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A Retrospective Analysis of Clinical Biomarkers for Olaparib Maintenance Therapy in Patients with Recurrent Ovarian Cancer

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Poly(ADP-ribose) polymerase (PARP) inhibitors theoretically promote synthetic lethality in cancer cells with homologous recombination deficiency (HRD). However, clinical evidence indicates that PARP inhibitors are also effective for treating HRD-negative ovarian cancer. The PARP inhibitor olaparib became available in Japan as a maintenance therapy for platinum-sensitive recurrent ovarian cancer regardless of homologous recombination status in April 2018. The purpose of this study was to identify potential clinical biomarkers for olaparib sensitivity in patients with recurrent ovarian cancer. Clinical information about the patients with recurrent ovarian cancer treated with olaparib maintenance therapy (OMT) was retrospectively collected. OMT duration was used as an indicator for olaparib sensitivity. The relationship between OMT duration and clinical parameters was statistically analyzed. We found a positive correlation between OMT duration and progression-free survival (PFS) or treatment free interval (TFI). In some cases, OMT duration exceeded PFS before olaparib introduction. We also found that more than half of the patients with measurable target lesions at the time of OMT introduction showed partial or complete response to OMT. These results validated the effectiveness of OMT and identified PFS and TFI as potential clinical markers for olaparib sensitivity in the patients with recurrent ovarian cancer.

Keywords: homologous recombination deficiency; olaparib; PARP inhibitor; progression free survival; recurrent ovarian cancer

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Introduction

Ovarian cancer is the 18th most common cancer worldwide, but the eighth leading cause of cancer death in women (World Cancer Research Fund International 2020), with high-grade serous carcinoma (HGSC) being the most frequently observed histologic subtype of ovarian cancer (Matz et al. 2017). Because patients with HGSC do not present any symptoms until their disease is advanced (Goff et al. 2004), many cases are detected at advanced stages (Audibert et al. 2017). Thus, the mortality rate of ovarian cancer is the highest among major gynecological cancers (Labidi-Galy et al. 2017).

Hereditary Breast and Ovarian Cancer syndrome (HBOC) is an inherited autosomal disorder caused by a pathogenic variants of germline *BRCA1* or *BRCA2* genes. Approximately 1 in 400-500 Japanese individuals carry a pathogenic variant of the *BRCA1/2* genes (Momozawa et al. 2018; Tokunaga et al. 2021a). Approximately 10-15% of ovarian, fallopian tube, and peritoneal cancers are reported to be associated with HBOC in Japan and the USA (Norquist et al. 2016; Hirasawa et al. 2017; Enomoto et al. 2019). Deleterious *BRCA* mutations disrupt homologous recombination, a key mechanism of DNA double-strand repair, resulting in homologous recombination deficiency (HRD). HRD is caused by other genomic or epigenomic alterations as well as deleterious *BRCA* mutations. Approximately 50% of HGSC exhibit HRD (Cancer Genome Atlas Research Network 2011; Ray-Coquard et al. 2019) and importantly, poly(ADP-ribose) polymerase (PARP) inhibition can facilitate synthetic lethality in cancer cells presenting HRD. Consistent with these previous

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reports, the international phase III clinical trial (SOLO-2) demonstrated that PARP inhibitor olaparib maintenance therapy (OMT) significantly improved progression-free survival (PFS) when compared with placebo (Ledermann et al. 2012) in patients with platinum-sensitive recurrent ovarian cancer harboring deleterious *BRCA* mutations. However, another clinical trial reported that OMT was effective in recurrent ovarian cancer regardless of *BRCA* mutation or HRD (Ledermann et al. 2014). Based on these backgrounds, the latest guideline for the treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer published by the Japan Society of Gynecologic Oncology proposes OMT for platinum-sensitive recurrent ovarian cancer (Tokunaga et al. 2021b). Additionally, clinicians frequently experience a heterogeneous response to PARP inhibitor maintenance therapy among patients with recurrent ovarian cancer presenting HRD (Heo and Dhillon 2018; Coleman et al. 2019; Ray-Coquard et al. 2019; González-Martín et al. 2019).

We hypothesized that *BRCA* mutation or HRD is not an absolute marker for PARP inhibitor sensitivity in clinical settings. Therefore, we conducted a single-center retrospective study to investigate potential clinical markers that can predict OMT sensitivity in patients with recurrent ovarian cancer.

Materials and Methods

Patient selection and data collection

Patients with recurrent ovarian cancer administered OMT at Tohoku University Hospital before the end of December 2020 were enrolled in this study. Patients with fallopian tube or primary peritoneal carcinoma were also included because these cancers are clinically considered to be the same disease category as ovarian cancer (Jordan et al. 2008; NCCN, National Comprehensive Cancer Network 2022). Clinical information was retrospectively collected in January 2022 and analyzed with approval from the Independent Review Committee of Tohoku University School of Medicine (Approval number 2021-1-854).

Data handling and analysis

Survey items included patient age at the time of OMT introduction, diagnosis, International Federation of Gynecology and Obstetrics (FIGO) cancer stage, histology, germline or somatic *BRCA* mutation status if inspected, platinum sensitivity, history of bevacizumab or PARP inhibitors treatment, successful maintenance period with olaparib (hereafter called "OMT duration"), progression-free survival (PFS) and treatment-free interval (TFI) after the primary treatment, the latest PFS and TFI before OMT introduction, number of chemotherapy cycles before OMT introduction, and number of recurrences. In the current study, both PFS and TFI were defined as the day from the end of the prior treatment to the day of recurrence diagnosis. While the period of maintenance therapy was excluded in TFI, it was included in PFS. Fig. 1 summarizes the relationship between PFI after the primary treatment and the latest PFS. For patients who were treated with olaparib after the first recurrence, PFS and TFI after the primary treatment was the same as the latest PFS and TFI before OMT introduction. OMT duration was used as a quantitative indicator for olaparib sensitivity in this study. In patients with measurable tumor on clinical imaging at the time of OMT introduction, best tumor response was also evaluated based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; Eisenhauer et al. 2009).

Statistical analysis

All statistical analyses were performed with the JMP 5.0 software (SAS, Cary, NC, USA). We used the Shapiro-Wilk's test to investigate if a continuous variable was normally distributed. Spearman's trend test was used to test for bivariate correlations. A Wilcoxon test was performed

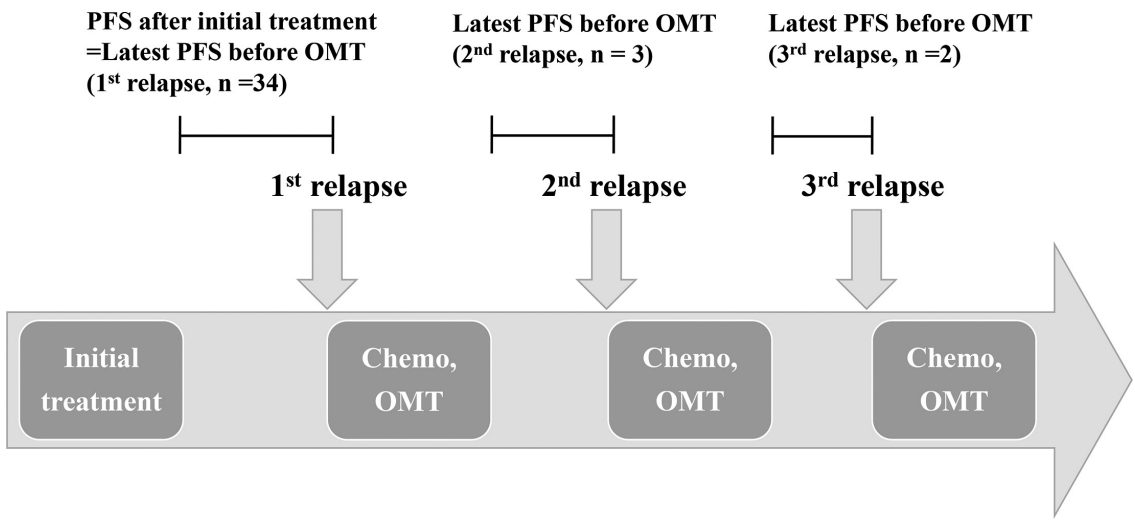

Fig. 1. A summary of the latest progression-free survival (PFS) after initial treatment. Chemo, chemotherapy; OMT, olaparib maintenance therapy.

to compare OMT duration within each nominal parameter. A P-value < 0.05 was considered to be statistically significant in this study.

Results

Patient characteristics

A total of 39 patients were eligible for this retrospective analysis. The baseline clinical characteristics of these patients are shown in Table 1. The median age of this group was 61 years. Thirty-four patients were diagnosed with primary ovarian cancer, three with fallopian tube cancer, and two with peritoneal cancer, while 37 out of 39 patients (95%) presented high-grade serous histology. Most of the patients were diagnosed as FIGO stage III or IV. Among the nine patients who received genetic *BRCA* mutation analysis, deleterious *BRCA1* mutations were detected in five patients. No deleterious *BRCA* mutation was found in the other four patients and *BRCA* mutation was not examined in the other 30 patients. Platinum sensitivity could not be assessed in five patients, mostly due to a carboplatin allergy. A total of 15 patients received prior maintenance therapy with bevacizumab and three patients received maintenance therapy with PARP inhibitors. Of the 39 patients, 20 and 15 patients showed a complete response (CR) or partial response (PR) to chemotherapy just before OMT introduction, respectively.

Analysis of OMT duration, the latest PFS and TFI, and those after the primary treatment, as well as the number of chemotherapy courses and recurrences before introduction of OMT are also summarized in Table 1 and are shown as a median with range. All of these parameters had a non-normal distribution.

Correlation between OMT duration and clinical parameters

In order to explore the clinical factors associated with OMT duration, we statistically investigated the relationship between various clinical parameters and OMT duration. We found that the distribution of OMT duration indicated that the sensitivity to OMT was heterogenous among the study population (Fig. 2). While 14 (35.9%) patients experienced relapse within six months after OMT introduction, OMT duration of 12 months or more was observed in 17 (43.6%) patients. Bivariate correlation analyses were performed to assess the relationship between OMT duration and PFS or TFI. Both the latest PFS and TFI as well as those after primary treatment showed a positive correlation with OMT duration (Fig. 3). There was not statistically significant association between OMT duration and *BRCA* mutation status, platinum sensitivity, chemotherapy response before OMT introduction, or the history of prior bevacizumab treatment (Fig. 4). It should be noted that *BRCA* mutation status was not examined in more than three-quarters of the patients in this study. Taken together, these results indicated that PFS and TFI can be sensitivity markers for OMT.

Comparison of OMT duration and the latest PFS in each patient

Before maintenance therapy became widely available, PFS in patients with recurrent ovarian cancer rarely exceeded the latest PFS (Blackledge et al. 1989; Markman et al. 1991). Thus, we compared the OMT duration and the latest PFS to evaluate the impact of OMT on the prognosis of patients with recurrent ovarian cancer. We found that the OMT duration exceeded the latest PFS in about 30% of the cases; however, six patients whose OMT duration did not exceed the latest PFS at the time of analysis were under OMT without relapse, suggesting that OMT may have exceeded the latest PFS in some of the additional patients (Fig. 5).

Optimal tumor response after olaparib introduction

Another PARP inhibitor, niraparib, is effective as maintenance therapy as well as a single anti-tumor agent as a late-line chemotherapeutic (Moore et al. 2019). Thus, we asked if olaparib had a tumor-shrinkage effect by assessing the tumor responses among the patients harboring target lesions defined by RECIST analysis. Of the 39 patients included in this study, 17 had target lesions at the time of OMT introduction. We found that 11 patients (64.7%) had partial or complete response toward olaparib. Notably, six patients (35.3%) experienced complete response with olaparib monotherapy (Fig. 6).

Discussion

In this study, we confirmed that the OMT duration was positively correlated with PFS and TFI in patients with recurrent ovarian cancer. The results suggest that PFS and TFI can be used as new predictors of responses to OMT in recurrent ovarian cancer. In addition, we also demonstrated that OMT suppressed tumor progression for a longer period than the latest PFS in a large number of patients with recurrent ovarian cancer. Furthermore, the best response rate with OMT indicated that olaparib treatment functioned not only as a maintenance therapy but also as an anti-tumor chemotherapy.

Although it was not able to assess the influence of *BRCA* mutation on olaparib sensitivity in this study because the majority of the patients did not receive genomic analysis, deleterious *BRCA* mutations or HRD is not consistent biomarkers for predicting PARP inhibitor sensitivity in patients with platinum sensitive recurrent ovarian cancer as mentioned in the Introduction. One possible reason for this may be fluctuation in the homologous recombination status observed in cancer. One of the major mechanisms of action for the development of PARP inhibitor resistance is the restoration of homologous recombination due to a reversion mutation or epigenetic alterations in the *BRCA* genes (Sakai et al. 2008; Swisher et al. 2008; Ashworth 2008; Wang and Figg 2008) or loss of *53BP1* (Bouwman et al. 2010; Jaspers et al. 2013), which lead to acquired homologous recombination proficiency. More generally, clonal evolution in can-

Table 1. Patient characteristics.

Parameters		Median	Range
Age		61	42-74
		No. of patients	%
Diagnosis			
	Ovarian cancer	34	87.2
	Fallopian tube cancer	3	7.7
	Primary peritoneal cancer	2	5.1
Histology			
	Serous	37	94.9
	Endometrioid	1	2.6
	Clear cell	1	2.6
Stage (FIGO) at diagnosis			
	II	2	5.1
	III	29	74.4
	IV	8	20.5
BRCA status			
	Deleterious *BRCA1* mutation detected	5	12.8
	No mutation detected	4	10.3
	Not examined	30	76.9
Platinum sensitivity			
	Sensitive	34	87.2
	Unknown	5	12.8
History of bevacizumab treatment			
	Yes	15	38.5
	No	24	61.5
History of PARP inhibitor treatment			
	Olaparib	2	5.1
	Veliparib	1	2.6
	No	36	92.3
Response to chemotherapy before OMT introduction			
	Complete response	20	51.3
	Partial response	15	38.5
	Stable disease	2	5.1
	Progressive disease	2	5.1
		Median	Range
No. of chemotheraapy cycle before OMT		3	2-10
No. of recurrence before OMT		1	1-3
		Median (months)	Range
OMT duration		8	1-36
PFS after initial treatment		13	3-120
TFI after initial treatment		12	0-120
PFS before OMT introduction		13	0-92
TFI before OMT introduction		11	0-92

OMT, olaparib maintenance therapy; PFS, progression-free survival; TFI, treatment-free interval.

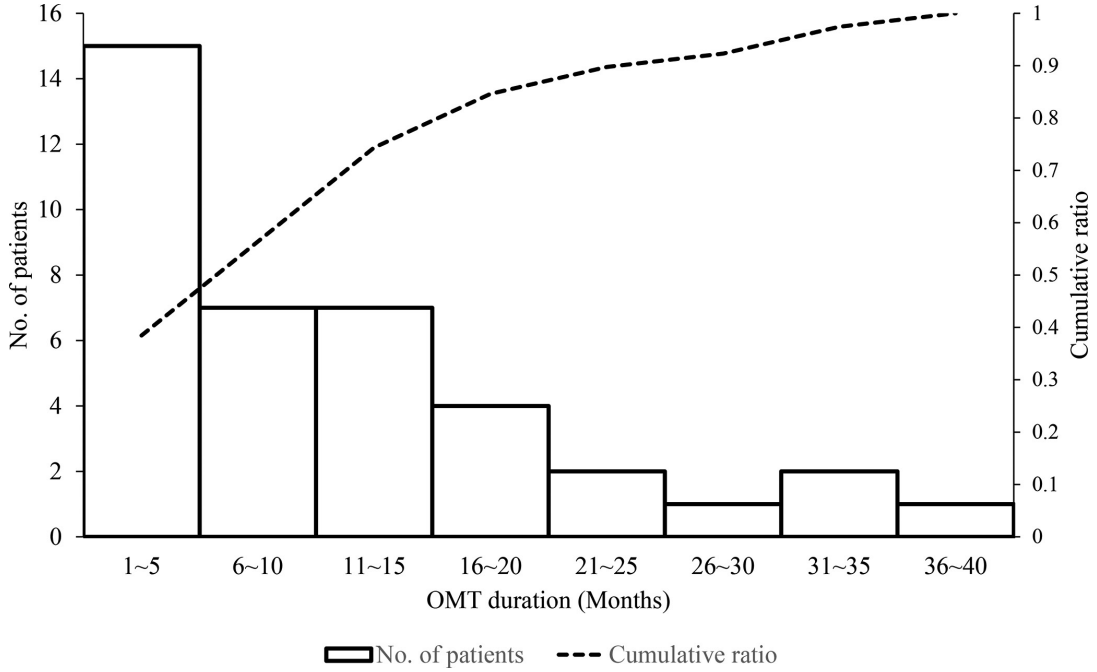

Fig. 2. Distribution of olaparib maintenance therapy (OMT) duration.
OMT duration shows a non-normal distribution using the Shapiro-Wilk's test.

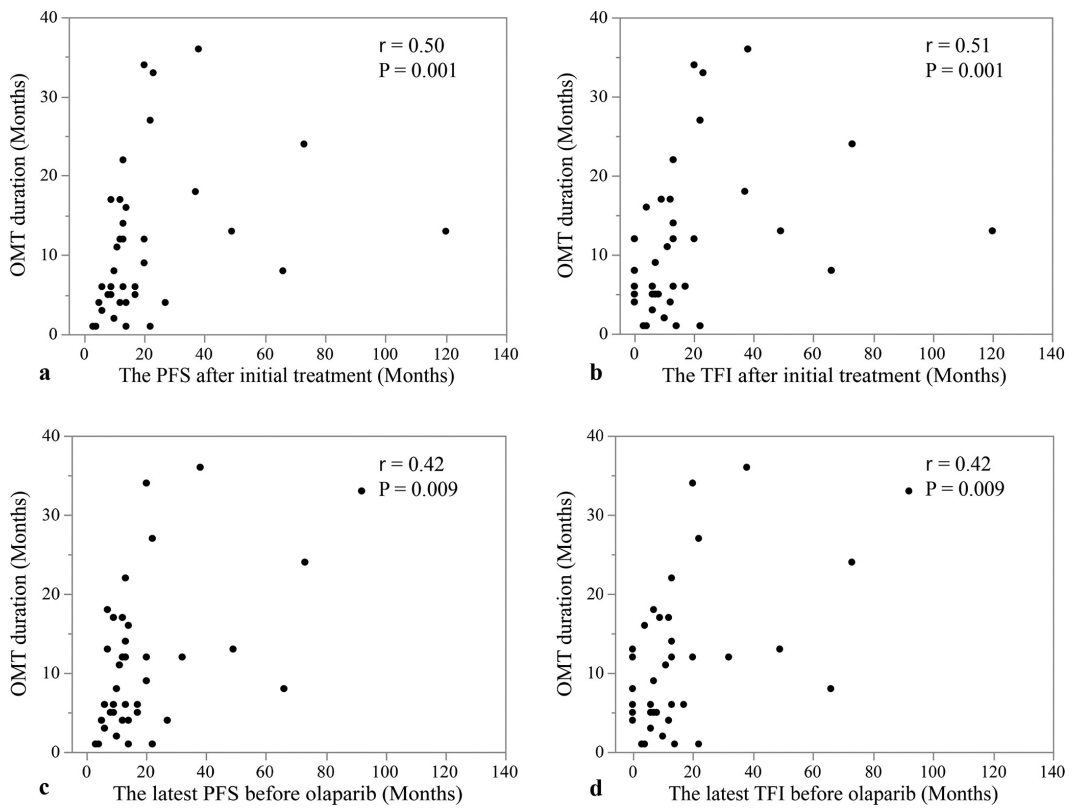

Fig. 3. Scattergrams illustrating the relationship between OMT duration and progression free survival (PFS) or treatment free interval (TFI).
a) OMT duration and PFS after initial treatment. b) OMT duration and TFI after initial treatment. c) OMT duration and the latest PFS. d) OMT duration and the latest TFI. All of the parameters show a non-normal distribution using the Shapiro-Wilk's test. A Spearman's trend test was used to examine bivariate correlations.
r, Spearman's rank correlation coefficient; PFS, progression free survival; TFI, treatment free interval; OMT, olaparib maintenance therapy.

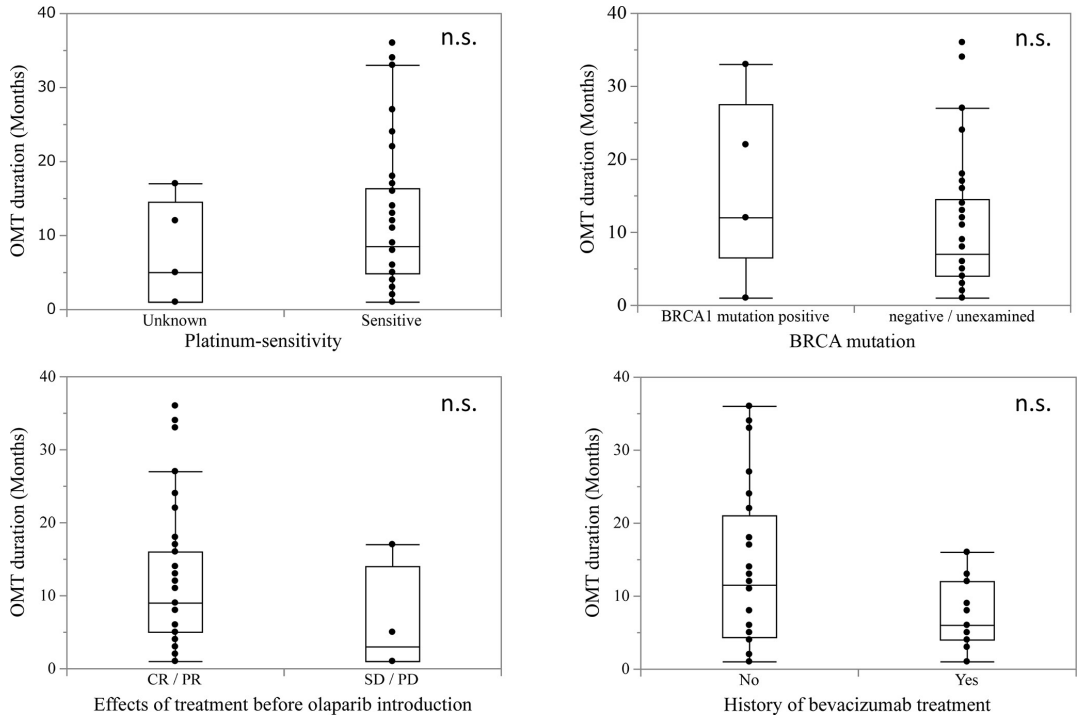

Fig. 4. The association of olaparib maintenance therapy (OMT) duration and each clinical parameter tested.
The association of OMT duration and platinum sensitivity, *BRCA* mutation status, response to the chemotherapy just before OMT introduction, and the history of bevacizumab treatment was examined using a Wilcoxon test.
n.s., not significant.

cer in relation to intratumor heterogeneity may result in the sequential change in homologous recombination status (Marusyk and Polyak 2010). Thus, it is possible that homologous recombination status at a previous time point does not appropriately reflect that of the current time point observation.

It is widely recognized that patients presenting longer PFS are more likely to respond to platinum-based chemotherapy (Markman et al. 1991). Recurrence with a latest PFS longer than six months is defined as platinum-sensitive recurrence (Mateo et al. 2015; Golan et al. 2019). Importantly, homologous recombination status is tightly associated with platinum sensitivity (Tan et al. 2008; Bowtell 2010; Patch et al. 2015). In fact, a variety of malignant tumors including ovarian cancer harboring HRD is clinically sensitive to platinum agents (Telli et al. 2016). Taken together, we hypothesized that the latest PFS or TFI, which predicted platinum sensitivity, were significantly associated with olaparib sensitivity because these factors reflect the real-time homologous recombination status of cancer. Therefore, the latest PFS or TFI may be a more important clinical marker to predict OMT sensitivity than that after primary treatment, even though both are statistically positively associated with OMT duration.

One of the problems with carboplatin, which is the most widely used platinum agent for ovarian cancer treatment, is the high prevalence of anaphylactic reactions that lead to the discontinuation of platinum-based chemotherapy (Makrilia et al. 2010). Because the allergy risk of carboplatin is dependent on the number of exposures, patients receiving treatment for recurrent ovarian cancer is more likely to experience or to have already experienced an anaphylactic event. As platinum sensitivity was undecidable in these patients, we believe the latest PFS or TFI might be a feasible surrogate marker for OMT introduction.

We identified some super-responders to OMT in our analysis of patients with recurrent ovarian cancer that were consistent with previous clinical trials and thus, successfully validated the benefit of OMT among this Japanese population. Interestingly, about one third of patients with target lesions at the start of OMT changed to CR after OMT. In the SOLO2 trial, 9.3% of patients with target lesions transitioned from PR to CR after OMT introduction (Ledermann et al. 2012). Although further investigation is required, our report indicates that OMT may be introduced to the patients who have measurable platinum sensitive lesions in certain situations.

The major limitations of this study were the inevitable biases of a retrospective study design and small sample size. Unknown HRD or *BRCA* status in the majority of the patients was another limitation to the analysis of PARP sensitivity. In addition, unlike the patients enrolled in this study, the majority of patients with ovarian cancer will be treated to PARP inhibitors prior to their first recurrence, as olaparib and other PARP inhibitors are now being introduced as a maintenance therapy after primary treatment. Evaluating whether PFS or TFI is an appropriate sensitivity marker for olaparib among the patients who have already

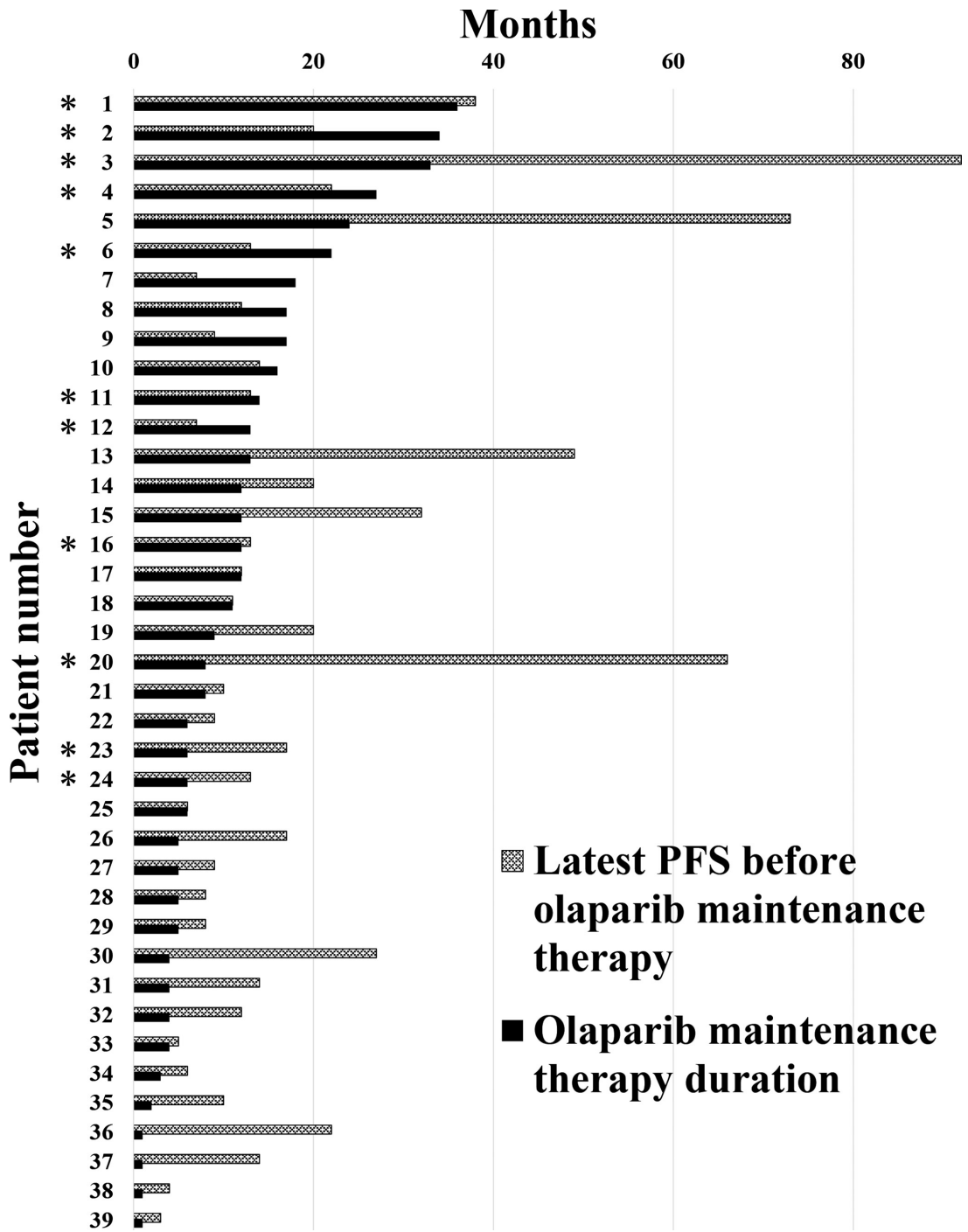

Fig. 5. Relationship between latest progression-free survival (PFS) before and after olaparib maintenance therapy (OMT) duration in individual patients.
Eleven patients were treated with olaparib without disease progression at the time of data collection. These patients are highlighted with*. Patients 3, 6, 14, and 38 harbor deleterious *BRCA1* mutations.

been prescribed PARP inhibitors should be part of future clinical trials and research.

In conclusion, the current study suggests that PFS and TFI before OMT introduction are potential clinical biomarkers for OMT sensitivity in patients with recurrent ovarian cancer.

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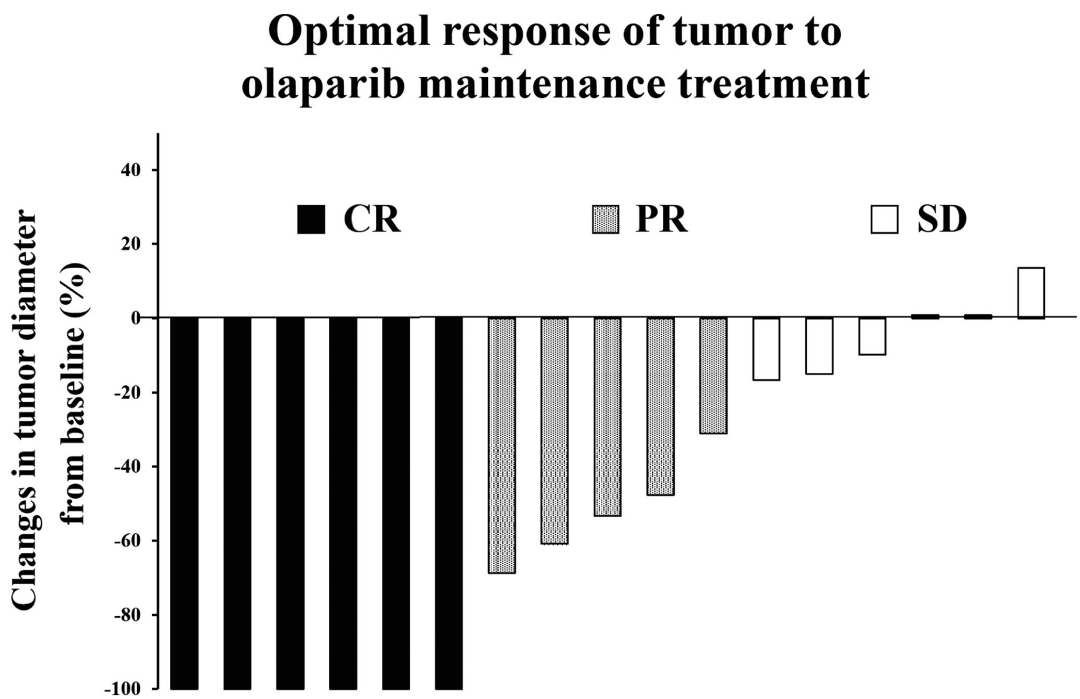

Fig. 6. Optimal tumor response to olaparib observed in patients with measurable tumors.
Optimal tumor response in 17 patients who had measurable residual tumors at the time of olaparib introduction. Patients 4, 6, 10, 14, 18, and 20 from Fig. 5 correspond to the patients who experienced complete response (CR). Similarly, patients 8, 15, 24, 30, and 34; and patients 11, 19, 31, 32, and 35 from Fig. 5 correspond to those who show partial response (PR) and stable disease (SD) in this figure, respectively.

Conflict of Interest

M.S. received honoraria from AztraZeneca, Takeda Pharmaceutical, and Chugai Pharmaceutical. The other authors declare no conflict of interest.

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