

Rechallenge with Anti-PD-1 Inhibitors in Patients with Recurrent Gynecologic Malignancies

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Purpose: We investigated the treatment outcomes of immune checkpoint inhibitor (ICI) rechallenge in patients with recurrent gynecologic cancers.

Materials and Methods: We retrospectively reviewed the medical records of 20 patients who underwent rechallenge with PD-1 inhibitors for recurrent gynecologic cancers at two tertiary centers between January 2018 and September 2022.

Results: The median age of the patients was 56 years (range, 35–79). Seven (35%), 1 (5%), 11 (55%), and 1 (5%) patients presented with cervical, vulvar, ovarian, and endometrial cancers, respectively. Sixteen (80%) patients received pembrolizumab and 4 (20%) received nivolumab at first treatment. Eight (40%) and 12 (60%) patients received pembrolizumab and nivolumab, respectively, at second treatment. At initial ICI treatment, 1 (5%) and 4 (20%) cases of a complete response (CR) and a partial response (PR) were observed, respectively, with a median progression-free survival (PFS) of 2.8 months (range, 1.4–49.6). Reasons for first ICI discontinuation were disease progression (n=16), severe adverse events (AEs) (n=2), and treatment withdrawal (n=2). During second ICI treatment, 1 (5%) patient achieved CR, 2 (10%) showed PR, and 5 (25%) experienced stable disease. The median PFS to second ICI was 1.8 months (range, 0.4–10.4). The median overall survival was 21.3 months (range, 10.1–52.7). Neither patient who discontinued ICI treatment due to AEs experienced AE relapse during second ICI treatment.

Conclusion: These results suggest that responses to ICI rechallenge are not as intolerable as responses to previous ICI. Clinicians should carefully consider rechallenge with PD-1 inhibitors outside of clinical trials until there are sufficient data to routinely support this practice.

Key Words: Gynecologic malignancy, immune checkpoint inhibitor, recurrence, rechallenge

INTRODUCTION

The introduction of immune checkpoint inhibitors (ICIs) over

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the last decade represents a major advancement in the treatment of many types of solid tumors and has enabled sustained recovery and possible tumor remission in limited numbers of patients.¹ Patients exposed to ICIs have increased in number in recent years and will continue to increase as indications for this therapy are extended.²⁻⁴ When chemo-resistance or serious adverse events (AEs) occur during chemotherapy, subsequent chemotherapy usually proceeds with a change in chemotherapeutic agents. ICIs are administered until there is evidence of tumor progression, unacceptable toxicity, or treatment completion.⁵ Upon ICI discontinuation for any reason, the possibility of retreatment with ICIs is debated because the balance between the efficacy and safety of rechallenge with ICIs has not yet been clarified.

No strategies have been established to overcome acquired resistance when ICIs are discontinued due to tumor progression.⁶ Re-try from one type of ICI to another may be an empir-

ical attempt to restore a tumor response to immunotherapy. When an ICI is discontinued due to immune-related AEs, restarting it once these AEs have fully resolved or a significant improvement has been achieved could potentially improve tumor control; however, this could increase the risk of reappearance of the same AE.^{7,8} The results of clinical trials indicate that it is possible to administer another course of ICI following treatment completion; however, the evidence with which to draw definitive conclusions is still limited.⁹

Even under these circumstances, a recent meta-analysis suggested that rechallenge with ICIs may represent a feasible and effective strategy for select patients with solid tumors [mainly non-small cell lung cancer (NSCLC) and melanoma] who have previously discontinued ICIs due to disease progression or AEs.¹⁰ To date, however, there have been no reports of ICI rechallenge as a treatment option in the field of gynecologic cancer. Thus, in the present study, we aimed to assess the efficacy and safety of rechallenge with ICIs among patients with recurrent gynecologic malignancies.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients with recurrent gynecologic cancers who underwent ICI rechallenge during their clinical course between January 2018 and September 2022 at two tertiary centers. The study protocol was approved by our Institutional Review Board (no. CHA IRB 2021-12-035). The inclusion criteria were histologically confirmed recurrent gynecologic malignancies, including those of the cervix, vulva, vagina, ovaries, fallopian tubes, peritoneum, or uterus, and the receipt of at least two lines of ICI during the clinical course (regardless of the number of lines or sequence of treatment). We investigated baseline patient characteristics, such as age, origin of cancer, histologic subtype, stage, mismatch repair (MMR) status, programmed death-ligand 1 (PD-L1) expression, Eastern Cooperative Oncology Group (ECOG) performance status, and history of prior chemotherapy, surgery, or radiation therapy. Patients with cervical or uterine cancer received 200 mg of pembrolizumab every 3 weeks or 240 mg of nivolumab every 2 weeks, while those with cancers of the ovary, fallopian tube, or peritoneum received 3 mg/kg of nivolumab every 2 weeks until the occurrence of disease progression, unacceptable toxicity, or patient withdrawal.

Tumor MMR status was determined by assessing the loss of protein expression via immunohistochemistry (IHC) staining of four MMR enzymes. MMR deficiency was defined as the loss of MMR expression in at least one marker in a tumor. Tumor PD-L1 expression was analyzed using PD-L1 IHC 22C3 antibody (Dako, Santa Clara, CA, USA) to determine the tumor proportion score (TPS), defined as the percentage of viable tumor cells, or using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies, Carpinteria, CA, USA) to determine the com-

bined positive score (CPS), defined as the ratio of PD-L1 positive cells (tumor cells, lymphocytes, and macrophages) to the total number of viable tumor cells multiplied by 100. PD-L1 positivity was defined as a TPS $\geq 1\%$ or a CPS ≥ 1 .

Responses to each ICI treatment were evaluated using the Response Evaluation Criteria in Solid Tumors version 1.1. Progression-free survival (PFS) was defined as the time from initiation of each ICI treatment to the first instance of documented disease progression or the date of death. Overall survival (OS) was defined as the duration between the date of initiation of the first ICI therapy to the date of death, irrespective of the cause of death. Patients who did not present with disease progression or had not died at the time of the analysis were censored at the date of last follow up. PFS and OS were estimated using the Kaplan-Meier method. Safety was assessed via a retrospective chart review of laboratory test results and physical examinations performed before each treatment cycle to detect any possible AEs characterized according to the Common Terminology Criteria for Adverse Events version 5.0.

RESULTS

Patient characteristics

Twenty patients received anti-PD-1 inhibitors in ICI rechallenge during their clinical courses. Table 1 lists the characteristics of these patients. The median age at first ICI treatment was 56 years (range, 35–79). Regarding origin, 7 (35%), 1 (5%), 11 (55%), and 1 (5%) patients presented with cancers of the cervix, vulva, ovary/fallopian tube/peritoneum, and endometrium, respectively. Three (15%) patients had MMR-deficient tumors, and PD-L1 positivity was confirmed in 16 (80%) patients. Seventeen (85%) patients had an ECOG performance status of ≤ 1 at first ICI treatment, and 8 (40%) patients had an ECOG performance status of ≤ 1 at second ICI treatment. Fourteen (70%) patients had received fewer than two prior lines of treatment at first ICI administration, while 2 (10%) patients had received fewer than two previous treatment lines at second ICI administration. The median sum of target lesion diameters was 45 mm (range, 5–340) at first ICI treatment and 122 mm (range, 40–292) at second ICI treatment. These indicated that patients were treated in more advanced and poor general conditions at the time of second ICI treatment. Pembrolizumab was administered in 16 (80%) patients at first treatment and in 8 (40%) patients at second treatment. Nivolumab was administered in 4 (20%) and 12 (60%) patients at first and second ICI treatments, respectively.

Efficacy

Upon the initial ICI treatment, 1 (5%) patient achieved a complete response (CR), 4 (20%) showed a partial response (PR), and 4 (20%) showed stable disease (SD) (Table 2). The median PFS was 2.8 months (range, 1.4–49.6). The reasons for treatment discontinuation were disease progression in 16 (80%),

Table 1. Clinical Characteristics of the Patients (n=20)

	First treatment	Second treatment
Age (yr)	56 (35–79)	57 (36–80)
Origin and histologic type		
Cervix		
Squamous cell carcinoma	7 (35)	
Vulvar		
Squamous cell carcinoma	1 (5)	
Ovary/tube/peritoneum		
High grade serous carcinoma	8 (40)	
Clear cell carcinoma	3 (15)	
Endometrium		
Mesonephric adenocarcinoma	1 (5)	
MMR status		
Deficiency	3 (15)	
Proficiency	13 (65)	
Not tested	4 (20)	
PD-L1 expression*		
≥1	16 (80)	
<1	2 (10)	
Not tested	2 (10)	
ECOG performance status		
0–1	17 (85)	8 (40)
2	2 (10)	8 (40)
3–4	1 (5)	4 (20)
Number of previous treatment		
1–2	14 (70)	2 (10)
3	3 (15)	5 (25)
4	1 (5)	4 (20)
5	1 (5)	4 (20)
>6	1 (5)	5 (25)
Sum of target lesion size, mm	45 (5–340)	122 (40–292)
Used ICI		
Pembrolizumab	16 (80)	8 (40)
Nivolumab	4 (20)	12 (60)

MMR, mismatch repair; PD-L1, programmed death-ligand 1; ECOG, Eastern Cooperative Oncology Group.

Data are presented as median (range) or n (%).

*Determined using either the tumor proportion score or the combined positive score.

immune-related AEs in 2 (10%), and withdrawal from treatment in 2 (10%) patients. During the second ICI treatment, 1 (5%) patient achieved CR, 2 (10%) showed PR, and 5 (25%) showed SD. The median PFS was 1.8 months (range, 0.4–10.4). Eleven (55%) patients died and 4 (20%) were lost to follow up. Three (15%) patients were undergoing second ICI treatment during the observation period, and 2 (10%) patients had received other treatments after experiencing disease progression following second ICI treatment. The median OS of the 20 patients was 21.3 months (range, 10.1–52.7). An overview of treatment progression is shown in Fig. 1.

Safety

During the first ICI treatment, AEs of grade 3 or higher included hypothyroidism, anemia, elevated liver enzyme levels, and abdominal pain (Table 3). The last two AEs led to ICI treatment discontinuation. During the second ICI treatment, AEs of grade 3 or higher included hypothyroidism, elevated liver enzyme levels, and pancytopenia. None of the two patients who discontinued first ICI treatment due to AEs experienced AE relapse during second ICI treatment. One patient (ID: BCHA08) experienced pancytopenia during second ICI treatment and was diagnosed with acute myeloid leukemia (AML) after a single cycle of nivolumab during second ICI. The AML was considered to have been caused by the accumulative effects of previous chemotherapy rather than ICI, and the patient died 3 months after diagnosis due to septic shock secondary to pneumonia, which was induced by pancytopenia.

DISCUSSION

ICI rechallenge refers to retreatment aimed at blocking the anti-programmed cell death protein (PD)-1 axis after a break period. Patients who undergo rechallenge may constitute a heterogeneous group, particularly in terms of the causes of previous ICI discontinuation. The three main causes of prior ICI discontinuation are toxicity, tumor progression, and treatment completion in the absence of progression.

In one meta-analysis of 49 studies (with 13027 patients) pertaining to ICI rechallenge strategies for the management of solid tumors (mainly NSCLC and melanoma), the overall response rate was 21.8% (range 0%–70%). In a subgroup of patients who had previously discontinued ICI treatment due to toxicity, the response rate was 44%, and patients who had previously discontinued ICI treatment due to disease progression achieved a 15.2% response rate.¹⁰ In the present study, the response rate of patients who had previously discontinued ICIs due to toxicity was 50% (1/2), and that of patients who had previously discontinued ICIs due to disease progression was 12.5% (2/16), resulting in a 15% overall response rate. These results are comparable to those observed in the aforementioned meta-analysis.

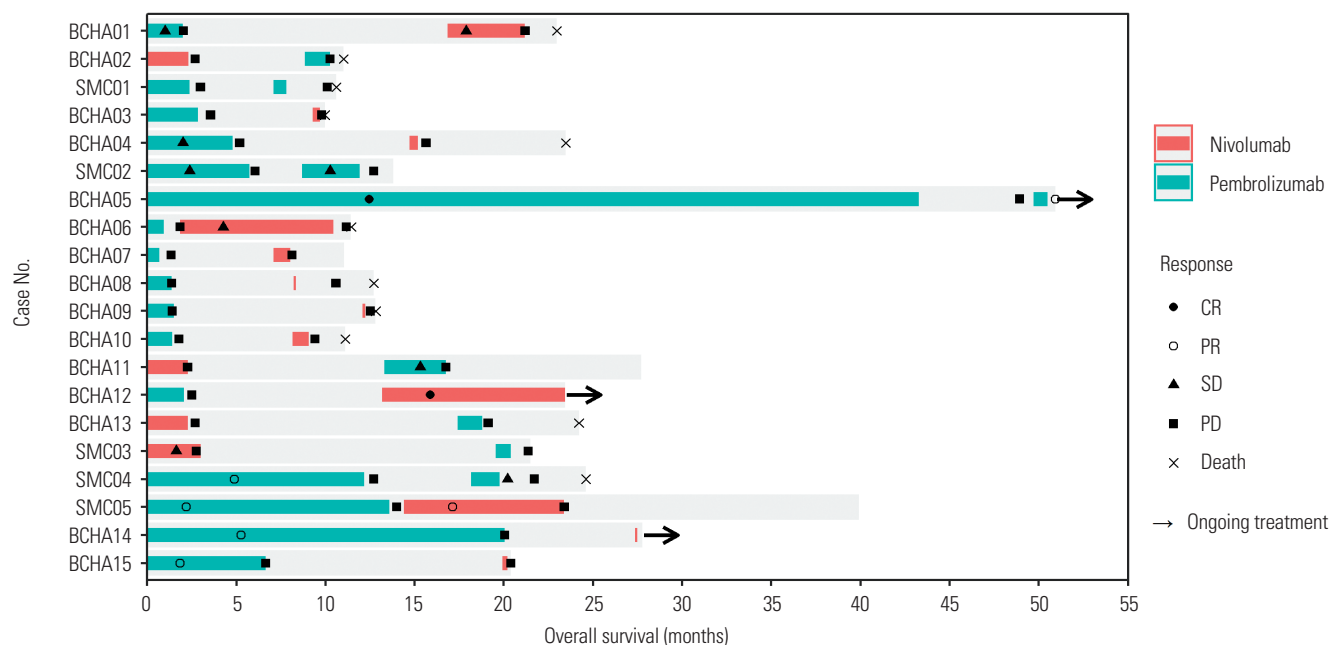
The small sample of patients included in the present study may limit conclusions based on these results. However, it is important to note that the patients in the prior meta-analysis were mainly diagnosed with NSCLC and melanoma, which are known to respond favorably to ICIs, whereas patients in the present study were diagnosed with gynecologic malignancies, which have been reported to respond to ICIs in approximately 20% of cases regardless of MMR status.^{11,12} Considering this, our results are encouraging, in that the response rate to ICI rechallenge among patients with recurrent gynecologic cancers, which have a relatively limited response to ICIs, was comparable to that reported in the prior meta-analysis.

Table 2. Clinical Courses of Patients Treated with First and Second ICIs (n=20)

Cases	Origin	OS (months)	First ICI				Second ICI			
			Type of ICI	Lines of therapy	BOR	PFS (months)	Type of ICI	Lines of therapy	BOR	PFS (months)
BCHA01	Cervix	23.3	P	1	SD [†]	2.1	N	3	SD	4.4
BCHA02	Cervix	11.2	N	2	PD	2.7	P	4	PD	1.4
SMC01	Cervix	10.8	P	3	PD	3.0	P	5	PD	3.0
BCHA03	Cervix	10.1	P	1	PD	3.6	N	4	PD	0.7
BCHA04	Cervix	23.8	P	1	SD	5.3	N	4	PD	0.9
SMC02	Cervix	14.0	P	1	SD	6.1	P	2	SD	4.1
BCHA05	Cervix	52.7	P	2	CR*	49.6	P	3	PR	1.2
BCHA06	Vulva	11.6	P	1	*	1.9	N	2	SD	9.7
BCHA07	Peritoneum	11.2	P	2	PD	1.4	N	5	PD	1.0
BCHA08	Ovary	12.9	P	2	PD	1.4	N	5	*	2.4
BCHA09	Ovary	13.0	P	3	PD	1.4	N	6	PD	0.7
BCHA10	Ovary	11.3	P	2	†	1.8	N	3	PD	1.3
BCHA11	Ovary	28.1	N	5	PD	2.3	P	7	SD	3.5
BCHA12	Peritoneum	24.7	P	2	PD	2.5	N	6	CR	10.4
BCHA13	Peritoneum	24.6	N	3	PD	2.7	P	6	PD	1.7
SMC03	Ovary	21.8	N	7	SD	2.8	P	11	PD	1.8
SMC04	Ovary	25.0	P	1	PR	12.9	P	3	SD	3.6
SMC05	Ovary	40.5	P	4	PR	14.2	N	5	PR	9.1
BCHA14	Ovary	28.7	P	2	PR	20.3	N	4	†	0.4
BCHA15	Endometrium	20.7	P	1	PR	6.7	N	3	PD	0.5

ICI, immune checkpoint inhibitor; OS, overall survival; BOR, best overall response; PFS, progression-free survival; P, pembrolizumab; N, nivolumab; SD, stable disease; PD, progressive disease; CR, complete response; PR, partial response.

*Discontinued due to adverse events; †Discontinued due to patient withdrawal; ‡Before treatment assessment.

**Fig. 1.** The overall treatment process since treatment initiation. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Regarding AEs resulting from ICI rechallenge, one recent large cohort study found a 28.8% recurrence rate of the same immune-related AEs associated with ICI discontinuation after rechallenge with the same ICI.¹³ In the previously described meta-analysis,¹⁰ the overall recurrence rate of immune-related AEs

of any grade was 52.2%, while that of immune-related AEs of grade 3–4 was 21.5%. In the present study, recurrence of the same AE was not observed in both patients who previously discontinued ICIs because of AEs. Only one patient experienced recurrent grade 3 hypothyroidism at ICI rechallenge, following

Table 3. Adverse Events Recorded During Treatment with ICIs (n=20)

Grade	First ICI		Second ICI	
	1/2	3/4	1/2	3/4
Hypothyroidism	2	1	1	1
Anemia	1	1	0	0
Increased liver enzymes	0	1*	0	1
Fatigue	1	0	0	0
Abdominal pain	0	1*	0	0
Pancytopenia	0	0	0	1*

ICI, immune checkpoint inhibitors.

*Led to treatment discontinuation.

prior discontinuation due to tumor progression. The frequency of AEs in this study was relatively low, which is likely due to the limitations of this retrospective study, which was conducted using chart reviews, because minor AEs might not have been recorded. Nevertheless, ICI resumption in patients who previously discontinued ICIs due to AEs could be considered for select patients with appropriate monitoring and use of standard treatment protocols to identify and treat AEs.

Two (40%) out of five responders to initial ICI in the present study responded to the second ICI, and only one (ID: BCHA12) (6.7%) patient responded to second ICI out of 15 previous non-responders (Table 2, Fig. 1). The therapeutic progress of the patient with ID: BCHA12 was as follows; This patient was a 79-year-old female diagnosed with high-grade serous peritoneal carcinoma carrying BRCA mutation, MMR deficiency, and positive PD-L1 expression. The patient received three cycles of pembrolizumab after second line chemotherapy. Upon confirming tumor progression, three more lines of chemotherapy failed, and she eventually received nivolumab as the seventh line of treatment. After six cycles of nivolumab, she experienced CR and is still undergoing treatment.

Since this patient's tumor was deficient for MMR, which is well known to be a significant prognostic marker of ICI treatment regardless of tumor origin,¹⁴⁻¹⁶ it was expected to respond favorably to ICI. However, it is questionable as to why she responded only to the second ICI, nivolumab, and not to the first ICI, pembrolizumab, even though they belong to the same class of PD-1 inhibitors. Pseudoprogression¹⁷ actually occurred with the first ICI treatment but may not have been properly evaluated. It is known that pembrolizumab and nivolumab share the same mechanism of action, but show subtle differences in pharmacodynamics and pharmacokinetics in terms of binding epitope and affinity.¹⁸ We wonder whether these differences between the two drugs resulted in the differences in response or resulted from immunological alterations following previous treatments. We also question whether prior pembrolizumab and several lines of chemotherapy may have resulted in a positive conformational change in the patient's PD-1/PD-L1 axis, rendering the subsequent nivolumab treatment effective. The additional therapeutic agents between the first ICI and the second ICIs are listed in Supplementary Table 1 (only online).

It is not known whether switching from one monoclonal antibody to another would be justified in cases of treatment failure. Also, we do not exactly know the best treatment sequence and the main structural, functional, and clinical differences between currently approved ICIs. Further studies are needed to confirm these differences.

The present study has several limitations. This retrospective study was conducted using data from a small number of patients. Also, possible selection bias might have existed because ICI rechallenge was based on the discretion of the physician. In this study, the tumors were heterogeneous in origin. However, as seen in previous studies,^{12,19} patients with gynecological cancers treated with ICI are not limited by tumor origin, and it is reasonable to classify them by MMR status. ICI rechallenge after an intervening treatment in patients who progressed during ICI treatment should be regarded as investigational, and enrollment in clinical trials is highly encouraged.⁵ However, in the present study, patients were rechallenged with the same class of PD-1 inhibitors (pembrolizumab and nivolumab). In Korea, few clinical trials can be registered on ICI rechallenge, and only two ICIs can be prescribed as off-label treatments for patients with gynecological cancers. We did not assess responses based on immune RECIST or immune-related RECIST criteria to assess the immune response. This could be regarded as a limitation of the retrospective study. Although none of the patients in this study raised concerns regarding potential pseudoprogression or hyperprogression, even when assessed by the RECIST criteria, the implementation of immune-related response criteria might have portrayed different results.

There are pending clinical trials that allow prior treatment with a PD-1 or PD-L1 inhibitor in renal cell carcinoma, NSCLC, and melanoma, but not in gynecologic malignancies. To the best of our knowledge, the present study is the first to evaluate ICI rechallenge in patients with gynecologic cancer, mainly an Asian cohort, in a real-world setting. Until a definite guideline for ICI rechallenge is established, the choice of rechallenge should be made weighing benefits and risks carefully on an individual basis, taking into account several factors, including performance status, tumor status, financial toxicity, response to previous ICIs, the type and grade of previously experienced AEs, and alternative available options.

AUTHOR CONTRIBUTIONS

Conceptualization: Min Chul Choi and Jeong-Won Lee. **Data curation:** Chi-Son Chang, Hyun Park, and Won Duk Joo. **Formal analysis:** Min Chul Choi. **Investigation:** Chi-Son Chang, Hyun Park, and Won Duk Joo. **Methodology:** Min Chul Choi and Jeong-Won Lee. **Project administration:** Min Chul Choi and Jeong-Won Lee. **Resources:** Min Chul Choi, Jeong-Won Lee, Hyun Park, and Won Duk Joo. **Software:** Min Chul Choi and Migang Kim. **Supervision:** Min Chul Choi and Jeong-Won Lee. **Validation:** Jeong-Won Lee, Hyun Park, and Won Duk Joo. **Visualization:** Migang Kim. **Writing—original draft:** Min Chul Choi and Chi-Son Chang. **Writing—review & editing:** Jeong-Won Lee and Migang Kim. **Approval of final manuscript:** all authors.

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