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Review

New treatment strategy for ovarian cancer with a *BRCA* gene mutation

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Mutated *BRCA1/2* genes have been identified as causative genes for ovarian cancer, and it has been reported that 10%–20% of all epithelial ovarian cancers have a *BRCA* mutation. As novel treatment drugs utilizing this *BRCA* gene mutation, significant attention has been paid to adenine dinucleotide poly (ADP-ribose) polymerase inhibitors. Among them, olaparib has been reported to be useful in patients with a *BRCA* mutation in Study 19 and SOLO-2 trials. It is important to establish a system for genetic counseling and to perform *BRCA* gene testing in patients with ovarian cancer. For patients with *BRCA*-mutated advanced cancer, if adequate response to chemotherapy has been achieved, olaparib is recommended as maintenance therapy for both advanced and recurrent cases. For patients without *BRCA* gene mutation, bevacizumab combined with chemotherapy or as maintenance therapy is also an option.

Keywords

Ovarian cancer; *BRCA* mutation; PARP inhibitor

1. Introduction

The incidence of ovarian cancer is increasing every year, and one of the most common malignancies of the gynecological disease, ranking third after cervical and uterine cancer. In 2017, there were 22,440 estimated new diagnoses of ovarian cancer and 14,080 deaths from the disease in the USA; deaths were higher than from endometrial cancer but lower than from cervical cancer [1].

In Japan, the *BRCA* gene test was previously covered by health insurance only for "patients with recurrent or metastatic breast cancer or newly diagnosed advanced ovarian cancer", but its eligibility criteria were expanded in 2020. Particularly in the treatment of advanced ovarian cancer, *BRCA* gene testing has increased treatment options for new and recurrent cases, and it is anticipated to help improve the prognosis. This article outlines a new treatment strategy for patients with a *BRCA* gene mutation, based on the association between ovarian cancer and *BRCA* genes and the results of related clinical trials conducted to date.

2. Ovarian cancer and *BRCA* gene diagnosis

In the USA, Norquist *et al.* reported that the frequency of germline mutations in 1915 cases of epithelial ovarian cancer was 15% for *BRCA1* and *BRCA2* combined (*BRCA1*: 8.5%, *BRCA2*: 6.3%). By histological type, the frequencies were 16% in high-grade serous carcinoma, 6% in low-grade serous carcinoma, 9% in endometrioid carcinoma, and 7% in clear cell carcinoma. No mutation was noted in mucinous carcinoma [2]. In Japan, Sakamoto *et al.* reported that germline *BRCA* mutations were identified in 12.6% of 95 patients with ovarian cancer (*BRCA1*: 5 patients, *BRCA2*: 7 patients) [3]. In the analysis of 230 patients by Hirasawa *et al.*, the frequency was 11.8% (*BRCA1*: 19 patients, *BRCA2*: 8 patients). By histological type, 22 of the 27 patients (81.5%) had high-grade serous carcinoma, 2 patients had endometrioid carcinoma, and 2 patients had clear cell carcinoma (7.4% each) [4].

Guidelines on the recommendations for the *BRCA* gene test are slightly different among countries. The National Comprehensive Cancer Network (NCCN) [5], Society of Gynecologic Oncology [6], and American College of Obstetricians and Gynecologists [7] guidelines propose that *BRCA* gene testing should be considered in all ovarian cancer patients, regardless of family history. However, the guidelines of the European Society for Medical Oncology, France, Germany, Netherlands, Spain, and the UK (the National Institute for Health and Care Excellence) state that testing should be considered on the basis of whether the patient has a family history of breast or ovarian cancer [8–11]. The guidelines published by the Scottish Intercollegiate Guidelines Network in Scotland also state that the test should be considered for all patients with non-mucinous ovarian or fallopian tube cancer, regardless of family history [12].

Thus, there are several issues that need to be discussed in the future, such as whether *BRCA* gene testing should be recommended for all patients with ovarian cancer or for patients who are likely to test positive due to their family history or histological type and the point in time when the test should be performed.

3. *BRCA1* and *BRCA2* gene mutations and cancer risk

BRCA1 is a gene located on chromosome 17 (at 17q21.32) cloned by Miki *et al.* The gene is characterized by a very large exon 1 and plays an important role in DNA repair [13]. *BRCA2* is a gene located on chromosome 13 (at 13q12.3) iden-

Table 1. Indication of PARP inhibitor

	United States	European Union	Japan
Olaparib	· maintenance treatment with platinum sensitive relapsed (g/s BRCA m) · first-line maintenance treatment for advanced ovarian cancer (g/s BRCA m)	· maintenance treatment with platinum sensitive relapsed · first-line maintenance treatment for advanced ovarian cancer (g/s BRCA m)	· maintenance treatment with platinum sensitive relapsed · first-line maintenance treatment for advanced ovarian cancer (g BRCA m)
Niraparib	· maintenance treatment with platinum sensitive relapsed (< prior 2 regimens) · maintenance treatment with platinum sensitive relapsed (> prior 3 regimens, HRD positive) · first-line maintenance treatment for advanced ovarian cancer	· maintenance treatment with platinum sensitive relapsed (HGSC)	Applying
Rucaparib	· monotherapy treatment with platinum sensitive, relapsed or progressive, (g/s BRCA m, HGSC, EM) · maintenance treatment with platinum sensitive relapsed (HGSC, EM)	· monotherapy treatment with platinum sensitive, relapsed or progressive, (g/s BRCA m, HGSC, EM) · maintenance treatment with platinum sensitive relapsed (HGSC, EM)	Ongoing clinical trial

Abbreviations g/s BRCA m: germline or somatic BRCA mutation, HRD: Homologous recombination deficiency, PSRC: Platinum-sensitive recurrent carcinoma, HGSC: high-grade serous carcinoma, EM: endometrioid carcinoma.

tified by Wooster *et al.* [14].

According to a report by Chen *et al.*, the proportions of people with a *BRCA1* mutation who develop breast cancer and ovarian cancer by the age of 70 years are estimated to be 57% (95% confidence interval [CI]: 47%-66%) and 40% (95% CI: 35%-46%), respectively, whereas those of people with a *BRCA2* mutation are 49% (95% CI: 40%-57%) and 18% (95% CI: 13%-23%), respectively [15]. Additionally, the Consortium of Investigators of Modifiers of *BRCA1/2* published a report on the positions of gene mutations and the risks of breast and ovarian cancers in 19581 *BRCA1* mutation carriers and 11900 *BRCA2* mutation carriers. According to this report, the occurrence of nonsense or frameshift mutations in the central part of the coding region of *BRCA1/2* increases the risk of ovarian cancer and decreases the risk of breast cancer. However, mutations in the 5' and 3' regions increase the risk of breast cancer and decrease the risk of ovarian cancer [16]. As the mechanism causing these differences in the risks of breast and ovarian cancers, the possible involvement of gene repair is considered; however, the whole picture is yet to be elucidated.

4. Necessity of genetic counseling

Genetic counseling for patients with a *BRCA* mutation is important for their blood relatives. When there are multiple breast cancer patients within a family, the breast cancer is called "familial breast cancer". Familial breast cancer caused by single-gene abnormality is called "hereditary breast cancer". Of all hereditary breast cancers, 60%-70% are hereditary breast and ovarian cancer (HBOC) caused by *BRCA1/2* mutations, which includes a high rate of ovarian cancer. In Japan, a surveillance system has been established for the treatment of HBOC by linking genetic and cancer treatments. This has increased the number of treatment options based on *BRCA* gene diagnosis, contributing to significant advances in cancer treatment.

The greatest benefit of the *BRCA* gene test in people at risk for HBOC is the option of risk reduction surgery. According to the NCCN guidelines, risk-reducing salpingo-oophorectomy (RRSO) is recommended in patients with a *BRCA* gene mutation at the age of 35-40 years. If the patient has a family member with a history of ovarian cancer at a younger age, their age should be considered to determine the appropriate timing for RRSO [17]. In 2009, Rebbeck *et al.* reported that RRSO can reduce the risk of ovarian cancer by 79% [18]. In a prospective cohort study of 2482 patients with a *BRCA* mutation, Domeckek *et al.* reported that RRSO reduced all-cause mortality by 60%. A meta-analysis by Marchetti *et al.* also reported 68% reduction in all-cause mortality [19, 20]. However, because early menopause increases the risk of cardiovascular events, hormone replacement therapy after RRSO is essential. To obtain fully informed consent from the patients about the procedure, genetic counseling is crucial.

Indeed, germline genetic testing should be ordered to all newly diagnosed patients with epithelial ovarian cancer to detect germline pathogenic variants (gPVs) in all genes associated with epithelial ovarian cancer susceptibility. What about the somatic mutations? The last decade, tumor sequencing to identify potentially targetable somatic mutations is increasingly being used in high-grade serous epithelial ovarian cancer and influences decisions on patient treatment. Beyond germline, poly ADP-ribose polymerase (PARP) inhibitors may be effective in somatic *BRCA1/2* mutations as well [21].

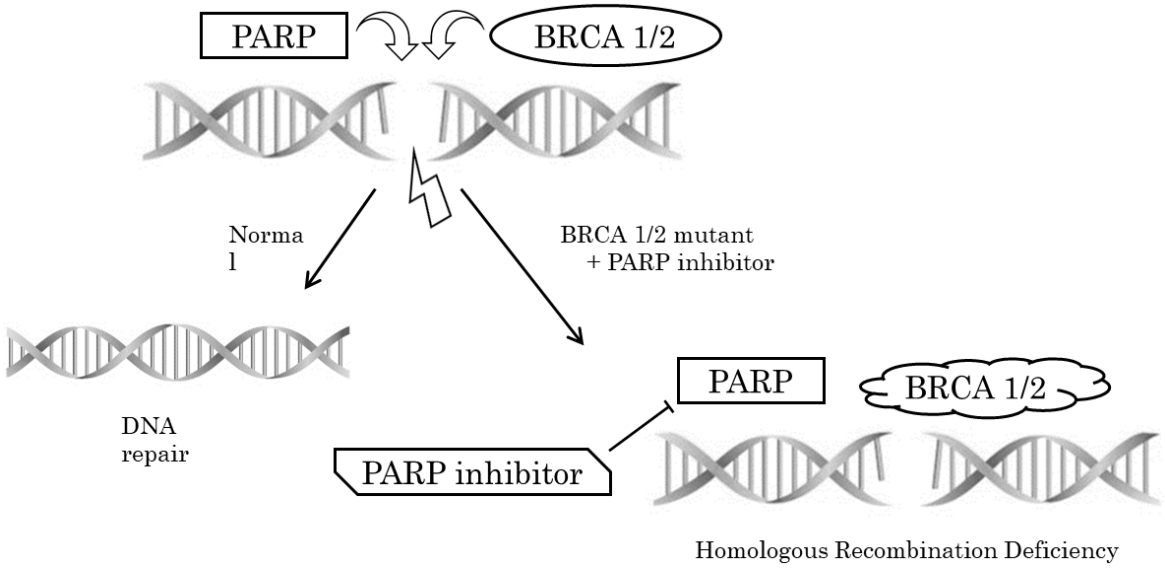

Fig. 1. Mechanism of synthetic lethality by PARP inhibitors. *BRCA1/2* genes play an important role in the repair of DNA double-strand breaks. In cells with disrupted *BRCA1/2* gene function, poly (ADP-ribose) polymerase inhibition causes a failure in the DNA repair mechanism by homologous recombination. This leads to synthetic lethality.

5. Poly ADP-ribose polymerase inhibitors

Adenine dinucleotide poly (ADP-ribose) polymerase (PARP) is an enzyme involved in DNA repair. PARP plays a part in the repair of both single-strand breaks and double-strand breaks (DSB) in DNA, which occurs by base excision repair and homologous recombination (HR), respectively [22–24]. To date, 17 members of the PARP family have been identified, with PARP1 being the most abundant in cells. PARP2 and PARP3 are also involved in DNA repair. *BRCA1/2* genes play an important role in DNA DSB repair. In cells in which *BRCA1/2* gene function is disrupted, the inhibition of PARP causes a failure in the mechanism of DNA repair via HR, resulting in cell death (Fig. 1). Cell death caused by the simultaneous damage of two mechanisms, such as PARP and *BRCA1/2* as described here, is called synthetic lethality. Accordingly, PARP inhibitors are considered to be effective in patients with mutations in *BRCA1/2* genes.

PARP inhibitors for ovarian cancer include olaparib, rucaparib, and niraparib, but their indications differ from country to country (Table 1).

In Japan, only olaparib is covered by health insurance. *BRCA* gene testing is not required for maintenance therapy in platinum-sensitive recurrent cancers. However, for maintenance therapy following initial chemotherapy, PARP inhibitors can be used only in patients with germline *BRCA* mutations, but with no restriction on histological types.

In contrast, in the USA, relapse treatment with PARP inhibitors is indicated for "maintenance therapy for platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or peritoneal cancer with a germline or somatic *BRCA* mutation", whereas in Europe, it is indicated for "maintenance therapy for platinum-sensitive recurrent high-grade serous epithelial ovarian, fallopian tube, or peritoneal cancer regardless of *BRCA* mutation status". In other words, in the USA, patients with platinum-sensitive recurrent cancer are not allowed to receive olaparib unless they have a germline *BRCA* mutation. Recently, the indications for maintenance therapy after initial chemotherapy have been expanded to include patients with high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have a germline or somatic *BRCA* mutation in both the USA and European countries.

Although rucaparib and niraparib have been approved for use in platinum-sensitive recurrences in the USA, they are currently used in global clinical trials in Japan and are highly anticipated to contribute to the future treatment of ovarian cancer.

In the USA, niraparib has been approved for use in maintenance therapy after initial and relapse treatment, but with no restriction on whether the patient has a *BRCA* mutation. However, in patients with a history of three or more regimens of chemotherapy, the use of niraparib is allowed only in patients who are positive for homologous recombination deficiency. In Europe, the drug has not been approved for use in maintenance therapy following the first-time chemotherapy and can be used only as maintenance therapy in relapse treatment. Recurrent patients eligible for niraparib are only those with platinum-sensitive recurrent high-grade serous epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer.

In both the USA and Europe, rucaparib has been approved for the treatment of germline or somatic *BRCA* mutation-positive epithelial ovarian, fallopian tube, and peritoneal cancer with a history of two or more chemotherapy regimens.

However, in Europe, the use is limited to the treatment of platinum-sensitive recurrences. Rucaparib can also be used for maintenance therapy in recurrent disease, regardless of germline or somatic *BRCA* mutation status, but its use is limited to platinum-sensitive recurrences in Europe. The histological type is also limited to high-grade serous carcinoma and endometrioid carcinoma.

In addition, veliparib is a promising molecular-targeted agent for high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer [25]. VELIA/GOG-3005 (an international, phase 3, placebo-controlled trial) involved patients with previously untreated stage III or IV high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer. VELIA/GOG-3005 assessed the efficacy of veliparib added to first-line induction chemotherapy with paclitaxel and carboplatin and continued as maintenance monotherapy. Patients were randomly assigned, in a 1 : 1 : 1 ratio, to one of the three arms: the control arm (patients treated with chemotherapy plus placebo followed by placebo maintenance), the veliparib-combination-only arm (those treated with chemotherapy plus veliparib followed by placebo maintenance), and the veliparib-throughout arm (those treated with chemotherapy plus veliparib followed by veliparib maintenance). Combination chemotherapy and maintenance therapy consisted of 6 and 30 cycles, respectively. The primary endpoint was progression-free survival (PFS) in the veliparib-throughout arm relative to the control arm, as assessed by the investigator based on the hierarchical testing in *BRCA* mutation, HRD (including *BRCA* mutation), and whole populations by log-rank tests.

Of the 1140 patients enrolled in the study, 26% had *BRCA* mutations and 55% had HRD. In the *BRCA* mutation cohort, the median PFS in the veliparib-throughout arm (108 patients) was 34.7 months, as compared with 22.0 months in the control arm (92 patients; hazard ratio [HR] for progression or death, 0.44; 95% confidence interval [CI], 0.28-0.68; $P < 0.001$) [26].

However, at this stage, the number of overall survival (OS) events is not sufficiently accumulated, so Japan, USA and Europe are waiting for approval application until the OS becomes mature.

6. Clinical trials with olaparib

In Japan, olaparib is the only PARP inhibitor approved for coverage by health insurance. This section describes the clinical trials that verified the usefulness of olaparib maintenance therapy in patients with *BRCA* gene mutation-positive ovarian cancer (Table 2).

6.1 Study 19

In this phase II study of patients with platinum-sensitive recurrent ovarian cancer who responded to platinum-based chemotherapy, 265 patients were assigned to olaparib (136 patients, 400 mg × 2) or placebo (129 patients) as maintenance therapy. The median PFS was 8.4 months in the olaparib group and 4.8 months in the placebo group, with the former being significantly longer than the latter (by 3.6 months) (HR: 0.35, 95% CI: 0.25-0.49, $P < 0.00001$) [27]. In the germline *BRCA* mutation -positive subgroup, the median PFS was significantly longer in the olaparib group (53 patients, 11.2 months) than in the placebo group (43 patients, 4.1 months) (HR: 0.17, 95% CI: 0.09-0.31, $P < 0.0001$). In patients without a germline *BRCA* mutation, the median PFS was 8.3 months in the olaparib group (50 patients) and 5.5 months in the placebo group (64 patients) (HR: 0.50, 95% CI: 0.29-0.82, $P = 0.0075$) [28]. In the follow-up report of OS in Study 19, the median OS was 29.8 months in the olaparib group and 27.8 months in the placebo group (HR: 0.73, 95% CI: 0.55-0.96, nominal $P = 0.025$). In patients with a germline *BRCA* mutation, the median OS was 34.9 months in the olaparib group and 30.2 months in the placebo group (HR: 0.62, 95% CI: 0.41-0.94, nominal $P = 0.025$), showing slight prolongation in the olaparib group [29].

6.2 SOLO-1 trial

The clinical trial was conducted in 391 patients with stage III/IV ovarian cancer with a *BRCA* mutation who showed platinum sensitivity to the first-line treatment. The subjects were assigned in a ratio of 2 : 1 to receive oral olaparib (260 patients, 300 mg × 2) or placebo (131 patients). The median PFS was not reached in the olaparib group, and it was 13.8 months in the placebo group (HR: 0.30, 95% CI: 0.23-0.41, $P < 0.0001$), showing significant prolongation in the olaparib group. The rate of freedom from disease progression at 3 years was 60.4% in the olaparib group and 26.9% in the placebo group [30].

6.3 SOLO-2 (NCT01874353) trial

A phase III study was conducted in 295 patients with *BRCA* mutation -positive high-grade serous or endometrioid platinum-sensitive recurrent ovarian cancer who were assigned to the olaparib group (196 patients, 600 mg/day) or the placebo group (99 patients) as maintenance therapy after platinum-based chemotherapy to compare the PFS between the two groups. The median PFS was 19.1 months in the olaparib group and 5.5 months in the placebo group, showing substantial prolongation in the olaparib group (HR: 0.30, 95% CI: 0.22-0.41, $P < 0.0001$). In this study, significant prolongation of PFS was observed not only in patients who achieved complete response (CR) but also in those who achieved partial response (PR) after the last chemotherapy [31].

6.4 PAOLA-1/ENGOT-ov2 trial

This was a phase III study that compared maintenance therapy with olaparib in combination with bevacizumab versus bevacizumab alone in patients with advanced ovarian cancer who responded to the first-line treatment with a platinating agent, taxane, and bevacizumab. The subjects were 806 patients diagnosed with the International Federation of Gynecology and Obstetrics stage III/IV high-grade serous or endometrioid ovarian cancer, fallopian tube cancer, or peritoneal cancer who received 3 cycles or more of platinum- and taxane-based chemotherapy with bevacizumab and were

Table 2. Previous clinical trials using olaparib

Trials	Patients	N	Arms	Median PFS (months)	PFS HR (95% CI): *P* value
Study19 [27]	· stageIII· IV · HGSC or EM	265	1) Placebo 2) Olaparib400 mg BID	4.8 8.4	0.35 (0.25∼0.49): $P < 0.00001$
SOLO-1 [30]	· stageIII· IV · HGSC or EM · gBRCAm	391	1) Placebo 2) Olaparib300 mg BID	13.8 NR	0.30 (0.23∼0.41): $P < 0.0001$
SOLO-2 [31]	· PSRC · HGSC or EM · gBRCAm	264	1) Placebo 2) Olaparib300 mg BID	5.5 19.1	0.30 (0.22∼0.41): $P < 0.0001$
PAOLA-1[32]	· StageIII· IV · HGSC	806	1)Platinum/taxane/Bev→ Bev maintenance 2) Platinum/taxane/Bev→Bev/olaparib maintenance	16.6 22.1	0.59 (0.49∼0.72): $P < 0.0001$

Abbreviations: gBRCA m: germline BRCA mutation, PSRC: platinum-sensitive recurrent carcinoma, HGSC : high-grade serous carcinoma, EM: endometrioid carcinoma, BID: twice a day, Bev:bevacizumab, PFS: progression-free survival, NR: not reached, HR:hazard ratio.

determined to have achieved CR or PR. The experimental group (537 patients) received olaparib (300 mg × 2/day) + bevacizumab (15 mg/kg, every 3 weeks), and the control group (269 patients) received placebo + bevacizumab (15 mg/kg, every 3 weeks). The median PFS (intention-to-treat population), the primary endpoint, was 22.1 months in the experimental group and 16.6 months in the control group, showing significant prolongation in the experimental group (HR: 0.59, 95% CI: 0.49-0.72, $P < 0.0001$). Additionally, among the patients with a *BRCA* mutation, the median PFS was 37.2 months in the experimental group (161 patients) and 21.7 months in the control group (80 patients) (HR: 0.31, 95% CI: 0.20-0.47). Among the patients without a *BRCA* mutation, the median PFS was 18.9 months in the experimental group (376 patients) and 16.0 months in the control group (189 patients) (HR: 0.71, 95% CI: 0.58-0.88). The incidences of treatment-related adverse events were 99% in the experimental group and 96% in the control group. Patients who had grade 3 or higher treatment-related adverse events accounted for 57% in the experimental group and 51% in the control group. The most common adverse reactions were fatigue/asthenia, nausea, and hypertension in the experimental group and hypertension, fatigue/asthenia, and arthralgia in the control group. Notably, grade 3 or higher anemia was reported by 17% patients in the experimental group compared to less than 1% in the control group [32].

7. Combination therapy with cediranib and olaparib

There are available studies evaluating the antiangiogenic agent cediranib with the PARP inhibitor olaparib in the ovarian cancer patients. This session describes the completed or ongoing clinical trials (Table 3).

NCT01116648, a randomized, open-label, phase II study designed to evaluate the combination of cediranib, an antiangiogenic agent, and olaparib versus olaparib alone, has been completed. First, preclinical synergy between olaparib and cediranib was explored to determine whether ovarian cancer cell invasion and microvascular endothelial cell tube formation were inhibited in vitro. Women with relapsed platinum-sensitive ovarian cancer of high-grade serous or endometrioid histology or with deleterious germline *BRCA1/2* mutations were enrolled in the study. Patients were randomly assigned to the single-agent arm (olaparib capsules 400 mg twice daily) or the experimental arm (cediranib 30 mg daily and olaparib capsules 200 mg twice daily) until disease progression.

The interim analysis showed that the experimental arm exhibited significantly longer PFS (17.7 months) than the single-agent arm did (9.0 months; HR: 0.42; $P = 0.005$). However, these results should be meticulously interpreted owing to the small size of each subgroup. Moreover, it would be interesting if a single-agent arm of cediranib, which could act as a comparator for the experimental arm, was included in the study design. A post-hoc exploratory analysis revealed that in the subset of patients with wild-type or unknown *BRCA* status, the experimental arm showed a statistically significant improvement compared with the single-agent arm for both median PFS (16.5 versus 5.7 months, HR 0.32; $P = 0.008$) and objective response rate (ORR; 76% versus 32%; $P = 0.006$). The authors proposed that this difference could be attributed to great synergy between olaparib and cediranib in the setting of hypoxia, potentially leading to alterations in the expression of DNA damage response genes. Patients with *BRCA* mutation showed a reduced tendency toward increased activity in the experimental arm and reduced impact on the endpoints of PFS (19.4 versus 16.5 months) and ORR (84% versus 63% benefit). Overall, ideal administration of the combination of cediranib plus olaparib may be possible for patients with an intact HR repair phenotype [33]. Finally, the most recently updated analysis showed that OS did not differ significantly in the entire study population (44.2 versus 33.3 months, HR 0.64; $P = 0.11$) [34].

Additional trials are ongoing to evaluate combined treatment with PARP inhibitors and anti-angiogenic agents. In the GY004 trial, olaparib monotherapy or olaparib plus cedi-

Table 3. Combination trials with cediranib and olaparib

Trials	Patients	Phase	N	Arms
NCT01116648 [33, 34]	· PSRC · HGSC/HGEC · g/s*BRCA* m	II	162	1) Olaparib 400 mg alone 2) Olaparib 200 mg + cediranib 30 mg
NRG-GY004 [35]	· PSRC · g*BRCA1/2* m · Any *BRCA* mutation status	III	549	1) Olaparib 400 mg alone 2) Olaparib 200 mg + cediranib 30 mg 3) Physician choice chemotherapy
ICON 9 [36]	· PR or CR with platinum chemotherapy · Any *BRCA* mutation status	III	618	1) Olaparib + cediranib 2) Cediranib + placebo (maintenance therapy)
COCOS [37]	· Platinum-resistant or–refractory · HGSC · g*BRCA* m	II/III	680	1) Olaparib alone 2) Cediranib alone 3) Olaparib + cediranib 4) Physician choice chemotherapy
OCTOVA [38]	· Relapsed platinum resistant OC · Stratification for prior PARP use · Stratification for prior anti-angiogenic use · *BRCA* status	II	138	1) Paclitaxel alone 2) Olaparib alone 3) Olaparib + cediranib
CONCERTO [39]	· Relapsed HGSC/HGEC · No germline mutation in *BRCA1/2*	IIb	62	Single arm: Olaparib + cediranib

Abbreviations: g/s *BRCA* m: germline or somatic *BRCA* mutation, g*BRCA* m: germline *BRCA* mutation, HGSC: high-grade serous carcinoma, HGEC: high-grade endometrioid carcinoma, OC:Ovarian cancer, PSRC: platinum-sensitive recurrent carcinoma.

Table 4. Combination trials with PARP inhibitors and the immune checkpoint inhibitors

Trials	Patients	Phase	N	Arms
MEDIOLA (NCT02734004) [40, 41]	Basket study in: · g*BRCA* m, OC · g*BRCA* m HER2(–) breast cancer · Relapsed platinum-sensitive SCLC · Metastatic or relapsed gastric cancer	I/II	427	Single arm: Olaparib + durvalumab
TOPACIO/Keynote-162 [42]	Basket study in: · Recurrent platinum-resistant OC · *HER2*(–) breast cancer	I/II	121	Single arm: Niraparib + pembrolizumab

Abbreviations: g/s *BRCA* m: germline or somatic *BRCA* mutation , g*BRCA* m: germline BRCA mutation, SCLC: small cell lung cancer, HGSC: high-grade serous carcinoma, HGEC: high-grade endometrioid carcinoma, PSRC: platinum-sensitive recurrent carcinoma, OC: ovarian cancer.

ranib therapy was compared with standard platinum-based chemotherapy in patients with platinum-sensitive recurrent ovarian cancer [35]. In the ICON 9 trial, maintenance therapy with cediranib plus olaparib was compared with olaparib alone within the same setting [36]. Three other phase II/III trials are currently ongoing for patients with platinum-resistant disease.

The COCOS study randomly assigned patients to one of four treatment groups: single-agent group (either olaparib or cedilanib), combination group, or standard chemotherapy group [37]. In the OCTOVA study, patients with germline *BRCA* mutations were randomly assigned to receive olaparib alone, olaparib plus cediranib, or weekly paclitaxel [38]. Finally, only patients with wild-type *BRCA* treated with at least three prior lines of therapy were recruited into the CONCERTO trial (study of cediranib in combination with olaparib) [39].

8. Combination of PARP inhibitors with the immune checkpoint inhibitors

Current studies have raised important concerns regarding whether PARP inhibitors may help enhance the response to immune checkpoint inhibition or other immunotherapeutic approaches. Recently, the MEDIOLA study and the TOPACIO trial (combination trials of immune checkpoint blockade with PARP inhibitors) were presented at the European Society of Gynaecological Oncology Congress in 2018 (Table 4). This section briefly describes these two clinical trials.

8.1 MEDIOLA trial (NCT02734004)

The phase I/II basket trial, evaluated the combination of olaparib and durvalumab in selected advanced solid cancers [40]. Efficacy of durvalumab and olaparib combination was demonstrated in the phase II trial which enrolled 32 *BRCA*-mutated platinum-sensitive ovarian cancer patients. Updated

results from this trial revealed an ORR of 71.9% and median PFS of 11.1 months while median OS was not reached at that time [41].

8.2 TOPACIO/Keynote-162

This is a phase I/II study investigating the combination of pembrolizumab and niraparib by enrolling a cohort population of heavily pretreated platinum-resistant or secondarily platinum-refractory patients. Based on the dose escalation phase I study, the recommended phase II dose was 200 mg orally once daily for niraparib and 200 mg intravenously three times a week for pembrolizumab. The initial response assessment showed that among the 60 evaluable patients, 64%, 19%, and 17% with platinum-resistant, platinum-refractory, and platinum-sensitive ovarian cancers, respectively, responded to the treatment [42]. Among the entire population, the estimated ORR was 25%, and disease control rate was 68%. Furthermore, 77% and 52% of enrolled patients had wild-type *BRCA* and were negative for HR deficiency, respectively. The ORRs for these two subgroups were 24% and 27%, respectively. This may have implications regarding therapeutic effects in patients not typically responsive to single-agent PARP inhibitors. Moreover, the *BRCA1/2* mutant cohort of 11 patients showed an ORR of 45% and a disease control rate of 73%. With regard to safety concerns, preliminary data revealed adverse events to be compatible with those of single-agent strategies. The most frequently reported toxicities of grade 3 or more were anemia (17%), fatigue (6%), and thrombocytopenia (3%) [43].

9. The topic of PARP inhibitor resistance

Advances in our understanding of resistance to PARP inhibitors may yield novel insights into the basic mechanisms of the DNA damage response. Individual PARP inhibitors have different chemical structures and diverse off-target effects [44]. Thus, application of secondary PARP inhibitors may be useful for the treatment of resistant tumors. The most common mechanism underlying resistance is restoration of homology-directed DNA repair owing to secondary reversion mutations [45].

Many studies have evaluated pharmacological methods for reversing resistance to PARP inhibitors. Knockdown of cyclin-dependent kinase 12 (CDK12) results in concomitant downregulation of DNA repair proteins, thereby leading to the development of a "*BRCA*ness" phenotype [46]. In vitro evidence suggests that pharmacological inhibition of CDK12 with Dinaciclib reverses acquired resistance to PARP inhibitors [47]. Furthermore, inhibition of the cell cycle regulator WEE1 causes cells to enter the S-phase of the cell cycle, thereby accelerating the accumulation of DNA DSBs in the context of HRD and PARP inhibition [48]. With the aim of overcoming homologous recombination-induced resistance to PARP inhibitors, Boussios *et al.* reported that combined inhibition of CDK12 or WEE1 could be effective [49].

10. Treatment recommended for advanced/recurrent ovarian cancer

Indications for PARP inhibitors vary from country to country. The choice of treatment should be based on the indications specified in the country. Among them, olaparib has been shown to have favorable therapeutic outcomes as maintenance therapy for advanced/recurrent ovarian cancer as demonstrated by the aforementioned clinical studies. Additionally, when used in patients with a *BRCA* mutation, the outcomes are even more favorable [27–30]. In Japan, the initial treatment recommended for patients with advanced ovarian cancer is to establish a histological diagnosis followed by *BRCA* gene testing and administer olaparib as maintenance therapy to those with a *BRCA* mutation who had an adequate response to platinum-based chemotherapy. In contrast, for patients without a *BRCA* mutation, one of the treatment options is combination/maintenance therapy with bevacizumab, which has been shown to prolong PFS by GOG 218 [50] and ICON7 [51]. In recurrent patients, indications differ among countries. In Japan, for patients with a *BRCA* mutation diagnosed with platinum-sensitive recurrent cancer, olaparib is recommended as maintenance therapy after an adequate response to platinum-based chemotherapy. For patients without a *BRCA* gene mutation, one of the treatment options is combination/maintenance therapy with bevacizumab, which has been shown to prolong PFS in GOG 213 [52] and OCEANS [53]. However, one important thing to consider is that bevacizumab can be administered even in patients with a platinum-resistant recurrence, while olaparib can be administered only in patients with a platinum-sensitive recurrence. The use of olaparib in patients with a *BRCA* gene mutation is useful as a new treatment strategy, and it is anticipated to help improve the prognosis of ovarian cancer. Furthermore, we look forward to future research on the usefulness of other molecular-targeted agents and immune checkpoint inhibitors.

Author contributions

T.S. contributed to the design and coordination of the review, and drafting the manuscript. T.B. contributed to the design of the review and drafting the manuscript. K.K., H.K., N.J., H.T., A. K., E.T., T. N., M.K. contributed to the conception, design, and coordination of the review and drafting the manuscript.

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Conflict of interest

The authors declare no conflict of interest.

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