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Original Article

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Niraparib in Japanese patients with heavily pretreated, homologous recombination-deficient ovarian cancer: final results of a multicenter phase 2 study

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Conflict of Interest
Daisuke Aoki declares the receipt of consulting fees from AstraZeneca, Chugai, MSD, and

ABSTRACT

Objective: To evaluate the long-term efficacy and safety of niraparib in Japanese women with heavily pretreated ovarian cancer.
Methods: This was the follow-up analysis of a phase 2, multicenter, open-label, single-arm study in Japanese women with homologous recombination-deficient, platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who had completed 3–4 lines of chemotherapy and were poly(ADP-ribose) polymerase inhibitor naïve. Participants received niraparib (starting dose, 300 mg) once daily in continuous 28-day cycles until objective disease progression, unacceptable toxicity, or consent withdrawal. The primary endpoint was confirmed objective response rate (ORR), as assessed using Response Evaluation Criteria in Solid Tumors version 1.1. Safety evaluations included treatment-emergent adverse events (TEAEs).
Results: 20 patients were enrolled in the study and included in both efficacy and safety analyses. Median total study duration was 759.5 days. Median dose intensity was 201.3 mg/day. Confirmed ORR was 60.0% (90% confidence interval [CI]=39.4–78.3); 2 patients had complete response and 10 patients had partial response. Median duration of response was 9.9 months (95% CI=3.9–26.9) and the disease control rate was 90.0% (95% CI=68.3–98.8). The most common TEAEs were anemia (n=15), nausea (n=12), and decreased platelet count (n=11). TEAEs leading to study drug dose reduction, interruption, or discontinuation were reported in 16 (80.0%), 15 (75.0%), and 2 patients (10.0%), respectively.
Conclusion: The long-term efficacy and safety profile of niraparib was consistent with previous findings in the equivalent population in non-Japanese patients. No new safety signals were identified.

Trial Registration: ClinicalTrials.gov Identifier: NCT03759600

Keywords: Clinical Trial, Phase II; Poly(ADP-ribose) Polymerase Inhibitors; Ovarian Cancer

Synopsis
We analyzed the long-term safety and efficacy of niraparib in Japanese patients with heavily pretreated, homologous recombination-deficient ovarian cancer. The objective response rate was 60.0% and no new safety signals were identified in this follow-up study. Efficacy and safety were consistent with previous findings in non-Japanese patients.

INTRODUCTION

Ovarian cancer is associated with high morbidity and mortality and is increasing in incidence in Japan [1]. Patients with advanced ovarian cancer have limited options for late-line therapy and median overall survival (OS) after third-line treatment is 5–9 months [2]. Poly(ADP-ribose) polymerase (PARP) is a DNA-binding enzyme that plays a key role in single-strand break (SSB) DNA repair [3]. Homologous recombination-deficient (HRd) cancer cells, such as those with *BRCA1/2* mutations, rely on intact SSB pathways to repair DNA damage and maintain cell viability. PARP inhibitors are a class of anticancer agents that exploit this synthetic lethality and induce tumor cell death by both inhibiting the catalytic activity of PARP and trapping it at the site of DNA damage [3]. Niraparib, an oral, highly selective PARP inhibitor [4], has been shown to be clinically efficacious in treating ovarian cancer in the NOVA [5], PRIMA [6], and QUADRA [2] clinical trials. It has marketing approval in

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several countries and territories, including Europe, the USA, and Japan. In Japan, niraparib is indicated for maintenance treatment of ovarian cancer after initial chemotherapy, maintenance treatment of platinum-sensitive recurrent ovarian cancer, and treatment of platinum-sensitive recurrent ovarian cancer with homologous recombination deficiency [7].

In a single-arm, open-label, phase 2 trial conducted in the USA and Canada (QUADRA), niraparib met its primary endpoint, with an objective response rate (ORR), as assessed by the investigator, of 27.7% (95% confidence interval [CI]=15.6–42.6; p<0.001) in platinum-sensitive, HRd-positive, PARP inhibitor-naive women with heavily pretreated ovarian cancer (n=47) [2]. In addition to this primary analysis population, QUADRA also included patients with platinum-resistant or refractory ovarian cancer, HRd-negative tumors, and both mutated *BRCA* and wild-type *BRCA* tumors. Exploratory analyses found that the clinical benefit of niraparib extended to patients beyond the primary group, including those with wild-type *BRCA* disease [2]. Based on the results of QUADRA, niraparib was also approved in the USA for the treatment of adults with advanced ovarian, fallopian tube, or primary peritoneal cancer who have received ≥3 previous chemotherapy regimens and who have HRd-positive cancer; however, this indication was voluntarily withdrawn by GSK in September 2022. This decision was made in consultation with the US Food and Drug Administration (FDA) and based on a totality of information on PARP inhibitors in the late-line treatment setting in ovarian cancer. A potential detrimental effect on OS had been observed with other PARP inhibitors in 2 independent randomized, active-controlled clinical trials conducted in women with *BRCA*-mutated, advanced ovarian cancer who had received ≥3 previous chemotherapy regimens [8,9]. Given the design of the QUADRA trial (single arm, uncontrolled), no comparative OS information can be obtained from the study, and it is difficult to assess any potential effect of niraparib on time-to-event endpoints. Unlike in the USA, niraparib retains this indication in Japan, although it is limited to patients sensitive to platinum-based chemotherapy. The American Society of Clinical Oncology (ASCO) also updated its guidelines for ovarian cancer to no longer recommend routinely offering niraparib to patients [10]. However, the guidelines also state that evidence on PARP inhibitor use in this setting is evolving and data continue to emerge. Thus, it is becoming increasingly important to collect further data on the use of PARP inhibitors in ovarian cancer.

Niraparib-2002 was a phase 2 study designed to evaluate the efficacy and safety of niraparib in a population of Japanese women equivalent to the primary analysis population in QUADRA. The study enrolled 20 patients, all with HRd-positive tumors and 65.0% of whom had *BRCA*-mutated tumors [11]. Primary data (median study duration, 120.5 days) have already been reported [11]. The confirmed ORR in the full analysis set (FAS) was 35.0% (7/20 patients; 1 had complete response [CR] and 6 had partial response [PR]), similar to that in the QUADRA study, and the disease control rate (DCR) was 90.0%. No new safety signals were identified and the short-term safety profile of niraparib in Japanese patients was considered acceptable and consistent with previous experience in non-Japanese patients [11]. Here, we report long-term follow-up data for Niraparib-2002.

MATERIALS AND METHODS

1. Study design and treatment

This was a phase 2, multicenter, open-label, single-arm study to evaluate the safety and efficacy of niraparib in heavily pretreated Japanese patients with advanced, relapsed, high-

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Data Availability

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

Author Contributions

Conceptualization: K.Y.; Formal analysis: A.D., T.T., Y.S, N.T., K.E., H.J., [1]H.K., [2]H.K., H.T., [3]H.K., K.S., M.M., [1]N.H., [2]N.H., S.J., T.K., T.M., Y.Y., K.Y., S.S., S.J., K.A, S.A., O.A., S.T.; Funding acquisition: K.Y.; Investigation: A.D., T.T., Y.S, N.T., K.E., H.J., [1]H.K., [2]H.K., H.T., [3]H.K., K.S., M.M., [1]N.H., [2]N.H., S.J., T.K., T.M., Y.Y., K.Y., S.S., S.J., K.A, S.A., O.A., S.T.; Methodology: K.Y., S.S., S.A.; Resources: K.Y.; Supervision: K.Y., S.T.; Validation: K.Y., S.S.; Writing - review & editing: A.D., T.T., Y.S, N.T., K.E., H.J., [1]H.K., [2]H.K., H.T., [3]H.K., K.S., M.M., [1]N.H., [2]N.H., S.J., T.K., T.M., Y.Y., K.Y., S.S., S.J., K.A, S.A., O.A., S.T.

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grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer (ClinicalTrials.gov: NCT03759600). The study design and patient inclusion and exclusion criteria have been described in detail previously [11]. Briefly, eligible participants were Japanese women ≥20 years old, with HRd-positive, relapsed, high-grade, serous epithelial ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease, who had completed 3 or 4 previous chemotherapy regimens and were platinum-sensitive to the last platinum-based therapy. Patients had to have ≥1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and an Eastern Cooperative Oncology Group performance status of 0 or 1. HRd testing was performed on tumor tissue using the Myriad myChoice® HRD diagnostic test (Myriad Genetics), which uses next generation sequencing to assess genomic instability and detect rearrangements and variants in the *BRCA1/2* genes. Individuals who had received other PARP inhibitors were excluded from participation.

The study was conducted at 17 sites in Japan, with data for the final analysis collected between December 26, 2018 and December 6, 2021. Participants received niraparib 300 mg (3×100 mg hard capsules) orally once daily, in continuous 28-day cycles until objective disease progression, unacceptable toxicity, or withdrawal of consent, as described previously [11]. The starting dose was set at 300 mg for consistency with the 300 mg starting dose of the QUADRA trial [2]. The choice of 300 mg as the starting dose was also based on the maximum dose at which tolerability was observed in Japanese patients and was agreed upon with the Pharmaceuticals and Medical Devices Agency. Clinic visits were conducted weekly during cycle 1 and then approximately every 4 weeks for subsequent cycles. Dose interruption of up to 28 days and dose reduction of up to 100 mg per day were permitted for any toxicity deemed intolerable to the patient. Patients discontinued niraparib if dose interruption did not resolve toxicity completely or to grade 1 toxicity during the 28-day dose interruption period and/or the patient had already undergone the maximum dose reductions. Dose intensity (mg/day) was calculated as the sum of the total daily dose ingested divided by the overall treatment exposure.

All patients provided written informed consent before participating. The study was conducted in accordance with the Declaration of Helsinki and the International Council on Harmonisation Tripartite Guideline on the ethical principles of Good Clinical Practice. The clinical study protocol, investigator's brochure, a sample informed consent form, and other study-related documents were reviewed and approved by the local or central Institutional Review Boards of all study sites.

2. Outcomes

Tumor assessment was performed using computed tomography or magnetic resonance imaging of the abdomen/pelvis and at clinically indicated areas. Imaging was performed at baseline, at the end of every 2 cycles until cycle 6, then at the end of every 3 cycles until cycle 39, and at the end of every 6 cycles until progression. Patients were classified as CR, PR, progressive disease (PD) or stable disease (SD) as assessed by the investigator using RECIST version 1.1. The primary endpoint was the confirmed ORR, defined as the proportion of patients classified as CR or PR. Secondary efficacy endpoints were duration of response (DOR), DCR (proportion of patients with CR, PR, or SD), progression-free survival (PFS), and OS. DOR was defined as the time from the earliest date of initial response (confirmed CR or PR) until the first date of radiological PD or death by any cause. PFS was defined as the time from the first dose of niraparib until the first date of documented disease progression as determined by RECIST version 1.1, clinical criteria, or death by any cause. OS was defined as the time from the first dose of niraparib to death by any cause. Secondary safety endpoints

were incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, severe (grade ≥3 according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03) TEAEs, and TEAEs that led to study drug dose reduction, interruption, or discontinuation.

3. Statistics

A sample size of 16 patients was planned for this study, with data from some patients anticipated to be non-evaluable (NE). A total of 14 enrolled patients was considered to provide ≥80% power to detect an ORR ≥29% when testing a null hypothesis of ORR ≤5% at a 1-sided significance level of 5% (binomial test). The FAS (efficacy analyses) included all patients who received ≥1 dose of study drug and had measurable disease at baseline. The safety analysis set (SAS) included all patients who received ≥1 dose of study drug. For analysis of the primary endpoint, ORR and its 2-sided 90% CI were calculated based on binomial distribution. DCR and its 2-sided 95% CI were also calculated based on binomial distribution. PFS and OS were analyzed using the Kaplan–Meier method to provide quartiles and progression/survival rate at specified points with 2-sided 95% CI. DOR was analyzed in the same way, using the population who responded to niraparib. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

1. Patient disposition and baseline characteristics

In total, 20 patients were enrolled in the study and included in both the FAS and SAS. Baseline characteristics have been described previously [11] and are shown in **Table 1**. At data cutoff, 17 patients had discontinued treatment, either owing to PD (n=15) or an adverse event (n=2). Median (range) total study duration and overall treatment exposure were 759.5 (237–1010) days and 254.5 (14–1,033) days, respectively. The median niraparib dose intensity was 201.3 mg/day and the median relative dose intensity was 67.1%.

2. Primary endpoint

Confirmed ORR in the FAS was 60.0% (90% CI=39.4–78.3). Out of 12 responders, 2 patients (10.0%) had CR and 10 patients (50.0%) had PR. In the remaining patients, the responses observed were SD (n=6) and PD (n=2) (**Fig. 1A**). In patients who had *BRCA1/2* mutations (n=13), the ORR was 69.2% (90% CI=42.7–88.7), whereas in patients without *BRCA1/2* mutations (n=7, includes 1 patient with unknown mutation status) the ORR was 42.9% (90% CI=12.9–77.5). The ORR in patients aged 18 to <65 years (n=11) was 45.5% (90% CI=20.0–72.9) and the ORR in patients aged ≥65 years (n=9) was 77.8% (90% CI=45.0–95.9). Patients for whom the primary tumor site was ovarian (n=13), primary peritoneal (n=5), and fallopian tube (n=2) had ORRs of 61.5% (90% CI=35.5–83.4), 60.0% (90% CI=18.9–92.4), and 50.0% (90% CI=2.5–97.5), respectively. Changes from baseline in target lesion size are shown for each patient in **Fig. 1B**.

3. Secondary endpoints

Median DOR in ORR responders (n=12) was 9.9 months (95% CI=3.9–26.9) across a median follow-up period of 31.3 months (**Fig. 2**). DCR in the FAS was 90.0% (95% CI=68.3–98.8). Kaplan–Meier plots for PFS and OS in the FAS are shown in **Fig. 3**. Median PFS was 8.3 months (95% CI=5.6–13.8), with 16 patients (80.0%) experiencing disease progression and 4 patients censored (either at last assessment [n=3] or last assessment before new anticancer

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Table 1. Demographics and baseline clinical characteristics

Characteristics	Niraparib 300 mg (n=20)
Age (yr)	62.0 (47.0–85.0)
Weight (kg)	54.5 (36.4–80.2)
<58	14 (70.0)
≥58, <77	5 (25.0)
≥77	1 (5.0)
Mean±standard deviation	53.7±9.7
Primary tumor site	
Ovarian	13 (65.0)
Primary peritoneal	5 (25.0)
Fallopian tube	2 (10.0)
ECOG status	
0	15 (75.0)
1	5 (25.0)
Tumor *BRCA1/2* mutation status	
Negative	6 (30.0)
Positive	13 (65.0)
Unknown	1 (5.0)
Cancer stage (FIGO) at initial diagnosis	
IA	1 (5.0)
IC	1 (5.0)
IIB	1 (5.0)
IIC	1 (5.0)
IIIA	1 (5.0)
IIIC	12 (60.0)
IV	3 (15.0)
Number of previous chemotherapy lines	
3	12 (60.0)
4	8 (40.0)
Type of previous chemotherapy	
Taxane	20 (100.0)
Bevacizumab	10 (50.0)
Doxorubicin	9 (45.0)
Gemcitabine	11 (55.0)
Liposomal doxorubicin	0
Best response to most recent platinum therapy	
CR	9 (45.0)
PR	8 (40.0)
SD	2 (10.0)
Unknown	1 (5.0)

Values are presented as median (min–max) or number (%) unless otherwise indicated. Table adapted from Okamoto et al. [11].
CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PR, partial response; SD, stable disease.

therapy [n=1]). At data cutoff, median OS was 24.9 months (95% CI=14.9–NE); 9 patients were censored at their last known alive date and 11 patients had died. The median follow-up periods for PFS and OS were 33.1 months and 31.8 months, respectively.

All patients experienced ≥1 TEAE during the study (**Table 2**). Of the 286 TEAEs that occurred, 202 were considered treatment-related. The most common TEAEs were anemia, nausea, and decreased platelet count. The most common TEAEs leading to study drug dose reduction (experienced by ≥10% of patients) were anemia (n=11, 55.0%), decreased platelet count (n=8, 40.0%), decreased neutrophil count (n=3, 15.0%), nausea (n=2, 10.0%), and vomiting (n=2, 10.0%). TEAEs leading to study drug interruption experienced by ≥10% of patients were anemia (n=10, 50.0%), decreased platelet count (n=9, 45.0%), decreased neutrophil count (n=4, 20.0%), and decreased white blood cell count (n=2, 10.0%). TEAEs leading to study

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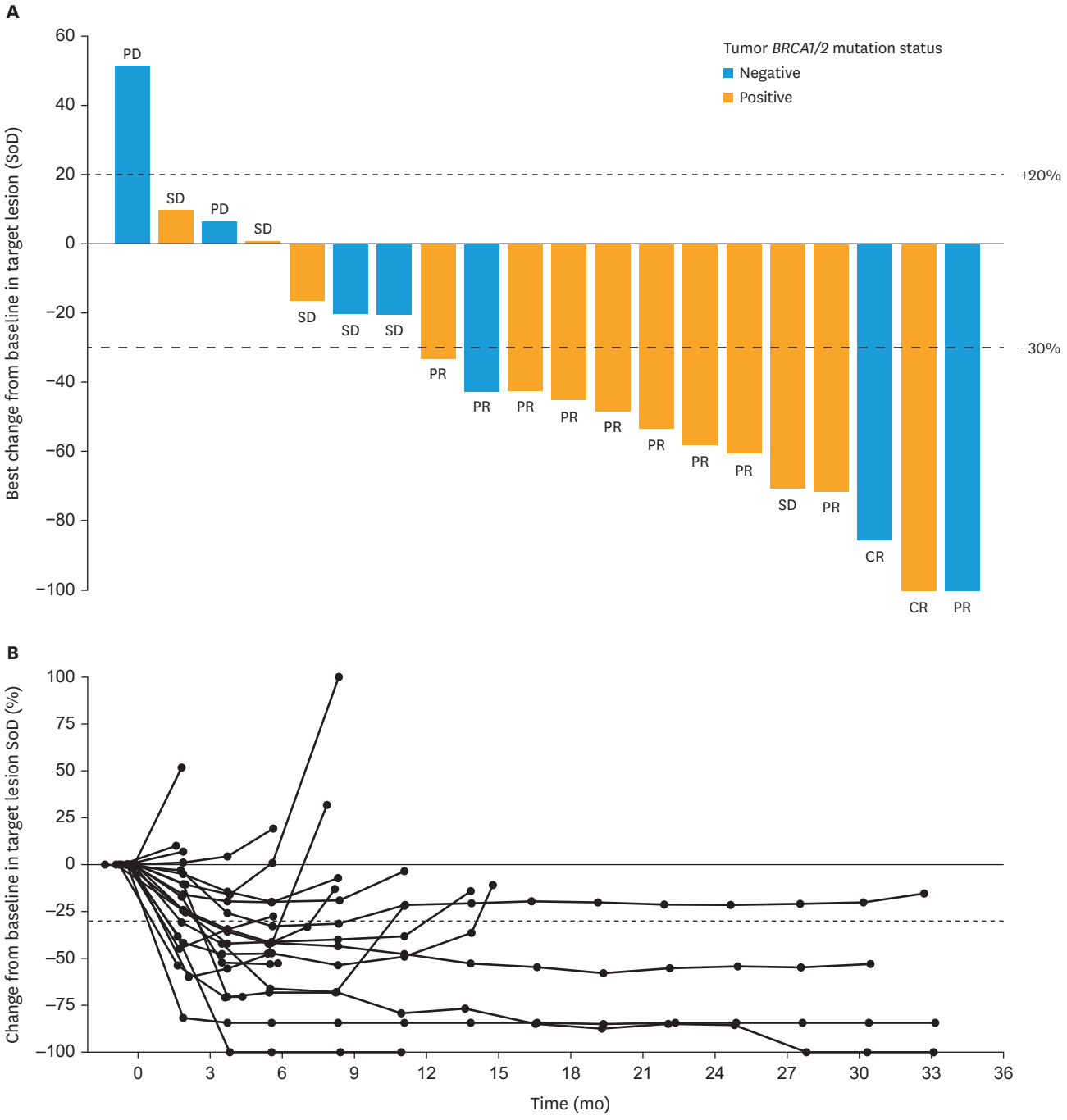

Fig. 1. Tumor responses. (A) Waterfall plot of ORR in the FAS. Includes all patients who had evaluable post-baseline target lesion(s). Tumor *BRCA1/2* mutation status is dichotomized as 'positive' or 'negative' (includes 'unknown'). The individual bars show the reduction rate at the time when the sum of the target lesion size decreased the most after starting administration of niraparib for each patient. The best overall response based on RECIST v1.1 shown at the end of each bar takes into account not only changes in the size of target lesions, but also evaluation of non-target lesions and the presence or absence of new lesions. (B) Change from baseline in target lesion size over time.
CR, complete response; FAS, full analysis set; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SoD, sum of diameters.

drug discontinuation were each only reported in 1 patient. Serious TEAEs were recorded for 8 patients (40.0%). TEAEs rated as Grade ≥3 severity, and serious TEAEs experienced by ≥10% of patients are shown in **Table 3**. No TEAEs leading to death were reported.

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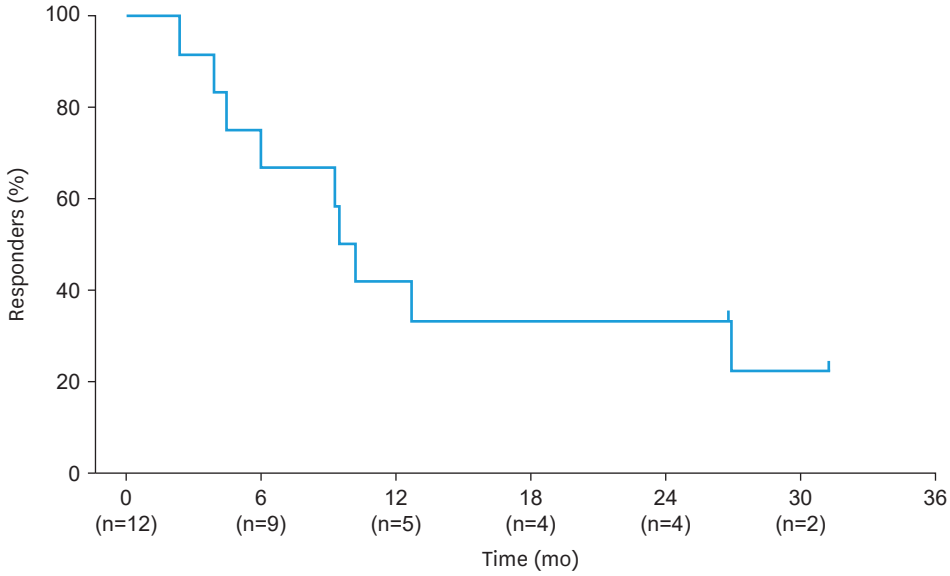

Fig. 2. Kaplan–Meier plot of duration of response in responders.

DISCUSSION

Patients with ovarian cancer who have received ≥3 lines of chemotherapy have high unmet medical needs. These patients typically have few late-line treatment options available to them and low (<10%) overall response to therapy [2]. This long-term follow-up of a phase 2, multicenter, open-label, single-arm study (Niraparib-2002) investigated the efficacy and safety of niraparib in 20 heavily pretreated Japanese women with relapsed, HRd-positive, high-grade, serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. Study participants were selected to represent a similar patient population to the non-Japanese primary analysis population in the QUADRA study [2,11].

The primary endpoint of confirmed ORR, as assessed by the investigator using RECIST version 1.1, was 60.0% at final data cutoff (median study duration, 759.5 days), compared with 35.0% in the initial report (median study duration, 120.5 days) [11] and 27.7% in QUADRA [2]. This apparent improvement in ORR compared with the initial report may be related to the timing of the initial data cutoff, which was executed very early in order to accelerate regulatory approval. At the time of data cutoff for the initial report, only 2 radiological tumor assessments (cycle 3 and cycle 5) at most had been performed for each patient after initiation of niraparib. Seven patients who had an initial response at cycle 3 were confirmed to have a lasting response at cycle 5 and were reported as responders. There were, however, several patients for whom a response was observed for the first time at cycle 5 or later, and therefore confirmation of response occurred after the data cutoff for the initial report and they were counted as non-responders. In this follow-up, 5 additional responders were reported versus the initial report, 4 of whom had their first response at cycle 5 and one who had their first response at cycle 6. Responders included patients with and without *BRCA1/2* mutations. Median DOR, which was not evaluable in the initial analysis, was 9.9 months, with the disease controlled for about 2 years in 4 patients. DCR was 90.0% and the median PFS and OS in this study were 8.3 months and 24.9 months, respectively. Together, these findings indicate clinically meaningful efficacy of niraparib in Japanese patients with ovarian cancer, particularly given the late-line setting.

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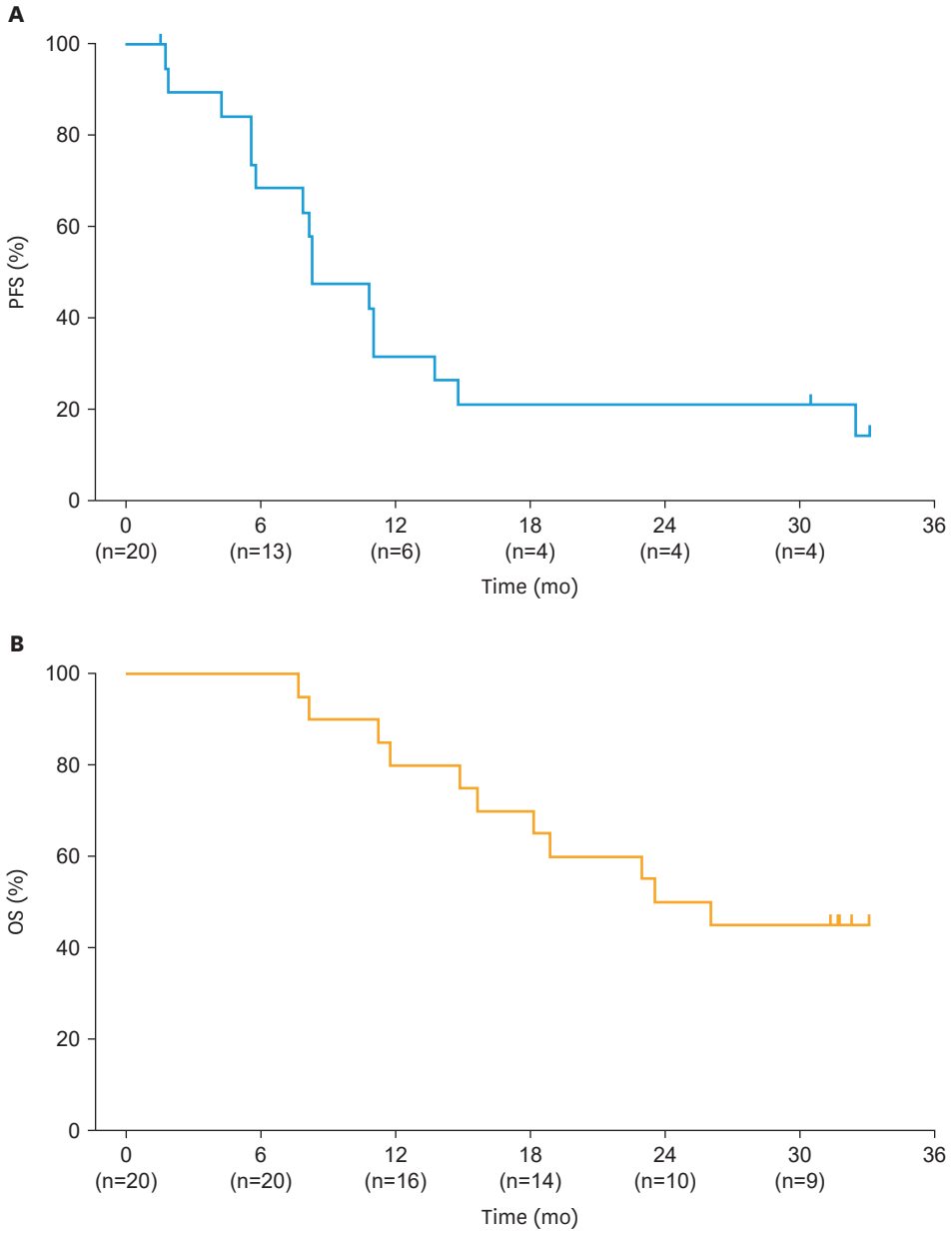

Fig. 3. Kaplan–Meier plot of (A) PFS and (B) OS in the FAS.
FAS, full analysis set; OS, overall survival; PFS, progression-free survival.

The safety profile of niraparib in this study was consistent with the initial report [11], as well as with previous studies of niraparib in Japanese and non-Japanese patients [2,12]. The most common TEAEs, experienced by ≥30% of patients, were anemia, nausea, decreased platelet count, constipation, vomiting, headache, malaise, decreased neutrophil count, decreased white blood cell count, and hypertension. Participants initially received niraparib 300 mg once daily; following dose modification, the median niraparib dose intensity was 201.3 mg/day. This is in line with the most commonly administered dose of 200 mg after initial dose adjustment in the pivotal phase 3 NOVA trial [13]. The niraparib dosing approved in Japan is an individualized starting dose determined by body weight and platelet count, rather than the fixed starting dose used in the QUADRA study and Niraparib-2002.

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Table 2. Summary of TEAEs

Adverse events	Niraparib 300 mg (n=20)
Any TEAEs	20 (100.0)
Related to study drug	20 (100.0)
Leading to study drug dose reduction	16 (80.0)
Leading to study drug interruption	15 (75.0)
Leading to study drug discontinuation	2 (10.0)
Serious TEAEs	8 (40.0)
Related to study drug	4 (20.0)
TEAEs observed in ≥20% of patients	
Blood and lymphatic system disorders	15 (75.0)
Anemia	15 (75.0)
Cardiac disorders	4 (20.0)
Palpitations	4 (20.0)
Gastrointestinal disorders	20 (100.0)
Nausea	12 (60.0)
Constipation	9 (45.0)
Vomiting	8 (40.0)
Stomatitis	5 (25.0)
General disorders and administration site conditions	7 (35.0)
Malaise	6 (30.0)
Infections and infestations	9 (45.0)
Investigations	17 (85.0)
Platelet count decreased	11 (55.0)
Neutrophil count decreased	6 (30.0)
White blood cell count decreased	6 (30.0)
Blood creatinine increased	4 (20.0)
Weight decreased	4 (20.0)
Metabolism and nutrition disorders	5 (25.0)
Decreased appetite	5 (25.0)
Musculoskeletal and connective tissue disorders	8 (40.0)
Nervous system disorders	14 (70.0)
Headache	7 (35.0)
Dysgeusia	4 (20.0)
Respiratory, thoracic, and mediastinal disorders	9 (45.0)
Skin and subcutaneous tissue disorders	8 (40.0)
Vascular disorders	8 (40.0)
Hypertension	6 (30.0)

Values are presented as number (%) of patients. TEAEs were defined as adverse events that occurred after administration of the first dose of study drug and are shown by MedDRA System Organ Class and Preferred Term.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Table 3. Grade ≥3 TEAEs and serious TEAEs with ≥10% incidence

Adverse events	Niraparib 300 mg (n=20)
Grade ≥3 TEAEs	17 (85.0)
Anemia	11 (55.0)
Platelet count decreased	6 (30.0)
Neutrophil count decreased	4 (20.0)
Lymphocyte count decreased	2 (10.0)
Weight decreased	2 (10.0)
White blood cell count decreased	2 (10.0)
Serious TEAEs observed in ≥10% of patients	8 (40.0)
Anemia	2 (10.0)
Platelet count decreased	2 (10.0)

Values are presented as number (%) of patients. TEAEs were defined as adverse events that occurred after administration of the first dose of study drug and are shown by MedDRA Preferred Term.
MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event.

Overall, the efficacy and safety profile of niraparib in Japanese patients was considered similar to results in the equivalent non-Japanese population in the QUADRA study [2]. As found in QUADRA, clinical benefit was observed in patients with and without *BRCA*

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mutations, providing further evidence of clinical utility in heavily pretreated patients with HRd-positive ovarian cancer beyond those with *BRCA* mutations.

PARP inhibitors are widely used in clinical practice in Japan and are recommended by the Japanese guidelines for use in first-line maintenance [14]. However, there is also a role for PARP inhibitor treatment in a later-line setting, given the unmet needs of patients who are ineligible to receive chemotherapy owing to past platinum hypersensitivity reactions. ASCO guidelines recommend that treatment decisions for late-line therapy are based on a thorough risk–benefit assessment in individual patients, taking into account a comprehensive understanding of available data, the patient's condition, and their preferences [10]. Niraparib is the only approved PARP inhibitor in these later treatment lines in Japan, and this study is one of very few clinical trials in Japanese patients receiving late-line treatment. In addition to Niraparib-2002, clinical trials investigating PARP inhibitor combination or rechallenge are also taking place in platinum-sensitive patients. Thus, data from this study will support physicians and patients in making treatment decisions for late-line therapy.

Based on the unmet needs of heavily pretreated patients, the efficacy data in Japanese patients and the different dosage to the US label (which may lead to a different risk–benefit profile in Japanese clinical practice to that seen in the QUADRA study), the Japan Society of Gynecologic Oncology requested that the Ministry of Health, Labour and Welfare maintain the indication for niraparib in this setting in Japan, contrary to the decision of the FDA, under the condition that patients are well informed about the benefits and risks, as well as the FDA decision. Data from this present study provide further support for the clinical utility of niraparib in Japan. However, given the different niraparib indications and dosing in Japan compared with the USA, as well as the rarity of the late-line patient population, it is still important to generate real-world data on niraparib use in Japan. The efficacy and safety of niraparib in Japanese patients will be further investigated in an ongoing observational study (UMIN Clinical Trial Registry: JGOG3031).

This trial has several limitations typically associated with local phase 2 oncology studies, including the lack of a comparator arm and a small sample size. However, the lower limit of the 90% CI of the primary endpoint in this study (39.4%) was higher than the threshold response (5%) based on historical cases, which suggests that data were collected from enough patients to be able to draw meaningful conclusions.

In conclusion, the final results of this phase 2 study demonstrate efficacy of niraparib in Japanese women with heavily pretreated ovarian cancer and support our initial report, which had similar findings to those seen in the equivalent population of non-Japanese patients. The long-term safety profile of niraparib in Japanese patients was considered acceptable and consistent with previous studies, with no new safety signals identified.

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