J Gynecol Oncol. 2021 Mar;32(2):e16
https://doi.org/10.3802/jgo.2021.32.e16
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Phase 2 single-arm study on the efficacy and safety of niraparib in Japanese patients with heavily pretreated, homologous recombination-deficient ovarian cancer

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Received: Jul 17, 2020
Revised: Oct 16, 2020
Accepted: Nov 8, 2020

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ABSTRACT

Objective: To evaluate the efficacy and safety of niraparib in Japanese women with heavily pretreated ovarian cancer.
Methods: This Phase 2 open-label, single-arm study enrolled Japanese women with homologous recombination deficiency-positive relapsed, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who had completed 3–4 lines of therapy.

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Presentation
Content included in this manuscript has been previously presented online at the 72nd Annual Congress of the Japan Society of Obstetrics and Gynecology, 23–28 April 2020, Abstract P-32-2.

Funding
This study was funded by Takeda Pharmaceutical Company Ltd.

Trial Registration
ClinicalTrials.gov Identifier: NCT03759600

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

The starting dose of niraparib was 300 mg administered once daily in continuous 28-day cycles until objective progressive disease, unacceptable toxicity, consent withdrawal or discontinuation. The primary endpoint, objective response rate (ORR), was assessed by the investigator using RECIST version 1.1. Safety evaluations included the incidence of treatment-emergent adverse events (TEAEs), including serious TEAEs.
Results: Twenty women were enrolled and the confirmed ORR in the full analysis set (FAS) was 35.0% (7/20), consisting of 1 complete response and 6 partial responses. Disease control rate in the FAS was 90.0%. The most frequently reported TEAEs (>50%) were anemia, nausea, and platelet count decreased. One patient (5.0%) had TEAEs leading to discontinuation of niraparib whereas reductions or interruptions were reported in 14 (70.0%) and 15 (75.0%) patients, respectively. The median dose intensity (202.9 mg daily) corresponded to a relative dose intensity of 67.6%.
Conclusion: Efficacy and safety of niraparib in heavily pretreated Japanese women was comparable to that seen in an equivalent population of non-Japanese women. No new safety signals were identified.

Trial Registration: ClinicalTrials.gov Identifier: NCT03759600

Keywords: Late-line Treatment; Japanese; Niraparib; Ovarian Cancer; Phase 2; Salvage

INTRODUCTION

Poly(ADP-ribose) polymerase (PARP) inhibitors are a relatively new class of anti-tumor agents that impair the ability of tumor cells with deficient DNA repair mechanisms associated with homologous recombination deficiency (HRd; e.g., *BRCA*1/2 mutations) to repair DNA damage [1,2]. This leads to an accumulation of irreparable double-strand DNA breaks and forces susceptible tumor cells to depend on an error-prone non-homologous end-joining mechanism for damage repair which promotes genetic instability and subsequent apoptosis [1,2].

Niraparib, a potent and selective inhibitor of PARP-1 and PARP-2, showed activity against ovarian, breast, and castrate-resistant prostate cancer in Phase 1 studies [2]. Niraparib is approved in the United States, Europe, Japan and certain other countries. Based on results from the NOVA [3], PRIMA [4], and QUADRA [5], trials, niraparib is currently indicated in the United States for the maintenance treatment of adult patients with either recurrent or advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete response (CR) or partial response (PR) to platinum-based chemotherapy, and for the treatment of adult patients with ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more previous chemotherapy regimens and associated with HRd-positive status [6].

A pharmacokinetic preclinical tumor model study demonstrated that niraparib preferentially concentrates in tumor tissue compared with plasma and also displays high tumor growth inhibition in *BRCA* wild-type tumors [7]. Of note, the favorable pharmacokinetic profile of niraparib has been associated with the broader clinical effect in patients with ovarian, fallopian tube and primary peritoneal cancers, irrespective of mutation or biomarker status. Recently, an open-label, single-arm, Phase 2 study (QUADRA) investigated the potential of niraparib monotherapy as a treatment in patients with 3 or more lines of therapy [5]. The heavily pretreated ovarian cancer (OC) population of QUADRA was particularly broad in that

Y.S., H.J., H.K.[1], H.K.[2], H.T., H.K.[3], K.S., M.M., N.H.[1], N.H.[2], S.J.,[1] T.T., T.K., T.M., Y.Y., K.Y., S.S., S.J.[2], S.A., A.D., S.T.
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it not only included patients with HRd-positive platinum-sensitive disease but also those with platinum-resistant or refractory high-grade OC, homologous recombination proficient (HRd-negative) tumors, and *BRCA* mutated or *BRCA* wild-type tumors. Although patients with HRd-positive platinum-sensitive disease, corresponding to the primary analysis population, met the primary endpoint with a statistically significant overall response of 28% (95% confidence interval [CI]=15.6–42.6, p<0.001), exploratory analyses showed that clinical benefit extended to other patients according to clinical and molecular biomarkers. In particular, the QUADRA study verified that clinically relevant activity was not only seen in patients with a *BRCA* mutation but also those with *BRCA* wild-type disease.

Based on this background, this Phase 2 study (Niraparib-2002) was designed to evaluate the efficacy and safety of niraparib in the equivalent population of Japanese women to the primary analysis population in the QUADRA study.

MATERIALS AND METHODS

1. Study design

This was a Phase 2, multicenter, open-label, single-arm study designed to evaluate the efficacy and safety of niraparib in chemotherapy-treated patients with relapsed, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer, who had received 3 or 4 previous lines of chemotherapy. The study was conducted with the aim of obtaining Japanese local regulatory approval and the study population was set in accordance with the primary analysis population in the QUADRA study, which contained the following 3 key elements for eligibility: HRd-positive, platinum-sensitive disease with 3 or 4 prior lines of chemotherapy, and PARP inhibitor-naïve. HRd-positive status was determined by the myChoice® (Myriad Genetics, Inc., Salt Lake City, UT, USA) HRd test such that any tumor which scored ≥42 or had a deleterious or suspected deleterious *BRCA*1/2 mutation was considered HRd-positive [3]. This study was registered at ClinicalTrials.gov (NCT03759600).

Patients were enrolled at 17 sites in Japan and data were collected between 26 December 2018 and 1 July 2019. Eligible patients were Japanese women (20 years or older) with HRd-positive relapsed, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer with recurrent disease. All patients were required to undergo tumor sample testing via the myChoice® test to determine if they had a HRd-positive tumor as defined by the Myriad Genetics myChoice test. Patients also must have completed 3 or 4 previous chemotherapy regimens with their last regimen >4 weeks before niraparib initiation and have been sensitive to the last platinum-based therapy, defined as having not experienced disease progression for at least 6 months following the last chemotherapy containing platinum-based anticancer agents. To evaluate the objective response rate (ORR), patients also had to have at least one measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Other inclusion criteria included Eastern Cooperative Oncology Group performance status of ≤1 and adequate organ function based on laboratory testing.

Key exclusion criteria included a history of known, persistent, Grade ≥3 hematologic toxicity from the last cancer therapy, palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the first dose of niraparib, and pelvic radiotherapy as treatment for primary or recurrent disease within 1 year of niraparib, in terms of minimizing the influence of pre-existing myelosuppression and securing bone marrow function reserve before

study treatment. Patients who had prior treatment with a known PARP inhibitor were also ineligible. Other exclusion criteria included symptomatic, uncontrolled medical conditions.

This study was conducted in accordance with ethical principles of the Declaration of Helsinki, the International Council for Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice, and the Institutional Review Board (IRB) regulations. 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 IRBs of all study sites. Each investigator conducted the study according to applicable local or regional regulatory requirements and in accordance with the responsibilities listed in the protocol. All patients provided written informed consent to participate in the study.

2. Treatment

Niraparib 300 mg (3×100 mg hard capsules) once daily was administered orally in continuous 28-day cycles until patients experienced objective progressive disease (PD), unacceptable toxicity, withdrawal of consent or until study discontinuation for any other specified reason.

Clinical visits were conducted weekly during cycle 1 and then approximately every 4 weeks for subsequent cycles. RECIST version 1.1 was used for tumor assessment using computed tomography (CT) or magnetic resonance imaging (MRI) scanning at the end of every 2 cycles through 6 months then at the end of every 3 cycles until progression.

Dose interruption of up to 28 days and dose reduction to a maximum 100 mg per day were permitted and implemented for any toxicity deemed intolerable to the patient. For non-hematologic toxicities, treatment was interrupted for any NCI CTCAE version 4.03 grade 3 or 4 non-hematologic toxicity considered related to niraparib. Treatment was restarted at 300 mg daily if the toxicity was resolved using adverse event prophylaxis to baseline or grade ≤1 within 28 days, or at 200 mg daily or 100 mg daily for first and second reductions, respectively, when adverse event prophylaxis was not considered feasible. 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. For hematologic toxicities, dose interruption/modification criteria were based on predefined platelet, neutrophil, and hemoglobin counts monitored by weekly blood draws until resolution or permanent discontinuation, if deemed necessary.

3. Outcomes

The primary endpoint was the confirmed ORR, defined as the proportion of patients achieving a CR or PR as assessed by the investigator using RECIST version 1.1.

Secondary endpoints of this study related to the efficacy and safety of niraparib. Secondary efficacy measures were the duration of response (DOR), disease control rate (DCR, proportion of patients achieving CR, PR or stable disease), progression-free survival (PFS), and overall survival (OS). DOR was defined as the time from the earliest date of initial response date of confirmed CR or PR until the earlier date of radiological PD or death by any cause. PFS was defined as the time from the first dose of niraparib to the earliest date of disease progression as determined by CT/MRI RECIST [8], clinical criteria, or death by any cause. Clinical criteria included positive findings via diagnostic tests (e.g., histology/cytology, ultrasound techniques, endoscopy, positron emission tomography) and cancer antigen 125 (CA-125) progression according to Gynecologic Cancer Intergroup criteria. However, disease

progression was not diagnosed in case of CA-125 progression in the absence of at least 1 other criterion. OS was defined as the time from the first dose of niraparib to death by any cause.

Secondary safety endpoints were assessed by the incidence of treatment-emergent adverse events (TEAEs), serious TEAEs, severe (grade 3 or higher) TEAEs, and TEAEs that led to drug reduction, interruption or discontinuation. TEAEs were defined as AEs that occurred after administration of the first dose of study drug and were coded using MedDRA criteria and were tabulated by Preferred Term and System Organ Class. Adverse events, including laboratory abnormalities, were considered according to severity (according to NCI CTCAE, version 4.03), seriousness, and causality in terms of relation to study drug administration. A serious TEAE referred to an untoward medical occurrence at any dose that resulted in death, inpatient hospitalization or prolongation of an existing hospitalization, persistent or significant disability or incapacity, or that was life-threatening, a congenital anomaly/birth defect, or otherwise a medically important event (such as allergic bronchospasm that required intensive treatment at home rather than in hospital). Further, a comprehensive set of serum chemistry and hematology tests were performed on samples collected before study drug administration at the start of each cycle; in cycle 1, serum chemistry was assessed at day 1 and 15, and hematology also assessed at days 1, 8, 15 and 22. Physical examinations and assessment of vital signs (blood pressure, pulse rate, body temperature) were also conducted at specified times during the study period.

4. Statistics

In terms of planned enrolment, 14 enrolled patients were considered to provide a ≥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). Accordingly, 16 patients were planned to be enrolled considering that some patients would be non evaluable (NE).

The safety analysis set was defined as patients who received ≥1 dose of study drug whereas the full analysis set (FAS) was defined as all patients who received ≥1 dose of study drug and had measurable disease at baseline. Based on the FAS, the ORR and 2-sided 90% CI and the DCR and 2-sided 95% CI were provided with the CIs calculated based on the binominal 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. The Kaplan-Meier plot for PFS and OS was also provided. The DOR was analyzed using the population who responded to niraparib.

RESULTS

1. Subject disposition and baseline characteristics

A total of 20 patients were enrolled and included in both the FAS and safety analysis set. At data cutoff, 4 patients had discontinued treatment either due to an adverse event (n=1) or PD (n=3).

Baseline demographic and clinical characteristics of enrolled patients are shown in **Table 1**. Overall, patients had a median age of 62.0 years and mean body weight of 53.7 kg. The primary tumor site was ovarian in 13 (65.0%) patients, primary peritoneal in 5 (25.0%) patients, and fallopian tube in 2 (10.0%) patients. All tumors were HRd-positive based on the inclusion criteria and *BRCA* mutations were detected in tumors from 13 (65.0%) patients.

https://doi.org/10.3802/jgo.2021.32.e16

Table 1. Demographic and baseline clinical characteristics (full analysis set)

Characteristics	Niraparib 300 mg (n=20)
Age (yr)	62.0 (47.0, 85.0)
Weight (kg)	
<58	14 (70.0)
58≤weight<77	5 (25.0)
≥77	1 (5.0)
Mean (standard deviation)	53.7 (9.7)
Median (min, max)	54.5 (36.4, 80.2)
Time from initial diagnosis (yr)	4.7 (2.5, 16.2)
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)
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)
No. of previous chemotherapy lines	
3	12 (60.0)
4	8 (40.0)
Time to progression after last platinum therapy (mo)	
6–12	12 (60.0)
>12	8 (40.0)
Best response to last platinum therapy	
CR	9 (45.0)
PR	8 (40.0)
SD	2 (10.0)
Unknown	1 (5.0)
Duration between the end date of the last chemotherapy regimen and the first dose of study treatment (mo)	2.1 (1.0, 27.0)*

Values are presented as median (min, max) or number (%).
CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PR, partial response; SD, stable disease.
*Includes non-platinum chemotherapy and so duration may be less than 6 months for some patients.

All patients received niraparib 300 mg once daily as the initial dose in cycle 1. Modifications to the initial dose in cycles 2 to 6 were conducted as shown in **Supplementary Fig. 1**. The median total study duration and overall treatment exposure of the study drug were 120.5 days and 118.5 days, respectively. Further, the median dose intensity was 202.9 mg daily and the median relative dose intensity (RDI) was 67.6%.

2. Primary endpoint

Confirmed ORR in the FAS was 35.0% (90% CI=17.7–55.8), for which the lower limit of the 90% CI of the ORR was higher than the prespecified threshold response (5%) (**Table 2**). Subgroup analysis found that responders were seen in patients with both positive and negative *BRCA* mutation status (**Table 2**). **Fig. 1** shows the waterfall plot for ORR in the FAS. Out of 7 responders, 1 (5.0%) patient achieved CR and 6 (30.0%) patients achieved PR.

Subgroup analysis of ORR based on age (<65 years and ≥65 years of age), primary tumor site (ovarian, primary peritoneal, and fallopian tube) and platinum-free interval after last

https://doi.org/10.3802/jgo.2021.32.e16

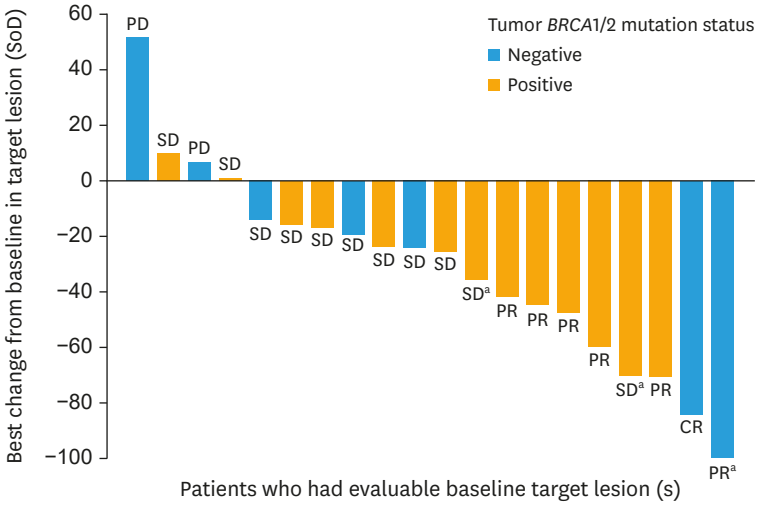

Fig. 1. Waterfall plot of ORR in FAS. Tumor *BRCA*1/2 mutation status is dichotomized as "Positive" or "Negative" (includes "Unknown").
CR, complete response; FAS, full analysis set; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters.
*Best overall response was determined as SD/PR as tumor shrinkage corresponding to PR/CR was observed at only one time point but was not confirmed at a subsequent time point before data cut-off as required for confirmation of CR or PR.

Table 2. Summary of overall response for primary endpoint for the total population and subgroup analysis based on *BRCA* mutation status

Efficacy	Niraparib 300 mg (n=20)
ORR	35.0 (17.7–55.8)
Best overall response	
CR	1 (5.0)
PR	6 (30.0)
SD	11 (55.0)
PD	2 (10.0)
NE	0 (0.0)
Tumor *BRCA*1/2 mutation status, response*	
Negative (n=7)	2 (28.6)
90% CI	5.3–65.9
Positive (n=13)	5 (38.5)
90% CI	16.6–64.5

Values are presented as number (90% CI) or number (%).
CI, confidence interval; CR, complete response; NE, non evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
*Tumor *BRCA*1/2 mutation status is dichotomized as "Positive" or "Negative", which includes "Unknown".

platinum-based treatment (6–12 months and ≥12 months) also found that responders were found in these subgroups (**Supplementary Table 1**).

3. Secondary endpoints

In terms of secondary efficacy measures, all ORR responders (7 patients) were censored for DOR at last assessment with no relevant DOR events recorded. PFS was considered in the FAS (20 patients) with documented progression noted in 3 patients (15.0%) during the follow-up period and 17 patients censored at either the last assessment (n=16) or last assessment before new anticancer therapy (n=1). The median (95% CI) PFS was 4.3 (NE–NE) months and the median (95% CI) follow-up for PFS was 3.7 (3.5–3.7) months. **Fig. 2** shows the Kaplan-Meier plot for PFS. OS was also considered in the FAS (20 patients) and, at the data cutoff, no patients had died (i.e., no survival events) and all were censored at their last known alive

https://doi.org/10.3802/jgo.2021.32.e16

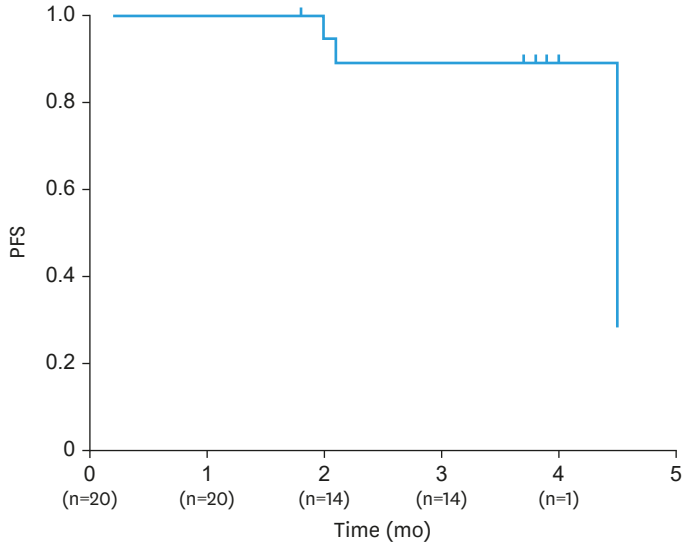

Fig. 2. Kaplan-Meier plot of PFS in FAS.
FAS, full analysis set; PFS, progression-free survival.

date. The median (95% CI) follow-up for DOR and OS were 1.9 (1.6–2.0) and 3.8 (3.7–4.3) months, respectively. The DCR in the FAS was 90.0% (95% CI=68.3–98.8).

Regarding safety endpoints, at least one TEAE occurred in all 20 (100%) enrolled patients and 171 of the total 204 TEAEs that occurred were considered treatment-related. Serious TEAEs were recorded in 4 (20%) patients who experienced a total of 6 TEAEs, of which 4 TEAEs were considered drug-related. One patient had a total of 3 TEAEs that led to discontinuation of niraparib whereas reductions or interruptions of the niraparib were reported in 14 (70.0%) and 15 (75.0%) patients respectively; the most common causes of either event were anemia, platelet count decreased, and neutrophil count decreased. The most common TEAEs of any grade were anemia, nausea, platelet count decreased, constipation, vomiting, neutrophil count decreased, malaise and headache (**Table 3**). Grade 3 or higher TEAEs were reported in 15 patients and the most common drug-related grade 3 or higher TEAEs (≥10% patients) were anemia (11 patients, 55.0%), platelet count decreased (6 patients, 30.0%), neutrophil count decreased (4 patients, 20.0%), and white blood cell count decreased (2 patients, 10.0%).

In terms of laboratory examination and other findings, several changes in hematology values were noted separately to that of TEAEs, including shifts to higher grades of decreased hemoglobin, leukocytes, absolute neutrophil count, lymphocytes, and platelets. These shifts were consistent with the appearance of grade 3 or higher TEAEs noted above. Most laboratory value shifts related to hematology parameters and shifts in serum chemistry (increased amylase, increased γ-glutamyl transferase and decreased phosphorus) were considered less clinically meaningful.

DISCUSSION

This was a Phase 2, multicenter, open-label, single-arm study to evaluate the efficacy and safety of niraparib in Japanese women with relapsed, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who have received 3 or 4 previous chemotherapy regimens.

https://doi.org/10.3802/jgo.2021.32.e16

Table 3. Overall incidence of TEAEs occurring in ≥10% of patients and the corresponding incidence of grade 3 or higher TEAEs by MedDRA System Organ Class and Preferred Term

Adverse events	Niraparib (n=20)	
	Any grade	Grade 3 or higher
Any TEAEs	20 (100.0)	15 (75.0)
Blood and lymphatic system disorders	14 (70.0)	11 (55.0)
Anemia	14 (70.0)	11 (55.0)
Cardiac disorders	4 (20.0)	-
Palpitations	4 (20.0)	-
Gastrointestinal disorders	19 (95.0)	-
Nausea	12 (60.0)	-
Constipation	7 (35.0)	-
Vomiting	7 (35.0)	-
Stomatitis	3 (15.0)	-
General disorders and administration site conditions	7 (35.0)	-
Malaise	6 (30.0)	-
Infections and infestations	5 (25.0)	-
Nasopharyngitis	3 (15.0)	-
Investigations	14 (70.0)	8 (40.0)
Platelet count decreased	11 (55.0)	6 (30.0)
Neutrophil count decreased	6 (30.0)	4 (20.0)
Blood creatinine increased	4 (20.0)	-
White blood cell count decreased	4 (20.0)	2 (10.0)
γ-glutamyl transferase increased	2 (10.0)	-
Weight decrease	2 (10.0)	-
Metabolism and nutrition disorders	5 (25.0)	-
Decreased appetite	5 (25.0)	-
Musculoskeletal and connective tissue disorders	2 (10.0)	-
Nervous system disorders	10 (50.0)	-
Headache	6 (30.0)	-
Dysgeusia	3 (15.0)	-
Respiratory, thoracic and mediastinal disorders	7 (35.0)	-
Epistaxis	3 (15.0)	-
Dyspnea	2 (10.0)	-
Skin and subcutaneous tissue disorders	4 (20.0)	-
Alopecia	2 (10.0)	-
Vascular disorders	4 (20.0)	-

Values are presented as number (%).
TEAE, treatment-emergent adverse event.

All enrolled patients had 3 or 4 prior lines of chemotherapy, with 40.0% of subjects having had 4 prior lines of chemotherapy, and thus represented a population with high unmet medical needs. As noted in the QUADRA study conducted among a similar population of non-Japanese women, such high unmet needs refers to those women with OC who have few late-line treatment options and, as a proportion of patients, typically have an overall response of less than 10% [5]. A total of 20 patients were treated with niraparib; all with HRd-positive tumors, and the proportion of patients with *BRCA* mutation tumors was similar to that of the biomarker-defined population in the QUADRA study (64.3%). The median RDI was 67.6%, which was slightly lower than that (76.9%) in biomarker-defined population in the QUADRA study [5]. Confirmed ORR, the primary endpoint in this study, assessed by the investigator using RECIST was 35.0% in the FAS. This is comparable to the confirmed ORR (27.7%) as assessed by the investigator, which represents the equivalent primary endpoint of the QUADRA registration study. The lower limit of the 90% CI of the ORR (17.7%) was higher than the threshold response (5%) based on historical cases. In this study, the median PFS was 4.3 months and 3 patients (15.0%) experienced the PFS event of progression. OS was not estimable for any of the enrolled patients because no subjects died and all subjects were censored at their last known alive date at the data cutoff.

https://doi.org/10.3802/jgo.2021.32.e16

All subjects in the safety analysis set experienced at least one TEAE, with treatment-related TEAEs reported in all subjects. The most frequently reported TEAEs in ≥30% of enrolled subjects were anemia, nausea, platelet count decreased, constipation, vomiting, neutrophil count decreased, malaise and headache. Six serious TEAEs occurred in 4 (20.0%) patients and 4 out of 6 serious AEs were considered related to study treatment by the investigator. TEAEs leading to study drug reduction, study drug interruption and study drug discontinuation were reported in 14 patients, 15 patients, and one patient, respectively. Although the incidence of TEAEs leading to study drug dose reduction and study drug dose interruption were relatively higher in this study, fewer TEAEs leading to study drug discontinuation were observed in this study than in the safety population of the QUADRA study (47.1%, 62.2% and 21.2%, respectively). Individualized dosing regimens (allowing for 200 mg or 300 mg niraparib starting doses) based on baseline body weight and platelet count have been reported to reduce AEs in similar studies conducted in non-Japanese women [4]. Given the relatively lower body weight of Japanese woman, individualized dosing might be considered.

The findings from this Phase 2 study add to the evolving body of evidence related to niraparib and provide additional specific support for its use in patients with ovarian, primary peritoneal, or fallopian tube cancer, especially in Japanese patients. The results of the QUADRA study recapitulated the continuum of increasing clinical benefit observed in previous studies including the pivotal NOVA study, and provide substantial evidence of a favorable efficacy and safety profile for niraparib in heavily pretreated patients who either have *BRCA* mutation or HRd-positive platinum-sensitive disease. Further, the results of the present Japanese Phase 2 study showed efficacy and safety profile in Japanese women in a late-line setting consistent with those observed in the QUADRA study. Previous Phase 1 and Phase 2 studies established a niraparib dose of 300 mg once daily as the dose for the pivotal Phase 3 NOVA trial. However, post hoc analysis of NOVA trial data at this dose identified low baseline body weight (<77 kg) and low platelet count (<150,000/μL) as risk factors for grade ≥3 thrombocytopenia, which is the major dose-limiting toxicity for niraparib [9]. In response, a Phase 2, multicenter, open-label, single-arm study (Niraparib-2001), evaluated the safety of niraparib 300 mg once daily in 19 Japanese women with platinum-sensitive, relapsed OC, fallopian tube cancer, or primary peritoneal cancer [10]. Almost all enrolled patients had a baseline body weight <77 kg and an incidence of grade ≥3 thrombocytopenia as expected from the previous analysis. However, the overall safety profile was generally consistent with the known safety profile of niraparib and previous experience with niraparib in non-Japanese patients [10]. All patients in the present study also initially received niraparib 300 mg once daily but, following required dose modification, the median dose intensity lowered to 202.9 mg daily, which likely reflects the dose-limiting factors noted previously. Other studies of niraparib in this indication, including those that are ongoing, recruiting or planned, relate to the use of niraparib in combination with other chemotherapy agents. Results from these trials reported to date show promising efficacy for patients who often have limited treatment options.

One limitation of this study is the small number of patients and lack of a comparator arm, as common to open-label, single-arm local Phase 2 oncology studies. The sample size of this study was justified by the lower limit of the 90% CI of ORR being higher than the threshold response (5%) based on historical cases. In the post-approval setting, post-marketing surveillance will provide real-world safety and efficacy data in a larger population of Japanese women with late-line OC.

https://doi.org/10.3802/jgo.2021.32.e16

In conclusion, the study results demonstrated efficacy of niraparib in Japanese women who are heavily pretreated, which was considered comparable to that in the equivalent population in non-Japanese patients. Additionally, the safety profile was acceptable and consistent with the known safety profile of niraparib and previous experience with niraparib in non-Japanese patients. No new safety signals were identified in this study.

ACKNOWLEDGEMENTS

The authors thank the patients, their families, caregivers and all clinicians for their involvement and contribution to the study. The authors also thank: the Japanese Gynecologic Oncology Group (JGOG) for providing valuable advice regarding study design and support for subject enrollment; TESARO, a GSK company, for providing valuable advice during manuscript development; Yuka Yamamoto, medical expert for Takeda Pharmaceutical Company Ltd., for providing valuable advice regarding study design and data interpretation during manuscript development; and Mark Snape, MBBS, CMPP of inScience Communications, Springer Healthcare, for writing the outline and the first draft of the manuscript. This medical writing assistance was funded by Takeda Pharmaceutical Company Ltd.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Subgroup analysis for ORR with niraparib 300 mg

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Supplementary Fig. 1

Initial niraparib dose for each cycle in the safety analysis set. Cycle 6 contained only 1 patient (received niraparib 100 mg) and is not shown.

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