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Olaparib Plus Abiraterone in Asian Patients With Metastatic Castration-Resistant Prostate Cancer: PROpel Subset Analysis

Mototsugu Oya[1] | Jae Young Joung[2] | Ji Youl Lee[3] | Mikio Sugimoto[4] | Young Deuk Choi[5] | Jun Hyuk Hong[6] | Hiroji Uemura[7] | Kazuo Nishimura[8] | Hideyasu Tsumura[9] | Satoru Kawakami[10] | Yukiyoshi Hirayama[11] | Tae Gyun Kwon[12] | Cheol Kwak[13] | Hiroyoshi Suzuki[14] | Tomoko Fujita[15] | Masahiro Nii[15] | David McGuinness[16] | Melanie Dujka[17] | Christian Poehlein[18] | Fred Saad[19] | Noel Clarke[20]

[1]Keio University Hospital, Tokyo, Japan | [2]Center for Prostate Cancer, National Cancer Center, Goyang, South Korea | [3]Seoul St Mary's Hospital, The Catholic University of Korea, Seoul, South Korea | [4]Kagawa University Hospital, Kagawa, Japan | [5]Yonsei University College of Medicine, Seoul, South Korea | [6]Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea | [7]Yokohama City University Medical Center, Yokohama, Japan | [8]Osaka International Cancer Institute, Osaka, Japan | [9]Kitasato University School of Medicine, Sagamihara, Kanagawa, Japan | [10]Saitama Medical Center, Saitama Medical University, Kawagoe, Japan | [11]Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan | [12]Chilgok Kyungpook National University Medical Center, Daegu, South Korea | [13]Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea | [14]Toho University Sakura Medical Center, Chiba, Japan | [15]AstraZeneca, Osaka, Japan | [16]AstraZeneca, Cambridge, UK | [17]AstraZeneca, Gaithersburg, Maryland, USA | [18]Merck & Co. Inc., Rahway, New Jersey, USA | [19]Centre Hospitalier de l'Université de Montréal, Montreal, Quebec, Canada | [20]The Christie and Salford Royal Hospital NHS Foundation Trusts and University of Manchester, Manchester, UK

Correspondence: Mototsugu Oya (moto-oya@keio.jp)

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Keywords: abiraterone | Asian | metastatic castration-resistant prostate cancer | olaparib | progression-free survival

ABSTRACT

In the phase 3 PROpel trial (NCT03732820) patients with metastatic castration-resistant prostate cancer (mCRPC) treated with olaparib plus abiraterone in the first-line setting showed significantly prolonged radiographic progression-free survival (rPFS; primary data cutoff [DCO]: 30 July 2021; hazard ratio [HR] 0.66, 95% confidence interval [CI], 0.54–0.81; $p < 0.001$), and at prespecified final OS analysis DCO (12 October 2022) numerically prolonged overall survival (OS; HR 0.81, 95% CI, 0.67–1.00; $p = 0.054$), versus placebo plus abiraterone for the global population. Here, we report efficacy, safety, and patient-reported outcome data for the Asian subset in PROpel. Eligible patients were randomly assigned (1:1) to either olaparib (300 mg twice daily) or placebo in combination with abiraterone (1000 mg once daily). The primary endpoint was investigator-assessed rPFS, and a key secondary endpoint was OS. In the Asian subset ($n = 133$) at primary analysis, median rPFS was 27.6 months in the olaparib plus abiraterone arm ($n = 63$), compared with 19.3 months in the placebo plus abiraterone arm ($n = 70$; HR 0.55, 95% CI, 0.32–0.95). Median OS at the final analysis was not reached in the olaparib plus abiraterone arm versus 43.7 months in the placebo plus abiraterone arm (HR 0.59, 95% CI, 0.32–1.06). The safety profile was generally similar in the Asian subset and the global population.

Abbreviations: AE, adverse event; bid, twice daily (dosing); BRCAm, *BRCA1* and/or *BRCA2* mutation; CI, confidence interval; ctDNA, circulating tumor DNA; DCO, data cutoff; FACT-P, Functional Assessment of Cancer Therapy–Prostate; HR, hazard ratio; HRQoL, health-related quality of life; HRRm, homologous recombination repair mutation; ITT, intention-to-treat; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NHA, next-generation hormonal agent; ORR, objective response rate; OS, overall survival; PARP, poly(ADP-ribose) polymerase; PFS2, time to second progression; PRO, patient-reported outcome; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival; TFST, time to first subsequent therapy.

Efficacy and safety results for olaparib plus abiraterone in the Asian subset were generally consistent with the global PROpel population supporting the combination of olaparib plus abiraterone as an important first-line treatment for consideration in Asian patients with mCRPC.
Trial Registration: Clinicaltrials.gov identifier: NCT03732820

1 | Introduction

Patients with metastatic castration-resistant prostate cancer (mCRPC) have a poor prognosis; clinical trials in the first-line treatment setting have reported median overall survival (OS) rates of approximately 3 and 5-year overall survival of approximately 30% [1, 2]. Data are limited for Asian populations because of small numbers included in pivotal studies; however, comparable rates have been reported [3]. Next-generation hormonal agents (NHAs), including abiraterone and enzalutamide, and taxane-based chemotherapies are current standard-of-care treatments in the first-line mCRPC treatment setting in both global and Asian populations [4]. However, there is an unmet need for improved treatments for a broad first-line mCRPC population to further increase OS rates. Any new mCRPC treatment options should be evaluated specifically in Asian patients.

Recent global studies demonstrated that combining poly(ADP-ribose) polymerase (PARP) inhibitor treatment with NHAs can improve outcomes in patients with mCRPC [5–9]. The PROpel trial (NCT03732820), a randomized, double-blind, phase 3 trial, investigated the efficacy and safety of olaparib plus abiraterone versus placebo plus abiraterone for first-line treatment in patients with mCRPC [6, 7]. PROpel met its primary endpoint (investigator-assessed radiographic progression-free survival [rPFS]); median rPFS was 24.8 versus 16.6 months (primary data cutoff: 30 July 2021; hazard ratio [HR] 0.66, 95% confidence interval [CI], 0.54–0.81; $p < 0.001$) [6]. In addition, for the key secondary endpoint of OS at the prespecified final OS analysis cutoff (12 October 2022), median OS was 42.1 months in the olaparib plus abiraterone arm and 34.7 months in the placebo plus abiraterone arm, a median 7.4-month improvement over life-prolonging standard-of-care abiraterone (HR 0.81, 95% CI, 0.67–1.00; $p = 0.054$ [alpha threshold at prespecified final OS analysis: two-sided boundary for significance 0.0377]) [7]. Additional secondary and exploratory endpoints from PROpel, including time to first subsequent therapy (TFST), time to second progression (PFS2), time to prostate-specific antigen (PSA) progression, objective response rate (ORR), and PSA response also supported the clinical benefit of olaparib plus abiraterone in the global population [6, 7]. The patient-reported outcome (PRO) of Functional Assessment of Cancer Therapy–Prostate (FACT-P) total score, derived from a questionnaire developed specifically to assess health-related quality of life (HRQoL) in men with prostate cancer, showed no detrimental effect on patient's HRQoL from the addition of olaparib to abiraterone, compared with abiraterone alone.

The combination of olaparib plus abiraterone has received approval by the European Medicines Agency for patients with mCRPC for whom chemotherapy is not clinically indicated [10], and by the South Korean Ministry of Food and Drug Safety for patients who have not received chemotherapy after diagnosis of mCRPC. The combination is also approved in *BRCA1* and/or *BRCA2* mutation (BRCAm) patients with mCRPC by the US Food and Drugs Administration [11], and the Japanese Ministry of Health, Labour and Welfare [12].

Here, the efficacy, safety, and PRO data for the Asian subset in PROpel are reported.

2 | Methods

2.1 | Patients

The study design and patient eligibility criteria have been described in detail previously [6]. To summarize, patients aged ≥ 18 years (≥ 19 years in South Korea) who had histologically or cytologically confirmed prostate adenocarcinoma with at least one documented metastatic lesion on a bone scan or computed tomography or MRI scan were eligible for inclusion in the phase 3 PROpel trial. Prior systemic treatment in the mCRPC first-line setting was not allowed (except for androgen deprivation therapy and first-generation antiandrogen agents with a 4-week washout period). Patients were included irrespective of homologous recombination repair mutation (HRRm) status; HRRm and BRCAm status was established after randomization, but before primary analysis, by tumor tissue and circulating tumor DNA (ctDNA) testing. Data are presented here using aggregate test results (i.e., tumor tissue and ctDNA; see further details in the Supplementary Methods Doc 1: Appendix S1). Exploratory analyses for the Asian subset reported here included patients from Japan and South Korea (the principal investigators and study sites are shown in Table S1). A Chinese cohort included in the PROpel study will be analyzed and reported separately from the previously reported global population and current Asian subset [6].

2.2 | Trial Design and Interventions

Eligible patients were randomly assigned (1:1) to either olaparib (300 mg twice daily [bid]) or placebo in combination with abiraterone (1000 mg once daily) plus prednisone or prednisolone (5 mg bid). Random assignment was stratified by distant metastasis type (bone only, visceral, or other) at baseline and by docetaxel treatment at the metastatic hormone-sensitive prostate cancer (mHSPC) stage of disease (yes or no). Study treatment continued until objective imaging-based progressive disease, as assessed by the investigator (using Response Evaluation Criteria in Solid Tumors 1.1 for soft tissue lesions and Prostate Cancer Working Group 3 criteria for bone lesions), unacceptable toxicity, or withdrawal of consent. Following objective disease

progression, further treatment was at the discretion of the investigator. Crossover from placebo plus abiraterone to receive olaparib plus abiraterone was not allowed. However, patients could be unblinded to HRRm and treatment status at disease progression and any PARP inhibitor monotherapy as standard-of-care was permitted.

2.3 | Endpoints

The preplanned Asian subset analyses of rPFS and the exploratory endpoints of ORR and PSA response are presented at primary analysis data cutoff [DCO]: 30 July 2021. Secondary endpoints, including OS (defined as the time from randomization to death from any cause), TFST (defined as time from randomization to the start of the first subsequent anticancer therapy or death from any cause [whichever was earlier]), and PFS2 (time from randomization to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression, or death) as well as PROs (FACT-P total score; see the Supplementary Methods Doc 1: Appendix S1 for further details), are presented at the final prespecified DCO (12 October 2022). FACT-P total score was derived from a questionnaire developed specifically to assess HRQoL in men with prostate cancer, and a clinically meaningful change in FACT-P total score was defined as a change of at least 10 points [13]. Post hoc exploratory analyses of rPFS and OS were undertaken for biomarker subgroups (HRRm/non-HRRm and BRCAm/non-BRCAm) on the basis of aggregate testing (tumor and ctDNA testing; see Supplementary Methods Doc 1: Appendix S1 for further details).

2.4 | Safety

Safety was assessed by reporting of adverse events (AEs) and serious AEs (according to Common Terminology Criteria for Adverse Events v.4.03) on the basis of vital signs, physical examination, electrocardiogram, and laboratory test findings.

2.5 | Trial Oversight

This trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca and Merck policies on bioethics.

2.6 | Statistical Analysis

A detailed description of the statistical methods used in the PROpel study have been described previously [6]; the same methods were used in the preplanned exploratory analyses of the Asian subset.

For time-to-event endpoints, HRs and 95% CIs were calculated using the Cox proportional hazards model, adjusted for the variables selected in the primary pooling strategy: metastases and docetaxel treatment at mHSPC stage and Kaplan–Meier curves were used to estimate medians. All analyses of the Asian subset presented here were exploratory and not powered for significance.

3 | Results

3.1 | Patients

Of the 796 patients randomized in the global population, 133 comprised the Asian subset, of which 77 were from Japan and 56 from South Korea. Within this subset, 63 patients were randomized to olaparib plus abiraterone and 70 to placebo plus abiraterone. Demographic and baseline characteristics of patients in the Asian subset were generally balanced between treatment arms and consistent with those in the intention-to-treat (ITT) global population although a few differences were reported (Table 1).

3.2 | Efficacy

3.2.1 | Progression-Free Survival

Investigator-assessed rPFS (DCO: 30 July 2021) favored patients treated in the Asian subset with olaparib plus abiraterone, compared with placebo plus abiraterone, with a median difference of 8.3 months (HR 0.55 95% CI, 0.32–0.95; Figure 1). Median duration of follow-up in censored patients was 21.9 months (range: 1.6–30.6) in the olaparib plus abiraterone arm versus 19.4 months (range: 1.8–27.7) in the placebo plus abiraterone arm.

The sensitivity analysis of rPFS by blinded independent central review showed consistent results (median 27.6 vs. 16.4 months; HR 0.40, 95% CI, 0.23–0.70; Figure S1). Post hoc exploratory analyses of rPFS in the HRRm and non-HRRm subgroups for the Asian subset favored the combination of olaparib plus abiraterone versus placebo plus abiraterone (HR 0.39; 95% CI, 0.16–0.86 for HRRm and HR 0.85; 95% CI, 0.42–1.69 for non-HRRm). Additional data, including by BRCAm status, are shown in Table S2.

3.2.2 | Overall Survival

Median OS at the final OS analysis DCO (12 October 2022) was not calculable for the olaparib plus abiraterone arm but was 43.7 months for the placebo plus abiraterone arm (HR 0.59, 95% CI, 0.32–1.06) (Figure 2). In addition, the proportion of patients alive at 24 months was 83.8% (95% CI, 71.9–90.9) in the olaparib plus abiraterone arm and 77.1% (95% CI, 64.9–85.6) in the placebo plus abiraterone arm, and at 42 months was 70.6% (95% CI, 56.8–80.7) in the olaparib plus abiraterone arm and 55.0% (95% CI, 41.2–66.9) in the placebo plus abiraterone arm. The median duration of follow-up in censored patients was 38.7 (range: 10.1–47.0) months in the olaparib plus abiraterone arm and 36.5 (range: 3.5–45.3) months in the placebo plus abiraterone arm. Post hoc exploratory analysis of OS for Asian patients in the aggregate HRRm and non-HRRm subgroup populations favored the combination of olaparib plus abiraterone versus placebo plus abiraterone (HR 0.41,

TABLE 1 | Baseline demographics characteristics of the Asian subset and overall global population randomized in PROpel (DCO: 30 July 2021).

	Asian subset		Global population [6, 7]	
	Olaparib plus abiraterone	Placebo plus abiraterone	Olaparib plus abiraterone	Placebo plus abiraterone
Characteristic	***n* = 63**	***n* = 70**	***n* = 399**	***n* = 397**
Age at randomization (median [range]), years	69.0 (52–85)	71.0 (50–87)	69.0 (43–91)	70.0 (46–88)
Prior docetaxel treatment at mHSPC stage	4 (6.3)	5 (7.1)	90 (22.6)	89 (22.4)
ECOG performance status				
0 (normal activity)	53 (84.1)	53 (75.7)	286 (71.7)	272 (68.5)
1 (restricted activity)	10 (15.9)	17 (24.3)	112 (28.1)	124 (31.2)
Missing	0	0	1 (0.3)	1 (0.3)
Gleason score ≥ 8	53 (84.1)	54 (77.1)	265 (66.4)	258 (65.0)
Missing	1 (1.6)	1 (1.4)	13 (3.3)	5 (1.3)
PSA at baseline (median [IQR]), μg/L	6.36 (2.53–26.82)	6.04 (3.10–25.20)	17.90 (6.09–67.00)	16.81 (6.26–53.30)
Symptomatic/asymptomatic status				
Symptomatic (BPI-SF #3 score ≥ 4 or opiate use)[a]	7 (11.1)	10 (14.3)	103 (25.8)	80 (20.2)
Asymptomatic or mildly symptomatic (BPI-SF #3 score < 4 and no opiate use)	55 (87.3)	60 (85.7)	266 (66.7)	294 (74.1)
Missing data	1 (1.6)	0 (0)	30 (7.5)	23 (5.8)
Disease site[b]				
Bone	56 (88.9)	64 (91.4)	349 (87.5)	339 (85.4)
Distant lymph nodes	17 (27.0)	13 (18.6)	133 (33.3)	119 (30.0)
Locoregional lymph nodes	9 (14.3)	9 (12.9)	82 (20.6)	89 (22.4)
Prostate and adjacent structures	14 (22.2)	15 (21.4)	47 (11.8)	46 (11.6)
Respiratory (including lung)	4 (6.3)	6 (8.6)	40 (10.0)	42 (10.6)
Liver	2 (3.2)	1 (1.4)	15 (3.8)	18 (4.5)
HRRm status (aggregate)[c]				
HRRm	23 (36.5)	26 (37.1)	111 (27.8)	115 (29.0)
Non-HRRm	40 (63.5)	44 (62.9)	279 (69.9)	273 (68.7)
HRRm unknown	0	0	9 (2.3)	9 (2.3)
BRCAm status (aggregate)[c]				
BRCAm	7 (11.1)	10 (14.3)	47 (11.8)	38 (9.6)
Non-BRCAm	56 (88.9)	60 (85.7)	343 (86.0)	350 (88.2)

Note: Data are presented as *n* (%) unless otherwise specified.
Abbreviations: BPI-SF, Brief Pain Inventory–Short Form questionnaire; BRCAm, *BRCA1* and/or *BRCA2* mutation; ctDNA, circulating tumor DNA; DCO, data cutoff; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; HRRm, homologous recombination repair mutation; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen.
[a]Baseline pain score was based on a patient completing the BPI-SF item 3 (worst pain) at least once during the 7-day baseline period and was determined as an average.
[b]Investigators could select more than one disease site. Entries for "other locally advanced sites," "other distant sites," and "other" have been excluded.
[c]HRRm group included patients with at least one HRR gene mutation detected by either tumor tissue or ctDNA-based test. Non-HRRm group comprised patients with no HRR gene mutation detected by either tumor tissue or ctDNA-based test with at least one test obtaining a result, and HRRm unknown denotes patients for whom mutation testing was not performed, mutation testing failed because of insufficient quantity or quality of sample, or technical failure occurred at sequencing or post-sequencing steps on analysis.

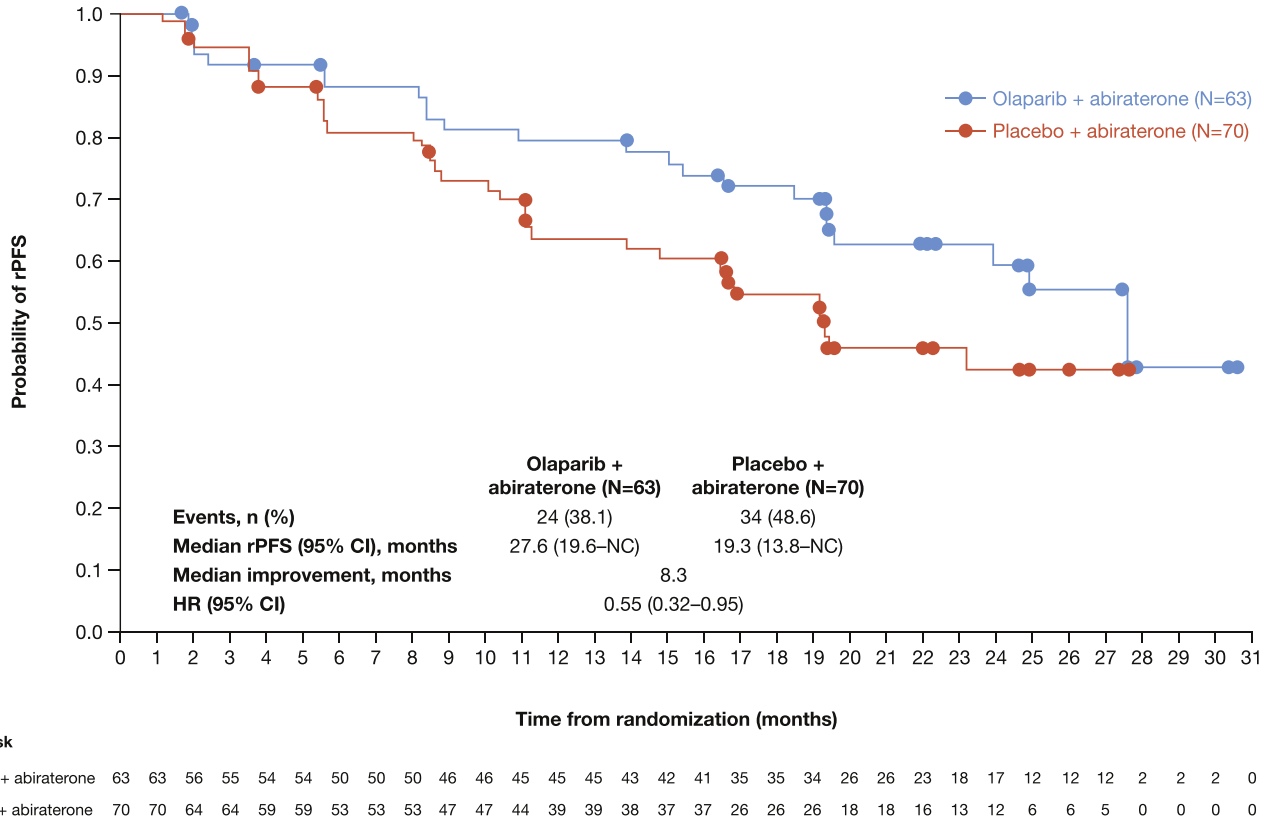


FIGURE 1 | Kaplan–Meier estimate curves for rPFS by investigator assessment in the Asian subset (DCO: 30 July 2021). A circle indicates a censored observation. HR and CIs were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases and docetaxel treatment at mHSPC stage. CI, confidence interval; DCO, data cutoff; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NC, not calculable; rPFS, radiographic progression-free survival.

95% CI, 0.16–1.00 for HRRm and HR 0.78, 95% CI, 0.35–1.72 for non-HRRm). Additional data, including by BRCAm status, are shown in Table S2.

3.2.3 | Additional Endpoints

Among the 33 patients with measurable disease at baseline, ORR (DCO: 30 July 2021) was 53.3% (8/15 patients) in the olaparib plus abiraterone arm, and 27.8% (5/18 patients) in the placebo plus abiraterone arm (odds ratio 2.97, 95% CI, 0.72–13.47). Confirmed PSA response was 85.7% ($n = 54/63$ patients) in the olaparib plus abiraterone arm, and 74.3% ($n = 52/70$) in the placebo plus abiraterone arm.

At the prespecified final OS DCO (12 October 2022), 25 (39.7%) patients in the olaparib plus abiraterone arm, and 33 (47.1%) in the placebo plus abiraterone arm had received a subsequent therapy. Higher proportions of Asian patients in both treatment arms had hormonal treatment, and lower proportions had cytotoxic chemotherapy as first subsequent therapies than among the global population (Table 1 and Table S3).

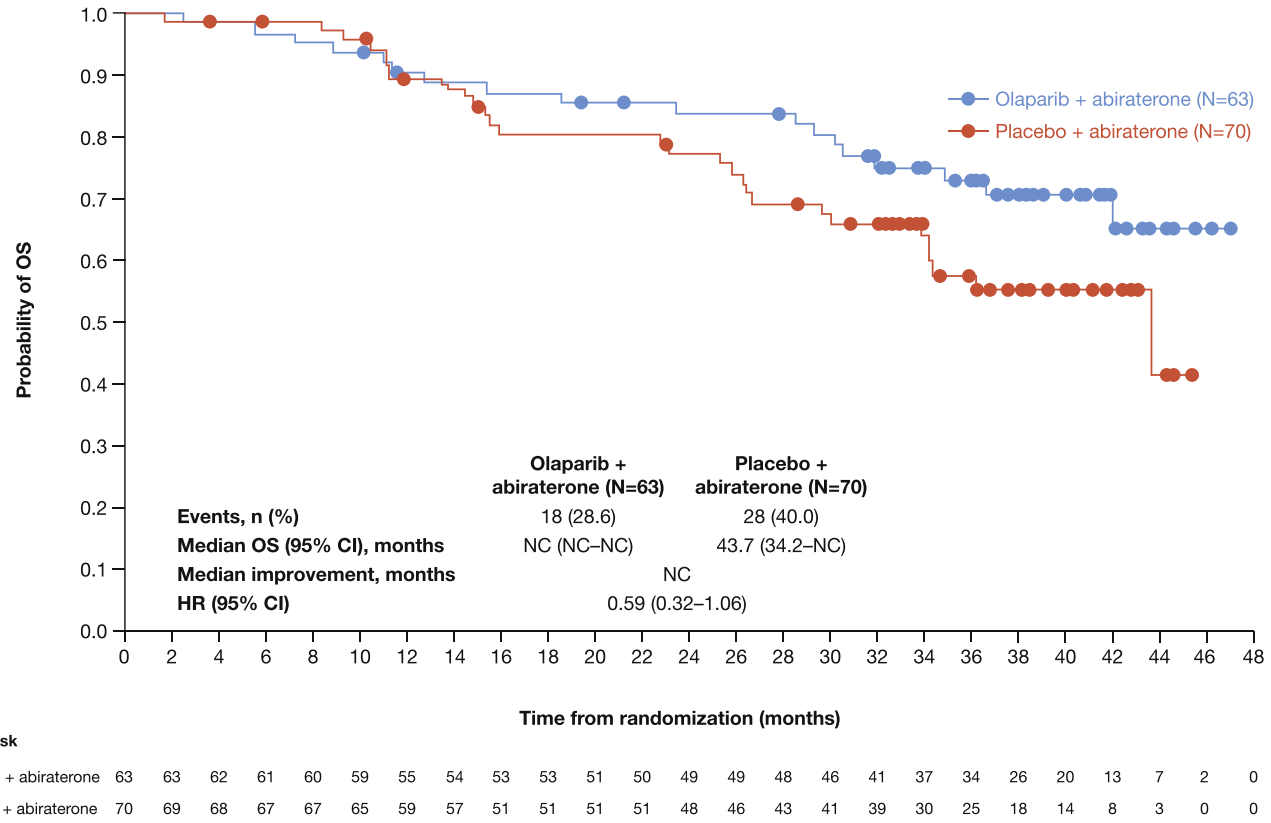
Median TFST was 41.0 months in the olaparib plus abiraterone arm and 22.2 months in the placebo plus abiraterone arm (HR 0.66, 95% CI, 0.41–1.07; Figure 3). Median PFS2 was not reached in either arm, and second progression events were reported for 14 (22.2%) patients in the olaparib plus abiraterone arm and 22 (31.4%) in the placebo plus abiraterone arm (HR 0.59, 95% CI, 0.29–1.15; Figure S2). In total, 19 (30.2%) patients in the olaparib plus abiraterone arm and 40 (57.1%) in the placebo plus abiraterone arm had a PSA progression event. Median time to PSA progression was not reached in the olaparib plus abiraterone arm and was 13.9 months in the placebo plus abiraterone arm (HR 0.30, 95% CI, 0.16–0.52).

3.2.4 | Patient-Reported Outcomes

For PROs, least-squares mean changes from baseline in FACT-P total score were similar between treatment arms throughout the treatment period; the overall changes from baseline were −12.53 in the olaparib plus abiraterone arm ($n = 56$) and −10.47 in the placebo plus abiraterone arm ($n = 66$), with a difference between treatment arms of −2.06 (95% CI, −7.12, 2.99). These findings are consistent with the global population showing no clinically meaningful difference between treatment arms.

3.3 | Safety

At the prespecified final OS analysis DCO (12 October 2022), median total duration of exposure was 22.1 months for olaparib, 30.4 months for abiraterone in the olaparib plus abiraterone group, 17.7 months for placebo, and 18.2 months for abiraterone in the placebo plus abiraterone group in the Asian subset. The



No. at risk

Olaparib + abiraterone	63	63	62	61	60	59	55	54	53	53	51	50	49	49	48	46	41	37	34	26	20	13	7	2	0
Placebo + abiraterone	70	69	68	67	67	65	59	57	51	51	51	51	48	46	43	41	39	30	25	18	14	8	3	0	0

FIGURE 2 | Kaplan–Meier estimate curves for OS in the Asian subset (DCO: 12 October 2022). A circle indicates a censored observation. HR and CIs were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases and docetaxel treatment at mHSPC stage. CI, confidence interval; DCO, data cutoff; HR, hazard ratio; NC, not calculable; mHSPC, metastatic hormone-sensitive prostate cancer; OS, overall survival.

median duration of treatment exposure was longer than in the global population (global: median total duration of exposure was 18.5 months for olaparib, 20.1 months for abiraterone in the olaparib plus abiraterone group, 15.7 months for placebo, and 15.7 months for abiraterone in the placebo plus abiraterone group) [7].

The safety and tolerability profile of olaparib plus abiraterone among the Asian subset was generally consistent with that reported previously in the global population, although the proportion of patients with dose interruptions due to an AE was higher for the Asian subset than for the global population (Table 2). The rates of the most commonly reported AEs in the Asian subset were generally comparable with those for the global population; however, nausea and fatigue/asthenia were lower in the Asian subset (17.5% and 15.9%, respectively) than in the global population (30.7% and 38.7%, respectively) [7]. A higher proportion of patients reported that lymphocyte count decreased in the Asian subset (14.3% vs. 8.5% for global population; Table 3). Furthermore, a higher proportion of patients reported Grade ≥ 3 neutropenia in the Asian subset (11.1% vs. 4.8% for the global population). The rate of cardiovascular (myocardial infarction, congestive heart failure, and ischemic stroke) and thromboembolic events (arterial and venous) was similar between arms (Table 3, Tables S4 and S5) and was also consistent with that seen in the global population. There were no cases of acute myeloid leukemia in the Asian subset or global population, but there were two cases of myelodysplastic syndrome in the olaparib plus abiraterone arm of the global population, neither of which were among the Asian subset.

4 | Discussion

In PROpel, a phase 3 trial of a PARP inhibitor in combination with a standard-of-care NHA in a biomarker-unselected first-line mCRPC global population, olaparib plus abiraterone resulted in a statistically significant and clinically meaningful rPFS benefit versus abiraterone at primary DCO (30 July 2021). Furthermore, although survival data were not mature, statistical significance was not reached but there was a median 7.4-month improvement in OS for olaparib plus abiraterone versus placebo plus abiraterone at the prespecified final OS analysis DCO (12 October 2022).

The exploratory analyses reported here, which were not powered for statistical significance, demonstrated that the rPFS and OS findings in the smaller Asian subset were consistent with those for the global population [6, 7]. Median rPFS was 8.3 months longer for the olaparib plus abiraterone arm than the placebo plus abiraterone arm, and the HR favored the olaparib plus abiraterone combination. In addition, although the median improvement in OS for olaparib plus abiraterone at final analysis DCO was not reached, the HR favored olaparib plus abiraterone versus placebo plus abiraterone. Furthermore, a higher proportion of patients were alive in

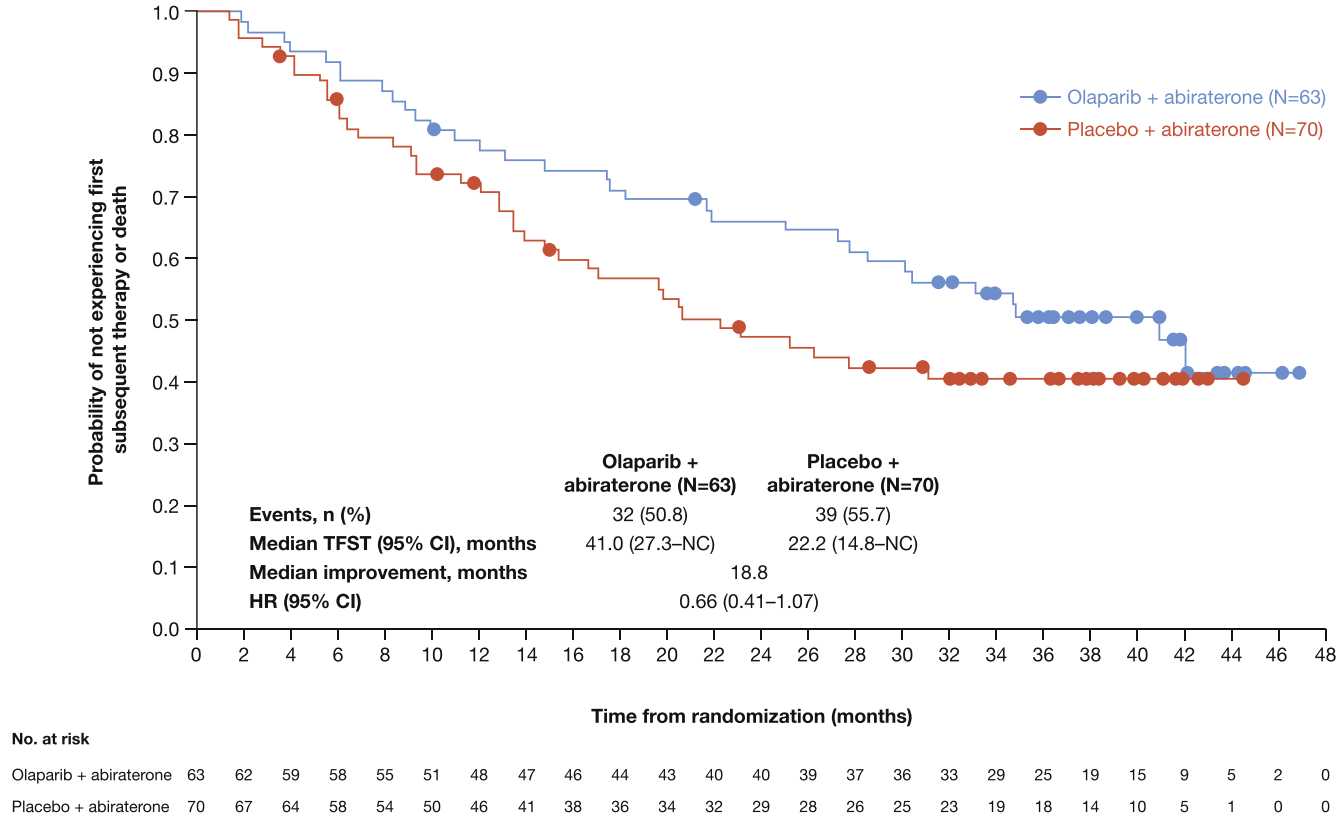


FIGURE 3 | Kaplan–Meier estimate curves for TFST in the Asian subset (DCO: 12 October 2022). A circle indicates a censored observation. HR and CIs were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases and docetaxel treatment at mHSPC stage. CI, confidence interval; DCO, data cutoff; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NC, not calculable; TFST, time to first subsequent therapy.

TABLE 2 | Summary of treatment-emergent AEs, SAEs, dose modifications, and discontinuations in the Asian subset and global population (DCO: 12 October 2022).

	Asian subset		Global population [7]	
	Olaparib plus abiraterone	Placebo plus abiraterone	Olaparib plus abiraterone	Placebo plus abiraterone
	n = 70	*n* = 398	*n* = 396	*n* = 396
Any AE (any grade)	63 (100)	64 (91.4)	389 (97.7)	380 (96.0)
Grade ≥ 3	39 (61.9)	34 (48.6)	222 (55.8)	171 (43.2)
Any SAE	25 (39.7)	23 (32.9)	161 (40.5)	126 (31.8)
Dose interruption because of an AE				
Olaparib/placebo	40 (63.5)	17 (24.3)	195 (49.0)	112 (28.3)
Abiraterone	28 (44.4)	16 (22.9)	145 (36.4)	95 (24.0)
Dose reduction due to an AE				
Olaparib/placebo	17 (27.0)	1 (1.4)	90 (22.6)	24 (6.1)
Abiraterone	6 (9.5)	5 (7.1)	10 (2.5)	17 (4.3)
Discontinuation due to an AE				
Olaparib/placebo	13 (20.6)	4 (5.7)	69 (17.3)	34 (8.6)
Abiraterone	8 (12.7)	3 (4.3)	45 (11.3)	37 (9.3)
Death due to an AE	0	1 (1.4)	26 (6.5)	20 (5.1)

Abbreviations: AE, adverse event; DCO, data cutoff; SAE, serious adverse event.

TABLE 3 | Treatment-emergent AEs in either arm in the Asian subset, and global population (DCO: 12 October 2022).

	Asian subset				Global population [7]			
	Olaparib plus abiraterone		Placebo plus abiraterone		Olaparib plus abiraterone		Placebo plus abiraterone	
	n = 63		*n* = 70		*n* = 398		*n* = 396	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Any AE	63 (100)	39 (61.9)	64 (91.4)	34 (48.6)	389 (97.7)	222 (55.8)	380 (96.0)	171 (43.2)
AEs reported by ≥ 10% of participants[a]								
Anemia[b]	29 (46.0)	10 (15.9)	6 (8.6)	2 (2.9)	198 (49.7)	64 (16.1)	70 (17.7)	13 (3.3)
Nausea	11 (17.5)	0	5 (7.1)	0	122 (30.7)	1 (0.3)	57 (14.4)	1 (0.3)
Fatigue/ asthenia	10 (15.9)	1 (1.6)	8 (11.4)	1 (1.4)	154 (38.7)	10 (2.5)	120 (30.3)	6 (1.5)
Diarrhea	10 (15.9)	1 (1.6)	5 (7.1)	0	82 (20.6)	5 (1.3)	42 (10.6)	1 (0.3)
Lymphocyte count decreased	9 (14.3)	7 (11.1)	5 (7.1)	3 (4.3)	34 (8.5)	15 (3.8)	17 (4.3)	6 (1.5)
Neutropenia[c]	8 (12.7)	7 (11.1)	5 (7.1)	4 (5.7)	40 (10.0)	19 (4.8)	14 (3.5)	7 (1.8)
Constipation	8 (12.7)	0	12 (17.1)	0	74 (18.6)	0	59 (14.9)	1 (0.3)
Peripheral edema	8 (12.7)	0	8 (11.4)	0	49 (12.3)	0	50 (12.6)	1 (0.3)
Malaise	8 (12.7)	0	7 (10.0)	0	15 (3.8)	1 (0.3)	10 (2.5)	0
Pyrexia	8 (12.7)	0	6 (8.6)	0	29 (7.3)	1 (0.3)	21 (5.3)	0
Decreased appetite	7 (11.1)	1 (1.6)	8 (11.4)	0	66 (16.6)	4 (1.0)	31 (7.8)	0
Vomiting	7 (11.1)	1 (1.6)	7 (10.0)	0	62 (15.6)	6 (1.5)	37 (9.3)	1 (0.3)
Back pain	7 (11.1)	0	4 (5.7)	0	86 (21.6)	4 (1.0)	79 (19.9)	6 (1.5)
Cataract	5 (7.9)	1 (1.6)	7 (10.0)	2 (2.9)	10 (2.5)	1 (0.3)	9 (2.3)	2 (0.5)
Hypertension	2 (2.3)	0	7 (10.0)	4 (5.7)	61 (15.3)	15 (3.8)	74 (18.7)	18 (4.5)
Other AEs of interest								
Cardiac failure events[d]	1 (1.6)	0	1 (1.4)	0	7 (1.8)	5 (1.3)	7 (1.8)	2 (0.5)
Embolic and thrombotic events								
Arterial[d]	3 (4.8)	3 (4.8)	3 (4.3)	1 (1.4)	10 (2.5)	8 (2.0)	14 (3.5)	10 (2.5)
Venous[d]	2 (3.2)	2 (3.2)	1 (1.4)	1 (1.4)	34 (8.5)	31 (7.8)	16 (4.0)	10 (2.5)

Note: Data are presented as *n* (%).
Abbreviations: AE, adverse event; DCO, data cutoff; MedDRA, Medical Dictionary for Regulatory Activities.
[a]AEs, regardless of the investigators' assessment of causality, are reported for those that occurred in at least 10% of patients in either treatment arm for Asian subset. Patients were counted once for each type of AE. AEs with an onset date, or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomized treatment, are included.
[b]Anemia category includes anemia, decreased hemoglobin level, decreased red blood cell count, decreased hematocrit level, erythropenia, macrocytic anemia, normochromic anemia, normochromic normocytic anemia, and normocytic anemia.
[c]Neutropenia category includes febrile neutropenia, granulocyte count decreased, neutropenia, neutropenic infection, neutropenic sepsis, neutrophil count decreased, idiopathic neutropenia, and agranulocytosis.
[d]Based on standardized MedDRA query.

the olaparib plus abiraterone arm than the placebo plus abiraterone arm at 24 and 42 months.

There was a trend in favor of olaparib plus abiraterone versus placebo plus abiraterone for other secondary endpoints, including TFST and PFS2 in this Asian subset, which is consistent with the global population [7]. Findings from the PRO assessment using the FACT-P questionnaire also showed no clinically meaningful difference in FACT-P total score between treatment arms in the Asian subset, indicating no detrimental effect on HRQoL with the addition of olaparib to abiraterone.

Post hoc analysis of aggregate HRRm and non-HRRm subgroups for the Asian subset showed that HRs directionally favored olaparib plus abiraterone, which is also consistent with results for the global population in the HRRm (rPFS, HR 0.50, 95% CI 0.34–0.73; OS, HR 0.66, 95% CI 0.45–0.95) and non-HRRm subgroups (rPFS, HR 0.76, 95% CI 0.60–0.97; OS, HR 0.89, 95% CI 0.70–1.14) [6, 7]. Hazard ratios are not reported for the BRCAm subgroup in the Asian subset as there were too few events for this to be calculated for rPFS or OS. It should be noted that there are limitations to these findings as analyses of biomarker subgroups within the PROpel Asian population were post hoc and exploratory, and based on small sample sizes. Therefore, these findings should be interpreted with caution.

There were some differences in baseline demographics for the Asian subset compared with the global population, including lower docetaxel use in the mHSPC setting and lower PSA levels. However, these differences in the baseline characteristics do not appear to have had any meaningful effect on the rPFS and OS results. The lower use of docetaxel treatment in Asian patients, compared with the global population may be due to the later approval of docetaxel in the mHSPC setting in Japan; additionally, docetaxel-related toxicity has been found to be more prominent in Asian than Western patients [14]. A higher proportion of Asian patients also had a Gleason score ≥ 8 and had HRRm, compared with the global population.

In the Asian subset of PROpel, the safety profile of olaparib plus abiraterone was generally consistent with that reported for the global population and for the known profiles of olaparib and abiraterone alone. There were some differences in AEs between the Asian subset and global population, with a higher proportion in the olaparib plus abiraterone arm of the Asian subset reporting a lymphocyte count decrease and Grade ≥ 3 neutropenia, and a lower proportion reporting nausea and fatigue/asthenia. However, there was no difference in the proportion of patients in the olaparib plus abiraterone arm with Grade ≥ 3 anemia between the Asian subset and global population; and the incidence was lower than observed in other trials of PARP inhibitors in combination with an NHA [8, 9]. In addition the higher proportion of patients in the Asian subset than the global population with dose interruptions due to an AE may be due to a several factors, including differences in ethnicity, body mass index, tolerability of AEs and drug absorption/metabolization between Asian and non-Asian populations, as has been reported in other cancer settings [15–17] However, no new safety signals were identified and there were no cases of acute myeloid leukemia or myelodysplastic syndrome in this Asian subset. Race-related differences in tolerability and response to other anticancer drugs, such as taxanes and NHAs, have previously been reported in Asian patients with mCRPC [14, 18]. Differences in the safety profile of abiraterone between Asian and Western populations have been reported [19, 20]. However, there were no notable differences in AEs between the Asian subset and global population in the placebo plus abiraterone arm in PROpel.

In conclusion, a clinically relevant rPFS benefit and numerically improved OS with olaparib plus abiraterone treatment was observed in this Asian subset of patients in PROpel. Results in the HRRm and non-HRRm subgroups were consistent with those observed for the global population. Furthermore, safety findings in the Asian subset were generally consistent with those reported for the ITT global population. Overall, results from this subset analysis support the use of olaparib plus abiraterone as an important first-line treatment consideration for Asian patients with mCRPC in Japan and South Korea.

Author Contributions

Mototsugu Oya: conceptualization, investigation, resources, supervision, validation, visualization, writing – review and editing. **Jae Young Joung:** investigation, resources, writing – review and editing. **Ji Youl Lee:** investigation, resources, writing – review and editing. **Mikio Sugimoto:** investigation, resources, writing – review and editing. **Young Deuk Choi:** investigation, resources, writing – review and editing. **Jun Hyuk Hong:** investigation, resources, writing – review and editing. **Hiroji Uemura:** investigation, resources, writing – review and editing. **Kazuo Nishimura:** investigation, resources, writing – review and editing. **Hideyasu Tsumura:** investigation, resources, writing – review and editing. **Satoru Kawakami:** investigation, resources, writing – review and editing. **Yukiyoshi Hirayama:** investigation, resources, writing – review and editing. **Tae Gyun Kwon:** investigation, resources, writing – review and editing. **Cheol Kwak:** investigation, resources, writing – review and editing. **Hiroyoshi Suzuki:** investigation, resources, writing – review and editing. **Tomoko Fujita:** conceptualization, resources, validation, writing – original draft, writing – review and editing. **Masahiro Nii:** conceptualization, resources, validation, writing – original draft, writing – review and editing. **David McGuinness:** conceptualization, data curation, formal analysis, resources, validation, writing – original draft, writing – review and editing. **Melanie Dujka:** conceptualization, resources, validation, writing – original draft, writing – review and editing. **Christian Poehlein:** conceptualization, resources, validation, writing – original draft, writing – review and editing. **Fred Saad:** conceptualization, investigation, resources, supervision, validation, visualization, writing – review and editing. **Noel Clarke:** conceptualization, investigation, resources, supervision, validation, visualization, writing – original draft, writing – review and editing.

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Ethics Statement

Approval of the research protocol by an Institutional Review Board: The study protocol was approved by the Institutional Review Boards or ethics committee at all participating institutions.

Registry and the Registration No. of the study/trial: Clinicaltrials.gov; NCT03732820. This trial was performed in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and the AstraZeneca and Merck policies on bioethics.

Animal Studies: None.

Consent

Informed consent: All patient provided written informed consent.

Conflicts of Interest

Mototsugu Oya received honoraria from Astellas, AstraZeneca, Bayer, Janssen, MSD, Nippon Kayaku, and Takeda, and research funding from AstraZeneca and Bayer, and is an editorial board member of *Cancer Science*. **Mikio Sugimoto** received honoraria from AstraZeneca,

Janssen, and Takeda. **Hiroji Uemura** performed a consultancy role for Janssen and Novartis; received honoraria from AstraZeneca, Bayer, Chugai, Janssen, Kissei, Sanofi, and Takeda; donations from Chugai, FDR, and travel expenses/gifts from Astellas, AstraZeneca, Bayer, Chugai, Janssen, Sanofi, and Takeda. **Kazuo Nishimura** received honoraria from AstraZeneca, Astellas, Bayer, and Janssen; and research funding from Bayer. **Hideyasu Tsumura** received honoraria from Astellas, AstraZeneca, Bayer, Janssen, Kissei, and Sanofi, research funding from AstraZeneca, Janssen, and Merck Sharp & Dohme LLC. **Satoru Kawakami** received honoraria from Astellas, AstraZeneca, Bayer, and Janssen. **Hiroyoshi Suzuki** received honoraria from Astellas, AstraZeneca, Bayer, Eli-Lilly, Ferring, Janssen, Novartis, Pfizer, and Sanofi; research funding from Astellas, AstraZeneca, Bayer, Eli-Lilly, Janssen, and Takeda; and donations from Aska, Bayer, Chugai, and Nihon Kayaku. **Tomoko Fujita** was an employee of AstraZeneca KK at the time of this study and is now an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co. Inc., Rahway, NJ, USA and owns stock in Merck & Co. Inc., Rahway, NJ, USA. **Masahiro Nii** is an employee of AstraZeneca KK. **Melanie Dujka** is an employee of AstraZeneca and owns stock in AstraZeneca. **David McGuinness** was a consultant for AstraZeneca and his current affiliation is DM Stat Consulting. **Christian Poehlein** is an employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co. Inc., Rahway, NJ, USA and owns stock in Merck & Co. Inc., Rahway, NJ, USA. **Fred Saad** received honoraria from AbbVie, Advanced Accelerator Applications, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen Oncology, Knight Therapeutics, Merck Inc. & Co, Myovant Sciences, Novartis, Pfizer, and Sanofi, acted in a consulting or advisory role for Advanced Accelerator Applications, AbbVie, Astellas Pharma, AstraZeneca, MedImmune, Bayer, Janssen Oncology, Knight Therapeutics, Myovant Sciences, Novartis, Pfizer, and Sanofi, and received research funding (institutional) from Advanced Accelerator Applications, Astellas Pharma, AstraZeneca, Bayer, Bristol Myers Squibb, Janssen Oncology, Merck Inc. & Co, Novartis, Pfizer, and Sanofi. **Noel Clarke** received honoraria for consultation and lectures from AstraZeneca, Bayer, Ipsen, Janssen, and Pfizer; acted in a consulting or advisory role for AstraZeneca; and received travel and accommodation expenses from AstraZeneca. **Jae Young Joung, Ji Youl Lee, Young Deuk Choi, Jun Hyuk Hong, Yukiyoshi Hirayama, Tae Gyun Kwon**, and **Cheol Kwak** have nothing to disclose.

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