ABSTRACT

Background: Poly (adenosine diphosphate)-ribose polymerase (PARP) inhibitors for tumors with homologous recombination deficiency (HRD), including pathogenic mutations in BRCA1/2, have been developed. Genomic analysis revealed that about 20% of uterine leiomyosarcoma (uLMS) have HRD, including 7.5%–10% of BRCA1/2 alterations and 4%–6% of carcinomas of the uterine corpus, and 2.5%–4% of the uterine cervix have alterations of BRCA1/2. Preclinical and clinical case reports suggest that PARP inhibitors may be effective against those targets. The Japanese Gynecologic Oncology Group (JGOG) is now planning to conduct a new investigator-initiated clinical trial, JGOG2052.

Methods: JGOG2052 is a single-arm, open-label, multi-center, phase 2 clinical trial to evaluate the efficacy and safety of niraparib monotherapy for a recurrent or persistent rare fraction of gynecologic malignancies with BRCA1/2 mutations except for ovarian cancers. We will independently consider the effect of niraparib for uLMS or other gynecologic malignancies with BRCA1/2 mutations (cohort A, C) and HRD positive uLMS without BRCA1/2 mutations (cohort B). Participants must have 1–3 lines of previous chemotherapy and at least one measurable lesion according to RECIST (v.1.1). Niraparib will be orally administered once a day until lesion exacerbation or unacceptable adverse events occur. Efficacy will be evaluated by imaging through an additional computed tomography scan every 8 weeks. Safety will be measured weekly in cycle 1 and every 4 weeks after cycle 2 by blood tests and physical examinations. The sample size is 16–20 in each of cohort A and B, and 31 in cohort C. The primary endpoint is the objective response rate.

Trial Registration: Japan Primary Registries Network (JPRN) Identifier: JRCT2031210264
**Keywords:** Gynecologic Neoplasms; Leiomyosarcoma; Homologous Recombination Repair; Gene; Mutation; Poly(ADP-ribose) Polymerase Inhibitors

**INTRODUCTION**

Recent advantages in genomic analysis using next-generation sequencing have revealed that molecular biological characteristics of various malignancies may be emerging therapeutic agents. Poly (adenosine diphosphate)-ribose polymerase (PARP) inhibitors for tumors with homologous recombination deficiency (HRD), including pathogenic mutations or likely pathogenic mutations in BRCA1/2 genes have been developed. In gynecologic malignancies, olaparib and niraparib for ovarian cancer are covered by medical insurance in most countries in the US, EU, and Asian countries, including Japan, because of a high incidence of HRD in ovarian cancers. Olaparib is therapeutically effective as a maintenance therapy based on germline or somatic BRCA1/2 mutations, HRD, or platinum sensitivity [1,2]. Niraparib is also one of the PARP inhibitors with higher PARP-trapping potency [3]. In addition to being used as maintenance therapy for newly diagnosed ovarian cancers with or without HRD [4] and recurrent ovarian cancers with HRD [5], niraparib exhibited an antitumor effect when used as a single agent for recurrent ovarian cancers with HRD in tumor tissue as an index, independent of platinum sensitivity [6]. However, the incidence of HRD in non-ovarian gynecologic malignancies is low, and the development of new treatments for these malignancies is difficult due to their rarity.

BRCA1/2 biallelic inactivation is one of the strongest biomarkers for the response of PARP inhibitors. Pan-cancer analysis revealed that uterine leiomyosarcoma (uLMS) has characteristic alterations in these genes and the major alterations in uLMS are somatic homozygous deletion in BRCA2, whereas germline pathogenic or likely pathogenic mutations along with loss of heterozygosity (LOH) are major biallelic inactivation of BRCA1/2 in other gynecologic malignancies, including ovarian cancer [7].

uLMS is located near the non-uterine LMS (nuLMS) in the phylogenetic tree of soft-tissue sarcomas (STS) [8], and it became clear that some of the uLMS have HRD, including alterations of BRCA1/2 and other homologous recombination repair (HRR)-related genes such as ATM and CDK11 [9]. Mutations of BRCA2 were observed more frequently in uLMS than in nuLMS (around 10% vs. 1%) [10,11]. In a study that conducted a cancer genome profile test on 80 cases of uLMS, Hensley et al. [11] reported that homozygous deletions and truncating mutations in BRCA2 were observed in 5% and 2.5% of the cases, respectively. Therefore, the mutation rate of BRCA1/2 in uLMS reported to date ranges from 7.5% to 10%, and abnormalities in the HRR gene are reported to be about 18% overall [12]. Choi et al. [13] reported that 25% (12 out of 48 samples) of uLMS showed clinically actionable mutation signatures of HRD. Furthermore, in an analysis of HRD score in 214 STS samples of The Cancer Genome Atlas database, which calculated an unweighted sum of LOH, telomeric allelic imbalance (TAI), and largescale state transitions (LST), the optimal cut-off value correlated with clinical HRD was 34.5 of HRD score [14]. Thus, HRD in uLMS may be estimated by scores based on LOH, TAI, and LST.

Genomic analysis in other gynecologic cancers revealed that mutations of BRCA1/2 were not limited to ovarian cancers and uLMS. The mutation rates of BRCA1/2 were estimated at 4%–6% in endometrial cancer and 2.5%–4% in cervical cancer. The BRCA1/2 mutations...
were also reported in vulvar cancer [15]. Those pathogenic (or likely pathogenic) mutations (either germline or somatic) may result in HRD through biallelic loss of BRCA1/2 [16]. Especially, uterine serous carcinoma is morphologically and biologically similar to ovarian serous carcinoma [17], and the mutation rate of BRCA1/2 in uterine serous carcinoma has been reported to be 9.1% and 6.3% [18]. Moreover, clinical studies that searched for cancer-related gene mutations in recurrent endometrial cancer in Japan were conducted in the medical institutions of the Japanese Gynecologic Oncology Group (JGOG), and the results were announced at American Society of Clinical Oncology in 2020 [19]. Among 102 cases of recurrent endometrial cancer, pathogenic or likely pathogenic variants of BRCA1/2 were detected in 8 cases (7.8%) (6 cases of the BRCA1 mutation, 2 cases of the BRCA2 mutation, and 2 duplicate cases). Therefore, BRCA1/2 mutated (i.e., a rare fraction of) gynecologic malignancies may be good candidates for PARP inhibitors.

In preclinical studies, PARP inhibitors showed antitumor effects not only on ovarian cancers but also on uterine sarcoma cell lines with BRCA2 gene mutations (SK-UT-1 and SK-UT-1B) in a concentration-dependent manner [9]. Furthermore, in a report examining the efficacy of niraparib on cell lines of HRD positive (HRd) STS without BRCA1/2 pathogenic mutations, the concentration-dependent antitumor effect was also observed both in vitro and in vivo on fibrosarcoma cell line (HT-1080) and uLMS cell line (SK-LMS-1) [14]. The PDX model of HRd uLMS without BRCA1/2 pathogenic mutations exhibited significant suppression of tumor growth by olaparib [13]. Thus, the antitumor effect of niraparib can be expected for HRd uLMS with or without BRCA1/2 alterations. Among rare gynecologic malignancies other than uLMS, it has been suggested that HeLa cells that have acquired cisplatin (CDDP) resistance may have increased sensitivity to PARP inhibitors than CDDP-sensitive cells because they overexpressed PARP1, which is a target of PARP inhibitors [20].

A recent case report of dramatic tumor shrinkage for uLMS with alterations of BRCA2 by administration of PARP inhibitor was published [21]. She experienced disease recurrence after gemcitabine plus docetaxel therapy (GD therapy), doxorubicin (Dox) monotherapy, and temozolomide, and had deep deletions of somatic BRCA2, TP53, and PTEN. The partial response (PR) was achieved 6 weeks after olaparib administration, and the response was maintained for 8 months. Furthermore, 2 case series have reported that PARP inhibitors were clinically useful in uLMS with BRCA2 alterations [10,11]. In one case series, Seligson et al. [10] reported the experience of PARP inhibitors for a total of 4 uLMS patients with a previous history of at least 4 lines of chemotherapy. Three patients had deletion, one a truncating mutation in BRCA2, and PR was noted in 1 case, while all remaining cases maintained stable disease (SD) for a period of 12 months or longer [10]. Another group also reported the effect of PARP inhibitors in a total of 6 cases of uLMS with BRCA2 alterations (4 cases with homozygous deletion and 2 cases with truncating mutations accompanied by LOH). Complete response (CR) was noted in 1 case and PR was observed in 1 case. The treatment period of 6 cases was 6 to 28 months [11]. In addition, it was reported that the recurrent case of cervical small cell neuroendocrine carcinoma with BRCA2 mutation in tumor tissues had a long SD of 15 months upon administration of a PARP inhibitor [22].

Ewing sarcoma and osteosarcoma were highly sensitive to PARP inhibitors in vitro [23]. It may be because the fusion gene EWS–FLI1 that causes Ewing sarcoma suppressed the function of BRCA1 and might have conferred the characteristics similar to HRd tumors [24]. However, a PARP inhibitor alone did not obtain the expected efficacy in a clinical trial [25]. Unlike uLMS, BRCA1/2 pathogenic mutations themselves are rare in Ewing sarcoma and
osteosarcoma [7]. It may be necessary to consider clinical trials targeting genomic alterations of HRD, including BRCA1/2 pathogenic mutations.

Based on the aforementioned preclinical and clinical studies, JGOG is now planning to conduct a new investigator-initiated phase 2 clinical trial to evaluate the efficacy and safety of niraparib monotherapy for recurrent and persistent rare fraction of gynecologic malignancies with HRD except for ovarian cancers (i.e., uLMS with HRD and “rare fraction” of other gynecologic cancers with BRCA1/2 mutations) (JGOG2052, Japan Primary Registries Network - jRCT20312I0264).

**METHODS**

1. **Trial design**

JGOG2052 is a single-arm, open-label, multi-center, phase 2 clinical trial conducted in 14 medical centers in Japan. We prospectively evaluate each of the following 3 cohorts independently; cohort A, BRCA1/2-mutated uLMS; cohort B, HRd uLMS without BRCA1/2 mutations; cohort C, BRCA1/2-mutated, rare fraction of gynecologic malignancies other than uLMS (Fig. 1). For uLMS patients, we will perform HRD testing of the tumor tissues using myChoice® CDx PLUS (Myriad, Salt Lake City, UT, USA) after confirming eligibility and obtaining written informed consent. uLMS with BRCA1/2 mutation in myChoice® CDx PLUS register into cohort A, and HRd uLMS without BRCA1/2 mutation into cohort B. We

![Study design diagram](https://ejgo.org)

**Endpoints**

- **Primary:** Objective response rate in each cohort (evaluating independently)
- **Secondary:** (Efficacy) Progression-free survival, overall survival, etc. (Safety) Number and percentage of subjects with adverse events, etc.
- **Exploratory:** Correlation between the efficacy of niraparib and HRD score, etc.

Fig. 1. Study design. For uLMS, myChoice® CDx PLUS is performed as an HRD test, and divided into cohort A and B; uLMS with BRCA1/2 mutation and HRd uLMS without BRCA1/2 mutation, respectively. Patients with BRCA1/2 mutation in cancer genomic profiling tests can register cohort A and C. HRd, homologous recombination deficiency positive; uLMS, uterine leiomyosarcoma; HRD, homologous recombination deficiency.
defined HRd uLMS as ≥33 of Genomic Instability Score in myChoice® CDx PLUS, calculated by LOH, TAI, and LST and correlated with HRD in STS [14]. This value is the same cut-off value as the VELIA study [26]. Patients in cohort A can be enrolled before obtaining the result of the HRD test if pathogenic or likely pathogenic mutations in BRCA1/2 are identified in the tumor tissue by the cancer genomic profiling tests (CGPs), covered by health insurance in Japan (FoundationOne® CDx, Foundation Medicine, Cambridge, MA; or OncoGuide™ NCC Oncopanel System, Sysmex Corporation, Kobe, Japan). As well, BRCA1/2 mutations must be confirmed by CGPs for registration in cohort C.

A 200 mg dose of niraparib will be orally administered once a day from the 1st day with 28 days per cycle until lesion exacerbation or unacceptable adverse events (AEs) occur. If the body weight before the first administration of this drug is at least 77 kg and the platelet count is at least 150,000/μL, 300 mg of niraparib should be orally administered once a day. Efficacy will be evaluated by imaging through an additional computed tomography scan every 8 weeks. Safety will be evaluated weekly in cycle 1 and every 4 weeks after cycle 2 by tests, including blood tests, and physical examinations.

2. Eligibility criteria
Patients who must meet all of the following inclusion criteria:

(1) Participants aged 20 years or older.
(2) Voluntary written consent must be given before the performance of any study-related procedure.
(3) Participants must have formalin-fixed, paraffin-embedded tumor samples available from the primary or recurrent lesions or agree to undergo fresh biopsy before study treatment initiation.
(4) Participants with uLMS must agree to undergo tumor HRD testing, and the result must show BRCA1/2 mutation (cohort A) or HRd without BRCA1/2 mutation (cohort B).
(5) Participants (in cohort C) must have been histologically diagnosed as gynecologic malignancies (except for uLMS, and primary ovarian, tubal and peritoneal carcinomas), whose tumors must have been genetically diagnosed as BRCA1/2-mutated (pathogenic or likely pathogenic).
(6) Participants must have been previously treated with chemotherapy including adjuvant settings.
(7) Participants must have at least one measurable lesion according to RECIST (v.1.1).
(8) Participants must have completed their last chemotherapy regimen >4 weeks before protocol treatment initiation.
(9) Participants must have a performance status of ≤1 on the Eastern Cooperative Oncology Group Performance Status Scale.
(10) Participants must have adequate organ function as indicated by the following laboratory values
  - Absolute neutrophil count ≥1,500/μL,
  - Platelets ≥150,000/μL,
  - Hemoglobin ≥10 g/dL,
  - Serum creatinine ≤1.5 × upper limit of normal (ULN) or calculated creatinine clearance ≥50 mL/min using the Cockcroft-Gault equation,
  - Total bilirubin ≤1.5 × ULN or direct bilirubin ≤1 × ULN,
  - Aspartate aminotransferase and alanine aminotransferase ≤2.5 × ULN unless liver metastases are present, in which case they must be ≤5 × ULN).
(11) Participants must be able to take oral medications.
(12) Female participants of childbearing potential must be negative for a pregnancy test.
(13) Female participants of childbearing potential agree to practice an effective contraception from the time of signing the informed consent through 180 days after the last dose of study drug.

Subjects will be excluded from the trial if they meet any of the following exclusion criteria:
(1) Participants whose lesions can be completely resected.
(2) Participants who have had prior treatment with 4 and more regimens of chemotherapy.
(3) Participants in cohort C who have recurrence with a last platinum-free interval (PFI) of 6 months or more if the participants treated by platinum-based regimens.
(4) Participants who have had palliative radiotherapy encompassing >20% of the bone marrow within 1 week of the study treatment.
(5) Participants who have any known, persistent (>4 weeks), grade ≥3 hematologic toxicity from last cancer therapy.
(6) Participants who have any known, persistent (>4 weeks), grade ≥3 fatigue during the last cancer therapy.
(7) Participants who have received pelvic radiotherapy as treatment within 1 year.
(8) Participants who have symptomatic, uncontrolled brain or leptomeningeal metastases.
(9) Participants who have known hypersensitivity to the components of niraparib or other PARP inhibitors.
(10) Participants who have had treatment with any investigational products within 28 days.
(11) Participants who have had major surgery within 3 weeks.
(12) Participants who have a diagnosis, detection, or treatment of invasive second primary malignancy other than the target cancer of this trial ≤24 months before study enrollment.
(13) Participants who are considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection.
(14) Participants who have received a transfusion within 4 weeks.
(15) Participants who have received a live virus or bacterial vaccines within 4 weeks.
(16) Participants who have a history or current evidence of any condition, therapy, or lab abnormality.
(17) Participants who are regular users or have a recent history of drug or alcohol abuse.
(18) Participants who are pregnant or breast feeding or expecting to conceive within the planned duration of the study.
(19) Participants who are immunocompromised.
(20) Participants who have known human immunodeficiency virus positive.
(21) Participants who have known hepatitis B surface antigen positive, or known or suspected active hepatitis C virus (HCV) infection. Participants who are positive for hepatitis B core antibody or hepatitis B surface antibody can be enrolled but must have an undetectable hepatitis B virus viral load. Participants who have positive HCV antibody must have an undetectable HCV viral load.
(22) Participants who are judged inappropriate by the physician-in-charge to safely conduct this study.

3. Primary endpoint
The primary endpoint is the objective response rate (ORR), which will be evaluate independently in each cohort. ORR is defined as the percentage of subjects who achieved CR or PR in the evaluation of objective response according to RECIST (v1.1) evaluated by central image evaluation physicians.
4. Secondary endpoints
Secondary endpoints include efficacy outcomes and safety outcomes. For efficacy outcomes, (1) Progression-free survival (PFS) rate at 6 months, which is defined as the percentage of subjects who have not experienced exacerbation or died 6 months after the date of enrollment in this trial; (2) Disease control rate, which is defined as the percentage of subjects whose therapeutic intervention has led to a CR, PR, or SD; (3) Duration of response, as the length of time that a tumor continues to respond to treatment without the lesions growing or spreading; (4) PFS, as the period starting from the date of enrollment in this study until the date of exacerbation or the date of death for any reason; and (5) Overall survival (OS), the period from the enrollment date until the date of death due to any cause in each cohort are evaluated. For safety outcomes, (1) Number and percentage of subjects with AE that occurred after administration of the investigational drug; (2) Number and percentage of subjects with grade 3 or higher AE; (3) Number and percentage of subjects with serious AE; (4) Number and percentage of subjects who had to discontinue the investigational drug due to AE; (5) Number and percentage of subjects who were suspended from the investigational drug due to AE; and (6) Number and percentage of subjects whose dose of the investigational drug was reduced due to AE are evaluated.

5. Exploratory endpoints
We investigate the following things exploratorily: (1) Correlation between the efficacy of niraparib and HRD score; (2) Incidence of BRCA1/2 alterations in uLMS, and the type of BRCA1/2 alterations; (3) Positive rate of Genomic Instability Score in myChoice® CDx PLUS, and the correlation between these scores and BRCA1/2 alterations in uLMS; and (4) Genomic analysis related to sensitivity and resistance to niraparib.

6. Sample size
The sample size was calculated independently for each cohort by an exact binomial test. A retrospective observational study examining the actual treatment of uLMS in Japan, JGOG 2049s, revealed that 186/256 patients (71.8%) underwent complete resection as primary surgery, and 159/256 (62.1%) received adjuvant chemotherapy, of which the most frequent regimen was GD therapy [27]. Because Dox-based chemotherapy is the first-choice regimen in the recurrent setting [28], we assume that many of the participants in this trial will have a previous history of chemotherapy with adjuvant chemotherapy, including GD therapy, and Dox-based chemotherapy after their recurrence. There is no standard regimen for uLMS in this setting at present. Drugs covered by health insurance in Japan include pazopanib [29], trabectedin [30], and eribulin [31], but the therapeutic effects of these drugs in phase 3 trials for uLMS are not sufficient; the ORR is only 4% to 11%. In the post-marketing surveillance in Japan, only eribulin showed the tumor shrinkage effect on LMS patients, but both pazopanib and trabectedin did not [32-34]. Therefore, eribulin is considered the most effective drug for the study subjects. The ORR of eribulin in the phase 3 study was 4% for the entire study, but it was 5% in the subgroup analysis for LMS. At present, reports on the efficacy of PARP inhibitors for BRCA mutation-positive uLMS include a series of 4 cases in 2019 and 6 cases reported by another group in 2020, as described above. Even when considering off-label regimens in Japan, the ORR is around 25% for GD therapy [35] or gemcitabine (GEM) monotherapy [36] for patients with a history of only one regimen, and this value is deemed to be clinically effective. Therefore, the ORR is expected to improve by 20% from the threshold when the threshold ORR is set to 5% for cohort A and B. To have an 80% power to reject the null hypothesis of a threshold ORR of 5%, we needed to enroll 16 patients, assuming a one-sided alpha level of 5%.
In cohort C, based on the mutation rate of BRCA1/2, cases of endometrial and cervical cancer unresponsive to standard platinum-containing chemotherapy regimen are the main targets of this cohort. There is only limited data on the treatment results of endometrial and cervical cancer resistant or unresponsive to platinum-containing chemotherapy. In retrospective studies, the therapeutic effect of second-line platinum-based chemotherapies on the patients with a PFI <6 months was significantly worse in endometrial and cervical cancer other than ovarian cancer [37-39]. Thus, non-platinum regimens are used in this setting [28]. Recently, a randomized phase 3 trial of lenvatinib plus pembrolizumab for recurrent endometrial cancer reported that the ORR in chemotherapy arm (either Dox or paclitaxel monotherapy) was 14.7%. The phase 3 trial allowed only one prior platinum-based chemotherapy regimen after the recurrence, including endometrioid histology at 59% [40]. There was also a phase 2 trial from Japan to evaluate the efficacy of non-platinum regimen for recurrent endometrial cancer with PFI of less than 6 months, presenting that the ORR was only 7.1% [41]. The ratio of BRCA1/2 mutations is higher in serous endometrial carcinomas (more aggressive and poor-prognostic subtype), and 2 or 3 prior regimens are allowed in the eligibility criteria, including the lenvatinib plus pembrolizumab regimen after failure to platinum-based regimens. Thus, the ORR in this study setting (with heavily-treated, and more likely to be high-grade subtype) is expected to be lower than 10%. In recurrent cervical cancer, the response rate to second-line CDDP based (or CDDP analogue based) chemotherapy was reported to be 11.4% (4/35) in platinum resistant patients, including the patients with PFI <12 months [39]. Although clinical trial data are minimal, the ORR in this setting was expected to be only about 10%, including a recent phase 2 trial investigating the effects of molecular-targeted drugs, for most participants with 2 or 3 prior regimens [42,43]. In addition, it was even less effective in a rare subtype of the cervix, such as neuroendocrine carcinoma [44]. In this study, all the patients in cohort C will be recruited after a CGP under health insurance coverage, which is applicable only for patients after the standardized treatment (i.e., heavily treated). Taken together, we assume that the ORR in cohort C (mainly composed of endometrial and cervical cancers) is 10%. The test results for recurrent ovarian cancer unresponsive to platinum drugs can also be a reference. In the QUADRA trial [6], which is a phase 2 study that verified the efficacy and safety of niraparib for recurrent ovarian cancer, the ORR was 27% in platinum-resistant ovarian cancer with BRCA1/2 mutation. When the expected ORR is set to 25%, the required sample size was 27 patients for rejecting the null hypothesis of a threshold ORR of 10% with a 70% power, assuming a one-sided alpha-level of 10%. Assuming that 4 patients would drop out, the target total number of patients was set at 31.

7. Participating institutions
This trial will be conducted at the following 14 medical institutions: Hokkaido University Hospital, Tohoku University Hospital, Niigata University Medical & Dental Hospital, The University of Tokyo Hospital, Keio University Hospital, The Jikei University Hospital, Cancer Institute Hospital of JFCR, Shizuoka Cancer Center, Nagoya University Hospital, Osaka University Hospital, Kindai University Hospital, Hyogo Cancer Center, Shikoku Cancer Center, Kurume University Hospital.

8. Randomization and blinding
Not applicable.

9. Statistical methods
The Full Analysis Set is the main target of efficacy analysis. In addition, the Per Protocol Set conforming to the trial protocol will undergo secondary analysis to examine the robustness
of the conclusions. Safety analysis set is defined as the set of subjects enrolled in the trial excluding those who fall under any of the following: (1) Subjects who have never been treated with the investigational drug; and (2) Serious GCP violations (e.g., consent or serious trial violations). AE is graded according to common terminology criteria for adverse events version 5.0.

DISCUSSION

In JGOG2052, participants are selected by BRCA1/2 mutations or HRD, which are high-evidence biomarkers for PARP inhibitors, to examine the safety and efficacy of niraparib. This trial focuses on recurrent and intractable uLMS with a previous history of chemotherapy, and other rare gynecologic malignancies without platinum-drug sensitivity, who have a poor prognosis and limited effects of existing chemotherapy regimens. Considering that there is no standard chemotherapy regimen for these targets, precision medicine for targeting rare gynecologic malignancies with these genomic alterations is emerging as important therapeutic targets. Based on the preclinical and clinical studies of PARP inhibitors for those patients, prolongation of OS can be largely expected. Although randomized control trials for these targets are difficult to perform due to their rarity, it is expected that the effect of niraparib on rare fraction of gynecologic malignancies with a common genomic background can be clarified in this trial. Therefore, it is significant to verify the efficacy of PARP inhibitors for BRCA1/2 mutation-positive cases or BRCA1/2 mutation-negative and HRd cases among chemotherapy-resistant, unresectable advanced or persistent rare fraction of gynecologic malignancies.

ACKNOWLEDGEMENTS

We thank the staff of Clinical Research and Medical Innovation Center, Promotion Unit, Institute of Health Science Innovation for Medical Care, Hokkaido University Hospital for assisting the study design, and at Medical Research Support Limited for data management.

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