Management of ovarian cancer associated with BRCA and other genetic mutations

AUTHORS: Kathleen M Moore, MD, Merry Jennifer Markham, MD, FACP, FASCO
SECTION EDITORS: Barbara Goff, MD, Don S Dizon, MD, FACP
DEPUTY EDITOR: Sadhna R Vora, MD

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INTRODUCTION

In the United States, ovarian cancer is the second most common gynecologic cancer, but it is the deadliest of the gynecologic cancers [1]. A female's lifetime risk of developing ovarian cancer is 1.3 percent [2]. While the majority of diagnosed cases of epithelial ovarian cancer (EOC) are not associated with genetic mutations, an estimated 18 percent of cases are associated with germline mutations, most of which are attributable to breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*) mutations [3-5]. High-grade serous is the most common histology associated with germline *BRCA1/2* mutations, but germline mutations have been identified in all epithelial histologies, except for mucinous, supporting genetic testing of all patients with EOC [6]. Patients with Lynch syndrome, characterized by a mutation in a DNA mismatch-repair gene (eg, mutL homolog 1 [*MLH1*], mutS homolog 2 [*MSH2*], mutS homolog 6 [*MSH6*], or postmeiotic segregation increased 2 [*PMS2*]), however, are more likely to have nonserous EOC [7].

Management of *BRCA*-associated ovarian cancers is discussed here. Other issues, including management of ovarian cancer that is not associated with genetic mutations, as well as cancer risks among patients with *BRCA* mutations, are discussed elsewhere.

- (See "Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum".)
- (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer".)

- (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease".)
- (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease".)
- (See "Cancer of the ovary, fallopian tube, and peritoneum: Surgical options for recurrent cancer".)
- (See "Cancer risks in BRCA1/2 carriers".)

GERMLINE AND SOMATIC TESTING FOR GENETIC ALTERATIONS

All patients with a diagnosis of ovarian, fallopian tube, or peritoneal cancer should have a genetic risk evaluation, irrespective of their family history, as the results may impact treatment decisions. (See "Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum", section on 'Testing for hereditary cancer syndromes'.)

If germline testing is negative, we proceed with somatic *BRCA* testing to determine who may most benefit from a poly(ADP-ribose) polymerase (PARP) inhibitor. (See 'Those with somatic BRCA mutations' below.)

Multiple commercial and academic tumor genotyping assays exist for detection of somatic genetic alterations [8,9]. Guidelines favor testing patients for both germline and somatic mutations in order to optimize identification of germline mutations (which would open access to cascade testing of family members). Additionally, this strategy would expand identification of patients who may benefit from PARP inhibitors. Relying only on somatic testing to identify patients for "reflex" genetic testing historically may miss up to 5 percent of germline mutations due to differences in test coverage, variant classification, and the inability to detect large rearrangements by available commercial next-generation sequencing [10]. Relying only on germline testing will miss approximately 7 percent of patients who have somatic mutations only [11]. Improvement of testing sequencing and strategy remains an urgent area of investigation.

For patients with recurrent ovarian cancer, genomic testing for DNA mismatch repair-deficient or microsatellite-instable ovarian cancer should also be performed, given the option of immunotherapy as later-line treatment. (See 'Mismatch repair deficiency/high microsatellite instability' below.)

EPIDEMIOLOGY OF BRCA-ASSOCIATED OVARIAN CANCERS

Approximately 13 to 15 percent of ovarian cancers are attributable to heritable mutations in *BRCA1* and *2*, although somatic *BRCA* mutations have also been identified in ovarian cancer specimens.

The Cancer Genome Atlas Research Network evaluated 316 stage II through IV high-grade serous epithelial ovarian cancer specimens and found that 3 percent of the cases showed somatic *BRCA1/2* mutations, compared with germline *BRCA1* mutations in 9 percent and germline *BRCA2* mutations in 8 percent [12].

In another study, 367 individuals with 390 ovarian carcinomas were analyzed; 88 germline mutations were identified among these cases [11]. Of the 88 germline mutations, 49 (56 percent) were in *BRCA1*, 17 (19 percent) were in *BRCA2*, and 22 (25 percent) were in other homologous-recombination genes (*BRCA1*-associated RING domain 1 [*BARD1*], BRCA-interacting protein 1 [*BRIP1*], checkpoint kinase 1 [*CHEK1*], checkpoint kinase 2 [*CHEK2*], family with sequence similarity 175, member A [*FAM175A*], nibrin [*NBN*], partner and localizer of *BRCA2* [*PALB2*], RAD51 paralog C [*RAD51C*], RAD51 paralog D [*RAD51D*]). Thirty-two of the 367 patients had 35 somatic mutations, including 19 (54 percent) in *BRCA1* and 6 (17 percent) in *BRCA2*, for a total somatic *BRCA1/2* mutation rate of 7 percent out of 367.

Patients with *BRCA* gene mutations have a greatly increased risk of ovarian and breast cancer (table 1). Further details of *BRCA* mutations as a risk factor for ovarian cancer are found elsewhere. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors", section on 'BRCA variants'.)

The lifetime risks for other cancers found in *BRCA* mutation carriers are also discussed elsewhere. (See "Cancer risks in BRCA1/2 carriers", section on 'Cancer risks in BRCA1/2 carriers'.)

NEWLY DIAGNOSED BRCA-ASSOCIATED OVARIAN CANCERS

In general, the approach to newly diagnosed ovarian cancer among *BRCA* mutation carriers mirrors that for patients without a *BRCA* mutation. (See "Overview of epithelial carcinoma of the ovary, fallopian tube, and peritoneum".)

However, special considerations are present specific to this population; this is discussed in the sections below.

Components of therapy

Surgery — The surgical management of *BRCA* mutation carriers with ovarian cancer is the same as of those without *BRCA* mutations and is discussed elsewhere. (See "Epithelial carcinoma

of the ovary, fallopian tube, and peritoneum: Surgical staging".)

Surgical considerations, including risk-reducing salpingo-oophorectomy as well as the option of opportunistic salpingectomy, for *BRCA* mutation carriers without ovarian cancer are discussed elsewhere. (See "Cancer risks in BRCA1/2 carriers" and "Opportunistic salpingectomy for ovarian, fallopian tube, and peritoneal carcinoma risk reduction".)

Adjuvant chemotherapy

Approach — The indications and approach to adjuvant chemotherapy for those with newly diagnosed ovarian cancer, irrespective of *BRCA* mutation status, are discussed elsewhere. (See "Adjuvant therapy of early-stage (stage I and II) epithelial ovarian, fallopian tube, or peritoneal cancer", section on 'Selection of patients' and "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer".)

Briefly, for all patients with advanced epithelial ovarian cancer (EOC), we treat with a platinum-plus-taxane combination, which may be administered either via intravenous/intraperitoneal (IV/IP) or the IV only route for optimally reduced disease; or via the IV only route, if suboptimally reduced. (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer", section on 'Women with optimally cytoreduced disease'.)

For patients at higher risk of recurrence (eg, those with pleural effusions or ascites) we also incorporate bevacizumab, which is administered with a conventionally dosed IV chemotherapy regimen, followed by maintenance administration. The benefit of adding bevacizumab is not significantly modified by *BRCA* mutation status [6].

Irrespective of whether IV/IP or IV treatment is administered, we suggest that these patients receive maintenance olaparib after completion of first-line therapy. If patients receive IV chemotherapy plus bevacizumab, we suggest addition of olaparib to bevacizumab during maintenance therapy. These recommendations are based on SOLO1, discussed below. (See 'PARP inhibition' below.)

Data regarding IV/IP versus IV treatment — Retrospective data suggest that *BRCA* carriers with ovarian cancer may experience greater benefits with IP chemotherapy compared with noncarriers, and, in particular, with platinum agents (which cause DNA crosslinking, leading to cell death in *BRCA*-mutated tumors due to deficient cellular DNA repair mechanisms). It is unclear, however, if the benefit for IV/IP treatment persists if poly(ADP-ribose) polymerase (PARP) inhibitors are used as maintenance, given the absence of data addressing this question. Therefore, IV therapy without IP treatment is also acceptable.

In order to be actionable, the *BRCA* status of patients must be ascertained at initial diagnosis.

- In the randomized, phase III clinical trial, GOG 172, which tested intraperitoneal chemotherapy versus intravenous (IV) chemotherapy in stage IIIC EOC or primary peritoneal carcinoma, aberrant *BRCA1* expression was an independent predictor for improved survival in patients randomized to the intraperitoneal arm (hazard ratio [HR] 0.67, 95% CI 0.47-0.97) [13]. Of 393 patients with archival tissue available, 189 (48 percent) had aberrant *BRCA1* (evaluated by immunohistochemistry staining), and 204 (52 percent) had normal expression.

- One-hundred patients with high-grade ovarian cancer who were treated with adjuvant intraperitoneal chemotherapy at a single institution between 2005 and 2016 were identified and had median follow-up of 47 months [14]. Seventy-seven of the 100 patients underwent *BRCA* testing and 25 (32 percent) were *BRCA* positive, including 23 with germline mutations and two with somatic mutations. The median progression-free survival (PFS) was longer in the *BRCA* mutation arm: median PFS not reached compared with 17.3 months in *BRCA*-negative group (HR 0.38, 95% CI 0.11-0.73).

PARP inhibitor maintenance therapy — Poly(ADP-ribose) polymerase (PARP) inhibitors block the repair of DNA single-strand breaks, and, for tumors associated with *BRCA* mutations, they result in cell death due to inefficiencies in DNA cell repair mechanisms. Our approach is generally consistent with guidelines from the American Society of Clinical Oncology [15].

- All patients with newly diagnosed ovarian cancer require genetic counseling and genetic and somatic testing for *BRCA* mutations. We suggest maintenance PARP inhibition for patients with advanced ovarian cancer and a germline or somatic mutation in *BRCA1* or *BRCA2* and a response to front-line, platinum-based therapy. Some, but not all, UpToDate contributors also offer maintenance PARP inhibitors to such patients with earlier-stage disease, although they have not been evaluated in this setting.

- In addition, for patients with a *BRCA1* or *BRCA2* mutation deemed to be at a high risk of recurrence (eg, ascites, pleural effusion) in whom bevacizumab will be administered with a conventionally dosed IV chemotherapy regimen, we suggest the addition of olaparib during maintenance bevacizumab.

The following PARP inhibitors have been evaluated:

- **Olaparib, with or without bevacizumab,** has regulatory approval in the United States by the US Food and Drug Administration (FDA) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated

advanced EOC who are in complete or partial response to first-line platinum-based chemotherapy [16].

- Approval for olaparib monotherapy was based on the phase III SOLO1 trial, in which 391 patients with advanced, high-grade, *BRCA*-associated serous or endometrioid ovarian cancer who had a complete or partial response to front-line, platinum-based chemotherapy were randomly assigned to maintenance with olaparib or placebo [10]. Most (388) had a germline *BRCA* mutation, and no patients received bevacizumab. At a median follow-up of 41 months, olaparib resulted in a lower three-year rate of disease progression or death compared with placebo (60 versus 27 percent; HR for disease progression or death 0.30, 95% CI 0.23-0.41) [10], with no detriment in health-related quality of life [17]. At a median follow-up of five years, median PFS was 56 versus 14 months, in the olaparib versus placebo group [18]. In an interim analysis of overall survival (OS; data maturity, 21 percent), three-year rate of freedom from death for olaparib versus placebo was 84 versus 80 percent (HR for death 0.95, 95% CI 0.60-1.53) [10]. Grade 3 or 4 toxicities were frequent with olaparib (39 versus 18 percent), with anemia and neutropenia being the most common severe adverse events. Acute myeloid leukemia occurred in 3 of 260 patients (1 percent) in the olaparib group and in none of the 130 patients receiving placebo. Analysis of long-term toxicity data will further inform use of front-line maintenance PARP inhibition.

- The approval for olaparib plus bevacizumab was supported by results of the PAOLA-1 trial. In this trial, patients with advanced, high-grade, serous, or endometrioid cancers who had responded to chemotherapy plus bevacizumab were randomly assigned to maintenance bevacizumab with or without olaparib. Among the subgroup with *BRCA*-positive ovarian cancer, the combination of olaparib plus bevacizumab improved PFS over bevacizumab alone (37 versus 22 months; HR 0.31, 95% CI 0.20-0.47) [19]. The five-year OS rates in this population were 73 versus 54 percent, respectively (median OS 75 versus 67 months; HR 0.60, 95% CI 0.39-0.93), although data are immature. However, it is unclear whether bevacizumab improved efficacy relative to olaparib alone, a question this trial was not designed to answer.

The discussions above are largely driven by data in patients with germline *BRCA* mutations (eg, SOLO1 almost exclusively enrolled patients with germline *BRCA* mutations, with only 2 of 391 patients having a somatic mutation in *BRCA* only). Further rationale for expanding use of front-line olaparib maintenance to include those with somatic *BRCA* mutations is extrapolation from the recurrent setting, discussed above. (See 'Germline and somatic testing for genetic alterations' above.)

- **Niraparib** – Niraparib has FDA approval as maintenance therapy in the first-line setting, irrespective of tumor *BRCA* status [20]. In the PRIMA trial, patients with advanced ovarian cancer who had responded to first-line, platinum-based chemotherapy were randomly assigned to niraparib or placebo for 36 months. For the subgroup with *BRCA*-associated cancers, niraparib prolonged PFS compared with placebo (22.1 versus 10.9 months; HR 0.40, 95% CI 0.27-0.62) [21].

- **Rucaparib** – Rucaparib does not have regulatory approval in any country for use as front-line maintenance. A randomized phase III trial (ATHENA mono) evaluated monotherapy rucaparib compared with placebo in patients undergoing surgical cytoreduction and responding to platinum doublet chemotherapy [22]. The homologous recombination deficiency population experienced a PFS benefit with rucaparib versus placebo (29 versus 11 months; HR 0.47, 95% CI 0.31-0.72), as did the overall population (20 versus 9.2 months; HR 0.52, 95% CI 0.40-0.68). ATHENA has a second component of the study which compares rucaparib with rucaparib nivolumab. That portion of the study has not yet reported.

Further details of these trials, which also included patients whose cancers were not associated with *BRCA* mutations, are found elsewhere. Subset analysis for those with homologous recombination-deficient tumors is found further below in this topic. (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer", section on 'BRCA-wildtype cancers that are homologous recombination proficient' and 'Other homologous recombination deficiencies' below.)

Adverse effects of PARP inhibitors — Adverse effects of poly(ADP-ribose) polymerase (PARP) inhibitors are discussed elsewhere. (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer", section on 'Adverse effects'.)

RECURRENT BRCA-ASSOCIATED OVARIAN CANCERS

Definition of platinum-sensitive versus platinum-resistant recurrence — Patients with a platinum-free interval (PFI) of six months or longer are considered to have "platinum-sensitive" disease, while those with a PFI of less than six months are considered to have "platinum-resistant" disease. Many aspects of the management of recurrent *BRCA*-associated ovarian cancers, including initial chemotherapy selection, are similar to the management of non-*BRCA*-associated recurrent disease. These issues are discussed elsewhere. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease" and "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease".)

The sections below focus on specific differences between management of *BRCA*-associated recurrent ovarian cancer and such cancers without associated *BRCA* mutations. Importantly, much of the data below come from clinical trials of people with *BRCA*-associated ovarian cancer that had recurred and who were **not** treated with maintenance poly(ADP-ribose) polymerase (PARP) inhibitors in the adjuvant (or first-line) setting.

Platinum-sensitive disease

Retreatment with platinum-based chemotherapy — Patients who relapse six months or longer after receiving initial therapy with a platinum-based treatment are more likely than others to respond to retreatment with a chemotherapy regimen that contains a platinum agent (eg, carboplatin, cisplatin). This is regardless of whether they have *BRCA*-associated disease or not. Further details are discussed elsewhere. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease" and "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease".)

For *BRCA* carriers with platinum-sensitive disease who did not undergo maintenance PARP inhibitor therapy in the first-line (or adjuvant) setting and who are not deemed to be candidates for or prefer to avoid further treatment with platinum, an appropriate alternative is to administer a PARP inhibitor, which has shown a progression-free survival (PFS) benefit over nonplatinum chemotherapy in a randomized trial.

In the phase III SOLO3 trial, among 266 patients who were *BRCA* carriers; never treated with a PARP inhibitor previously; and had platinum-sensitive, recurrent ovarian cancer, olaparib improved both objective response rate (ORR; 72 versus 51 percent) and PFS (13 versus 9 months; hazard ratio [HR] 0.62, 95% CI 0.43-0.91) relative to nonplatinum chemotherapy (of the treating clinician's choice) [23]. The most common adverse events with olaparib were nausea (65 versus 34 percent) and anemia (50 versus 25 percent), and with chemotherapy were palmar-plantar erythrodysesthesia (36 versus 1 percent) and nausea. Most common grade ≥3 adverse events in either arm were anemia (21 versus 0 percent), palmar-plantar erythrodysesthesia (0 versus 12 percent), and neutropenia (6 versus 11 percent) for olaparib and chemotherapy, respectively.

The PARP inhibitor rucaparib has also demonstrated PFS improvements over chemotherapy in a randomized trial in PARP-inhibitor-naïve patients whose cancer had progressed on ≥2 prior chemotherapy regimens (7.4 versus 5.7 months; HR 0.67, 95% CI 0.52-0.86) [24]. Patients assigned to the chemotherapy arm of this trial received platinum-based chemotherapy if they

had platinum-sensitive disease, or weekly paclitaxel if they had partially platinum-sensitive disease or platinum-resistant disease.

- Among the 74 patients with platinum-sensitive disease (progression ≥12 months), PFS was 12.9 versus 9.6 months, respectively (HR 0.69, 95% CI 0.37-1.29). Those with partially platinum-sensitive disease (progression within ≥6 months to <12 months) experienced a PFS of 8.0 versus 5.5 months (HR 0.40, 95% CI 0.24-0.65).

- Among the 23 patients with reversion mutations (which restore function to *BRCA1 and BRCA2*), there was no benefit with PARP inhibitors over chemotherapy (HR 2.8 favoring chemotherapy, 95% CI 0.99-7.8).

- In the overall study, rucaparib resulted in serious adverse events in 27 percent, versus 12 percent in the chemotherapy group.

- It is not indicated to treat those with platinum-resistant disease as a later line therapy. These are discussed below.

Further data regarding olaparib, rucaparib, and niraparib, which come from trials enrolling patients with both platinum-sensitive and platinum-resistant relapse, are discussed below. (See 'Other homologous recombination deficiencies' below and 'PARP inhibitors no longer used in this setting' below.)

Maintenance — Several trials suggest that patients with platinum-sensitive disease achieve better response rates and PFS using maintenance after response to chemotherapy.

Data regarding available agents are discussed below, as is choosing between them. (See 'PARP inhibition' below and 'Angiogenesis inhibition' below and 'Choosing between a PARP inhibitor and an angiogenesis inhibitor' below.)

PARP inhibition — For patients with platinum-sensitive relapsed ovarian cancer with a partial or complete response to platinum-based chemotherapy without previous exposure to a poly(ADP-ribose) polymerase (PARP) inhibitor, maintenance PARP inhibition improves PFS, particularly among those with *BRCA* mutations.

- **Niraparib** – In the phase III NOVA study, 553 patients with platinum-sensitive, previously PARP-inhibitor-untreated, recurrent ovarian cancer were randomly assigned after completion of platinum-based chemotherapy in a 2:1 ratio to niraparib maintenance or placebo [25]. Compared with placebo, niraparib increased PFS in all cohorts, with improvements in the group with genomic *BRCA* mutations as follows: 21.0 versus 5.5 months (HR 0.27, 95% CI 0.17-0.41). In a subsequent letter to providers, these advantages

did not translate to overall survival (OS) benefits (44 versus 42 months with placebo in the genomic *BRCA* group) [26]. OS results were likely influenced by treatment crossover, however, as patients in the control group likely received a subsequent PARP inhibitor after progression.

The most common severe toxicities associated with niraparib were hematologic, but myelodysplastic syndrome occurred in a small percentage of patients. Overall results of this study are discussed elsewhere.

- **Olaparib** – Positive results were observed in the phase III SOLO2/ENGOT-Ov21 trial, in which 295 patients with relapsed, platinum-sensitive, germline *BRCA*-associated, high-grade serous ovarian cancer or high-grade endometrioid cancer who had received at least two lines of previous chemotherapy and were previously PARP-inhibitor-untreated were randomly assigned in a 2:1 ratio to olaparib maintenance or placebo [27]. Those receiving olaparib experienced improved PFS (19.1 versus 5.5 months; HR 0.30, 95% CI 0.22-0.41). In subsequent reporting, median OS was 52 months with olaparib versus 39 months with placebo (HR 0.74, 95% CI 0.54-1.00) [28].

  Grade 3 or higher adverse events occurred in 18 percent of those receiving olaparib versus 8 percent of those receiving placebo. Olaparib maintenance therapy did not have a detrimental effect on health-related quality of life outcomes compared with placebo [29].

  Similarly, a subanalysis of Study 19, which enrolled those with platinum-sensitive, high-grade, recurrent epithelial ovarian cancer, evaluated the outcomes of maintenance therapy of olaparib specifically in patients with a known *BRCA* mutation (either germline or somatic) and suggested that the clinical benefit was greatest among these patients [30]. Patients with a *BRCA* mutation had a benefit in PFS with olaparib compared with placebo (median, 11 versus 4 months; HR 0.18, 95% CI 0.10-0.31), with a trend toward improved OS (HR 0.73, 95% CI 0.45-1.17), which became more pronounced at longer follow-up (>5 years) [31,32]. By contrast, patients without a *BRCA* mutation had a smaller PFS benefit (median, 7 versus 5.5 months; HR 0.54, 95% CI 0.34-0.85), but no benefit in OS (HR 0.99, 95% CI 0.63-1.55). A post-hoc analysis of patients with *BRCA* mutations that excluded those from sites where any crossover occurred demonstrated an improved OS with olaparib (HR 0.52, 95% CI 0.28-0.970). This implies that later treatment with olaparib may have confounded the OS endpoint from the primary trial [33]. Full results of Study 19 are discussed elsewhere. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease", section on 'PARP inhibitors no longer used'.)

- **Rucaparib** – In the phase III ARIEL3 trial, 564 patients with relapsed, high-grade, serous or endometrioid ovarian carcinoma, all of whom had received ≥2 previous platinum-based therapies and achieved a complete or partial response to their most recent platinum-based treatment and were previously PARP-inhibitor-untreated, were randomly assigned in a 2:1 ratio to maintenance therapy with rucaparib or to placebo [34]. In contrast to other studies of PARP inhibitors, patients were permitted to enroll in this study even if they had residual bulky disease (≥2 cm). Rucaparib improved PFS among those with a known genomic or somatic *BRCA* mutation (16.6 versus 5.4 months; HR 0.23, 95% CI 0.16-0.34) [35].

Angiogenesis inhibition — Results of trials of the angiogenesis inhibitor bevacizumab with and following chemotherapy were not stratified according to *BRCA* mutation status. Results in the general population of patients with platinum-sensitive relapse are discussed elsewhere. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease", section on 'Angiogenesis inhibitors'.)

Choosing between a PARP inhibitor and an angiogenesis inhibitor — Choice between a poly(ADP-ribose) polymerase (PARP) inhibitor and an angiogenesis inhibitor as maintenance therapy depends on prior treatment history.

- **For those with prior exposure to a PARP inhibitor** – There are no data to inform use of PARP maintenance after platinum-sensitive relapse among patients who received a PARP inhibitor as maintenance treatment following first-line treatment. In the absence of prospective data, UpToDate contributors are divided in their approach:

  - Some UpToDate contributors opt for bevacizumab if the recurrence recurred on, or within 12 months of, the last dose of maintenance PARP inhibitor, and retreatment with a PARP inhibitor if the recurrence occurred more than 12 months from the last dose of maintenance PARP inhibitor.

  - However, other UpToDate contributors consider either bevacizumab or a PARP inhibitor to be an appropriate maintenance option for PARP-exposed patients with a platinum-sensitive recurrence, irrespective of interval since last dose of PARP inhibitor, although enthusiasm for reuse of PARP inhibitors is less if the patient progressed on prior PARP inhibitors.

- **For those without prior exposure to a PARP inhibitor** – For those with platinum-sensitive relapse of *BRCA*-associated cancers or with homologous recombination deficiency, without prior exposure to a poly(ADP-ribose) polymerase (PARP) inhibitor, we suggest a PARP inhibitor rather than bevacizumab as maintenance therapy (bevacizumab

being the preferred option for those without *BRCA* mutations). Considerations in patients who have **not** received prior PARP inhibitors are as follows.

There have been no trials directly comparing an antiangiogenesis inhibitor (bevacizumab) with and following platinum-based chemotherapy versus a PARP inhibitor following response to platinum-based chemotherapy.

With some caveats, which will be discussed, some observations based on cross-trial comparisons may be made. Among patients with *BRCA*-associated cancers, the PFS HRs favoring use of a PARP inhibitor as maintenance are overwhelmingly positive, and statistically significant, at 0.27, 0.23, and 0.30 for NOVA, ARIEL3, and SOLO2, respectively [25,27,34]. The median PFS for these three trials ranges from 16.6 to 21 months with use of a PARP inhibitor as compared with only 5.5 months for placebo.

Among patients **unselected** for *BRCA* mutation status, the HRs for PFS in favor of use of bevacizumab were 0.48 and 0.63 in OCEANS and GOG 213, respectively, and statistically significant. Importantly, GOG 213 also demonstrated a statistically significant improvement in OS with an HR of 0.823. Subsequently, preliminary results of AGO-OVAR 2.21 support carboplatin and pegylated liposomal doxorubicin plus bevacizumab as another standard-of-care option (although this trial did not compare treatments with versus without bevacizumab). When one looks at the median PFS for platinum doublets plus bevacizumab, they range from 11.7 to 13.8 months (from the start of chemotherapy, as discussed above).

Acknowledging the lack of data for *BRCA*-associated cancers that responded to induction chemotherapy and then received bevacizumab, the degree of benefit for use of PARP inhibitors makes this the preferred choice in a PARP inhibitor-naïve patient with a *BRCA*-associated cancer and response to induction chemotherapy.

However, comparisons of the trials that have reported on these two strategies must be interpreted with caution, given discrepant study designs and inclusion criteria. Notable differences between the trials were as follows:

- The three randomized phase III trials of maintenance PARP inhibitors (NOVA, ARIEL3, and SOLO2) only enrolled patients who had responded to induction chemotherapy. By contrast, the studies evaluating bevacizumab concurrently and following chemotherapy for platinum-sensitive relapse (OCEANS trial and GOG 213) included patients who responded, as well as those who did not respond, to platinum-based therapy.

- The time-to-event calculations for PFS in the PARP inhibitor trials start from the end of platinum-based chemotherapy. In the bevacizumab trials, they start from the

beginning of chemotherapy.

- The PARP inhibitor trials included subset analyses of *BRCA* versus non-*BRCA*-associated cancers, while these analyses are not available for the bevacizumab trials.
- The PARP inhibitor trials enrolled patients who had high-grade serous or high-grade endometrioid disease only. All histologies (including clear cell and mucinous) were allowed on the bevacizumab trials.

While recognizing the limitations in the data, we continue to prefer PARP inhibitors as maintenance therapy for patients with platinum-sensitive relapse and response to platinum-based chemotherapy, provided that they were not previously exposed to a PARP inhibitor.

Selection between the two regimens in *BRCA*-wildtype tumors is discussed elsewhere. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-sensitive disease", section on 'Choice of therapy'.)

Platinum-resistant disease

Preferred option: Chemotherapy — Chemotherapy is the preferred approach for *BRCA* carriers with platinum-resistant relapse. Selection of chemotherapy agents for *BRCA* carriers with platinum-resistant disease is similar to other patients and is discussed elsewhere. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease", section on 'Overview of the treatment approach'.)

PARP inhibitors no longer used in this setting — The PARP inhibitors olaparib, niraparib, and rucaparib previously had regulatory approval in the United States for patients with advanced ovarian cancer after multiple prior lines of chemotherapy, based on response rates of approximately 30 percent and PFS benefits over chemotherapy [24,36-38]. Nevertheless, with longer follow-up, the manufacturers voluntarily withdrew these agents given concerns regarding long-term outcomes and toxicities. We no longer use PARP inhibitors as treatment for multiply relapsed *BRCA*-associated advanced ovarian cancer, but they remain an appropriate option as maintenance therapy in patients with recurrent ovarian cancer who are in complete or partial response to platinum-based chemotherapy. (See 'Maintenance' above.)

PROGNOSIS

BRCA mutation carriers, particularly *BRCA2* carriers, appear to have a better prognosis than noncarriers. An analysis of 1213 epithelial ovarian cancer cases with germline mutations in *BRCA1* or *BRCA2* and 2666 noncarriers revealed a five-year overall survival rate of 36 percent

(95% CI 34-38 percent) for noncarriers, 44 percent (95% CI 40-48 percent) for *BRCA1* carriers, and 52 percent (95% CI 46-58 percent) for *BRCA2* carriers [39].

This improved survival appears to be due to a higher sensitivity of platinum-based treatment of these tumors relative to sporadic cases, which is maintained across repeated courses of chemotherapy [40-42]. (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer".)

Some data suggest that the improved prognosis for *BRCA* mutation carriers is only in the short term. The median follow-up in the analysis above was three years. By contrast, a registry study that compared 281 patients with *BRCA* mutations with other patients with ovarian cancer reported a higher survival rate in the *BRCA* group at three years (approximately 75 versus 65 percent), but no significant difference at five or more years [43].

SPECIAL CONSIDERATIONS

Those with somatic BRCA mutations — Rationale for poly(ADP-ribose) polymerase (PARP) inhibition in those with somatic *BRCA* alterations comes from Study 19 and NOVA, both in the setting of relapsed, platinum-sensitive disease. In these studies, the hazard ratio (HR) favoring maintenance PARP inhibition after response to platinum-based induction therapy for platinum-sensitive recurrence was almost identical between those with somatic and germline *BRCA*-associated tumors. In Study 19, the HR for somatic *BRCA* was 0.23 (95% CI 0.04-1.12) as compared with 0.17 (95% CI 0.09-0.34) for those with germline mutations [44]. In NOVA, the HR in favor of niraparib was 0.27 (95% CI 0.08-0.90) for somatic *BRCA* mutations as compared with 0.27 (95% CI 0.17-0.41) for germline [25].

Similarly, in the retreatment setting, as opposed to maintenance, the PARP inhibitor rucaparib has shown similar overall response rates in somatic and germline *BRCA*-associated tumors at 63 and 74 percent, respectively [45].

Other homologous recombination deficiencies — Homologous recombination deficiency (HRD) is being evaluated as a biomarker for selection of patients for PARP inhibitor maintenance after initial therapy, as well as for later-line treatment among those with platinum-sensitive relapse.

- Trials evaluating PARP inhibitor maintenance therapy in treatment-naïve disease have found greater benefits for those with HRD tumors relative to nongenetically altered ovarian cancers, and similar to those with *BRCA*-associated tumors. Olaparib plus bevacizumab has regulatory approval in the United States by the US Food and Drug

Administration (FDA) for the maintenance treatment of adult patients with advanced epithelial ovarian cancer who are in complete or partial response to first-line platinum-based chemotherapy, and whose cancer is associated with HRD-positive status defined by either: a deleterious or suspected deleterious *BRCA* mutation and/**or** genomic instability [16].

In the PAOLA trial, among patients with stage III to IV, high-grade serous or endometrioid ovarian cancer with a response to initial chemotherapy and bevacizumab, maintenance therapy with olaparib and bevacizumab improved progression-free survival (PFS) relative to bevacizumab alone in the overall trial population, and particularly in those with HRD (37.2 versus 17.7 months; HR 0.33, 95% CI 0.25-0.45) [19]. In the HRD-positive population, OS was longer with olaparib plus bevacizumab (five-year OS rate 66 versus 48 percent; HR 0.62, 95% CI 0.45-0.85) [46].

In a separate phase III trial in patients with newly diagnosed advanced ovarian cancer who had a response to platinum-based chemotherapy (PRIMA), maintenance with the PARP inhibitor niraparib also demonstrated PFS benefits over placebo in the overall trial population, with greater benefits among those with HRD [21]. In the subset of patients with HRD and no *BRCA* mutation, median PFS with niraparib versus placebo was 19.6 and 8.2 months, respectively (HR 0.50, 95% CI 0.31-0.83).

Overall results of these trials are discussed elsewhere, along with further details regarding toxicities. Data among those with *BRCA*-mutated cancers are discussed above. (See "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer", section on 'BRCA-wildtype cancers that are homologous recombination proficient' and 'PARP inhibitor maintenance therapy' above.)

While other mutations have been associated with an increased risk of ovarian cancer (eg, BRCA-interacting protein 1 [*BRIP1*], RAD51 paralog C [*RAD51C*], RAD51 paralog D [*RAD51D*], partner and localizer of *BRCA2* [*PALB2*], and *BRCA1*-associated RING domain 1 [*BARD1*]), strategies targeting these mutations have not been elaborated. Cancer risks for carriers of partner and localizer of BRCA2 (*PALB2*), *RAD51*, and other genes associated with hereditary ovarian cancer, and screening for such cancer susceptibility syndromes, are discussed elsewhere. (See "Overview of hereditary breast and ovarian cancer syndromes" and "Genetic testing and management of individuals at risk of hereditary breast and ovarian cancer syndromes".)

Mismatch repair deficiency/high microsatellite instability — For patients with recurrent ovarian cancer, genomic testing for DNA mismatch repair-deficient (dMMR) or microsatellite-instable (MSI) ovarian cancer should be performed. The immune checkpoint inhibitor

pembrolizumab is approved by the US Food and Drug Administration for the treatment of dMMR or MSI cancers, including ovarian cancer, that have progressed following prior treatment, and for which there are no satisfactory alternative treatment options [47].

In KEYNOTE-158, enrolling 233 patients with 27 tumor types with confirmed dMMR/MSI tumors refractory to prior therapy, the objective response rate (ORR) to pembrolizumab was 34 percent [48]. Among 15 patients with ovarian cancer, the ORR was similar (33 percent), including three complete responses. Further details of this study are found elsewhere. (See "Overview of advanced unresectable and metastatic solid tumors with DNA mismatch repair deficiency or high tumor mutational burden".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Ovarian, fallopian tube, and peritoneal cancer" and "Society guideline links: Hereditary breast and ovarian cancer".)

SUMMARY AND RECOMMENDATIONS

- **Overview** – Approximately one-fifth of cases of epithelial ovarian cancer (EOC) are associated with germline mutations, with most of these attributable to breast cancer susceptibility gene 1 (*BRCA1*) or breast cancer susceptibility gene 2 (*BRCA2*) mutations. (See 'Introduction' above.)

- **Surgical management** – The surgical management of *BRCA* mutation carriers with ovarian cancer is the same as of those without *BRCA* mutations. (See "Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Surgical staging".)

- **Systemic treatment for newly diagnosed disease** – For most patients with optimally cytoreduced, *BRCA*-associated EOC, either intravenous (IV)/intraperitoneal (IP) or IV chemotherapy only are acceptable options. (See 'Adjuvant chemotherapy' above.)

    - **Initial chemotherapy** – The indications and choice of adjuvant chemotherapy for those with newly diagnosed ovarian cancer, irrespective of *BRCA* mutation status, are discussed elsewhere. (See "Adjuvant therapy of early-stage (stage I and II) epithelial ovarian, fallopian tube, or peritoneal cancer", section on 'Selection of patients' and "First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tube, and peritoneal cancer".)

- **Maintenance therapy**

  - For patients with advanced *BRCA1*/2-associated EOC, or with homologous recombination-deficient (HRD) tumors, who experienced a response to front-line, platinum-based therapy, we suggest maintenance with a PARP inhibitor rather than observation (**Grade 2B**). Some UpToDate contributors also offer maintenance PARP inhibitors to those with earlier-stage, *BRCA*-associated EOC that has responded to platinum-based therapy, particularly stage II disease, extrapolating from data in advanced cancer. (See 'PARP inhibitor maintenance therapy' above.)

  - In addition, for patients with a *BRCA1* or *BRCA2* mutation deemed to be at a high risk of recurrence (eg, ascites, pleural effusion) in whom bevacizumab is being administered with a conventionally dosed IV chemotherapy regimen, we suggest the addition of olaparib during maintenance bevacizumab (**Grade 2C**).

- **Systemic treatment for relapsed disease**

  - **Platinum-sensitive relapse**

    - For patients with *BRCA1/2*-associated, platinum-sensitive, relapsed EOC, we suggest retreatment with platinum-based chemotherapy rather than a non-platinum-based chemotherapy (**Grade 2C**). For such patients who experience a complete or partial response to platinum-based therapy, and who did not receive PARP inhibitor maintenance in the front-line setting, we suggest maintenance with a PARP inhibitor rather than bevacizumab (**Grade 2C**). There are no data to inform use of PARP inhibitors (either as treatment or as maintenance) after platinum-sensitive relapse among patients with previous PARP exposure.

      F*or BRCA* carriers with platinum-sensitive disease who did not undergo maintenance PARP inhibitor therapy in the first-line (or adjuvant) setting, a PARP inhibitor is an appropriate alternative to chemotherapy. (See 'Maintenance' above.)

  - **Platinum-resistant relapse** – For patients with *BRCA*-associated ovarian cancer that is platinum resistant, chemotherapy selection is the same as for patients who are not *BRCA* carriers and is discussed elsewhere. (See "Medical treatment for relapsed epithelial ovarian, fallopian tube, or peritoneal cancer: Platinum-resistant disease", section on 'Overview of the treatment approach'.)

- **Prognosis** – *BRCA* mutation carriers with ovarian cancer, particularly *BRCA2* carriers, have a better prognosis than noncarriers. (See 'Prognosis' above.)

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GRAPHICS

Estimated cancer risks associated with *BRCA1* and *BRCA2* mutations

Cancer type	Risk in *BRCA1/2* carriers to age 70 years	General population risk to age 70 years	Comments
Breast	40 to 75 percent	7 percent	The range of risk reported in the literature is wide. In most studies, risk in *BRCA1* carriers is higher than that observed in *BRCA2* carriers. The incidence of breast cancer diagnosed younger than 50 years of age is higher in *BRCA* carriers compared with *BRCA2* carriers, but both groups have an increased risk of premenopausal breast cancer, as well as increased lifetime risks.
Contralateral (opposite) breast	*BRCA1*: Up to 65 percent *BRCA2*: Up to 50 percent	0.5 to 1 percent per year after diagnosis	Risk is affected by other factors such as tamoxifen use and oophorectomy (ovary removal). For *BRCA1/2* carriers who have had lumpectomy: Risk of developing a second breast cancer in the affected breast appears to be elevated over long follow-up periods.
Ovarian	*BRCA1*: Approximately 40 percent *BRCA2*: Approximately 15 percent	<1 percent	The risk estimates provided here are representative of

			findings from multiple studies. The incidence of ovarian cancer diagnosed younger than 50 years of age is higher in *BRCA* carriers, and overall rare in all carriers younger than 40 years old; risk of fallopian tube cancer is also substantially elevated.
Colon	Unclear	2 percent	If elevated, risk is small; studies have not been consistent about whether risk is elevated
Prostate	Elevated; absolute risk not well defined	8 percent White individuals 12 percent Black individuals	Risk appears to be higher in *BRCA2* carriers and possibly in men younger than 65 years old.
Male breast	Elevated but <10 percent	<1 percent	Risk appears to be higher in *BRCA2* carriers; rarely occurs in men younger than age 50.
Pancreatic	Elevated but <10 percent	<1 percent	Risk appears to be higher in *BRCA2* carriers
Other sites	To be determined	Varied	These sites may include cancer of the stomach and skin (melanoma).

These risks are estimates based upon review of the literature. Specific studies have reported risks that are lower or higher than the ranges or estimates quoted; however, the estimates reported here are representative of findings from high-quality studies. Risks will also vary based on an individual's current age and other risk factors.

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