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Research Article

Efficacy and safety of apalutamide in Japanese patients with nonmetastatic castration-resistant prostate cancer: a subgroup analysis of a randomized, double-blind, placebo-controlled, Phase-3 study

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ABSTRACT

Background: In the global Phase-3 Selective Prostate Androgen Receptor Targeting with ARN-509 study, apalutamide plus ongoing androgen deprivation therapy (ADT) significantly increased metastasis-free survival (MFS) and improved other clinical outcomes in men with nonmetastatic castration-resistant prostate cancer (nm-CRPC) who were at high risk of developing metastases. In this subpopulation analysis of Selective Prostate Androgen Receptor Targeting with ARN-509 study, the efficacy and safety of apalutamide plus ADT were evaluated in Japanese patients with nm-CRPC.

Methods: The primary efficacy end point was MFS. Secondary efficacy end points were time to metastasis, progression-free survival, symptomatic progression, initiation of cytotoxic chemotherapy, and overall survival. Safety and pharmacokinetic parameters were also assessed.

Results: Fifty-five Japanese patients with ongoing ADT were randomized (apalutamide: n = 34, placebo: n = 21). Median treatment duration was 5.7 months in the apalutamide group and 11.0 months in the placebo group. Median MFS was not reached in the apalutamide group (95% confidence interval: 10.97, not estimable) and was 18.23 months (95% confidence interval: 11.04, 18.50) in the placebo group. Secondary end points were improved in the apalutamide group. The safety profile of apalutamide with ADT was comparable with the global population, and no new safety signals were identified in this Japanese subpopulation. Although, apalutamide exposure tended to be higher in the Japanese subpopulation compared with the non-Japanese population, this was likely to be explained by body weight and considered not clinically meaningful.

Conclusion: In the Japanese subpopulation, treatment with apalutamide with ADT resulted in favorable efficacy outcomes with comparable benefit-risk profile to the global population with nm-CRPC who are at high-risk of developing metastases.

1. Introduction

Patients who have an increase in prostate-specific antigen (PSA) after primary therapy are often treated with androgen deprivation

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therapy (ADT). Although, patients initially respond to ADT, eventually most patients acquire resistance and develop nonmetastatic castration-resistant prostate cancer (nm-CRPC).[1,2] Patients with nm-CRPC are defined as those treated with ADT, with rising PSA levels despite castration levels of testosterone, and without evidence of metastatic disease on conventional imaging.[3] In such patients, distant metastatic disease may develop in approximately 2 years[4,5], with even a higher risk of metastatic progression in men with PSA doubling time (PSADT) of ≤10 months.

Apalutamide is a next-generation, orally administered, nonsteroidal antiandrogen, which shows potent and selective androgen receptor antagonist activity without significant agonist properties.[6] Apalutamide selectively binds to the ligand-binding domain of the androgen receptor thereby impairing its nuclear translocation and DNA binding to androgen response elements.[6,7]

Selective Prostate Androgen Receptor Targeting with ARN-509 (SPARTAN), a global, randomized Phase-3 study, assessed the efficacy of ongoing ADT with apalutamide compared with placebo in men with nm-CRPC at a high risk of developing metastases. In this study, apalutamide with ongoing ADT significantly increased metastasis-free survival (MFS) (40.5 months vs 16.2 months, hazard ratio [HR] for metastasis or death: 0.28, 95% confidence interval [CI]: 0.23, 0.35; $p < 0.001$) and time to symptomatic progression (HR: 0.45; 95% CI: 0.32, 0.63; $p < 0.001$) using ADT with apalutamide compared with placebo in patients with nm-CRPC.[8] Exploratory analysis of the SPARTAN study also revealed that the health-related quality of life was preserved after initiation of apalutamide treatment.[9] Based on the results of the SPARTAN study, the US Food and Drug Administration approved apalutamide on 14 February 2018 for patients with nm-CRPC.[10]

Currently, no recommendations have been provided for the treatment of nm-CRPC in the Japanese clinical practice guideline for prostate cancer, and to date no therapy has been shown to have efficacy in Japanese men with nm-CRPC.[11] Hence, a subpopulation analysis of the SPARTAN study to evaluate the efficacy and safety of apalutamide with ongoing ADT in Japanese men with nm-CRPC was undertaken.

2. Materials and Methods

2.1. Patients

Detailed methodology of this study has been published earlier.[8] Men with nm-CRPC aged ≥18 years were eligible. Patients were required to have no detectable distant metastases as determined on conventional imaging (computed tomography/magnetic resonance imaging or technetium bone scan) and evaluated by blinded independent central review (BICR), with a histologically or cytologically confirmed adenocarcinoma of the prostate and at a high risk for developing metastases (defined as PSADT ≤10 months during continuous ADT); with CRPC (defined as 3 PSA rises ≥1 week apart, with the last PSA >2 ng/mL) and testosterone levels of <50 ng/dL, demonstrated during continuous medical or surgical ADT was required. Gonadotropin-releasing hormone analog therapy was continued throughout the study to maintain castrate levels of testosterone in nonorchiectomized patients.

Patients were excluded if they had distant metastases (except pelvic lymph nodes <2 cm in the short axis (N1) located below the iliac bifurcation); symptomatic loco-regional disease requiring medical intervention; prior enzalutamide or abiraterone acetate treatment or; prior chemotherapy for prostate cancer; a history of seizures or condition that may predispose to seizures or concurrent treatment with medications known to have seizure potential; or any major medical condition or malignancy.

The institutional review board of each participating institution reviewed and approved the protocol, informed consent form, and amendments. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients provided written informed consent before enrollment. This trial was registered at ClinicalTrials.gov (NCT01946204).

2.2. Study design and medication

Patients with ongoing ADT were randomly assigned (2:1) to either apalutamide (240 mg/day) or matched placebo orally on a continuous daily dosing schedule until disease progression, withdrawal of consent, or unacceptable toxicity or death. This analysis was performed in the Japanese subpopulation and the data is reported from the first interim report with clinical cut-off date of 19 May 2017.

2.3. Efficacy end points

2.3.1. Primary

The primary end point was MFS defined as the time from randomization to the first evidence of bone or soft tissue distant metastasis (in accordance with BICR review) or death due to any cause, whichever occurred first.

2.3.2. Secondary

Secondary end points were time to metastasis (defined as the time from randomization to the first evidence of bone or soft tissue distant metastasis [in accordance with BICR review]), progression-free survival (PFS; defined as the time from randomization to first radiographic detection of progressive disease [distant or local/regional, determined by BICR review] or death due to any cause), time to symptomatic progression (defined as the time from randomization to development of: (1) a skeletal-related event [pathologic fracture, spinal cord compression, or need for surgical intervention or radiation therapy to the bone], or (2) pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anticancer therapy, or (3) clinically significant symptoms due to loco-regional tumor progression requiring surgery or radiation therapy), overall survival (OS), and time to the initiation of cytotoxic chemotherapy.

2.4. Assessments

Distant metastasis was assessed by imaging (computed tomography/magnetic resonance imaging or technetium bone scan) and assessed by BICR. Radiographic evaluations were performed every 16 weeks and for newly detected bone lesions, a second imaging study was performed to confirm metastasis. Evidence of distant metastases on imaging were determined on the basis of the Response Evaluation Criteria in Solid Tumors (version 1.1).

2.5. Safety analysis

Safety was evaluated based on adverse events (AEs) assessment, physical examinations, vital sign measurements, and clinical laboratory tests (hematology, serum chemistry, liver function tests, and thyroid stimulating hormone). All AEs were graded in accordance with National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.03.

2.6. Pharmacokinetic analysis

Nonlinear mixed effects modeling was used to develop a population pharmacokinetic (PK) model for plasma concentrations of apalutamide and its active metabolite N-desmethyl apalutamide. A covariate analysis was performed to investigate the potential effect of the intrinsic and extrinsic factor on the exposure of apalutamide and N-desmethyl apalutamide. In addition, the population PK model was used to derive individual exposure metrics for area under the curve at steady state during dosing-interval ($AUC_{0\text{-}24,ss}$) for apalutamide and N-desmethyl apalutamide.

2.7. Statistical methods

The primary statistical method of comparison for time-to-event end points was a nonstratified log-rank test. HRs (<1 favors active treatment) were calculated from a nonstratified proportional hazards model with a single factor of treatment group. The Kaplan–Meier method was used to estimate medians. Both primary and secondary efficacy end points were analyzed using intent-to-treat population that included all Japanese patients who were randomized into the study. The safety analysis set comprised all Japanese patients who received at least one dose of study medication. The PK analysis set comprised all Japanese patients who received at least one dose of study medication and had a sufficient number of quantifiable plasma samples for reliable estimation of PK parameters.

3. Results

3.1. Patient disposition and characteristics

Of the 1207 patients enrolled globally in the SPARTAN study[8], 55 (4.6%) were enrolled from Japan (ongoing ADT plus apalutamide: n = 34 or placebo: n = 21), and included in this subpopulation analysis (Fig. 1). All baseline characteristics of the Japanese subpopulation were consistent with the global population except for body weight, which was lower in the Japanese subpopulation (median [range]; apalutamide: 61.9 [46-84] kg; placebo: 67.5 [48-83] kg) in comparison with the global population (apalutamide: 85.0 [45-182] kg; placebo: 83.2 [43-161] kg) (Table 1). In Japan, the patient enrollment was delayed by almost 1.5 years while last patient enrollment was extended by 5 months in comparison with the global population (first patient enrollment: October 2013, last patient enrollment: June 2016). The median treatment duration from randomization to clinical cut-off date in the Japanese subpopulation was shorter (apalutamide: 5.67 [0.1; 22.1] months; placebo: 10.97 [3.7; 20.6] months) than the global population (apalutamide: 16.92 [0.1; 42.0] months; placebo: 11.17 [0.1; 37.1] months). At the cut-off date, 38.2% (13/34) patients in the apalutamide group and 52.4% (11/21) patients in the placebo group had already discontinued study-assigned treatment. The most common reason for treatment discontinuation was AEs in the apalutamide group and progressive disease in the placebo group. Till the clinical cut-off date, 26.5% of patients in the apalutamide group and 33.3% patients in the placebo group received treatment for at least 12 months and none in the two groups received treatment for 24 months.

3.2. Efficacy

3.2.1. Primary

In the Japanese subpopulation, median MFS was not reached in the apalutamide group (95% CI: 10.97, not estimable [NE]) compared with 18.23 months (95% CI: 11.04, 18.50) in the placebo group (Fig. 2, Supplementary Table 1). The HR for metastasis or death was 71% lower (HR: 0.29; 95% CI: 0.06, 1.48) in the apalutamide group (Supplementary Table 1), which is comparable to the HR in the global population (HR: 0.28; 95% CI: 0.23, 0.35). The proportion of patients who developed distant metastasis or died was 5.9% (2/34) in the apalutamide group compared with 33.3% (7/21) in the placebo group.

3.2.2. Secondary

In the Japanese subpopulation, apalutamide treatment was associated with improved outcomes for all the secondary end points. The median time to metastasis was not reached (95% CI: 10.97, NE) in the apalutamide group and was 18.23 months (95% CI: 11.07, 18.50) in the placebo group (HR: 0.34; 95% CI: 0.06, 1.75) (Fig. 3A, Supplementary Table 1). The median PFS was not reached (95% CI: 10.97, NE) in the apalutamide group and was 18.23 months (95% CI: 10.12, 18.50) in the placebo group (HR: 0.55; 95% CI: 0.17, 1.73) (Fig. 3B, Supplementary Table 1). The BICR-confirmed radiographic progressive disease or death was observed in 14.7% (5/34) patients in the apalutamide group and 38.1% (8/21) in the placebo group. The median time to symptomatic progression and median OS was not reached in both treatment groups. Time to symptomatic progression (HR: 0.38; 95% CI: 0.04, 4.22) (Fig. 3C) and OS (HR: 0.36; 95% CI: 0.03, 4.03) (Fig. 3D) were improved with apalutamide treatment

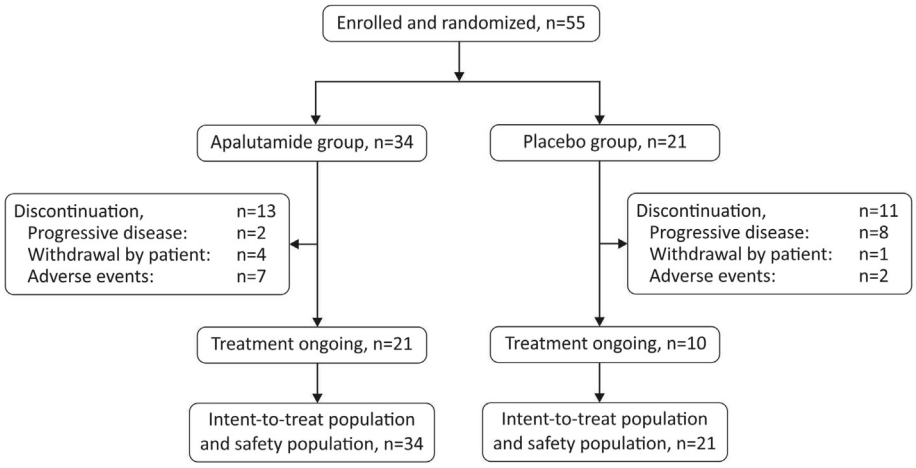

Fig. 1. Japanese patient disposition. Intent-to-treat (ITT) population included all patients who received at least one dose of study medication. The safety analysis set comprised all patients in the safety population. Safety population included all patients who received at least 1 dose of study drug. AEs, adverse events; n, number of patients.

Table 1
Demographics and baseline characteristics in the Japanese subpopulation versus global population (intent-to-treat population)

Charactaristics	Japanese subpopulation		Global population	
	Apalutamide (n = 34)	Placebo (n = 21)	Apalutamide (n = 806)	Placebo (n = 401)
Age, years	79.0 (61-90)	74.0 (63-86)	74.0 (48-94)	74.0 (52-97)
Weight, kg	61.9 (46-84)	67.5 (48-83)	85.0 (45-182)	83.2 (43-161)
Height, cm	163.5 (140-176)	164.2 (153-172)	173.0 (140-196)	172.0 (149-194)
Time from initial diagnosis to randomization, years	n = 34	n = 21	n = 806	n = 400
	7.26 (0.9-14.7)	7.53 (1.1-15.2)	7.95 (0.3-30.4)	7.85 (0.8-26.3)
PSA doubling time, months	4.10 (1.1-8.1)	4.30 (0.7-7.4)	4.40 (0.8-10.0)	4.50 (0.7-10.0)
ECOG performance status score, n (%)	n = 34	n = 21	n = 806	n = 400
0	30 (88.2)	20 (95.2)	623 (77.3)	311 (77.8)
1	4 (11.8)	1 (4.8)	183 (22.7)	89 (22.3)
Lymph node stage at diagnosis, n (%)	n = 34	n = 21	n = 799	n = 395
N0	28 (82.4)	20 (95.2)	550 (68.8)	273 (69.1)
N1	6 (17.6)	1 (4.8)	118 (14.8)	61 (15.4)
Gleason score at initial diagnosis, n (%)	n = 34	n = 21	n = 784	n = 387
<7	1 (2.9)	2 (9.5)	152 (19.4)	72 (18.6)
7	8 (23.5)	5 (23.8)	291 (37.1)	146 (37.7)
>7	25 (73.5)	14 (66.7)	341 (43.5)	169 (43.7)
Previous prostate cancer therapy, n (%)	n = 34	n = 21	n = 803	n = 401
Surgery or radiotherapy	33 (97.1)	21 (100.0)	617 (76.6)	307 (76.6)
Hormonal therapy				
GnRHa	34 (100.0)	21 (100.0)	780 (96.8)	387 (96.5)
First-generation antiandrogen	33 (97.1)	21 (100.0)	592 (73.4)	290 (72.3)
Orchiectomy	1 (2.9)	1 (4.8)	47 (5.8)	24 (6.0)
Baseline PSA, ng/mL	4.35 (0.5-21.7)	3.96 (1.9-21.7)	7.78 (0.1-294.8)	7.96 (1.1-291.8)
Baseline hemoglobin, g/L	129.50 (94.0-155.0)	134.00 (107.0-173.0)	133.00 (94.0-221.0)	134.00 (92.0-202.0)
Baseline alkaline phosphatase, U/L	73.50 (33.0-137.0)	75.00 (48.0-147.0)	77.00 (3.0-353.0)	78.00 (29.0-257.0)
Baseline testosterone, nmol/L	0.85 (0.3-2.2)	1.10 (0.5-2.0)	0.80 (0.3-3.1)	0.80 (0.3-2.8)

Data is presented as median (range) unless specified. ECOG, Eastern Cooperative Oncology Group; GnRHa, gonadotropin-releasing hormone analog; n, number of patients; N, nodal disease; PSA, prostate-specific antigen.

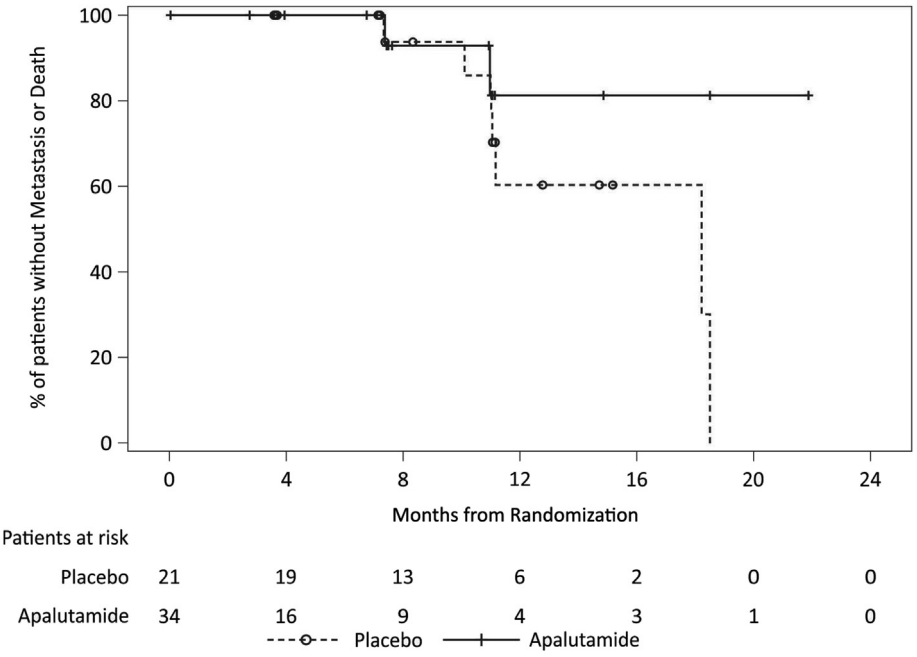

Fig. 2. Kaplan–Meier plot of the primary end-point metastasis-free survival (Japanese intent-to-treat population).

(Supplementary Table 1). The number of events were limited as symptomatic progression and death were observed in 2.9% (1/34) patients in the apalutamide group and 9.5% (2/21) patients in the placebo group. The median time to initiation of cytotoxic chemotherapy was not reached for both the apalutamide group and the placebo group (95% CI: 15.87, NE) (Fig. 3E, Supplementary Table 1). Cytotoxic chemotherapy was initiated in 9.5% (2/21) of patients in the placebo group and no patients in the apalutamide group. Although the number of events in Japanese patients was small, the treatment effect of apalutamide in Japanese subpopulation was nevertheless consistent with that of the global population.

3.3. *Safety*

The incidence of AEs occurred at similar frequencies between the Japanese subpopulation and the global population in the

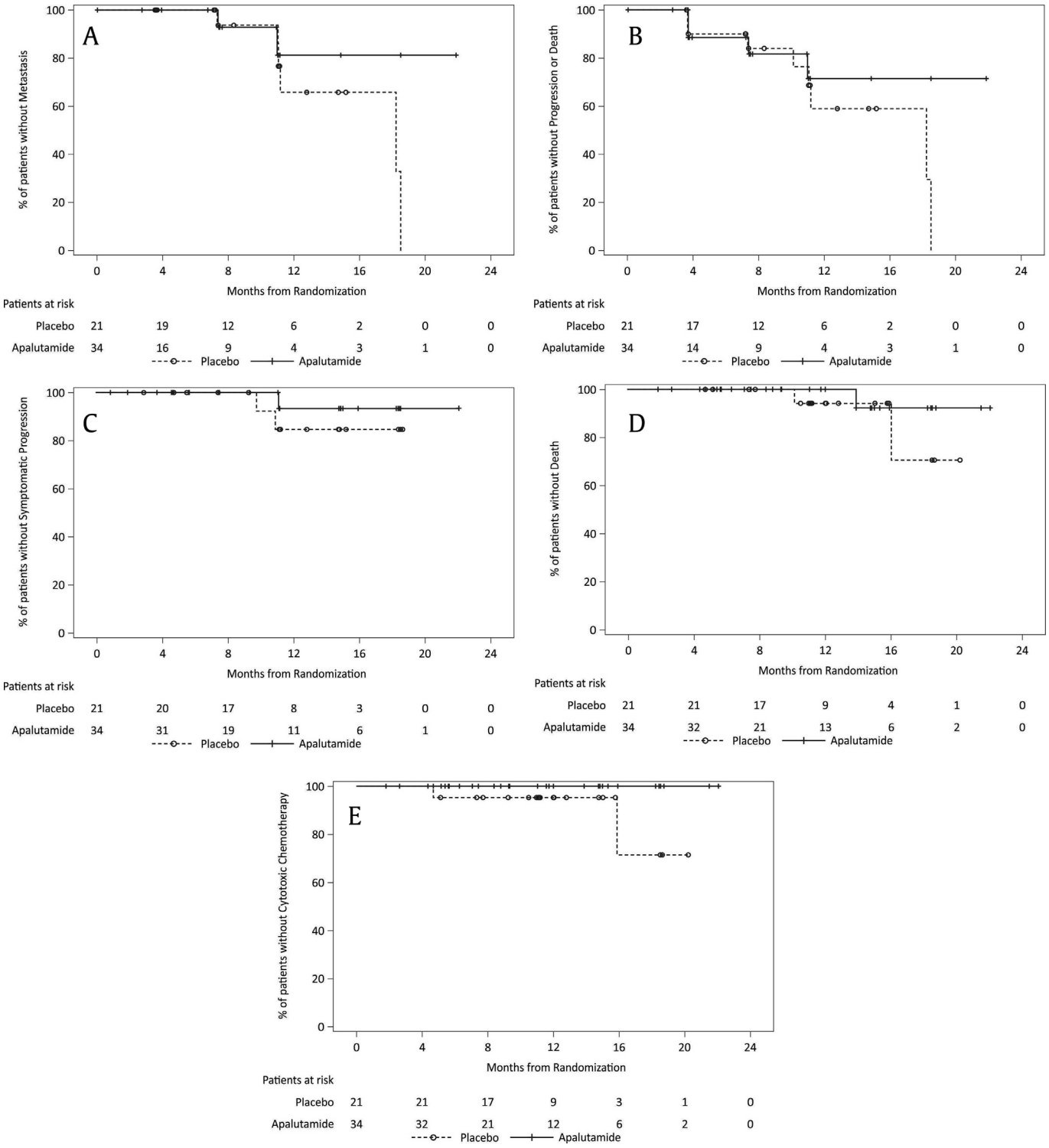

Fig. 3. Kaplan–Meier plot of the secondary end points. (A) Time to metastasis, (B) Progression-free survival, (C) Time to symptomatic progression, (D) Overall survival, and (E) Time to initiation of cytotoxic chemotherapy (Japanese intent-to-treat population).

apalutamide group (94.1% versus 96.5%) and the placebo group (85.7% versus 93.2%). In the Japanese subpopulation, the most frequently reported AEs (occurring in ≥15% of patients in either group) were nasopharyngitis (9% apalutamide vs 24% placebo), rash maculopapular (24% apalutamide vs 0% placebo), rash generalized (18% apalutamide vs 0% placebo), constipation (18% apalutamide vs 5% placebo), dysgeusia (18% apalutamide vs 5% placebo), and decreased appetite (18% apalutamide vs 10% placebo).

CTCAE Grade 3/4 AEs were reported in 44.1% (15/34) of patients in the apalutamide group and in 23.8% (5/21) of patients in the placebo group in the Japanese subpopulation (Table 2); compared with 45.1% (362/803) of patients in the apalutamide group and

Table 2
Summary of adverse events in the Japanese subpopulation versus global population (safety population)

n (%)	Japanese subpopulation		Global population	
	Apalutamide (n = 34)	Placebo (n = 21)	Apalutamide (n = 803)	Placebo (n = 398)
≥1 AEs	32 (94.1)	18 (85.7)	775 (96.5)	371 (93.2)
Grade 3 or 4 AEs	15 (44.1)	5 (23.8)	362 (45.1)	136 (34.2)
Any SAEs	8 (23.5)	5 (23.8)	199 (24.8)	92 (23.1)
Any AE leading to treatment discontinuation	7 (20.6)	2 (9.5)	85 (10.6)	28 (7.0)
AE leading to death	0	1 (4.8)	10 (1.2)	1 (0.3)

AE, adverse event; n, number of patients; SAE, serious adverse event.

Table 3
Summary of adverse events in the Japanese subpopulation (safety population)

Graded AEs in ≥2% patients	Apalutamide (n = 34)	Placebo (n = 21)
	Grade 3	Grade 3
Rash maculopapular	2 (5.9)	0
Hydronephrosis	1 (2.9)	1 (4.8)
Rash macular	1 (2.9)	0
Rash generalized	1 (2.9)	0
Drug eruption	1 (2.9)	0
Miliaria	1 (2.9)	0
Presyncope	1 (2.9)	0
Spinal cord compression	1 (2.9)	0
Thrombotic cerebral infarction	1 (2.9)	0
Decreased appetite	1 (2.9)	0
Hyperkalemia	1 (2.9)	0
Lumbar spinal stenosis	1 (2.9)	0
Lumbar vertebral fracture	1 (2.9)	0
Hypertension	1 (2.9)	0
Pleural effusion	1 (2.9)	0
Pneumonia aspiration	1 (2.9)	0
Weight decreased	1 (2.9)	0
Amylase increased	1 (2.9)	0
Anemia	1 (2.9)	0
Malignant neoplasm of renal pelvis	1 (2.9)	0
Renal impairment	1 (2.9)	0
Cystitis hemorrhagic	1 (2.9)	0
Cardiac failure	1 (2.9)	0
Cataract	1 (2.9)	0
Prostatitis	1 (2.9)	0
Pancreatitis	0	1 (4.8)
Cerebral infarction	0	1 (4.8)
Polymyalgia rheumatic	0	1 (4.8)
Calculus urinary	0	1 (4.8)
Cholangitis acute	0	1 (4.8)

Data is presented as n (%). No Grade 4 AEs were reported. AE, adverse event; n, number of patients.

34.2% (136/398) of patients in the placebo group in the global population.[8] The most frequently reported Grade 3/4 AE (occurring in ≥2 patients in either group) was rash maculopapular (5.9% in apalutamide vs 0% in placebo) (Table 3).

AEs of special interest with apalutamide included skin rash, falls, fractures, hypothyroidism and seizures, although the small sample size of Japanese patients makes it difficult to accurately assess each one of these. AEs in skin rash group (including rash maculopapular, rash generalized, and others) were reported in 56% of apalutamide-treated patients versus none in the placebo-treated patients. Among Grade 3/4 AEs of special interest in the Japanese subpopulation, the most commonly reported was skin rash (apalutamide: 15%, placebo: 0%); of these patients with skin rash, 58% had dose interruption and 21% had a dose reduction. Onset of skin rash typically occurred within the first 3 months of apalutamide treatment and most events of skin rash (apalutamide: 74%) were reported as resolved within approximately 2 months, which was consistent with the results in the global population. In the global population, a similar trend of higher events of skin rash in apalutamide group (apalutamide: 23.8%, placebo: 5.5%) was observed. Among Grade 1/2 AEs of special interest, falls (apalutamide: 2.9%, placebo: 9.5%) and fracture (apalutamide: 2.9%, placebo: 14.3%) were less frequent in the apalutamide group in the Japanese subpopulation in comparison with the placebo group and also in comparison with the global population (Grade 1/2 events: falls, apalutamide: 13.8%, placebo:8.3%; fracture, apalutamide: 8.9%, placebo: 5.8%; total events: falls, apalutamide: 15.6%, placebo: 9.0%; fracture, apalutamide: 11.7%, placebo: 6.5%). No events of seizure were reported in the Japanese population and only Grade 1 events of hypothyroidism were reported in placebo treated group (4.8%) of the Japanese population.

In the Japanese subpopulation, death due to AE within 28 days of the last dose of study drug was reported in one patient in the placebo group and no death was reported in the apalutamide group (Table 2). In the global population, death was reported in 1.2% (10/803) patients in the apalutamide group and 0.3% (1/398) patients in the placebo group. Proportions of patients with SAEs and AEs leading to treatment discontinuation were similar between the two groups in both Japanese subpopulation and global population.

3.4. *Pharmacokinetics*

Population PK modeling undertaken in overall study population including Japanese men, identified body weight and serum albumin concentration to be associated with apalutamide or N-desmethyl apalutamide exposure in patients with CPRC, although the magnitude of the effect was considered low.

Using the population PK model, individual $AUC_{0\text{-}24,ss}$ were estimated, and patients in the Japanese subgroup tended to show higher exposure of apalutamide and N-desmethyl apalutamide compared with the non-Japanese population (Fig. 4A). However, this is likely to be explained by the difference in body weight between the populations. No notable difference was observed in the relationship between body weight and $AUC_{0\text{-}24,ss}$ of apalutamide and N-desmethyl apalutamide in the Japanese patients (Fig. 4B). The exposures in the Japanese patients overlapped with the exposure range in the non-Japanese population, therefore, the difference was considered not clinically relevant.

4. Discussion

Apalutamide is the first Food and Drug Administration–approved drug for the treatment of patients with nm-CRPC[10], and National Comprehensive Cancer Network guidelines now include apalutamide as a systemic therapy option for nm-CRPC especially in patients with PSADT ≤10 months.[12] In this subgroup analysis of the SPARTAN study, the efficacy and safety of apalutamide with ongoing ADT in Japanese patients with nm-CRPC was similar to the overall patient population of the global study.[8] However, these results should be interpreted with caution, given the relatively small number of Japanese patients enrolled in the study. Moreover, being a post-hoc analysis of the global SPARTAN trial, our study was neither

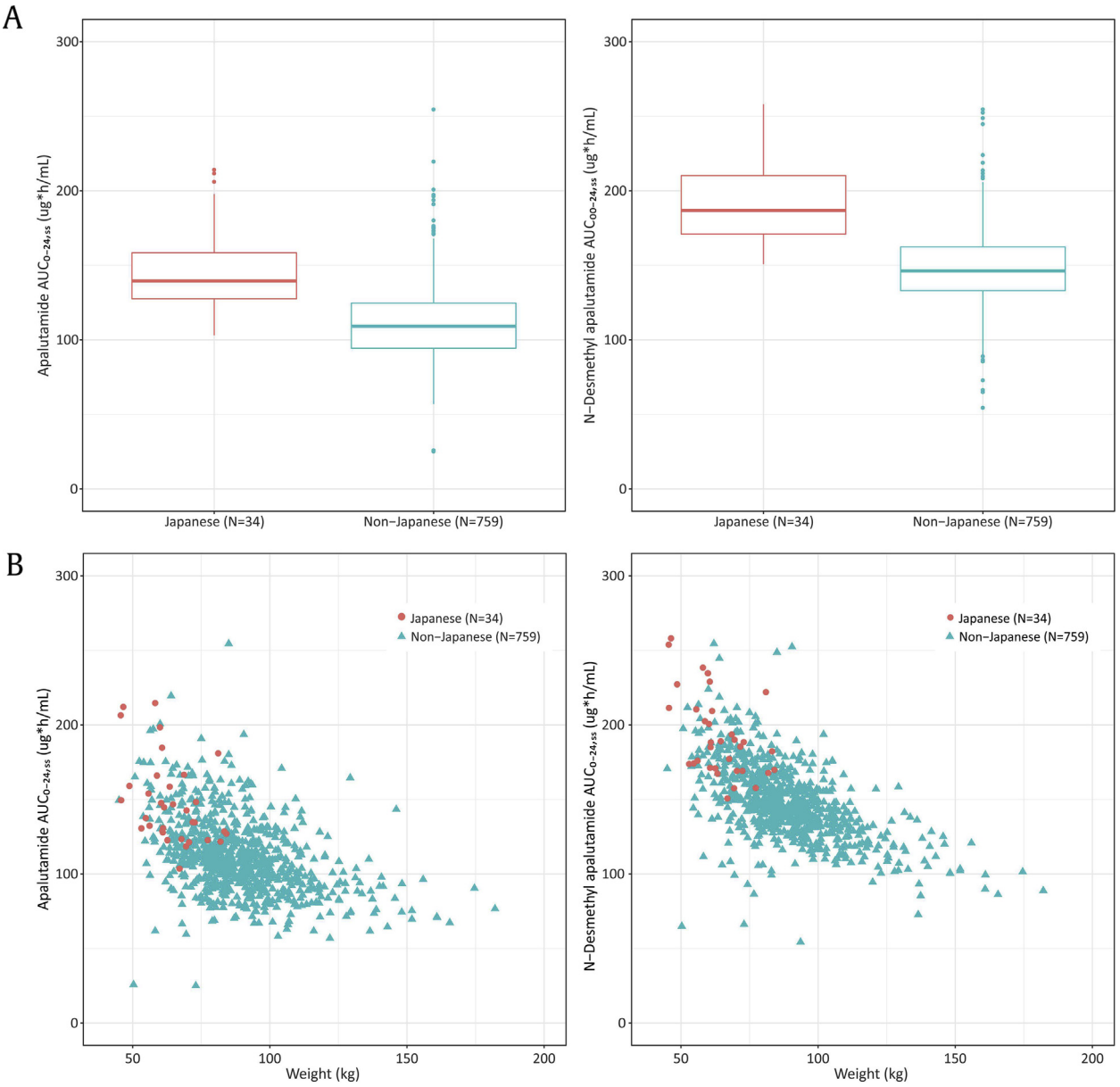

Fig. 4. Pharmacokinetic assessments evaluating apalutamide exposure in the Japanese patients versus the non-Japanese patients (pharmacokinetic analysis set) (A) Area under the curve at steady state ($AUC_{0\text{-}24,ss}$, μg*h/mL) (B) The influence of body weight (kg) on the exposure of apalutamide and N-desmethyl apalutamide.

designed nor powered to detect treatment effect differences between Japanese and non-Japanese patients.

In the current subpopulation analysis in Japanese men with high-risk nm-CRPC, the use of apalutamide with ongoing ADT resulted in an improvement in MFS, with a 71% lower risk of metastasis or death (HR: 0.29; 95% CI: 0.06, 1.48), consistent with the findings in the global population. Secondary end points, including time to metastasis, PFS, and time to symptomatic progression improved in the apalutamide group. Proportion of patients with symptomatic progression and cytotoxic chemotherapy was also lower in the apalutamide group. The outcomes for these secondary efficacy end points in the Japanese subpopulation demonstrated consistency with the results observed in global population.

In this subpopulation analysis with the Japanese patients, improvement in MFS was supported by a lower proportion of patients with symptomatic progression (2.9%, 1/34) in the apalutamide group thus corroborating the results observed in the global population (7.9%, 64/806). Although the timing of therapy was not formally tested in SPARTAN, these results indicate that it may be preferable to start early treatment with apalutamide in the patients with nm-CRPC and high risk of metastases rather than withholding the treatment until metastasis appears.

Although the frequency of first-generation antiandrogen use was slightly higher in Japan (~98%) compared with the global population data from SPARTAN (~72%), the efficacy outcomes in Japanese patients showed the same trend as observed in the global population. Moreover, based on the small percentage of Japanese patients included in this analysis, it is difficult to evaluate the effect of this difference in frequency of first-generation antiandrogen use on efficacy variables.

The frequency of AEs, Grade 3/4 AEs, SAEs, and AEs leading to death and treatment discontinuation was comparable between the global population and the Japanese subpopulation. Although skin rash (AE of special interest) was reported for a greater

proportion of the Japanese subpopulation (56%) than the global population (23.8%) in the apalutamide group, the following points in the Japanese subpopulation were generally consistent with the global population; most skin rashes in the apalutamide group were Grade 1 or 2 and manageable with the administration of antihistamines/topical steroids and dose reduction/interruptions, onset of skin rash occurred within the first 3 months of apalutamide treatment and most events were resolved within approximately 2 months. There were no substantial differences in the proportion of patients who had fall event or developed fracture and hypothyroidism between the Japanese subpopulation and the global population. No seizure was reported in the Japanese subpopulation.

As observed in the current subpopulation analysis, exposure of apalutamide and N-desmethyl apalutamide tended to be higher in Japanese patients compared with non-Japanese patients, which can be explained by lower body weight in the Japanese patients. However, the difference was considered not clinically relevant. Race (categorized as Black, White, Asian [non-Japanese], Japanese, and other) had no discernable impact on the PK parameters of apalutamide and N-desmethyl apalutamide.[13] The fact of higher prevalence of skin rash in Japanese population compared to non-Japanese populations needs further investigation. In this subpopulation analysis, apalutamide with ongoing ADT showed consistent efficacy outcomes in Japanese patients with high-risk nm-CRPC. Furthermore, based on the consistency of results in Japanese population with the outcomes in global population, Japanese patients may be expected to experience a consistent clinical benefit-risk profile of apalutamide therapy in nm-CRPC.

Author contributions

H.U., T.S., H.T., G.A., E.J.S., and M.S. were the investigators. K.S. was the project statistician. B.R., A.L.-G., and B.E. had primary roles in the study design and data interpretation; C.P.-R. and K.S. had primary role in analysis of data. All authors contributed to the data interpretation for the results.

All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data and made the final decision about where to publish these data and approved submission to this journal.

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Conflict of interest

H.U. reports receiving research grants from Janssen Pharmaceutical (during the conduct of the study) and lecture fees/subsidies from Bayer Yakuhin, Limited, Takeda Pharmaceutical Company Limited, AstraZeneca K.K., TAIHO Pharmaceutical Company Limited,. Astellas Pharma Inc. and Pfizer Inc. T.S. reports receiving research grants from Konica Minolta, Inc., educational lecture fee from Bayer AG, AstraZeneca K. K., Janssen Pharmaceutical K.K., Astellas Pharma Inc, Nihon Medi-Physics Co., Ltd. and Takeda Pharmaceutical Company Limited. M.S. reports receiving consulting fees from Astellas Pharma Inc. and Bayer Yakuhin, Limited. H.Tsumura. reporst receiving research grants from Janssen Pharmaceutical and Astellas Pharma Inc. G.A. reports receiving consulting fee from Janssen Pharmaceutical and lecture fee from Janssen Pharmaceutical, AstraZeneca K.K, Takeda Pharmaceutical Company Limited, Astellas Pharma Inc., Pfizer Japan Inc., Novartis Pharmaceutical, and Bayer Yakuhin Limited. E.J.S. reports receiving honoraria for lectures from Janssena and is a member of the consulting or advisory board of Janssen and Fortis; holds stocks for Fortis Therapeutics and Harpoon Therapeutics. The following authors declare a conflict of interest on the basis that they are full-time employees of Janssen Pharmaceutical K.K. of Johnson & Johnson: K. I., K.S., and K.F.; and Janssen Research and Development: Youyi Shu, B.R., A.L.-G., B.E., and C.P.-R.. The material presented in this article reflects authors own personal views and should not be interpreted as being representative of the views of their employers or institutions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2020.05.002.

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