79%
	High school	50	36.50%
	2-year college	4	2.92%
	4-year college	54	39.42%
	Graduate school	4	2.92%
	Decline to answer	1	0.73%
Employment status	Employed full-time	18	13.14%
	Self-employed	17	12.41%
	Part-time employed	6	4.38%
	Retired	62	45.26%
	Long-term disability	0	0.00%
	Short-term disability	0	0.00%
	Not employed (other than retired)	33	24.09%
Region of residence	Chubu	1	0.73%
	Kanto	105	76.64%
	Kyushu (including Okinawa)	30	21.90%
Household income	Less than ¥2,500,000	28	20.44%
	2,500,000 to ¥4,999,999	57	41.61%
	¥5,000,000 to ¥7,499,999	14	10.22%
	¥7,500,000 to ¥9,999,999	6	4.38%
	¥10,000,000 to ¥12,499,999	3	2.19%
	¥12,500,000 to ¥14,999,999	3	2.19%
	¥15,000,000 or more	2	1.46%
	Decline to answer	23	16.79%
Type of medical insurance	National health insurance	40	29.20%
	Late stage elderly insurance	76	55.47%
	Company/Social insurance	18	13.14%
	Welfare recipient	2	1.46%
	None of the above (all costs paid by myself/my family)	0	0.00%
Currently cared by a primary caregiver for prostate cancer	Yes	7	5.11%
	No	129	94.16%
Primary caregiver relationship	Wife	4	57.14%
	Child	1	14.29%

	Grandchild	0	0.00%
	Sibling	0	0.00%
	Other relative (parent, niece/nephew)	0	0.00%
	Hired professional caregiver	2	28.57%
	Other non-relative	0	0.00%
Physician-diagnosed comorbid condition	Cardiovascular disease	19	13.87%
	Chronic pulmonary disease	3	2.19%
	Rheumatologic disease	1	0.73%
	Peptic ulcer disease	16	11.68%
	Mild liver disease	13	9.49%
	Diabetes without chronic complications	16	11.68%
	Diabetes with chronic complications	5	3.65%
	Hemiplegia or paraplegia	1	0.73%
	Renal disease	4	2.92%
	Any malignancy, including leukemia and lymphoma	1	0.73%
	Moderate or severe liver disease	1	0.73%
	Other metastatic solid tumor currently being treated (other than that of the prostate)	1	0.73%
	AIDS/HIV	0	0.00%
	Hypertension	58	42.34%
	Prior malignancy, now in remission (malignancy other than that of the prostate)	10	7.30%
	None of the above	51	37.23%
		Mean	**SD**
Age		75.8	7.5

Supplementary table 2 List of attributes and levels in DCE

Attributes	Levels
i. Risk of fatigue as a side-effect of treatment	• 15% • 25% • 35%
ii. Risk of falls or fractures as a side-effect of treatment	• 3% • 10% • 20%
iii. Risk of cognitive impairment as a side-effect of treatment	• 0% • 5% • 10%
iv. Risk of hypertension as a side-effect of treatment	• 5% • 15% • 25%
v. Extension of time until cancer-related pain occurs	• 15 months • 35 months • 45 months
vi. Risk of rashes as a side-effect of treatment	• 5% • 15% • 25%

Supplementary table 3 Attribute-level preference weights: overall sample (N=137)

Attribute	Levels	Mean preference weight	SE	95% CI	p-value
Risk of fatigue as a side-effect of treatment	15%	0.633	0.035	0.564, 0.703	<0.001
	25%	0.034	0.013	0.009, 0.059	0.009
	35%	-0.667	0.043	-0.752, -0.582	<0.001
Risk of falls or fracture as a side- effect of treatment	3%	0.802	0.057	0.691, 0.913	<0.001
	10%	0.136	0.013	0.110, 0.161	<0.001
	20%	-0.938	0.054	-1.044, -0.831	<0.001
Risk of cognitive impairment as a side-effect of treatment	0%	1.385	0.058	1.271, 1.498	<0.001
	5%	0.035	0.012	0.012, 0.059	0.005
	10%	-1.420	0.056	-1.530, -1.310	<0.001
Risk of hypertension as a side-effect of treatment	5%	0.642	0.024	0.595, 0.689	<0.001
	15%	0.210	0.018	0.173, 0.246	<0.001
	25%	-0.852	0.037	-0.925, -0.779	<0.001
Extension of time until cancer-related pain occurs	15 months	-0.933	0.068	-1.066, -0.799	<0.001
	35 months	0.281	0.015	0.252, 0.309	<0.001
	45 months	0.652	0.064	0.526, 0.778	<0.001
Risk of rashes as a side-effect of treatment	5%	0.705	0.050	0.606, 0.803	<0.001
	15%	-0.056	0.016	-0.088, -0.024	<0.001
	25%	-0.648	0.051	-0.749, -0.548	<0.001

Supplementary table 4 Differences in preference weights across demographic and health history factors

			Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
		N	15%	25%	35%	3%	10%	20%	0%	5%	10%	5%	15%	25%	15 months	35 months	45 months	5%	15%	25%
Age group	<60	5	0.468	0.045	-0.513	0.429	0.123	-0.552	1.453	-0.083	-1.370	0.545	0.124	-0.669	-1.220	0.251	0.969	0.409	-0.093	-0.316
	60-<70	20	0.617	0.024	-0.641	0.755	0.170	-0.925	1.465	0.007	-1.472	0.646	0.174	-0.820	-1.015	0.274	0.741	0.728	-0.078	-0.651
	70-<80	65	0.620	0.021	-0.641	0.789	0.138	-0.927	1.362	0.055	-1.417	0.657	0.183	-0.840	-0.999	0.283	0.716	0.736	-0.037	-0.700
	≥80	46	0.691	0.059	-0.750	0.897	0.116	-1.013	1.353	0.031	-1.384	0.635	0.273	-0.908	-0.775	0.283	0.492	0.690	-0.074	-0.616
	p-value		0.621	0.602	0.595	0.455	0.621	0.479	0.922	0.119	0.966	0.849	0.096	0.625	0.380	0.978	0.297	0.683	0.689	0.548
Marital status	Married / Living with partner	117	0.646	0.034	-0.680	0.827	0.135	-0.961	1.373	0.043	-1.415	0.644	0.203	-0.848	-0.948	0.284	0.664	0.732	-0.060	-0.672
	Not	20	0.586	0.043	-0.629	0.686	0.135	-0.822	1.407	-0.012	-1.395	0.642	0.249	-0.891	-0.846	0.260	0.586	0.558	-0.040	-0.518
	p-value		0.558	0.797	0.687	0.394	0.980	0.377	0.837	0.113	0.902	0.975	0.396	0.690	0.608	0.568	0.679	0.234	0.681	0.303
Level of education	Completed university education	62	0.628	0.029	-0.657	0.785	0.141	-0.925	1.423	0.035	-1.457	0.625	0.219	-0.844	-0.899	0.290	0.609	0.699	-0.053	-0.646
	Not	75	0.647	0.040	-0.686	0.826	0.130	-0.956	1.339	0.035	-1.375	0.659	0.202	-0.862	-0.963	0.273	0.690	0.715	-0.061	-0.654
	p-value		0.790	0.677	0.733	0.721	0.681	0.784	0.476	0.970	0.467	0.487	0.656	0.820	0.640	0.566	0.532	0.879	0.821	0.939
Employment status	Employed	41	0.706	0.047	-0.753	0.879	0.149	-1.028	1.358	0.024	-1.382	0.667	0.228	-0.895	-0.994	0.279	0.714	0.740	-0.058	-0.682
	Not employed	96	0.609	0.030	-0.638	0.776	0.128	-0.905	1.386	0.040	-1.426	0.634	0.202	-0.836	-0.908	0.281	0.627	0.694	-0.057	-0.636
	p-value		0.211	0.533	0.228	0.409	0.476	0.301	0.824	0.555	0.723	0.532	0.531	0.476	0.569	0.945	0.536	0.675	0.989	0.685
Household income	Less than ¥5,000,000	85	0.644	0.037	-0.681	0.817	0.148	-0.965	1.413	0.038	-1.451	0.642	0.220	-0.862	-0.849	0.284	0.566	0.699	-0.051	-0.647
	¥5,000,000 to ¥9,999,999	20	0.660	0.062	-0.722	0.786	0.080	-0.866	1.263	0.019	-1.282	0.699	0.267	-0.966	-0.917	0.248	0.669	0.682	-0.040	-0.642
	¥10,000,000 or more	8	0.797	0.019	-0.816	1.191	0.090	-1.281	0.975	0.115	-1.090	0.669	0.150	-0.819	-1.453	0.398	1.055	0.864	-0.148	-0.717
	Decline to answer	24	0.540	0.010	-0.550	0.656	0.150	-0.807	1.486	0.010	-1.497	0.595	0.144	-0.738	-1.080	0.258	0.823	0.707	-0.063	-0.644
	p-value		0.468	0.701	0.533	0.274	0.253	0.297	0.237	0.297	0.335	0.677	0.227	0.393	0.164	0.177	0.206	0.893	0.571	0.991
Type of medical insurance	National health insurance	40	0.605	0.022	-0.627	0.746	0.137	-0.883	1.408	0.044	-1.452	0.628	0.196	-0.824	-0.989	0.272	0.718	0.685	-0.026	-0.659
	Late stage elderly insurance	76	0.677	0.040	-0.717	0.875	0.129	-1.004	1.348	0.047	-1.396	0.648	0.226	-0.874	-0.879	0.294	0.586	0.731	-0.070	-0.662
	Company/Social insurance	18	0.505	0.009	-0.513	0.587	0.163	-0.749	1.484	-0.029	-1.455	0.634	0.158	-0.793	-1.095	0.252	0.843	0.592	-0.067	-0.525
	Welfare recipient	2	1.017	0.342	-1.359	1.428	0.058	-1.486	0.904	-0.023	-0.880	0.894	0.343	-1.236	-0.445	0.225	0.221	1.292	-0.125	-1.167
	p-value		0.214	0.022	0.094	0.181	0.749	0.245	0.651	0.175	0.666	0.635	0.505	0.531	0.573	0.737	0.444	0.418	0.645	0.518
Currently cared by a primary caregiver for prostate cancer	Yes	7	0.665	0.058	-0.723	0.815	0.046	-0.861	1.137	0.071	-1.208	0.582	0.301	-0.883	-1.021	0.307	0.714	0.575	-0.062	-0.513
	No	129	0.636	0.034	-0.670	0.807	0.139	-0.946	1.390	0.033	-1.424	0.647	0.205	-0.852	-0.929	0.279	0.650	0.715	-0.057	-0.658
	p-value		0.858	0.678	0.789	0.975	0.116	0.731	0.334	0.480	0.398	0.551	0.254	0.858	0.769	0.681	0.827	0.542	0.944	0.536

Duration of prostate cancer (median split)	≤5 years	76	0.619	0.024	-0.643	0.808	0.135	-0.943	1.365	0.035	-1.401	0.635	0.197	-0.832	-0.994	0.295	0.699	0.700	-0.067	-0.633
	>5 years	60	0.662	0.049	-0.711	0.806	0.135	-0.941	1.393	0.035	-1.427	0.655	0.226	-0.882	-0.858	0.262	0.596	0.717	-0.045	-0.672
	p-value		0.553	0.337	0.443	0.984	0.990	0.986	0.815	0.969	0.815	0.676	0.427	0.508	0.327	0.270	0.431	0.867	0.511	0.709
ECOG grade at study enrolment	Grade 0	105	0.631	0.027	-0.658	0.811	0.135	-0.946	1.373	0.036	-1.409	0.639	0.205	-0.844	-0.973	0.282	0.690	0.719	-0.058	-0.661
	Grade 1	31	0.662	0.062	-0.724	0.796	0.132	-0.928	1.392	0.031	-1.423	0.661	0.227	-0.888	-0.802	0.275	0.527	0.669	-0.056	-0.613
	p-value		0.718	0.252	0.528	0.915	0.922	0.893	0.888	0.847	0.917	0.701	0.609	0.617	0.299	0.830	0.293	0.680	0.970	0.695
Symptomatic status at study enrolment	Symptomatic	3	0.853	-0.081	-0.772	0.979	0.097	-1.076	0.755	0.081	-0.836	0.547	0.124	-0.671	-1.990	0.252	1.739	1.039	-0.210	-0.829
	Asymptomatic	133	0.633	0.038	-0.671	0.803	0.136	-0.939	1.391	0.034	-1.425	0.646	0.212	-0.858	-0.910	0.281	0.629	0.700	-0.054	-0.646
	p-value		0.364	0.171	0.734	0.651	0.667	0.713	0.107	0.563	0.123	0.548	0.489	0.465	0.020	0.768	0.011	0.324	0.165	0.603

Supplementary table 5 Regression coefficients for preference weights and HRQoL sub-scale scores

		Risk of fatigue as a side-effect of treatment			Risk of falls or fracture as a side-effect of treatment			Risk of cognitive impairment as a side-effect of treatment			Risk of hypertension as a side-effect of treatment			Extension of time until cancer-related pain occurs			Risk of rashes as a side-effect of treatment		
	N	**15%**	**25%**	**35%**	**3%**	**10%**	**20%**	**0%**	**5%**	**10%**	**5%**	**15%**	**25%**	**15 months**	**35 months**	**45 months**	**5%**	**15%**	**25%**
Symptom scale: Urinary symptoms	137	0.002	0.000	-0.001	-0.001	0.001	0.000	0.003	0.000	-0.003	-0.001	0.002	-0.001	0.004	-0.001	-0.004	-0.001	0.000	0.001
p-value		0.455	0.896	0.567	0.848	0.500	0.970	0.375	0.865	0.380	0.367	0.065	0.745	0.291	0.530	0.329	0.722	0.938	0.709
Symptom item: Incontinence aid	36	-0.004	-0.001	0.006	-0.007	-0.002	0.009	-0.001	-0.001	0.002	-0.004	-0.001	0.004	-0.005	0.000	0.005	-0.009	-0.001	0.010
p-value		0.022	0.052	0.012	0.020	0.103	0.003	0.741	0.148	0.519	0.011	0.545	0.060	0.249	0.596	0.247	0.002	0.524	0.002
Symptom scale: Bowel symptoms	137	-0.004	-0.001	0.004	-0.007	-0.001	0.009	0.004	-0.001	-0.003	-0.005	0.002	0.003	0.006	0.001	-0.007	-0.011	-0.001	0.012
p-value		0.256	0.603	0.280	0.144	0.217	0.068	0.428	0.564	0.487	0.020	0.233	0.368	0.303	0.366	0.195	0.013	0.370	0.006
Symptom scale: Hormonal treatment-related symptoms	137	0.004	0.000	-0.004	0.004	0.000	-0.003	-0.001	0.001	0.000	-0.002	0.000	0.002	0.001	0.003	-0.004	-0.002	0.000	0.002
p-value		0.148	0.908	0.224	0.422	0.725	0.451	0.894	0.472	0.988	0.315	0.834	0.586	0.800	0.036	0.460	0.608	0.908	0.590
Functional scales: Sexual activity	137	-0.002	0.000	0.003	-0.004	0.000	0.005	0.001	-0.003	0.002	-0.004	-0.004	0.007	-0.002	-0.001	0.003	-0.002	-0.002	0.004
p-value		0.587	0.852	0.619	0.546	0.843	0.498	0.850	0.054	0.835	0.227	0.131	0.127	0.830	0.734	0.761	0.716	0.367	0.519
Functional scales: Sexual functioning	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA