Ovarian Cancer, Version 2.2020

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ABSTRACT

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women. A major challenge in treating ovarian cancer is that most patients have advanced disease at initial diagnosis. These NCCN Guidelines discuss cancers originating in the ovary, fallopian tube, or peritoneum, as these are all managed in a similar manner. Most of the recommendations are based on data from patients with the most common subtypes—high-grade serous and grade 2/3 endometrioid. The NCCN Guidelines also include recommendations specifically for patients with less common ovarian cancers, which in the guidelines include the following: carcinosarcoma, clear cell carcinoma, mucinous carcinoma, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal, and malignant germ cell tumors. This manuscript focuses on certain aspects of primary treatment, including primary surgery, adjuvant therapy, and maintenance therapy options (including PARP inhibitors) after completion of first-line chemotherapy.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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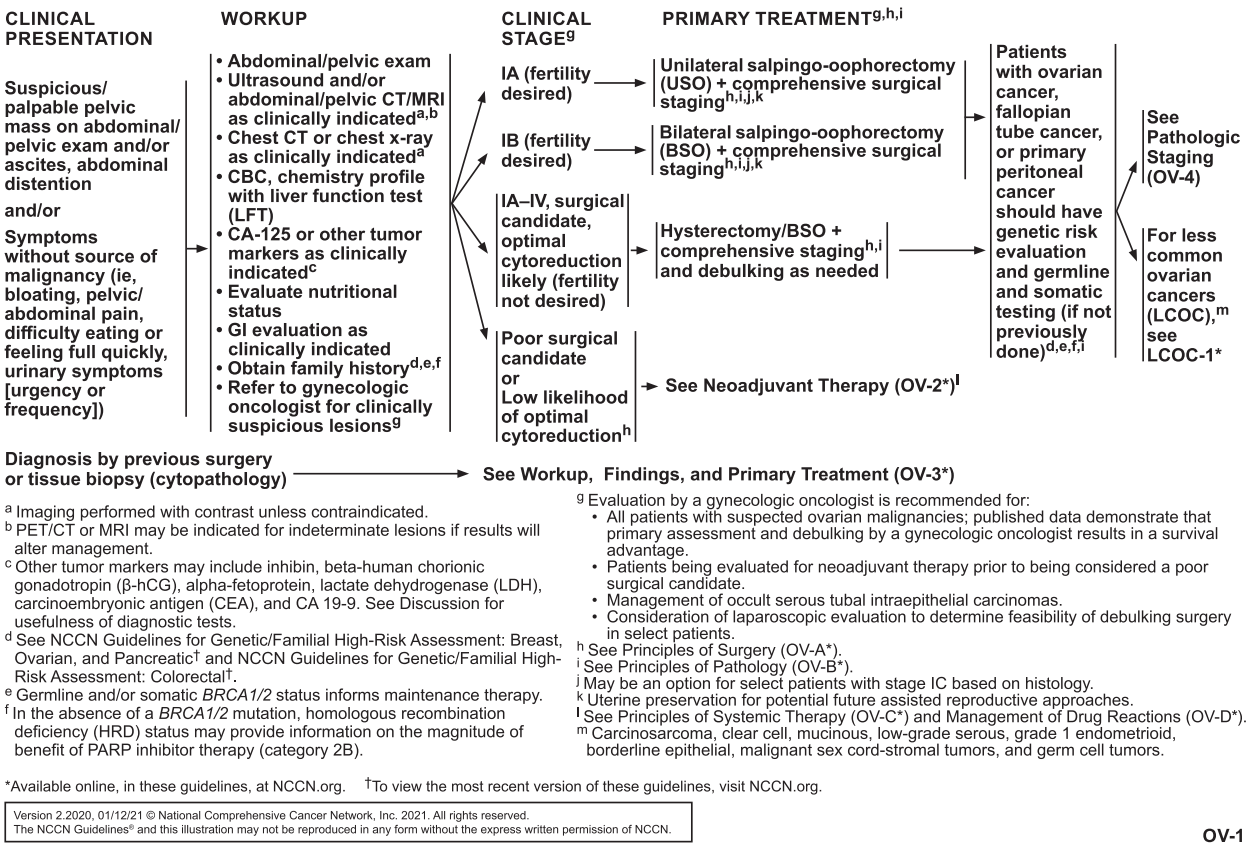
The complete NCCN Guidelines for Ovarian Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

Disclosures for the NCCN Ovarian Cancer Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Ovarian Cancer Panel members can be found on page 226. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[a] Imaging performed with contrast unless contraindicated.
[b] PET/CT or MRI may be indicated for indeterminate lesions if results will alter management.
[c] Other tumor markers may include inhibin, beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), and CA 19-9. See Discussion for usefulness of diagnostic tests.
[d] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic† and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal†.
[e] Germline and/or somatic *BRCA1/2* status informs maintenance therapy.
[f] In the absence of a *BRCA1/2* mutation, homologous recombination deficiency (HRD) status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).
[g] Evaluation by a gynecologic oncologist is recommended for:
- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
- Patients being evaluated for neoadjuvant therapy prior to being considered a poor surgical candidate.
- Management of occult serous tubal intraepithelial carcinomas.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.

[h] See Principles of Surgery (OV-A*).
[i] See Principles of Pathology (OV-B*).
[j] May be an option for select patients with stage IC based on histology.
[k] Uterine preservation for potential future assisted reproductive approaches.
[l] See Principles of Systemic Therapy (OV-C*) and Management of Drug Reactions (OV-D*).
[m] Carcinosarcoma, clear cell, mucinous, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal tumors, and germ cell tumors.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

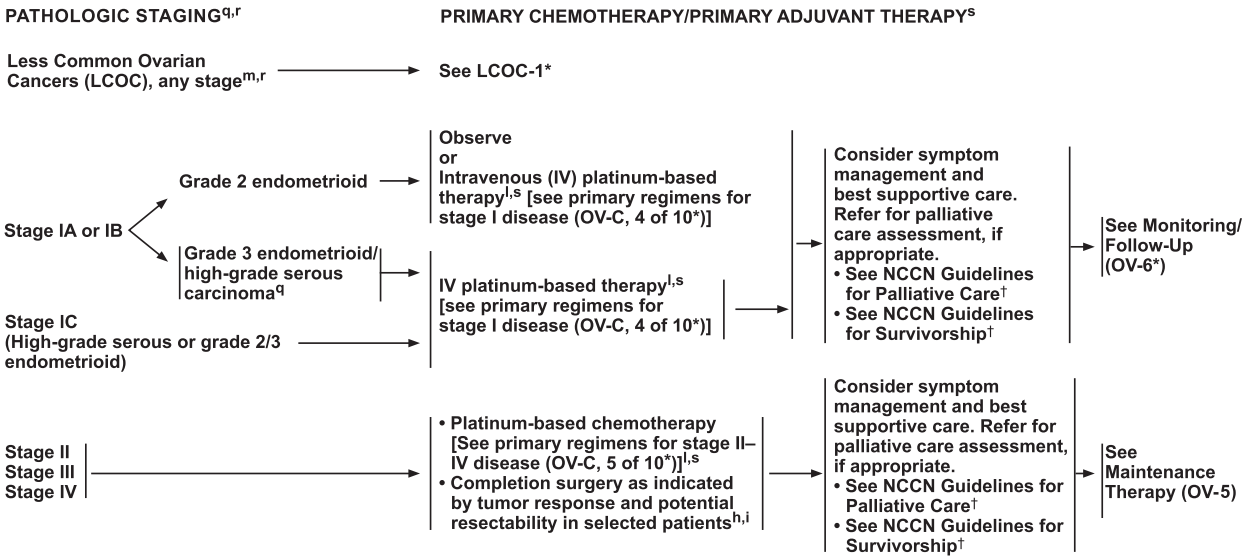
OV-1

Overview

Primary treatment of presumed ovarian, fallopian tube, or primary peritoneal cancer usually consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy (OV-1, OV-4, above and 193).[1–5] However, for some patients with early-stage disease, surgery alone (followed by observation) may be sufficient as primary treatment. In addition, for certain histologic subtypes, adjuvant therapy with hormonal agents are options that may be considered. Neoadjuvant chemotherapy (NACT) with interval debulking surgery (IDS) should be considered in patients with advanced-stage ovarian cancer who are not good candidates for upfront primary debulking surgery (PDS) due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced.[6,7] Emerging data supports an increasing role of PARP inhibitors in the management of ovarian cancer.[8] In the primary treatment setting, PARP inhibitors have been incorporated as NCCN recommended maintenance therapy options for select patients after first-line chemotherapy (see OV-5, page 194). Each of these primary treatment options, including maintenance therapy options after first-line chemotherapy, are described in more detail subsequently. For all patients with suspected or confirmed ovarian cancer, a gynecologic oncologist should be involved in assessing whether a patient is a suitable surgical candidate and/or an appropriate candidate for NACT and consideration of laparoscopic evaluation to determine feasibility of debulking surgery. The NCCN Guidelines recommend symptom management and best supportive care for all patients; women should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care, available at NCCN.org).[9–11] This text is written to reflect the recommendations in v1.2020; revisions for the 1.2021 version are underway. For the most recent and complete NCCN Guidelines for Ovarian Cancer, visit NCCN.org.

Primary Surgery

Based on published improved outcomes, it is recommended that a gynecologic oncologist be the provider to determine the best surgical approach and perform the appropriate primary surgery.[12–14] An open laparotomy is



[h] See Principles of Surgery (OV-A*).
[i] See Principles of Pathology (OV-B*).
[l] See Principles of Systemic Therapy (OV-C*) and Management of Drug Reactions (OV-D*).
[m] Carcinosarcoma, clear cell, mucinous, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal tumors, and germ cell tumors.
[q] Pathologists recommend categorizing serous ovarian cancer as either low-grade or high-grade. Grade 2 serous is considered high-grade.
[r] Consider expert pathologic review to confirm histologic diagnosis. See WHO Histologic Classification (OV-E*).

[s] Patients receiving primary chemotherapy will be monitored as follows:
1. Every 1–3 cycles: Physical exam and consider pelvic exam
2. Interim CBC with platelets as indicated
3. Chemistry profiles if indicated
4. CA-125 levels or other tumor markers as clinically indicated prior to each cycle of chemotherapy
5. Chest/abdominal/pelvic CT or MRI with contrast, PET/CT (skull base to mid-thigh), or PET as indicated

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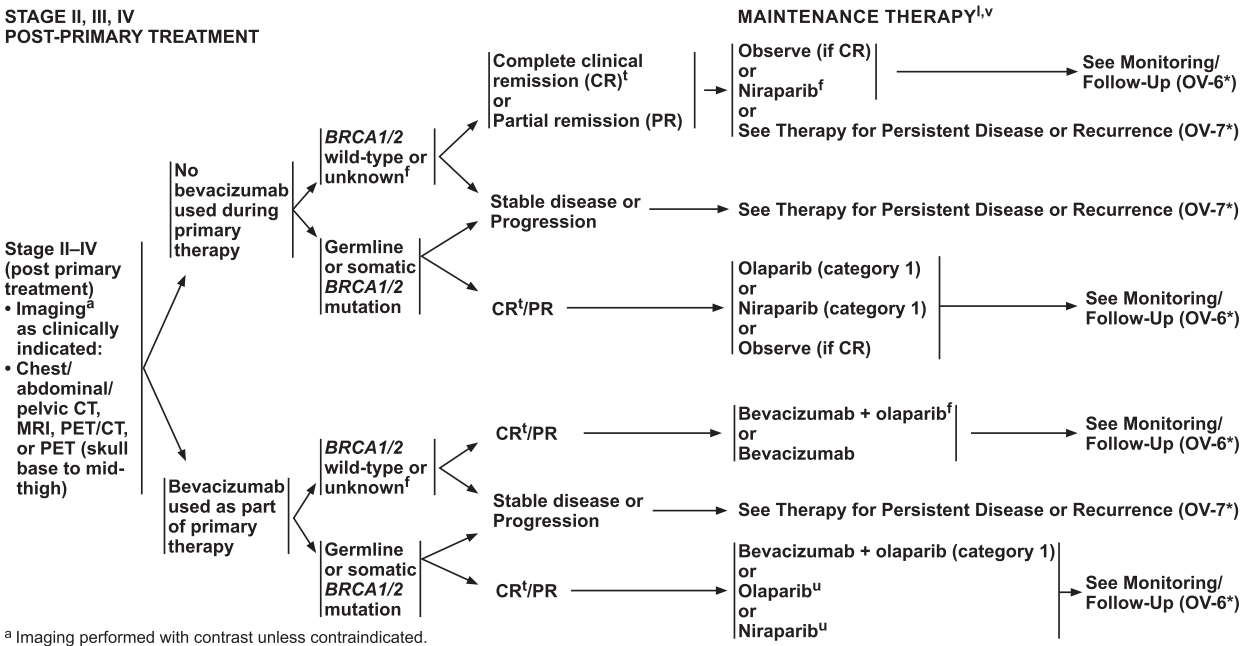
OV-4

recommended for most patients, but minimally invasive techniques may be appropriate in certain circumstances (see "Open Laparotomy Versus Minimally Invasive Techniques" on page 194). Prior to surgery, patients with advanced disease should be counseled about port placement if intraperitoneal (IP) chemotherapy is being considered. Intraoperative pathologic evaluation with frozen sections may assist in management by providing confirmation of diagnosis and cancer type and providing information about the extent of disease. For all procedures, the surgeon should describe the following in the operative report: (1) the extent of initial disease in the pelvis, mid abdomen, and upper abdomen before debulking; (2) whether a complete or incomplete resection was achieved, and (3) if resection was incomplete, the amount and size of residual disease in the aforementioned areas after debulking.[15]

For most patients presenting with suspected malignant ovarian, fallopian tube, or primary peritoneal neoplasm, initial surgery should include a hysterectomy (if uterus present) and bilateral salpingo-oophorectomy (BSO) with comprehensive staging and debulking as indicated.[5,16,17] This is the recommended approach for stage IA–IV if optimal cytoreduction appears feasible, the patient is a surgical candidate, and fertility is not a concern. It is described in greater detail in "Debulking Surgery for Newly-Diagnosed Disease" (page 195).

For patients with early stage disease who wish to preserve fertility, less-extensive surgery may be an option, as described in "Fertility Sparing Options for Stage I Disease" (page 195).

NACT with IDS should be considered for patients with advanced-stage ovarian cancer who are not good candidates for PDS due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced.[6,7] The anticipated benefit from NACT is to allow for medical improvement of the patient and/or clinical response that would increase the likelihood of optimal cytoreduction at IDS. Patients treated with NACT and IDS should also receive postoperative adjuvant chemotherapy. See sections entitled "Neoadjuvant Chemotherapy" and "Interval Debulking Surgery," in the full NCCN Guidelines for Ovarian Cancer (available online at NCCN.org). As



[a] Imaging performed with contrast unless contraindicated.
[f] In the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).
[l] See Principles of Systemic Therapy (OV-C*) and Management of Drug Reactions (OV-D*).
[t] No definitive evidence of disease.
[u] After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARP inhibitor (olaparib or niraparib) for patients with a germline or somatic *BRCA1/2* mutation. However, based on the magnitude of benefit of PARP inhibitor maintenance therapy for other subgroups, single-agent PARP inhibitors can be considered.
[v] Data are limited for maintenance therapy with a PARP inhibitor for patients with stage II disease.

*Available online, in these guidelines, at NCCN.org.

OV-5

described in "Laparoscopic Evaluation Prior to Resection" (page 195), for certain patients with bulky disease, a minimally invasive procedure may be appropriate for obtaining biopsy material to confirm diagnosis and/or for molecular testing, and for determining whether optimal cytoreduction is possible.

Open Laparotomy Versus Minimally Invasive Techniques

In most cases in which surgery is recommended as part of primary treatment of suspected malignant ovarian, fallopian tube, or primary peritoneal neoplasm, it should be performed by open laparotomy including a vertical midline abdominal incision. The surgical guidelines emphasize that an open laparotomy should be used for most patients undergoing surgical staging, primary debulking, interval debulking, or secondary cytoreduction.

Improvement of minimally invasive methods and selection of appropriate patients are the topics of much study and debate.[18–48] Minimally invasive techniques are commonly used for early-stage disease (or presumed early-stage disease), and some studies have shown no difference in surgical outcomes, recurrence rates, or survival for those who received minimally invasive versus open surgical staging.[19,21–23,26–28,32,39–42,49–53] If signs of lymph node metastasis or localized carcinomatosis are found, lymphadenectomy and complete pelvic peritonectomy may be feasible using minimally invasive techniques.[36] The NCCN Guidelines indicate that in early-stage disease, minimally invasive techniques to achieve the surgical goals may be considered in selected patients if performed by an experienced gynecologic oncologist.[16,29,54–56]

Studies in patients undergoing PDS for advanced disease have shown that debulking and surgical staging is technically feasible using minimally invasive techniques, and hysterectomy and unilateral salpingo-oophorectomy (USO) or BSO can be achieved using a minimally invasive approach.[25,30] Several studies have reported results for patients who received IDS via minimally invasive techniques, following NACT.[31,34,35,37,47] These studies have shown that for patients undergoing IDS, minimally invasive approaches are safe, technically feasible, and can achieve optimal cytoreduction, cancer-

specific survival may be worse (than with laparotomy) if patients are not carefully selected, and patients with extensive disease will likely need to be converted to open lapartomy.[31,34,35,37,47] The NCCN Guidelines recommend that in select patients (who have undergone NACT), minimally invasive procedures may be used for IDS, provided that optimal debulking can be achieved. If the patient cannot be optimally debulked using minimally invasive techniques, either in the PDS or IDS setting, then they should be converted to an open procedure.

Laparoscopic Evaluation Prior To Resection

In select patients with advanced-stage disease, minimally invasive procedures (assessment laparoscopy) may be used to assess whether optimal cytoreduction is likely to be achieved by PDS, to determine whether NACT may be a better initial treatment option.[57–68] A randomized trial assessed whether laparoscopy would be useful to predict the ability achieve optimal cytoreduction (<1 cm residual disease). Optimal cytoreduction was achieved in 90% (92/102) of patients randomized to the assessment laparoscopy arm compared with 61% (60/99) patients who were randomized to the laparotomy without assessment laparoscopy arm (relative risk, 0.25; 95% CI, 0.13– 0.47; $P<.001$).[63] Assessment laparoscopy to evaluate extent of disease and feasibility of resection was used frequently in the large prospective trials validating NACT and IDS and was required in one of these trials (SCORPION).[68–72]

Fertility Sparing Options for Stage I Disease

Fertility preservation is an evolving field and area of active research, with many approaches being explored, and many patient- and case-specific factors to consider, especially for those with malignancies.[73–75] Patients who wish to retain fertility options should be referred to a reproductive endocrinologist for preoperative evaluation and consultation. Large retrospective studies and meta-analyses have found that for stage I epithelial ovarian cancer, fertility-sparing surgery did not appear to compromise disease-free survival (DFS) or overall survival (OS) compared with radical surgery.[76–85] Although clear cell histology is associated with increased risk of poor outcomes,[83] some studies have shown that even among patients with stage I clear cell, fertility-sparing surgery does not increase risk of relapse or shorten survival compared with radical surgery.[77,78,81,82,85] Large retrospective studies among patients with stage I borderline ovarian tumors have found that recurrence rate and survival is similar for those treated with fertility sparing versus radical surgery.[86–89] In retrospective studies, including multivariate analyses, fertility sparing surgery does not appear to be associated with poorer outcomes (DFS, PFS, OS) compared with more extensive surgery in patients with stage I germ cell tumors and sex-cord stromal tumors.[90–105] Fertility-sparing surgery may be considered for patients who wish to preserve fertility and have apparent early-stage disease and/or low-risk tumors, such as early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, or malignant sex cord stromal tumors. Even if the contralateral ovary cannot be spared, uterine preservation can be considered as it allows for potential future assisted reproductive approaches. A USO (preserving the uterus and contralateral ovary/fallopian tube) and comprehensive surgical staging may be adequate for select patients who wish to preserve fertility and appear to have stage IA unilateral tumors.[106–111] For those with bilateral stage IB tumors who wish to maintain fertility, a BSO (preserving the uterus) and comprehensive surgical staging can be considered. In patients undergoing USO or BSO, comprehensive surgical staging should still be performed in most patients to rule out occult higher-stage disease, because data show that approximately 30% of patients (with presumed early-stage disease) are upstaged after undergoing complete staging surgery.[23,27,28,112–116] Comprehensive surgical staging may be omitted in pediatric/adolescent patients with clinically apparent early-stage malignant germ cell tumors based on the pediatric surgical literature suggesting that incomplete staging does not result in poorer outcomes (OS).[117] For adults with apparent stage I malignant ovarian germ cell tumors, comprehensive staging is recommended based on results from retrospective studies suggesting that incomplete surgical staging may be associated with increased risk of recurrence[118,119]; although others found no relationship between incomplete staging and DFS.[120]

Debulking Surgery for Newly-Diagnosed Disease

Debulking surgery is widely accepted as an important component of initial treatment of patients with clinical stage II, III, or IV disease, and multiple retrospective studies have contributed to the understanding of the extent of debulking needed to achieve maximal cytoreduction.[3,4,14,108,112,121–123] Optimal cytoreduction is defined as residual disease less than 1 cm in maximum diameter or thickness[17,108,124–126]; however, maximal effort should be made to remove all gross disease since resection to R0 offers superior survival outcomes.[121,127] Although debulking surgery is the standard of care, this recommendation is based on retrospective data (and thus is not a category 1 recommendation).[126] In general, the procedures described in this section should be part of the surgical management of patients with ovarian, fallopian tube, or primary peritoneal cancer in an effort to fully stage patients and to achieve maximal debulking preferable to resection of all visible disease

in appropriate circumstances and at least to less than 1-cm residual disease if complete cytoreduction is not feasible.[128–130] These procedures also apply to many of the LCOC.

For patients with newly-diagnosed epithelial ovarian cancer apparently confined to an ovary or to the pelvis, the goal of surgery is to achieve complete cytoreduction of all pelvic disease and to evaluate for occult disease in the upper abdomen or retroperitoneum. For patients with newly diagnosed invasive epithelial ovarian cancer involving the pelvis and upper abdomen, the goal is to achieve optimal cytoreduction of all abdominal, pelvic, and retroperitoneal disease.

On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations. For obvious disease beyond the ovaries, cytologic assessment of ascites and/or lavage specimens will not alter stage or management. For patients with disease apparently confined to an ovary or to the pelvis, all peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm.

Hysterectomy and BSO should be performed. Although hysterectomy is recommended for most patients, USO or BSO with uterine preservation may be considered for selected patients with apparent stage IA/IB disease desiring to preserve fertility (see "Fertility Sparing Options for Stage I Disease," page 195). Every effort should be made to keep an encapsulated ovarian mass intact during removal.[26,131] For young patients who will abruptly enter menopause after surgery, various supportive care measures may be used to help decrease hot flashes and other symptoms, and potentially reduce the risk of other systemic comorbidities that are more likely with surgical menopause.[132–135] Hormone replacement therapy has not been shown to worsen survival in premenopausal patients with gynecologic cancers, but limited perspective data exist.[136,137]

For patients with disease apparently confined to an ovary or to the pelvis (presumed stage I/II), omentectomy should be performed to rule out higher-stage disease. For patients with disease involving the pelvis and upper abdomen (stage III/IV), all involved omentum should be removed.

The use of systematic lymphadenectomy is an area of controversy. For patients with presumed early stage, a randomized trial showed that systematic aortic and pelvic lymphadenectomy improved detection of metastatic nodes compared with node sampling (positive nodes found in 9% vs 22%; P=.007), but was not associated with improved PFS or OS.[138] Operating time and the proportion of patients requiring blood transfusions was significantly higher for those who underwent systematic lymphadenectomy.[138] However, meta-analyses that included retrospective or observational studies have reported that systematic lymphadenectomy improves OS in patients with early stage disease, even though it does not improve PFS.[139,140] Similar to this randomized controlled trial, other prospective studies using systematic lymphadenectomy have found 3%–14% of patients had positive lymph nodes.[141–145]

For patients with advanced ovarian cancer, some early prospective studies suggested that systematic lymphadenectomy improved survival.[146,147] An early international randomized trial in patients with stage IIIB–IV (optimally debulked) epithelial ovarian cancer found that systematic lymphadenectomy improved PFS compared with resection of bulky nodes only, although OS was not improved, operating times were longer, and more patients required blood transfusions.[148] A randomized study of patients with stage IA–IV disease undergoing second look surgery found that although systematic lymphadenectomy increased detection of nodal metastases compared with resection of bulky nodes only (positive nodes found in 24% vs 13%; P=.02), this did not translate into improved PFS or OS in the whole population or in subpopulations based on stage or extent resection.[149] As in other studies, systematic lymphadenectomy was associated with longer operating times, more blood loss and transfusions, and longer hospital stays.[149] More recently, a large randomized trial (LION, NCT00712218) found that in patients with stage IIB–IV ovarian cancer who had macroscopically complete resection and normal nodes both before and during surgery, lymphadenectomy did not improve PFS or OS, and was associated with increased rates of serious postoperative complications and mortality within 60 days after surgery.[150] However, meta-analyses that included data from retrospective and observational studies have found that systematic lymphadenectomy improves OS in patients with advanced disease, even though PFS is not improved.[139,140,151–153]

Pelvic and para-aortic lymph node dissection is recommended for patients with disease confined to affected ovaries or to the pelvis, and for those with more extensive disease who have tumor nodules outside the pelvis that are 2 cm or less (presumed stage IIIB). Para-aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels. The preferred method of dissecting pelvic lymph nodes is removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to

the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve.[154]

For those with more extensive disease outside of the pelvis (nodules >2 cm), suspicious and/or enlarged nodes should be resected, if possible.[148,155] Systematic lymph node dissection and resection of clinically negative nodes is not required for these patients because results will not change staging and the procedure does not appear to impact OS, based on results from randomized trials (described previously).[148–150]

Some surgeons classify debulking based on the number of procedures. Procedures that may be considered for optimal surgical cytoreduction (in all stages) include: bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.[122,127,156]

Extensive resection of upper abdominal metastases is recommended as part of debulking for patients who can tolerate this surgery, as it is associated with improved PFS and OS.[122,127]

Select patients with low-volume residual disease after surgical cytoreduction for stage II or III invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy.[157,158] In these patients, consideration should be given to placement of an IP catheter with initial surgery.[16]

Ancillary Palliative Surgical Procedures

Patients presenting with symptoms may benefit from ancillary palliative procedures performed during primary or secondary cytoreductive surgery. Decisions on the use of ancillary procedures should be made in conjunction with a gynecologic oncology surgeon or a practitioner familiar with ovarian cancer patterns of recurrence. Palliative surgical procedures that may be appropriate in select patients include paracentesis or insertion of an indwelling peritoneal catheter, thoracentesis, pleurodesis, video-assisted thorascopy, or insertion of a pleural catheter, nephrostomy or use of ureteral stents, gastrostomy tube, intestinal stents, or surgical relief of intestinal obstruction.

Analysis of Surgical Specimens

As described in the section entitled "Diagnosis, Pathology and Staging" (in these NCCN Guidelines on NCCN.org), surgical specimens should undergo pathology assessment to determine/confirm diagnosis, determine histologic subtype, and stage. Molecular testing is also appropriate for most patients; see the "Molecular Testing" section (available on NCCN.org) for detailed recommendations.

Management After Primary Surgery

In the NCCN Guidelines for Ovarian Cancer, adjuvant therapy is defined as drugs or other forms of supplemental treatment after cancer surgery intended to decrease the risk of disease recurrence or to primarily treat residual disease, whether gross or microscopic, after surgical cytoreduction. Most patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer should receive adjuvant systemic chemotherapy after primary surgery (see OV-4, page 193). Postoperative observation is an option for select patients with stage I disease, depending on cancer histologic type and substage, as shown in Table 1. Observation is considered an option in these select groups of patients with stage I disease either because survival is ˃90% with surgical treatment alone or because for low-risk disease in certain cancer types it has not been demonstrated that adjuvant chemotherapy provides clear clinical benefit compared with observation alone for those who have had complete surgical staging.[159–165] Furthermore, postoperative observation should generally only be considered for patients who have had resection of all disease and complete surgical staging to rule out the possibility of clinically occult disease that would result in upstaging. For some of the less common epithelial cancer types (mucinous, grade 1 endometrioid, low-grade serous), the benefit of adjuvant systemic therapy has not been demonstrated and observation is an option (Table 1). If analysis of a biopsy or surgical specimen shows a nonepithelial cancer type, such as sex cord stromal or germ cell tumors, a patient should be treated according to separate pathways specific for nonepithelial cancers (See LCOC-10 through LCOC-13 and corresponding Discussion text, in these guidelines, at NCCN.org).

A large variety of regimens and approaches have been tested in prospective randomized trials as postoperative therapy for patients with newly-diagnosed ovarian cancer. Most of these regimens have included intravenous chemotherapy, but IP administration of chemotherapy has also been tested, as have targeted agents and drugs from other classes. Recent trials have shown that maintenance therapy after postoperative platinum-based chemotherapy can have a positive impact on PFS in patients with advanced disease, so integration of maintenance therapy as part of postoperative management is increasing in prevalence and importance.[166–169] Selection of immediate postoperative treatment should be informed by eligibility criteria for maintenance therapy. This is discussed in greater detail in "Options After First-Line Chemotherapy" (page 209).

Based on results of phase III randomized trials, the NCCN Guidelines include several options for postoperative treatment (within 6 weeks) in patients with advanced epithelial cancers: platinum-based

Table 1. NCCN Recommended Management Options Following Up-Front Primary Surgery for Stage I Disease, Epithelial Cancer Types

		Recommended Options (Category 2A Unless Otherwise Noted)		
Cancer Type	**Pathologic Stage[a]**	**Observation**	**Standard IV Platinum-Based Chemotherapy[b]**	**Other Adjuvant Systemic Therapy**
High-grade serous carcinoma	IA/B/C	NR	Yes	NR
Grade 2 endometrioid	IA/IB	Yes	Yes	NR
Grade 3 endometrioid	IA/B/C	NR	Yes	NR
Carcinosarcoma	IA/B/C	NR	Yes	Carboplatin/ifosfamide Cisplatin/ifosfamide Paclitaxel/ifosfamide (category 2B)
Clear cell carcinoma	IA	Yes	Yes	NR
Clear cell carcinoma	IB/IC	NR	Yes	NR
Mucinous carcinoma	IA/IB	Yes	NR	NR
Mucinous carcinoma	IC	Yes	Yes	5-FU/leucovorin/oxaliplatin Capecitabine/oxaliplatin
Grade 1 endometrioid	IA/IB	Yes	NR	NR
Grade 1 endometrioid	IC	Yes (category 2B)	Yes	Hormone therapy (category 2B)[c]
Low-grade serous carcinoma	IA/IB	Yes	NR	NR
Low-grade serous carcinoma	IC	Yes (category 2B)	Yes	Hormone therapy (category 2B)[c]

Abbreviations: IV, intravenous; NR, not recommended.
[a]Stage confirmed by a complete surgical staging procedure and pathologic analysis.
[b]Regimen options for all cancer types include paclitaxel 175/carboplatin, docetaxel/carboplatin, carboplatin/liposomal doxorubicin, as shown in Table 5. Not including options for those who are elderly, have poor performance score, or comorbidities.
[c]Hormone therapy options include aromatase inhibitors (anastrozole, letrozole, exemestane), leuprolide acetate, or tamoxifen.

intravenous chemotherapy, platinum-based IV/IP chemotherapy, and platinum-based IP chemotherapy plus bevacizumab, as outlined in Table 2. Specific options and supporting data for each of these categories of treatment are described in greater detail in the sections below. For stage I disease, data are more limited, and while the NCCN Guidelines include some platinum-based intravenous chemotherapy options, IP/intravenous chemotherapy and use of bevacizumab are not recommended approaches for stage I disease (Table 1). Specific options for stage I disease are also discussed below in "Options for Stage I, Epithelial Cancer Types," (page 202). For certain rarer cancer types, there are additional recommended adjuvant treatment options, including additional chemotherapy options, chemotherapy/bevacizumab regimens (stage II–IV only), and hormonal therapies (Tables 1 and 2). More information on these options can be found in subsequent sections for specific LCOCs.

For all patients, the goals of postoperative therapy and considerations for selection and management during therapy should be discussed prior to the initiation of therapy. As for all aspects of their diagnosis and treatment of ovarian, fallopian tube, or peritoneal cancer, patients should be encouraged to participate in clinical trials. Chemosensitivity/resistance and/or other biomarker assays have been proposed for informing decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available, but the current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3). Prior to recommending chemotherapy, requirements for adequate organ function and performance status should be met.

During drug-based therapy, patients should be observed closely and treated for any complications. Appropriate blood chemistry tests should be monitored. Appropriate dose reductions and modifications of chemotherapy should be performed depending on toxicities experienced and goals of therapy. Consider scalp cooling to reduce incidence of alopecia for patients receiving chemotherapy with high rates of alopecia.[170]

Options for Intravenous Chemotherapy

Comparison of intravenous chemotherapy regimens for postoperative treatment of newly-diagnosed ovarian cancer has been the subject of many prospective randomized trials. Most of these trials have failed to show significant differences between regimens in efficacy outcomes (eg, PFS, OS), but many have shown differences in toxicity profile, ability to complete the planned therapy, and quality of life (QOL). For this reason, the NCCN Guidelines includes a number of recommended options for postoperative intravenous chemotherapy in

Table 2. NCCN Recommended Management Options Following Up-Front Primary Surgery for Stage II–IV[a]

Cancer Type	Recommended Options (Category 2A Unless Otherwise Noted)	
	Standard IV Platinum-Based Chemotherapy ± Bevacizumab[b]	Other
High-grade serous	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only)
Grade 2/3 endometrioid	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only)
Carcinosarcoma	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only) Carboplatin/ifosfamide Cisplatin/ifosfamide Paclitaxel/ifosfamide (category 2B)
Clear cell carcinoma	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only)
Mucinous carcinoma	Yes	5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab) Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)
Low-grade serous	Yes	Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)
Grade 1 endometrioid	Yes	Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)

Abbreviations: IP, intraperitoneal; IV, intravenous.
[a]Not including options for those who are elderly, have poor performance score, or comorbidities.
[b]Paclitaxel 175/carboplatin, paclitaxel weekly/carboplatin weekly, docetaxel/carboplatin, carboplatin/liposomal doxorubicin, paclitaxel weekly/carboplatin q3wk, paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab (ICON-7 & GOG-218), as shown in Table 3 and Table 7.

patients with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer. The NCCN recommended options for platinum-based intravenous chemotherapy to treat stage II–IV epithelial disease are summarized in Table 3, along with the list of trials that tested these regimens (last column).[171–179] Supplemental eTable 1 and eTable 2 (available at JNCCN.org) and Table 4 summarize the results of randomized trials that tested these recommended regimens.[171–175,177–196] The most commonly-used regimen, paclitaxel 175/carboplatin, has been considered the standard postoperative chemotherapy for ovarian cancer for many years, so there are many studies in which it has been tested (eTable 1, eTable 2, and Table 4). The history supporting these options is summarized subsequently.

Results from multiple early trials suggested that regimens that included a platinum agent resulted in better response rates and PFS (compared with other chemotherapy options).[197,198] Subsequent trials aimed at determining which platinum-based combinations are the most effective and safe.

Selecting a Platinum Agent

Multiple randomized trials compared carboplatin versus cisplatin, either alone or in combination with other agents (examples in eTable 1, eTable 2).[181–184,199–204] All these trials showed equivalent efficacy, but differences in toxicity profiles and QOL. Cisplatin was associated with higher rates of neurotoxicity, gastrointestinal toxicities (nausea, emesis), renal toxicity, metabolic toxicities, anemia, and alopecia, while carboplatin was associated with higher rates of thrombocytopenia and granulocytopenia.[181–184,199–204] The AGO-OVAR-3 study found that QOL was significantly better with carboplatin/paclitaxel versus cisplatin/paclitaxel, both in global QOL metrics and on various subscales.[183,184] Several randomized studies tested alternating carboplatin and cisplatin every other course, but found that efficacy was similar and toxicity somewhat worse than using carboplatin for every course.[188,204] Based on results from all these studies carboplatin is the recommended platinum agent for postoperative intravenous chemotherapy in patients with newly-diagnosed ovarian, fallopian tube, and primary peritoneal cancers.

Selecting A Non-Platinum Agent (for Use in Combination With a Platinum Agent)

Many different chemotherapy agents have been tested in combination with platinum agents as options for intravenous chemotherapy in newly-diagnosed ovarian cancer. Large randomized trials have compared various platinum-based doublet, triplet, and quadruplet combinations with cyclophosphamide, paclitaxel, docetaxel, topotecan, doxorubicin, epirubicin, gemcitabine, topotecan, and melphalan.[178,179,187,189–191,193–196,205–211] Trials that compared platinum-based doublets with cyclophosphamide versus paclitaxel showed that paclitaxel was associated with significantly better response rate, PFS, and OS.[205–207] Thus, paclitaxel is preferred over cyclophosphamide for platinum-based combination therapy in the first-line setting. Based on results from

Table 3. IV Chemotherapy: NCCN Recommended Options for Stage II–IV, All Epithelial Cancer Types[a,b]

Regimen Short Name	Detailed Dosing per Cycle[c]	Cycle Length, wk	No. of Cycles	Category[d]	Preference Category	Randomized Trials
Paclitaxel 175/carboplatin	Paclitaxel, 175 mg/m² IV over 3 hr followed by carboplatin, AUC 5–6[e] IV over 30–60 min on D1	3	6	2A	Preferred	See eTables 1 and 2
Paclitaxel weekly/carboplatin weekly	Paclitaxel, 60 mg/m² IV over 1 hr followed by carboplatin, AUC 2 IV over 30 min, weekly	3	6 (18 wk)	2A	Other recommended	MITO-7[171] ICON8[172,173]
Paclitaxel weekly/carboplatin q3wk	Dose-dense paclitaxel, 80 mg/m² IV over 1 hr on D1, 8, and 15 followed by carboplatin, AUC 5–6[e] IV over 30–60 min on D1	3	6	2A	Other recommended	ICON8[172,173] JGOG-3016[174–176] GOG-0262[177]
Carboplatin/liposomal doxorubicin	Carboplatin, AUC, 5 IV over 30–60 min + pegylated liposomal doxorubicin, 30 mg/m² IV over 1 hr[f]	4	6	2A	Other recommended	MITO-2[178]
Docetaxel/carboplatin	Docetaxel, 60–75 mg/m² IV over 1 hr followed by carboplatin, AUC, 5–6 IV over 30–60 min on D1	3	6	2A	Other recommended	SCOTROC1[179]

Abbreviations: AUC, area under the curve; D, day of cycle; IV, intravenous.
[a]Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma; stage IC only for mucinous, low-grade serous, and grade 1 endometrioid.
[b]These options are primarily for patients with age ≤70 years, good performance status, and without comorbidities. For patients who are elderly, have poor performance score, or comorbidities, see alternate treatment options discussed in the section titled "Options for Patients Who Are Elderly or Have Comorbidities or Poor Performance Score" (available online, in these guidelines, at NCCN.org).
[c]Infusion times may need to be adjusted for patients with prior hypersensitivity reaction(s). See "Management of Drug Reactions" (page OV-D; available online, in these guidelines, at NCCN.org).
[d]NCCN category of evidence and consensus.
[e]Note that carboplatin dosing may be revised based on changes in serum creatinine methodology (see FDA carboplatin dosing statement; https://www.mskcc.org/clinical-updates/new-guidelines-carboplatin-dosing). The AUC of 5 to 6 for carboplatin reflects contemporary treatment.
[f]For the first cycle of pegylated liposomal doxorubicin, infuse at 1 mg/min and make sure that the patient does not have a reaction.

randomized trials showing improved safety and QOL with carboplatin/paclitaxel versus cisplatin/paclitaxel (eTable 1),[181–184] carboplatin/paclitaxel became the "standard" combination therapy option for postoperative first-line intravenous chemotherapy in patients with ovarian, fallopian tube, or primary peritoneal cancer. Most subsequent trials used this doublet, usually paclitaxel 175 mg/m² plus carboplatin AUC 5-6, given on day 1 of a 21-day cycle, as the control arm (see examples in eTable 1, eTable 2, and Table 4). This regimen is also a recommended option in the NCCN Guidelines (Table 3).

Two other platinum-based doublets have shown similar efficacy to carboplatin/paclitaxel, but with different safety profiles.[178,179] The SCOTROC1 study found that docetaxel/carboplatin resulted in similar PFS, OS, and global QOL scores as paclitaxel/carboplatin, and was associated with lower rates of neurotoxicity, arthralgia, myalgia, alopecia, and abdominal pain, but higher rates of other adverse events (AEs; gastrointestinal, peripheral edema, allergic reactions, and nail changes; Table 4).[179] The MITO-2 trial found that pegylated liposomal doxorubicin [PLD]/carboplatin was associated with a higher response rate but similar PFS and OS as paclitaxel/carboplatin (Table 4).[178] PLD/carboplatin was associated with higher rates of certain hematologic toxicities, skin toxicity, and stomatitis, but lower rates of neurotoxicity and alopecia than the paclitaxel/carboplatin control.[178] Global QOL and most functional domains and symptom scales were the same across treatment arms, PLD/carboplatin was associated with worse scores for certain patient-reported toxicities.[178] Therefore, this regimen may be useful in select patients at high risk for neurotoxicity or those who would like to avoid alopecia. The docetaxel/carboplatin and liposomal doxorubicin/carboplatin regimens are both recommended options in the NCCN Guidelines (Table 3), and may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes).[212]

Randomized trials testing platinum-based triplet or quadruplet regimens have generally found that these do not improve efficacy but are associated with worse toxicity when compared with platinum-based doublets[187,189–191,193–196] or single-agent platinum regimens.[208,209] Examples of platinum-based triplet and quadruplet regimens that have been compared with the standard paclitaxel/carboplatin regimen are in eTable 2. One study showed that adding gemcitabine to carboplatin/paclitaxel actually resulted in worse PFS compared with carboplatin/paclitaxel alone (eTable 2).[194]

Carboplatin/Paclitaxel Dosing Options

As noted above, for postoperative first-line treatment of ovarian cancer, the most commonly used dosing for intravenous carboplatin/paclitaxel combination therapy is Paclitaxel 175 mg/m² + carboplatin AUC 5-6, both given on day 1 of a 3-week cycle. As summarized in Table 4, multiple randomized studies have compared different dosing schedules for intravenous carboplatin

Table 4. IV Chemotherapy: Randomized Trials Comparing Paclitaxel 175/Carboplatin[a] With Other Recommended Regimens

Trial	Stage	N[b]	First-Line Systemic Therapy[c] Dosing per Cycle	Cycle Length, wk	No. of Cycles	Efficacy[d] HR [95% CI]	Safety/QoL[e]
ICON3[187]	IC–IV	1,421	Carboplatin, AUC ≥5[f] D1	3	6	NS	Less alopecia, grade 3/4; fever, grade 3/4; sensory neuropathy, grade 2/3; motor neuropathy, grade 3/4
SCOTROC1[179]	IC–IV	1,077	Docetaxel, 75 mg/m² D1 + carboplatin, AUC 5 D1	3	6[g]	NS	More GI, peripheral edema, allergic reactions, nail changes Less neurosensory and neuromotor toxicity, arthralgia, alopecia, abdominal pain Global QoL NS
MITO-2, NCT00326456[178]	IC–V	820	Carboplatin, AUC 5 D1 + PLD, 30 mg/m² D1	3	3–6[i]	NS	More anemia, thrombocytopenia, skin toxicity, stomatitis Less neuropathy, alopecia, diarrhea QoL: less diarrhea after 3 cycles and loss of appetite after 3 cycles
MITO-7, NCT00660842[171]	IC–IV	822	Paclitaxel, 60 mg/m² D1, 8, 15 + carboplatin, AUC 2 D1, 8, 15	3	6	NS	More pulmonary toxicity Less neutropenia, febrile neutropenia, thrombocytopenia, neuropathy, hair loss, vomiting Better QoL
JGOG-3016, NCT00226915[174,175]	II–IV	631	Paclitaxel, 80 mg/m² D1, 8, 15[h] + carboplatin, AUC 6 D1	3	6	Better PFS: 0.76 [0.62–0.91]; *P*=.0037 Better OS: 0.79 [0.63–0.99]; *P*=.039	More grade 3/4 anemia Global QoL NS; worse QoL on FACT-T subscale
GOG-0262; NCT01167712[177]	II–IV	112	Paclitaxel, 80 mg/m² D1, 8, 15 + carboplatin, AUC 6 D1	3	6	Better PFS: 0.62 [0.40–0.95]; *P*=.03	More anemia and sensory neuropathy Less neutropenia Worse QoL on FACT-O TOI
		580	Paclitaxel, 80 mg/m² D1, 8, 15 + carboplatin, AUC 6 D1 + bevacizumab, 15 m/kg D1 cycles 2–6[j]	3	6	NS	
ICON8, NCT01654146[172,173]	IC–IV	1,566	Paclitaxel, 80 mg/m² IV D1, 8, 15 + carboplatin, AUC 5–6 IV D1	3	6	NS	More grade 3/4 AEs, including uncomplicated neutropenia, anemia Worse Global QoL
			Paclitaxel, 80 mg/m² IV D1, 8, 15 + carboplatin, AUC 2 IV D1, 8, 15	3	6	NS	More grade 3/4 AEs, including uncomplicated neutropenia, carboplatin hypersensitivity reaction Worse Global QoL

Abbreviations: AE, adverse event; AUC, area under the curve; D, day of cycle; GI, gastrointestinal; HR, hazard ratio; IV, intravenous; NS, not significant; OS, overall survival; PLD, pegylated liposomal doxorubicin; PFS, progression-free survival; QoL, quality of life.

[a]Unless otherwise noted, each of the trials listed used the following regimen as comparator: paclitaxel, 175 mg/m² D1 + carboplatin, AUC 5–6 D1, q3wk x 6 cycles.

[b]Total number of patients randomized, including those in the paclitaxel 175/carboplatin control arm.

[c]Regimen compared with paclitaxel 175/carboplatin.

[d]Efficacy outcomes compared with paclitaxel 175/carboplatin; NS indicates no significant difference between regimens for PFS and/or OS. HR with 95% confidence interval and *P* value are provided if statistically significant.

[e]Toxicity or QoL compared with paclitaxel 175/carboplatin regimen.

[f]Both arms in ICON3 used carboplatin AUC ≥5.

[g]In SCOTROC1, patients responding after 6 cycles were allowed to continue on carboplatin alone for another 3 cycles.

[h]JGOG-3016, the paclitaxel dosage in the control arm was 180 mg/m² (instead of 175 mg/m² as in the other trials).

[i]For those with good response after 3 cycles, MITO-2 allowed an additional 3 cycles

[j]In GOG-0262, those who opted to have bevacizumab and were undergoing neoadjuvant chemotherapy (3 cycles) + interval debulking surgery + adjuvant chemotherapy (3 cycles), bevacizumab was administered cycles 2, 5, 6.

and paclitaxel regimens as first-line postoperative therapy for ovarian cancer.[171–175,177,213,214] Three different randomized trials (JGOG-3016, GOG-0262, and ICON8) tested "dose-dense" weekly paclitaxel dosing of 80 mg/m² combined with the standard carboplatin dosing (AUC 6, day 1, every 3 weeks).[172,174,175,177] JGOG-3016 results showed that this regimen improved PFS and OS, GOG-0262 showed that this regimen improved PFS (in the subset of patients who were not receiving concurrent bevacizumab), and ICON8 found no significant improvements in PFS or OS (Table 4). All 3 trials reported increased rates of neutropenia and signs of worse QOL among patients treated with the dose dense regimen.

Two randomized trials (MITO-7, ICON8) compared standard paclitaxel/carboplatin dosing with weekly paclitaxel (60 or 80 mg/m^2) plus weekly carboplatin (AUC 2), and found no significant differences in efficacy outcomes.[171–173] MITO-7, which tested 60 mg/m^2 paclitaxel, showed higher rates of pulmonary toxicity, but lower rates of neutropenia, febrile neutropenia, thrombocytopenia, neuropathy, hair loss, and vomiting, and significant improvement in QOL.[171] ICON8, which tested 80 mg/m^2 paclitaxel, showed higher rates of neutropenia and carboplatin hypersensitivity reaction, and worse global QOL compared with standard carboplatin/paclitaxel dosing.[172,173] Based on these results, if a weekly regimen is used, the paclitaxel weekly/carboplatin weekly regimen using 60 mg/m^2 paclitaxel is the recommended option (for stage II–IV disease; Table 3).

Options for Stage I, Epithelial Cancer Types

Most of the patients had stage III–IV disease in randomized trials testing intravenous chemotherapy as postoperative first-line treatment of ovarian cancer. More recent trials allowed patients with stage II–IV disease, but only some included patients with select stage I disease (eTable 1, eTable 2, and Table 4). Therefore, the list of recommended options is much shorter for patients with stage I disease, as summarized in Table 5, which also shows trials that tested the recommended regimens (last column).[171–173,178,179,187,194,215,216] Patients with stage I disease were included in randomized trials comparing intravenous paclitaxel/carboplatin (standard dosing) with single-agent carboplatin (ICON3),[187] docetaxel/carboplatin (SCOTROC1),[179] PLD/carboplatin (MITO-2),[178] and weekly paclitaxel/weekly carboplatin (MITO-7, ICON8).[171–173] Of these, the first three are recommended options for stage I disease in epithelial cancer types. Paclitaxel weekly/carboplatin weekly is more logistically challenging to administer and is therefore not often used in the setting of stage I disease, given the lower risk of recurrence (compared with more advanced disease). Patients with stage I disease have also been included in some randomized trials testing triplet or quadruplet regimens,[187,194,209,210] but the added toxicity of these regimens with no clear impact on efficacy makes options inappropriate for stage I.

Number of Cycles

Recommendations for the number of cycles of treatment vary with the stage of the disease. Panel members had an extensive discussion about the number of cycles of chemotherapy that should be recommended for patients with advanced-stage disease. There is no evidence confirming that more than 6 cycles of combination chemotherapy are required for initial chemotherapy. Early randomized studies showed that patients treated with 8 or 10 cycles of adjuvant first-line platinum-based intravenous chemotherapy had similar survival but experienced worse toxicity than those treated with only 5 cycles.[217,218] For the regimens recommended in the NCCN Guidelines (for postoperative first-line intravenous chemotherapy), most of the supporting phase III randomized trials tested 6 cycles of therapy (see eTable 1, eTable 2, and Table 4). Although cross-trial comparisons should be interpreted with caution, the few trials that used >6 cycles,[190,191,195,196] did not appear to show better outcomes than those that used 6 cycles. Also, it has been noted that among the 2 trials showing improved efficacy with first-line cisplatin/paclitaxel versus cisplatin/cyclophosphamide in patients with advanced ovarian cancer, the later trial that allowed continuation beyond 6 cycles, up to 9 cycles reported a smaller treatment effect (on PFS, OS) and had higher rates of neurotoxicity, suggesting that treatment beyond 6 cycles is unlikely to provide additional clinical benefit.[205,206] One randomized trial (NCT00102375) showed that adding 4 cycles of topotecan after 6 cycles of carboplatin/paclitaxel did not improve PFS or OS, or even response among those with measurable disease (eTable 2).[190] The phase III randomized trial GOG-157 compared 3 versus 6 cycles of paclitaxel/carboplatin as postoperative first-line intravenous chemotherapy for patients with stage I–II epithelial ovarian cancer at high risk, defined as stage IA/IB with grade 3 or clear cell, or stage IC/II with any grade.[215,216] For the ITT population, the number of cycles did not have a significant impact on RFS or OS, whereas 6 cycles was associated with higher rates of grade 3-4 neurotoxicity, grade 4 granulocytopenia, and grade 2–4 anemia.[215,216] After a median of 91 months of follow-up, exploratory analysis by cancer type showed that 6 cycles (versus 3) was associated with significant improvement in RFS for patients with serous histology (hazard ratio [HR], 0.30 [95% CI, 0.13-0.72]; P=.007), but this effect was not seen for any other cancer subtypes (endometrioid, clear cell, mucinous), and the number of cycles did not significantly impact OS for any subgroup.[216] Based on these data the NCCN Guidelines recommend 6 cycles adjuvant intravenous chemotherapy for stage I high-grade serous carcinoma, 3 cycle for other stage I epithelial cancers, and 6 cycles for stage II–IV epithelial disease (regardless of tumor type).

Targeted Agents

Bevacizumab in the First-Line Setting

Two phase 3 randomized trials, GOG-0218 and ICON7, tested the effects of adding bevacizumab during first-line platinum-based combination chemotherapy and as single-agent maintenance therapy after first-line chemotherapy (for patients who had not progressed during initial

Table 5. IV Chemotherapy: Regimens Recommended for Stage I, All Epithelial Cancer Types[a,b]

Regimen Short Name	Detailed Dosing per Cycle[c]	Cycle Length, wk	No. of Cycles	Category[d]	Preference Category	Randomized Trials
Paclitaxel 175/carboplatin	Paclitaxel, 175 mg/m² IV over 3 hr followed by carboplatin, AUC 5–6[e] IV over 30–60 min on D1	3	High-grade serous: 6 All other: 3	2A	Preferred	ICON3[187] GOG-157[215,216] du Bois et al, 2010 [194] SCOTROC1[179] MITO-2[178] MITO-7[171] ICON8[172,173]
Carboplatin/liposomal doxorubicin	Carboplatin, AUC 5 IV over 30–60 min+ PLD, 30 mg/m² IV over 1 hr[f]	4	High-grade serous: 6 All other: 3	2A	Other recommended	MITO-2[178]
Docetaxel/carboplatin	Docetaxel, 60–75 mg/m² IV over 1 hr followed by carboplatin, AUC 5–6 IV over 30–60 min on D1	3	High-grade serous: 6 All other: 3	2A	Other recommended	SCOTROC1[179]

Abbreviations: AUC, area under the curve; D, day of cycle; IV, intravenous; PLD, pegylated liposomal doxorubicin.
[a]Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma; stage IC only for mucinous, low-grade serous, and grade 1 endometrioid.
[b]These options are primarily for patients with age ≤70 years, good performance status, and without comorbidities. For patients who are elderly, have poor performance score or comorbidities, see alternate treatment options discussed in the section entitled "Options for Patients Who Are Elderly or Have Comorbidities or Poor Performance Score" (available online, in these Guidelines, at NCCN.org).
[c]Infusion times may need to be adjusted for patients with prior hypersensitivity reaction(s). See "Management of Drug Reactions" (OV-D, available online, in these Guidelines, at NCCN.org).
[d]NCCN category of evidence and consensus.
[e]Note that carboplatin dosing may be revised based on changes in serum creatinine methodology (see FDA carboplatin dosing statement; https://www.mskcc.org/clinical-updates/new-guidelines-carboplatin-dosing). The AUC of 5 to 6 for carboplatin reflects contemporary treatment.
[f]For the first cycle of PLD, infuse at 1 mg/min and make sure that the patient does not have a reaction.

treatment with chemotherapy + bevacizumab).[219–221] The study design and results from these trials are summarized in Table 6.[219–223]

Bevacizumab in the First-line Setting: Efficacy

In GOG-0218, although PFS was similar for patients treated with carboplatin/paclitaxel (Arm 1, control) versus those who also had bevacizumab during initial treatment (Arm 2, carboplatin/paclitaxel/bevacizumab), patients treated with carboplatin/paclitaxel/bevacizumab followed by maintenance with single-agent bevacizumab (Arm 3) had a 3-month improvement in median PFS compared with the control arm (See Table 6).[219,222] OS was not significantly different across all 3 arms (Table 6), even after long-term follow-up.[219,222,223] The effects of treatment on PFS and OS were nonproportional over time, however, with the greatest difference between arms around 15 months, and the Kaplan-Meier curves converging again about 9 months later. Results from ICON7 were similar, with results from the primary analysis (median follow-up 19.4 months) showing longer PFS with carboplatin/paclitaxel/bevacizumab, followed by single-agent bevacizumab maintenance therapy (Arm 2) compared with carboplatin/paclitaxel along (Arm 1).[220] Analyses after longer follow-up (median 48.9 months), however, showed no significant treatment-dependent differences in PFS or OS (Table 6).[221] Again the effects were nonproportional over time, with the treatment-dependent differences in PFS and OS increasing to a peak between 12–18 months, and the Kaplan-Meier curves subsequently converging.[221]

For both GOG-0218 and ICON7, outcomes with upfront paclitaxel/carboplatin/bevacizumab plus single-agent bevacizumab maintenance (Arm 3 in GOG-0218, Arm 2 in ICON7) were compared with control (paclitaxel/carboplatin alone, Arm 1) for a variety of patient subgroups to determine whether there are particular groups of patients that benefit from bevacizumab. Results across both studies showed that patients with features associated with poor prognosis tend to derive a greater benefit from the addition of bevacizumab.[219] Analyses of data from GOG 0218 showed that bevacizumab improved OS in patients with stage IV disease and in patients with ascites, another high-risk group (more likely to have poor performance score, high-grade serous histology, higher median pretreatment CA-125 level, suboptimal surgical cytoreduction).[222–224] For ICON7, although after long-term follow up (median 48.9 months) there were no significant effects of bevacizumab on PFS or OS for the total population, subgroup analyses identified a high-risk group for which bevacizumab improved both PFS (median PFS for Arm 1 vs Arm 2: 10.5 vs 16.0 months; HR, 0.73 [95% CI, 0.61-0.88]; P=.001) and OS (median OS for Arm 1 vs Arm 2: 30.2 vs 39.7 months; HR, 0.78 [95% CI, 0.63–0.97]; P=.03).[221] This high-risk group included those with either stage IV, inoperable stage III, or suboptimally debulked (residual disease >1 cm) stage III. Exploratory analyses suggest that stage may be more important than the extent of residual disease for identifying patients who may benefit from bevacizumab.[225] Although sample sizes were small, analyses found no significant impact of bevacizumab on OS for the following subgroups: clear cell carcinoma, low stage high-grade disease, low grade serous.[221]

Table 6. Bevacizumab in the First-Line Setting: Phase III Randomized Controlled Trials

Summary of Results

Trial	Patients[a]	First-Line Chemotherapy[b] → Maintenance	n	F/U, mo[c]	PFS Median, mo	PFS HR [95% CI]	PFS *P* Value[d]	OS Median, mo	OS HR [95% CI]	OS *P* Value[d]	AEs G3/4	AEs G5	AEs Dc'd[e]
GOG-0218 NCT00262847 Burger et al, 2011[219]	Stage III incompletely resected (34% ≤1 cm, 40% >1 cm) or stage IV (26%) Residual disease, R0/>0–≤1 cm/>1 cm:[230] 5%/41%/54% Cancer type: 85% serous Tumor G3: 73%	Arm 1: carbo/pac/placebo → placebo	625	17.4[f]	10.3			39.3			NR	1.0%	12%
		Arm 2: carbo/pac/bev → placebo	625		11.2	0.908 [0.795–1.040]	.16	38.7	1.036 [0.827–1.297]	.76	NR	1.6%	15%
		Arm 3: carbo/pac/bev → bev	623		14.1	0.717[f] [0.625–0.824]	<.001	39.7	0.915[f] [0.727–1.152]	.45	NR	2.3%	17%
GCIG ICON7 Perren et al, 2011[220] Oza et al, 2015[221]	High-risk early stage (I–IIA and clear cell or G3; 9%), IIB–IIIB (21%) or IIIC–IV (70%) Residual disease, R0/>0–≤1 cm/>1 cm: 48%/24%/26% Cancer type: 69% serous Tumor G3: 72%	Arm 1: carbo/pac → none	764	48.6	17.5			58.6			54%	1%	NR
		Arm 2: carbo/pac/bev → bev	764	48.8	19.9	0.93[g] [0.83–1.05]	.85	58.0	0.99[g] [0.85–1.14]	.85	65%	1%	NR

Treatment Regimens

Trial	Treatments
GOG-0218	Arm 1: Carbo, AUC 6 + pac, 175 mg/m² IV, q3wk x cycles 1–6 Arm 2: Carbo, AUC 6 + pac, 175 mg/m² IV, q3wk x cycles 1–6 + bev, 15 mg/kg q3wk x cycles 2–6 Arm 3[h]: Carbo, AUC 6 + pac, 175 mg/m² IV, q3wk x cycles 1–6 + bev, 15 mg/kg q3wk x cycles 2–6 → maintenance bev, 15 mg/kg q3wk x cycles 7–22
GCIG ICON7	Arm 1: Carbo, AUC 5–6 + pac, 175 mg/m², q3wk x 6 cycles Arm 2[h]: Carbo, AUC 5–6 + pac, 175 mg/m², q3wk x 6 cycles + bev, 7.5 m/kg q3wk x 5–6 cycles (omitted cycle 1 if <4 wk from surgery) → maintenance bev, 7.5 m/kg q3wk x 12 cycles

Abbreviations: AE, adverse event; AUC, area under the curve; carbo, carboplatin; bev, bevacizumab; dc'd, discontinued; f/u, follow-up; G, grade; HR, hazard ratio; NR, not reported; OS, overall survival; pac, paclitaxel; PFS, progression-free survival; R0, no visible residual disease.

[a]All patients had histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube cancer.

[b]All patients were treated with surgery followed by chemotherapy.

[c]Median follow-up duration, in months.

[d]HR and *P* values are for comparison with control arm (Arm 1).

[e]Patients that discontinued due to AEs.

[f]Multivariate analysis of GOG-0218 results after a median of 73.2 months follow-up confirmed that there was a significant difference in PFS between Arm 1 and Arm 3 (HR [95% CI], 0.74 [0.65–0.84]; *P*<.001) and no significant impact on OS (HR [95% CI], 0.87 [0.75–1.0]; *P*=.053).[222] Long-term follow-up results after a median of 102.9 months confirmed no significant difference in OS between control (median OS, 40.8 mo) and Arm 2 (median OS, 41.1 mo; HR [95% CI], 1.06 [0.94–1.20]) or Arm 3 (median OS, 43.4 mo; HR [95% CI], 0.96 [0.85–1.09]).[223] Exploratory analysis of disease-specific survival yielded similar results. Subgroup analysis showed no treatment-dependent differences in OS for patients with stage III disease, but did yield interesting results for patients with stage IV disease. Arm 1 and 2 had no significant difference in OS, but Arm 3 showed significantly longer OS compared with Arm 1 (42.8 vs 32.6 mo; HR [95% CI], 0.75 [0.59–0.95]).[223]

[g]Primary analysis of GCIG ICON7 after a median of 19.4 months follow-up showed improved PFS with bevacizumab (HR [95%CI], 0.81 [0.70–0.94]; *P*=.004). Both PFS and OS showed nonproportionality, with the maximum treatment-dependent differences for PFS and OS between 12 and 18 mo.[220]

[h]Regimen recommended in the NCCN Guidelines as an option for patients with newly diagnosed stage II–IV, following cytoreductive surgery.

An exploratory analysis of GOG-0218, including 1,195 patients with DNA samples that could be sequenced, showed that the presence of mutations in *BRCA1*, *BRCA2*, or non*BRCA* homologous recombination repair (HRR) genes was associated with longer PFS and OS relative to patients with no mutations in these genes, even after adjusting for treatment, stage, size of residual disease, and performance status at baseline.[226] For patients without mutations in any of these genes, the addition of bevacizumab (to up-front chemotherapy and as maintenance) was associated with improved PFS (median PFS for Arm 1 vs Arm 3: 10.6 vs 15.4 months; HR, 0.71 [95% CI, 0.60–0.85]; *P*=.0001). This treatment effect on PFS was not observed in the group of patients with mutations in *BRCA1/2* or a non*BRCA* HRR gene. These findings are consistent with those from other exploratory analyses suggesting that patients with poorer prognosis may derive the most benefit from bevacizumab.[226] Nonetheless, mutation status did not significantly modify the effect of bevacizumab on PFS, so these data are insufficient to support using mutation status to identify patients who may benefit from first-line and maintenance bevacizumab.

Bevacizumab Safety and QOL

Based on earlier studies, toxicities that may occur in patients treated with bevacizumab and are of particular concern, may require intervention and often lead to treatment discontinuation include the following: pain (grade ≥2), neutropenia (grade ≥4), febrile neutropenia, thrombocytopenia, bleeding (grade ≥2; various types), hypertension (grade ≥2), thromboembolism (grade ≥3, various types), gastrointestinal events (perforations, abscesses, and fistulas), reversible posterior leukoencephalopathy syndrome, renal injury and proteinuria (grade ≥3), and wound disruption.[227] In both GOG-0218 and ICON7, the following types of toxicities were more common in the bevacizumab arm: bleeding, hypertension, proteinuria, thromboembolic events (grade ≥3), gastrointestinal perforation (grade ≥3) and wound healing complications.[219,220] For some of these the difference between arms was smaller than expected. Neutropenia occurred with similar rates across arms, and reversible posterior leukoencephalopathy syndrome occurred in GOG-0218 in only the bevacizumab arms.

Data from both GOG-0218 and ICON7 showed that most toxicities developed during the chemotherapy phase of treatment, although there were a few AEs of concern that continued to develop during the bevacizumab maintenance phase, including hypertension, high-grade pain, proteinuria, and thromboembolism.[219] Exploratory analyses tried to identify factors that might be associated with increased risk bevacizumab-associated adverse events.[228,229] Analysis of GI-related adverse events in GOG-0218 identified inflammatory bowel disease, bowel resection at primary surgery as being associated with increased risk of grade ≥2 perforation, fistula, necrosis, or hemorrhage.[228] Another analysis of GOG-0218 reported that patients treated with bevacizumab had higher rates of readmission, and noted that most readmissions occur within the first 40 days after surgery but after the first cycle of chemotherapy was delivered.[229] Other factors associated with increased rates of readmission (across treatment arms) include baseline CA-125 level, disease stage, surgery involving bowel resection, residual disease, ascites, high body mass index and poor performance score. Whereas shorter time to start of chemotherapy after surgery was associated with increased rates of readmission,[229] time to initiation longer than 25 days was associated with poorer OS (across treatment arms).[230]

Both GOG-0218 and ICON7 reported some small but statistically significant differences between treatment arms in the global measures of QOL. Analyses of GOG-0218 showed that QOL improved somewhat during the course of the study across all arms (FACT-O TOI scores improved from ~67-68 to ~76-68).[219,231] Results showed slightly worse QOL for patients treated with bevacizumab during the chemotherapy phase (FACT-O TOI scores ≤3 points lower than for placebo; $P<.001$), but this difference did not persist in the maintenance phase.[219,231] There were no statistically significant differences in QOL scores for patients treated with bevacizumab during chemotherapy only (Arm 2) versus bevacizumab during chemotherapy plus maintenance (Arm 3),[231] which further supports the idea that bevacizumab maintenance did not impact QOL. For FACT-O TOI scores, the threshold for clinically meaningful differences has been suggested to be 5–7 points. Results from ICON7 showed that for both arms QOL improved somewhat over the course of the trial, during both the chemotherapy phase and the maintenance phase.[220,232] However, these increases were smaller in bevacizumab arm (Arm 2), such that QOL scores were better in the control arm (Arm 1) versus the bevacizumab arm (Arm 2) at the end of chemotherapy (week 18; mean QLQ-C30 score difference of 6.1 points; $P<.0001$) and at the end of the maintenance phase (week 54; 6.4 points; $P<.0001$).[232] Although differences between the two arms (favoring placebo) were consistently present and statistically significant, it is unclear whether they are clinically meaningful, as the threshold for clinical significance is a matter of debate, and some have argued that it should be 10 points.

NCCN Recommendations

Based on results from GOG-0218 and ICON7, the NCCN Guidelines include bevacizumab-containing regimens as options for first-line chemotherapy following cytoreductive surgery (Table 7).[219–221,223] The regimens recommended are those used in these trials that consist of upfront carboplatin/paclitaxel/bevacizumab, followed by bevacizumab maintenance (shown in Table 6, footnote h and Table 7). In both of these trials, treatment was discontinued upon disease progression, so the guidelines recommend single-agent bevacizumab maintenance only for those who have not progressed during the 6 cycles of upfront carboplatin/paclitaxel/bevacizumab (OV-5). Given that GOG-0218 found that patients treated with upfront carboplatin/paclitaxel/bevacizumab without single-agent bevacizumab maintenance did not have improved outcomes compare with control (carboplatin/paclitaxel), observation is not a recommended option for patients with response or stable disease following completion of a first-line regimen containing bevacizumab (OV-5, bottom two pathways). Currently there are no data to support introducing bevacizumab as maintenance therapy if bevacizumab was not included in the initial primary regimens used (see OV-5, top pathways).

GOG-0218 did not include patients with stage I–II disease, and ICON7 included patients with stage I–IIA disease only if they were considered "high risk" because

Table 7. NCCN Recommended IV Bevacizumab/Chemotherapy Options for Stage II–IV, All Epithelial Cancer Types[a,b]

Regimen Short Name	Detailed Dosing per Cycle	Cycle length, wk	No. of Cycles[c]	Category[d]	Preference Category	Supporting References
Paclitaxel/carboplatin/ bevacizumab + maintenance bevacizumab (ICON-7)	Paclitaxel, 175 mg/m^2 IV over 3 hr, followed by carboplatin, AUC 5–6 IV over 1 hr, and bevacizumab, 7.5 mg/kg IV over 30–90 min D1	3	5–6	2A	Preferred	ICON-7 Perren et al, 2011[220] Oza et al, 2015[221]
	(Maintenance) bevacizumab, 7.5 mg/kg IV over 30–90 min D1	3	≤12	*BRCA1/2* wild-type/unknown: 2A[e] *BRCA1/2* mutation: bevacizumab alone not recommended[f]		
Paclitaxel/carboplatin/ bevacizumab + maintenance bevacizumab (GOG-218)	Paclitaxel, 175 mg/m^2 IV over 3 hr, followed by carboplatin, AUC 6 IV over 1 hr, + bevacizumab (cycles 2–6), 15 mg/kg IV over 30–90 min D1	3	6	2A	Preferred	GOG-0218 Burger et al, 2011[219] Tewari et al, 2019[223]
	(Maintenance) bevacizumab, 15 mg/kg IV over 30–90 min D1	3	≤16	*BRCA1/2* wild-type/unknown: 2A[e] *BRCA1/2* mutation: bevacizumab alone not recommended[f]		

Abbreviations: AUC, area under the curve; D, day of cycle; IV, intravenous.
[a]Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma; stage IC only for mucinous, low-grade serous, and grade 1 endometrioid
[b]These options are primarily for patients with age ≤70 years, good performance status, and without comorbidities. For patients who are elderly, have poor performance score or comorbidities, see alternate treatment options discussed in the section titled "Options for Patients Who Are Elderly or Have Comorbidities or Poor Performance Score" (available online, in these guidelines, at NCCN.org).
[c]NCCN recommended number of cycles.
[d]NCCN category of evidence and consensus.
[e]For patients with *BRCA1/2* wild-type or unknown mutation status who are in complete or partial response (CR/PR) after chemotherapy + bevacizumab, maintenance options include bevacizumab alone (category 2A) or bevacizumab + olaparib (category 2A). See "Options After First-Line Chemotherapy" (page 209) for more information.
[f]For patients with a *BRCA1/2* mutation who are in CR/PR after chemotherapy + bevacizumab, maintenance therapy options include bevacizumab + olaparib (category 1), olaparib monotherapy (category 2A), or niraparib monotherapy (category 2A). See "Options After First-line Chemotherapy" (page 209) for more information.

of poor differentiation (high grade) or clear cell histology (Table 6). Due to these entry criteria and the results of subgroup analysis suggesting that bevacizumab may only be beneficial in patients with more advanced disease, the NCCN Guidelines do not include the bevacizumab-containing regimens (including bevacizumab maintenance) as options for stage I disease, but only recommend them for patients with stage II or higher.

GOG-0218 and ICON7 included patients primarily with ovarian cancer, but also some with primary peritoneal or fallopian tube cancer.[219,220] These trials mostly included patients with serous histology, but did include patients with other cancer types (mucinous, clear cell, endometrioid). Therefore, the NCCN recommendations regarding use of bevacizumab as part of first-line chemotherapy and maintenance apply to patients with any of these epithelial cancer types.

Intraperitoneal/Intravenous Regimen

IP chemotherapy has been explored as an option for ovarian cancer based on the idea that localized delivery could improve efficacy, particularly against microscopic spread and peritoneal carcinomatosis, with an acceptable safety profile. Although results from smaller randomized trials (n<120) suggested no clinical benefit (response rate, PFS, OS) with IP/intravenous compared with intravenous regimens,[233,234] three larger randomized trials (n>400) in newly diagnosed chemotherapy naïve patients with stage III disease and residual disease ≤1 cm after primary surgery compared intravenous regimens with IP/intravenous regimens using similar agents, and found that IP/intravenous chemotherapy resulted in improved PFS and/or OS, with at least borderline statistical significance (See Table 8).[158,235,236] One phase II randomized trial (n=218) in patients with stage IIIC–IV epithelial ovarian cancer with optimal debulking also showed that IP/intravenous administration improved PFS and OS compared with intravenous only.[237,238] Results from these trials suggest that IP/intravenous administration significantly increases risk of certain high-grade hematologic toxicities (eg, granulocytopenia, leukopenia, neutropenia, thrombocytopenia), and certain nonhematologic toxicities (eg, gastrointestinal and metabolic toxicities, renal toxicity, abdominal pain, neurologic toxicities, infection, fatigue).[158,235–237,239] The increased risk of toxicity was considered acceptable given the improvement in OS, which was greater than a year (16 months) in one of the trials (Table 8).[158,235,236] Pooled analyses of GOG-114 and GOG-172 data showed that the IP/intravenous regimen was associated with lower risk of relapse in the peritoneal space,[240] and long-term follow-up (>10 years) showed significant PFS benefit (P=.01) and OS benefit (P=.042), especially after adjusting for other prognostic factors (P=.003 for PFS, P=.002 for OS).[241] This analysis also showed that survival improves with each cycle of IP chemotherapy.[241] Although the extent of residual disease was

Table 8. IP/IV Versus IV Platinum-Based Chemotherapy: Randomized Trials

Trial	Patients[a]	First-Line Systemic Therapy[b]	n	PFS			OS			AEs	
				Median, mo	HR [95% CI]	*P* Value	Median, mo	HR [95% CI]	*P* Value	G5	DC'd[e]
GOG-0104[235]	Stage III OC/FTC/PPC: 100%, 0, 0 Cancer type, serous/endometrioid/ other: 67%/10%/23% Tumor grade, 1/2/3: 12%/30%/58% Residual disease, R0/>0–≤1 cm/>1 cm: 26%/73%/0	IP/IV: Cyclo, 600 mg/m² IV + cis, 100 mg/m² IP, q3wk x 6 cycles	267	NR			49	0.76 [0.61–0.96]	.02	1%	9%
		IV: Cyclo, 600 mg/m² IV + cis, 100 mg/m² IV, q3wk x 6 cycles	279	NR			41			0	5%
GOG-0114[236]	Stage III OC/FTC/PPC: 100%, 0, 0 Cancer type, serous/endometrioid/ other: 67%/12%/21% Tumor grade, 1/2/3: 12%/40%/48% Residual disease, R0/>0–≤1 cm/>1 cm: 35%/65%/0	IP/IV: Carbo, AUC 9 IV, q4wk x 2 cycles; then pac, 135 mg/m² IV, then cis, 100 mg/m² IP, q3wk x 6 cycles	227	18	0.78	.01	63	0.81	.05	1%	NR
		IV: Pac, 135 mg/m² IV + cis, 75 mg/m² IV, q3wk x 6 cycles	235	22			52			1%	NR
GOG-172 (NCT00003322)[158,239]	Stage III OC/FTC/PPC: 88%, 0, 12% Cancer type, serous/endometrioid/ other: 79%/7%/14% Tumor grade, 1/2/3: 10%/37%/51% Residual disease, R0/>0–≤1 cm/>1 cm: 63%/37%/0	IP/IV: Pac, 135 mg/m² IV D1 + cis, 100 mg/m² IP D2 + pac, 60 mg/m² IP D8, q3wk x 6 cycles	214	23.8	0.80 [0.64–1.00]	.05	65.6	0.75 [0.58–0.97]	.03	2.4%	NR
		IV: Pac, 135 mg/m² IV D1+ cis, 75 mg/m² IV D2, q3wk x 6 cycles	215	18.3			49.7			1.9%	NR
GOG-0252 (NCT00951496)[242]	Stage II/III/IV: 10%/84%/6% OC/FTC/PPC: NR[c] Cancer type, serous/endometrioid/ other: 83%/1%/16% Tumor grade, 1/2/3: NR/≥7%/≥72% Residual disease, R0/>0–≤1 cm/>1 cm: 58%/35%/7%	IV/IP pac/carbo bev: pac, 80 mg/m² IV D1, 8, 15 + carbo, AUC 6 IP D1, q3wk x 6 cycles; + bev, 15 mg/kg IV, q3wk cycles 2–22	518	27.4	0.925 [0.802–1.07]		78.9	0.949 [0.799–1.128]		1.4%	28%
		IV/IP pac/cis/bev: Pac, 135 mg/m² IV D1 + cis, 75 mg/m² IP D2 + pac, 60 mg/m² IP D8, q3wk x 6 cycles; + bev, 15 mg/kg IV, q3wk cycles 2–22	521	26.2	0.977 [0.847–1.13]		72.9	1.05 [0.884–1.24]		2.0%	29%
		IV pac/carbo/bev: Pac, 80 mg/m² IV D1, 8, 15 + carbo, AUC 6 IV D1, q3wk x 6 cycles; + bev, 15 mg/kg IV, q3wk cycles 2–22	521	24.9			75.5			1.6%	24%

Abbreviations: AE, adverse event; bev, bevacizumab; carbo, carboplatin; cis, cisplatin; cyclo, cyclophosphamide; D, day of cycle; Dc'd, discontinued study treatment; FTC, fallopian tube cancer; G, grade; HR, hazard ratio; IP, intraperitoneal; IV, intravenous; NR, not reported; OC, ovarian cancer; pac, paclitaxel; PPC, primary peritoneal cancer; R0, removal of all macroscopic disease.

[a]All trials enrolled newly diagnosed, previously untreated/chemotherapy-naïve patients, with an epithelial cancer type.

[b]All patients were treated with surgery followed by chemotherapy.

[c]Percentages for each cancer type were not reported, but trial inclusion criteria allowed OC, FTC, and PPC.

[d]HR and *P* values are for comparison with control arm (IV regimen).

[e]Patients who discontinued because of AEs.

prognostic for outcome, IP/intravenous chemotherapy still provided PFS benefit even among those with some gross residual disease (>0-≤1 cm).[241] Based on these results, an IP/intravenous option similar to the regimen used in GOG-172 was added to the NCCN Guidelines (Table 9) for patients with optimally debulked (<1 cm residual) stage III disease.[158] Women with optimally debulked stage II disease may also receive IP chemotherapy, as the NCCN Panel has decided that many of the regimens tested in stage III–IV should also be offered to patients with stage II disease. Patients with stage II were allowed in GOG-0252 and another (small) randomized trial, although in both of these studies the IP/intravenous regimens did not significantly improve PFS or OS compared with intravenous regimens.[234,242] IP chemotherapy is not recommended for stage I or IV disease.

In the large randomized trials that showed that IP/intravenous benefit, most of the patients had serous or endometrioid disease, and high-grade tumor histology (Table 8), so it is unclear whether patients with LCOCs will benefit from IP/intravenous chemotherapy. In the NCCN Guidelines, the clear cell carcinoma and carcinosarcoma are the only LCOCs for which IP/intravenous chemotherapy is a recommended option, as these cancer types are associated with higher risk of poor outcomes.[243–246] Patients with carcinosarcoma were not included in the randomized trials testing IP/intravenous chemotherapy, but 2%–6% of patients had clear cell carcinoma.[158,235,236,242] These trials included mostly patients with ovarian cancer, but in GOG-172, 12% of patients had primary peritoneal cancer. In the NCCN Guidelines the recommended IP/intravenous regimen is an option regardless of primary site (ovarian, fallopian, or primary peritoneal). All women should be counseled about the clinical benefit associated with combined IP/intravenous chemotherapy administration before undergoing surgery.

Enthusiasm for IP/intravenous chemotherapy has waned considerably due to the results of GOG-0252, a large randomized trial in patients with stage II/III optimally resected (≤1 cm), or stage III/IV suboptimally resected (>1 cm) disease (Table 8).[242] Results showed that for combination therapy with paclitaxel/carboplatin/bevacizumab, IP administration of the carboplatin did not improve PFS or OS compared with intravenous administration (Table 8).[242] An intravenous/IP paclitaxel/cisplatin/bevacizumab regimen also did not improve PFS for OS relative to the control intravenous paclitaxel/carboplatin/bevacizumab regimen (Table 8).[242] These results suggest that given the PFS benefit of adding bevacizumab (during chemotherapy and maintenance), IP administration does not further improve outcomes.

For the recommended IP chemotherapy regimen (Table 9), the IP paclitaxel was infused over 24 hours in the clinical trial (GOG-172).[158] A 3-hour infusion of paclitaxel has not been proven to be equivalent to a 24-hour infusion, although a 3-hour infusion has been reported to be more convenient, easier to tolerate, and less toxic.[247] Note that in all the supporting trials and in the NCCN Guidelines, IP regimens include intravenous regimens so that systemic disease can also be treated.

The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity.[158,235–237,239] In GOG-172, only 42% of women were able to complete all 6 treatment cycles of the IP regimen[158]; with more experience, this percentage has improved in the major cancer centers.[248] It has been suggested that a lower IP cisplatin dose of 75 mg/m^2 may help to decrease toxicity.[247,248] However, the chemotherapy portion of the intravenous/IP paclitaxel/cisplatin/bevacizumab regimen used in GOG-0252 was very similar to the intravenous/IP paclitaxel/cisplatin regimen used in GOG-172, but with a lower dose of cisplatin (75 mg/m^2 vs 100 mg/m^2), and did not improve PFS/OS relative to control (Table 8),[158,242] so it is unclear whether the intravenous/IP chemotherapy regimen with the lower cisplatin dose provides any benefit compared with intravenous administration.

Prior to the administration of the combined IP and intravenous regimen, patients must be apprised of the increased toxicities with the combined regimen when

Table 9. NCCN Recommended IP/IV Platinum-Based Chemotherapy Option for Optimally Debulked[a] Stage II–III, Selected Epithelial Cancer Types[b]

Regimen Short Name	Detailed Dosing per Cycle	Cycle Length, wk	No. of Cycles	Category[c]	Preference Category	Trials With Supporting Data
IV/IP paclitaxel/cisplatin	Paclitaxel, 135 mg/m^2 IV continuous infusion over 3 or 24 hr D1; Cisplatin, 75–100 mg/m^2 IP D2 after IV paclitaxel; Paclitaxel, 60 mg/m^2 IP D8	3	6	2A	Useful in certain circumstances	GOG-0172[158]

Abbreviations: D, day of cycle; IP, intraperitoneal; IV, intravenous.
[a]Optimally debulked is defined as <1 cm residual disease.
[b]Includes high-grade serous, grade 2/3 endometrioid, and clear cell carcinoma.
[c]NCCN category of evidence and consensus.

compared with using intravenous chemotherapy alone (increased myelosuppression, renal toxicities, abdominal pain, neuropathy, gastrointestinal toxicities, metabolic toxicities, and hepatic toxicities). Patients who are candidates for the IP cisplatin and IP/intravenous paclitaxel regimen should have normal renal function before starting, a medically appropriate PS based on the future toxicities of the IP/intravenous regimen, and no previous evidence of medical problems that could significantly worsen during chemotherapy, such as preexisting neuropathy. Reasons for discontinuing the IP regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain.[249] Women unable to complete IP therapy should receive intravenous therapy. Expert nursing care may help to decrease complications.[250] Giving intravenous hydration before and after IP chemotherapy is a useful strategy to prevent certain toxicities (nausea, vomiting, electrolyte imbalances, and metabolic toxicities).[248] Prior to receiving and after receiving each cycle of IP cisplatin, adequate amounts of intravenous fluids need to be administered to prevent renal toxicity. After each cycle has been completed, patients need to be monitored carefully for myelosuppression, dehydration, electrolyte loss, end-organ toxicities (such as renal and hepatic damage), and all other toxicities. After chemotherapy, patients often require intravenous fluids (5–7 days) in the outpatient setting to prevent or help treat dehydration.

Options After First-Line Chemotherapy

After initial treatment (eg, surgery followed by chemotherapy), patients should undergo regular clinical re-evaluation. Observation with follow-up is recommended for patients who had stage I disease at presentation and have no signs of new disease (OV-4, page 193). Recommendations for surveillance during observation are in the monitoring/follow-up section (OV-6; available at NCCN.org).

For patients who had stage II–IV disease at presentation, options following surgery and chemotherapy depend on the success of these interventions. These patients should be evaluated with imaging as clinically indicated to determine the extent of residual disease or progression and screen for new metastases. Imaging should include chest/abdominal/pelvic CT, MRI, PET/CT or PET (skull base to midthigh).

Patients with persistent disease or progression during initial treatment should be treated with second-line approaches (see "Therapy for Resistant Disease or Recurrence" on OV-7 and "Recurrent Disease," available at NCCN.org).[251,252]

For patients with advanced-stage (stages II–IV) disease who, after primary therapy (surgery plus chemotherapy), are in complete clinical remission (ie, complete response [CR], defined as no definitive evidence of disease[251,252]), partial remission (ie, partial response [PR]), or stable disease, recommended options depend on the extent of their response and the type of primary chemotherapy they received (see OV-5, page 194). These recommendations have been revised several times recently due to emerging data from clinical trials,[166–169] summarized in Tables 10, 11, and 12. These recent data and their impact on the recommendations are discussed in the subsequent sections.

Bevacizumab Maintenance Therapy

As described in detail in "Bevacizumab in the First-Line Setting" (page 202), results from the phase III GOG-0218 and ICON7 trials support the use of single-agent bevacizumab maintenance therapy for patients with stage II–IV disease who experience response or stable disease after postoperative chemotherapy with one of the carboplatin/paclitaxel/bevacizumab regimens used in these trials (and recommended by NCCN).[219–221] Based on these results, bevacizumab monotherapy was a recommended option for maintenance for patients with stage II–IV disease who were in CR/PR after a primary treatment with surgery and one of the bevacizumab-containing regimens recommended in the first-line setting. However, due to results from subsequent trials showing benefit from PARP inhibitors, as described subsequently, bevacizumab monotherapy is no longer recommended for patients with *BRCA1/2* mutations, but is still recommended as an option for patients who have wild-type or unknown *BRCA1/2* mutation status (in CR/PR after a recommended bevacizumab-containing first-line chemotherapy regimen), as these patients have fewer PARP inhibitor options (see OV-5, page 194).

PARP Inhibitor Maintenance Therapy After Primary Chemotherapy

Several PARP (poly ADP ribose polymerase) inhibitors have been shown to be active in recurrent ovarian cancer,[253–260] and have been FDA approved for multiple indications in ovarian cancer (summarized in Table 13)[261–263]; the corresponding recommendations can be found in the NCCN Guidelines algorithm for "Post-Primary Treatment: Maintenance Therapy" (OV-5, page 194), "Therapy for Persistent Disease or Recurrence" (OV-7, available at NCCN.org) and "Principles of Systemic Therapy: Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer" (OV-C 7 and 8 of 10, available at NCCN.org).

More recently, several phase III double-blind, randomized trials have tested PARP inhibitors as maintenance therapy for patients with newly-diagnosed, histologically confirmed, FIGO stage III–IV ovarian, fallopian tube, or primary peritoneal cancer who have completed first-line

Table 10. Phase III RCTs Testing PARP Inhibitors for Maintenance After First-Line Chemotherapy: Efficacy

Trial	Maintenance Therapy	Median Follow-Up, mo	PFS[a] (Arm A vs B)		
SOLO-1, NCT01844986[166]	Arm A (n=260): olaparib Arm B (n=131): placebo	Arm A vs B: 40.7 vs 41.2	**Population**	**3-Year**	**HR [95% CI]**
			Overall (all *BRCA1/2* mut)	60% vs 27%[d]	0.30 [0.23–0.41]
PAOLA-1/ENGOT-OV25, NCT02477644[167]	Arm A (n=537): olaparib + bevacizumab Arm A (n=269): placeb + bevacizumab	Arm A vs B: 22.7 vs 24.0	**Population**	**Median (mo)**	**HR [95% CI]**
			Overall	22.1 vs 16.6[e]	0.59 [0.49–0.72]
			BRCA1/2 mut	37.2 vs 21.7	0.31 [0.20–0.47]
			BRCA1/2-wt/ND	18.9 vs 16.0	0.71 [0.58–0.88]
			BRCA1/2-wt, HRD[b]	28.1 vs 16.6	0.43 [0.28–0.66]
			HRP	16.6 vs 16.2	1.00 [0.75–1.35]
PRIMA/ENGOT-OV26/GOG-3012, NCT02655016[168]	Arm A (n=487): niraparib Arm A (n=246): placebo	13.8	**Population**	**Median (mo)**	**HR [95% CI]**
			Overall	13.8 vs 8.2[e]	0.62 [0.50–0.76]
			HRD	21.9 vs 10.4[e]	0.43 [0.31–0.59]
			BRCA1/2 mut	22.1 vs 10.9	0.40 [0.27–0.62]
			BRCA1/2 wt, HRD[b]	19.6 vs 8.2	0.50 [0.31–0.83]
			HRP	8.1 vs 5.4	0.68 [0.48–0.94]
Trial	**First-Line → Maintenance Therapy[f]**	**Median Follow-Up, mo**	**PFS (Arm A vs C)**		
VELIA/GOG-3005, NCT02470585[169]	Arm A (n=375): carbo/pac/placebo → placebo Arm B (n=383): carbo/pac/veli → placebo Arm C (n=382): carbo/pac/veli → veli	28	**Population**	**Median (mo)**	**HR [95% CI]**
			Overall	17.3 vs 23.5[e]	0.68 [0.56–0.83]
			BRCA1/2 mut	22.0 vs 34.7[e]	0.44 [0.28–0.68]
			BRCA1/2 wt	15.1 vs 18.2	0.80 [0.64–1.00]
			HRD[b]	20.5 vs 31.9[e]	0.57 [0.43–0.76]
			HRP	11.5 vs 15.0	0.81 [0.69–1.09]

Abbreviations: carbo, carboplatin; HR, hazard ratio; HRD, homologous recombination deficient; HRP, homologous recombination proficient; GIS, genomic instability score; mut, mutation; ND, not determined (unknown); pac, paclitaxel; PFS, progression-free survival; RCT, randomized controlled trial; veli, veliparib; wt, wild-type.

[a]Outcomes were measured from time of randomization (after first-line therapy).

[b]For PAOLA-1 and PRIMA, homologous recombination deficient was defined as *BRCA1/2* mut or a GIS ≥42 on myChoice CDx assay (Myriad Genetic Laboratories). For VELIA, homologous recombination deficient was defined as *BRCA1/2* mut or a GIS ≥33 on myChoice CDx assay (Myriad Genetic Laboratories).

[d]$P<.0001$.

[e]$P<.001$.

[f]First-line therapy was for 6 cycles, maintenance for 30. Veliparib dose during chemotherapy was 150 mg twice daily. Only those who completed the 6 cycles of first-line therapy without progression were treated with single-agent maintenance veliparib, 300 mg (or placebo) twice daily x 2 weeks, then veliparib, 400 mg (or placebo) twice daily.

chemotherapy.[166–169] Characteristics of the patient populations in these trials are summarized in Table 11, and efficacy and safety results are summarized in Tables 10 and 12.

Olaparib Monotherapy

The SOLO-1 trial demonstrated a remarkable improvement in PFS with single-agent olaparib versus placebo as maintenance therapy for patients with a germline or somatic *BRCA1/2* mutation who had a CR or PR after first-line platinum-based chemotherapy (Table 10).[166] The risk of progression or death was 70% lower, with the median PFS (from randomization) of 13.8 months for placebo, and the median PFS for olaparib had not been reached after a median follow-up of 41 months; OS data are also immature. A subsequent subgroup analysis

Table 11. Phase III RCTs Testing PARP Inhibitors for Maintenance After First-Line Chemotherapy: Patient Characteristics[a]

	SOLO-1[166]	PAOLA-1[167]	PRIMA[168]	VELIA[169]
	Olaparib vs Placebo	Bevacizumab + Olaparib vs Bevacizumab + Placebo	Niraparib vs Placebo	Veliparib vs Placebo
Patient characteristics:				
• FIGO stage: III, IV	83%, 17%	70%, 30%	65%, 35%	77%, 23%
• Cancer type: high-grade serous, high-grade endometrioid, other[b]	96%, 2.3%, 1.5%	96%, 2.5%, 1.7%	95%, 2.7%, 2.3%	100%, 0, 0
• Primary cancer site: ovarian, primary peritoneal, fallopian-tube	85%, 8%, 6%	86%, 8%, 6%	80%, 6.4%, 13%	NR
• *BRCA1/2* status: mutation, wild-type, unknown	100%, 0, 0	29%, 67%, 4%	30%, NR, NR	26%, 65%, 9%
• Homologous recombination status: deficient, proficient, unknown[c]	100%, 0, 0	48%, 34%, 18%	51%, 34%, 15%	55%, 33%, 12%
Primary treatment and response:				
• Surgery: PDS, IDS, none	62%, 35%, 2%	51%, 42%, 7%	NR, 67%, NR	67%, 28%, 4%
• Macroscopic residual disease after surgery (PDS or IDS): none, some, unknown	76%, 19%, 1%	51%, 33%, 0	NR[d]	64%, 30%, 1%
• Systemic therapy	Platinum-based chemotherapy[e]	Platinum-taxane based chemotherapy[f] + bevacizumab	Platinum-based chemotherapy[f]	Paclitaxel/carboplatin/placebo vs paclitaxel/carboplatin/veliparib
• Cycles of systemic therapy: 6, 7–9, unknown	78%, 21%, 0[g]	6–9 chemotherapy, 2–3 bevacizumab[g]	69%, 25%, 6%	6[f]
• Response after systemic therapy: CR, PR[h]	82%, 18%	73%, 27%	69%, 31%	NR
• CA-125 ≤ULN after systemic therapy	95%	86%	92%	NR

Abbreviations: CR, complete response; GIS, genomic instability score; IDS, interval debulking surgery (after neoadjuvant chemotherapy); NED, no evidence of disease; NR, not reported; PDS, upfront primary debulking surgery; PR, partial response; RCT, randomized controlled trial; ULN, upper limit of normal.

[a]All patients had newly diagnosed, histologically confirmed disease. Data show percent of total randomized population (n=310 for SOLO-1; n=806 for PAOLA-1; n=733 for PRIMA; n=1,140 for VELIA).

[b]In SOLO-1, other cancer types were mixed endometrioid and serous. In PAOLA-1, other cancer types included clear cell, undifferentiated, or other; entry criteria allowed high-grade serous, high-grade endometrioid, and other nonmucinous with deleterious germline *BRCA1/2* mutation. In PRIMA, entry criteria required high-grade serous or high-grade endometrioid histology, yet 17 patients were listed as "other" without further explanation. VELIA entry criteria required histologic confirmation of high-grade serous, and no data on this were reported.

[c]For PAOLA-1 and PRIMA, homologous recombination deficient was defined as *BRCA1/2* mutation or a GIS ≥42 on myChoice CDx assay (Myriad Genetic Laboratories). For VELIA, homologous recombination deficient was defined as *BRCA1/2* mutation or a GIS ≥33 on myChoice CDx assay (Myriad Genetic Laboratories).

[d]Entry criteria for PRIMA required patients to have either (1) stage III disease with visible residual tumor after primary surgery, (2) inoperable stage III disease, or (3) any stage IV disease (residual disease after surgery not required); 23.1% of patients had stage III disease with residual disease after primary surgery.

[e]Chemotherapy agents used in both arms were paclitaxel (98% of patients), carboplatin (91%), cisplatin (20%), docetaxel (6%), and gemcitabine (<1%).

[f]Information based on entry criteria because data was not reported.

[g]In SOLO-1, 1% of patients had 4 cycles of chemotherapy.

[h]In SOLO-1 and PAOLA-1, CR was defined as NED on imaging (no measurable/assessable disease) and CA-125 ≤ULN. In SOLO-1, PR was defined as 30% reduction in tumor volume or NED on imaging with CA-125 >ULN. In PAOLA-1, PR was defined as radiologic evidence of disease, an abnormal CA-125 level, or both. In PRIMA, CR and PR were judged by "investigator assessment"; more specific criteria was not disclosed. In VELIA, the response rate for the whole population was not reported, and response was not required prior to maintenance therapy.

showed that the PFS benefit was significant regardless of *BRCA* mutation type (*BRCA1* vs *BRCA2*).[264] Based on results from SOLO-1, the NCCN Guidelines include olaparib monotherapy as a maintenance therapy option for patients who have a *BRCA1/2* mutation and have a CR or PR after completion of primary therapy including surgery and platinum-based chemotherapy (Table 14).

SOLO-1 excluded patients who received bevacizumab as part of primary systemic therapy, so the efficacy of single-agent olaparib in after chemotherapy/bevacizumab primary therapy is unknown. Nonetheless, the benefit from olaparib was sizeable and significant across many subgroups analyzed.[166,264] It is important to note that the effects of maintenance olaparib on PFS (70% improvement; Table 10)[166] are far greater than the effects on PFS reported for the addition of bevacizumab to both upfront and maintenance therapy (<30% improvement).[219,221,222] PFS curves from SOLO-1 show large separation between olaparib versus placebo throughout the time course of the study (median follow-up, 41 months),[166] in contrast to results from GOG-0218 and ICON7 showing PFS curves converging well before 40 months, even for the high-risk groups shown to benefit most from bevacizumab.[221,222] In addition, the exploratory analysis

Table 12. Adverse Events Associated With PARP Inhibitor Maintenance After First-Line Systemic Therapy[a]

	SOLO-1[166]	PAOLA-1[167]	PRIMA[168]	VELIA[169]
Maintenance therapy tested	Olaparib vs placebo	Bevacizumab + olaparib vs bevacizumab + placebo	Niraparib vs placebo	Veliparib vs placebo[b]
PARP inhibitor maintenance dose	300 mg twice daily	300 mg twice daily	300 mg once daily[c]	300 mg twice daily x 2 wk, then 400 mg twice daily
AEs grade 5	None	<1% vs 1%	0.4% vs 0.4%	None
AEs grade ≥3	39% vs 18%	57% vs 51%	71% vs 19%	45% vs 32%
AEs leading to discontinuation	12% vs 2%	20% vs 6%	12.0% vs 2.5%	17% vs 1%
Common nonhematologic AEs (>20%), any grade, differing between arms by ≥9%	Nausea: 77% vs 38% Fatigue/asthenia: 63% vs 42% Vomiting: 40% vs 15% Diarrhea: 34% vs 25% Constipation: 28% vs 19% Dysgeusia: 26% vs 4% Decreased appetite: 20% vs 10%	Nausea: 53% vs 22% Fatigue/asthenia: 53% vs 32% Vomiting: 22% vs 11% Hypertension: 46% vs 60%	Nausea: 57% vs 28% Vomiting: 22% vs 12% Constipation: 39% vs 19% Headache: 26% vs 15% Insomnia: 25% vs 15%	Nausea: 56% vs 24% Vomiting: 34% vs 12% Arthralgia: 16% vs 20%
Common nonhematologic AEs (>5%), grade ≥3	None	Fatigue/asthenia: 5% vs 1% Hypertension: 19% vs 30%	Hypertension: 6% vs 1%	Nausea: 5% vs 1% Fatigue: 6% vs 1%
Common hematologic AEs (>20%), any grade, differing between arms by ≥9%	Anemia: 39% vs 10% Neutropenia: 23% vs 12%	Anemia: 41% vs 10% Lymphopenia: 24% vs 9%	Anemia: 63% vs 18% Neutropenia: 26% vs 7% Neutrophil count decreased: 17% vs 2% Thrombocytopenia: 46% vs 4% Platelet count decreased: 28% vs 1%	Thrombocytopenia: 20% vs 5%
Common hematologic AEs (>5%), grade ≥3	Anemia: 22% vs 2% Neutropenia: 9% vs 5%	Anemia: 17% vs <1% Lymphopenia: 7% vs 1% Neutropenia: 6% vs 3%	Anemia: 31% vs 2% Neutropenia: 13% vs 1% Neutrophil count decreased: 8% vs 0 Thrombocytopenia: 29% vs <1% Platelet count decreased: 13% vs 0	Anemia: 7% vs 1% Thrombocytopenia: 7% vs <1% Neutropenia: 5% vs 4%

Abbreviation: AE, adverse event.
[a]Toxicities during the trial intervention or up to 30 days after discontinuation of the intervention.
[b]AEs during the maintenance phase only.
[c]Protocol revision allowed for 200 mg once daily starting dose in patients with baseline body weight <77 kg, a platelet count <15,000/mm^3, or both.

of GOG-0218 based on *BRCA* mutation status suggests that bevacizumab may not improve PFS in patients with *BRCA1/2* mutations.[226] The PAOLA-1 trial (described in the next section) suggested that maintenance olaparib could provide PFS benefit in patients who had bevacizumab during first-line chemotherapy.[167] For these reasons single-agent olaparib is a category 1 option only for patients who did not have bevacizumab as part or primary therapy, but is a category 2A option for patients who received prior bevacizumab, provided that they were in a CR or PR after completion of chemotherapy (Table 14). The NCCN Panel included a footnote to make it clear that data are limited on the use of single-agent olaparib after first-line platinum-based chemotherapy plus bevacizumab, but that evidence from other subgroups suggests that it should be considered as an option for these patients.

Olaparib + Bevacizumab

The phase III double-blind, randomized PAOLA-1 trial demonstrated a remarkable improvement in PFS (HR, 0.59) when olaparib (vs placebo) was added to maintenance bevacizumab in patients who have a CR or PR after first-line platinum-taxane chemotherapy plus bevacizumab for advanced disease (Table 10).[167] Unlike SOLO-1, PAOLA-1 included both patients with and without *BRCA1/2* mutations. Subgroup analyses showed that similar to the SOLO-1 trial, for patients with *BRCA1/2* mutations, maintenance olaparib

Table 13. FDA-Approved Indications for Bevacizumab and PARP Inhibitors in Ovarian Cancer

Agent USPI Date	First-Line Chemotherapy	Maintenance After First-Line Chemotherapy	Recurrence Therapy	Maintenance After Recurrence Therapy
Bevacizumab September 2020[227]	For epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with carboplatin and paclitaxel, followed by bevacizumab as a single agent, for stage III or IV disease following initial surgical resection.		For epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with paclitaxel, PLD, or topotecan, for platinum-resistant recurrent disease who received ≤2 prior chemotherapy regimens.	
			For epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum-sensitive recurrent disease.	
Niraparib April 2020[261]	None	For the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy.	For the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥3 prior chemotherapy regimens and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation[a], or • genomic instability[a] and who have progressed >6 months after response to the last platinum-based chemotherapy.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to platinum-based chemotherapy.
Olaparib May 2020[262]	None	For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated[b] advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy. In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR 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[b], and/or • genomic instability[b]	For the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated[b] advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in CR or PR to platinum-based chemotherapy.
Rucaparib October 2020[263]	None	None	For the treatment of adult patients with deleterious *BRCA* mutation[c] (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥2 prior lines of chemotherapies.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy.

Abbreviations: CR, complete response; HRD, homologous recombination deficiency; PLD, pegylated liposomal doxorubicin; PR, partial response; USPI, US prescribing information.
[a]Select patients for therapy based on an FDA-approved companion diagnostic for niraparib.
[b]Select patients for therapy based on an FDA-approved companion diagnostic for olaparib.
[c]Select patients for therapy based on an FDA-approved companion diagnostic for rucaparib.

reduced the risk of progression or death by approximately 70% (Table 10).[167] A subsequent subanalysis found that the PFS benefit of adding olaparib to bevacizumab maintenance was similar and significant regardless of *BRCA* mutation type (*BRCA1* vs *BRCA2*).[265] Based on these results, maintenance with bevacizumab + olaparib is a category 1 option for patients who have a CR/PR after completing bevacizumab-containing first-line therapy, and single-agent bevacizumab was removed as a maintenance therapy option in this setting.

PAOLA-1 also showed that adding olaparib to maintenance bevacizumab resulted in a smaller but still significant improvement in PFS for those with *BRCA1/2* wild-type or unknown (Table 10).[167] Due to the smaller magnitude of this effect, the NCCN Guidelines include olaparib + bevacizumab combination and bevacizumab monotherapy both as a

Table 14. NCCN Recommended Options for Maintenance After First-Line Chemotherapy[a]

Pathologic Stage	*BRCA1/2* Status	Primary Systemic Therapy[b]	Response to Primary Therapy	Recommended Options	Category	FDA Indication[e]	Supporting Trial
Any	Any	Any	SD/PD	Therapy for persistent disease or recurrence	2A	N/A	N/A
I	Any	Any	CR/PR	Observe	2A	N/A	N/A
II–IV	Mutated	Platinum-based chemotherapy	CR	Observe	2A	N/A	N/A
			CR/PR	Olaparib	1	Yes	SOLO-1[166]
				Bevacizumab + olaparib	NR	Yes	Extrapolation from PAOLA-1[167]
				Niraparib	1	Yes	PRIMA[168]
II–IV	Mutated	Platinum-based chemotherapy + bevacizumab	CR/PR	Bevacizumab	NR	Only for stage III–IV	GOG-0218[219], ICON7[220,221]
				Olaparib[d]	2A	Yes	Extrapolation from SOLO-1[166] and PAOLA-1[167]
				Bevacizumab + olaparib	1	Yes	PAOLA-1[167]
				Niraparib[d]	2A	Yes	Extrapolation from PRIMA[168]
II–IV	Wild-type or unknown	Platinum-based chemotherapy	CR	Observe	2A	N/A	N/A
			CR/PR	Bevacizumab + olaparib	NR	Yes for patients with genomic instability	Extrapolation from PAOLA-1[167]
				Niraparib[c]	2A	Yes	PRIMA[168]
			PR	Therapy for persistent disease or recurrence	2A	N/A	N/A
II–IV	Wild-type or unknown	Platinum-based chemotherapy + bevacizumab	CR/PR	Bevacizumab	2A	Only for stage III–IV	GOG-0218[219], ICON7[220,221]
				Bevacizumab + olaparib[c]	2A	Only for patients with genomic instability	PAOLA-1[167]
				Niraparib	NR	Yes	Extrapolation from PRIMA[168]

Abbreviations: CR, complete clinical remission (complete response), with no evidence of disease; N/A, not applicable; NR, not recommended by NCCN; PD, progressive disease; PR, partial remission (partial response); SD, stable disease

[a]Options shown in this table are for patients with ovarian, fallopian tube, or primary peritoneal cancer who have undergone primary treatment per NCCN Guidelines recommendations with either (1) up-front surgery plus adjuvant systemic therapy or (2) neoadjuvant chemotherapy, interval debulking surgery, and postoperative adjuvant systemic therapy.

[b]Recommended maintenance therapy options are for patients who have undergone primary systemic therapy with an NCCN recommended regimen. See page OV-C for options (available online, in these guidelines, at NCCN.org).

[c]In the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

[d]After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARP inhibitor (olaparib or niraparib) for patients with a *BRCA1/2* mutation. However, based on the magnitude of benefit of PARP inhibitor maintenance therapy for other subgroups, single-agent PARP inhibitors can be considered.

[e]FDA indication column indicates options consistent with an FDA-approved indication.

category 2A maintenance therapy options for patients with *BRCA1/2* wild-type or unknown mutation status who are in a CR or PR after completion of first-line platinum-based chemotherapy/bevacizumab combination (Table 14).

In PAOLA-1, the population without *BRCA1/2* mutations was further subdivided based on results of MyChoice CDx (Myriad Genetic Laboratories), a proprietary tumor tissue assay that uses multiple molecular tests and combines several metrics (loss of heterozygosity [LOH],[266] telomeric allelic imbalance,[267] and large scale state transitions[268] to determine the genomic instability score (GIS), a proxy measure for the presence of homologous recombination deficiency.[269,270] GIS cutoff of 42 was used to define homologous recombination deficiency status based on a prior analyses of a population of breast and ovarian cancer cases showing that this cutoff identified 95% of patients who had *BRCA1/2* deficiency, defined as either (1) one deleterious mutation in *BRCA1* or *BRCA2*, with LOH in the wild-type copy, (2) two deleterious mutations in the same gene, or (3) promoter methylation of *BRCA1* with LOH in the wild-type copy.[271] Among those without *BRCA1/2* mutations, the PFS benefit of maintenance olaparib was significant for those with homologous recombination deficiency (as defined by the proprietary assay) but was not significant for those who did not have homologous recombination deficiency (Table 10). For this reason, the NCCN Panel included the following footnote relating to the use of maintenance bevacizumab + olaparib: in the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may provide information

on the magnitude of benefit of PARP inhibitor therapy (category 2B). OS results from PAOLA-1 were not mature.

Niraparib Monotherapy

Similar to the SOLO-1 results for olaparib monotherapy, the PRIMA trial demonstrated a remarkable improvement in PFS with single-agent niraparib (versus placebo) as maintenance therapy for patients with a *BRCA1/2* mutation who were in a CR/PR after first-line platinum-based chemotherapy (Table 10).[168] Based on these results, the NCCN Guidelines include single-agent niraparib as a maintenance therapy option for patients with *BRCA1/2* mutations who have completed primary treatment including surgery and platinum-based first-line therapy (Table 14). PRIMA likely did not include many patients who had prior bevacizumab as part of primary systemic therapy, so for patients with a *BRCA1/2* mutation maintenance niraparib is a category 1 option for those who had first-line platinum-based chemotherapy without bevacizumab, and a category 2A option for those who had bevacizumab in conjunction with first-line platinum-based chemotherapy (Table 14).

Unlike SOLO-1, the presence of a *BRCA1/2* mutation was not part of the entry criteria for the PRIMA trial. PRIMA included patients who did not have deleterious mutations in *BRCA1/2*, and results showed significant PFS improvement with niraparib (versus placebo) for the overall population. Subgroup analyses showed that the effect of maintenance niraparib on PFS was still significant among patients without a *BRCA1/2* mutation (HR, 0.71 [95% CI, 0.58–0.88]), although the size of the effect appears smaller than that seen in patients with *BRCA1/2* mutations (Table 10). Based on these results, the NCCN Guidelines include single-agent niraparib as an option for maintenance therapy for patients with *BRCA1/2* wild-type or unknown, provided they are in a CR or PR after completion of primary platinum-based chemotherapy (without bevacizumab) (Table 14). Given the smaller magnitude of the PFS effect in patients without *BRCA1/2* mutation, and that PRIMA likely included very few patients who had bevacizumab as part of primary therapy, single-agent niraparib is not a recommended maintenance therapy option for those who have *BRCA1/2* wild-type or unknown and received bevacizumab as part of primary therapy (Table 14).

As in PAOLA-1, in PRIMA the patient group without *BRCA1/2* mutation was further subdivided into homologous recombination deficient and proficient based on a GIS cutoff of 42 using the MyChoice CDx (Myriad Genetic Laboratories).[168] Results showed that the PFS effect of niraparib (versus placebo) remained significant for the smaller subgroup of patients with homologous recombination deficiency but no *BRCA1/2* mutation, and was significant, with a trend toward smaller magnitude, for the homologous recombination proficient subgroup (Table 10).[168] Because of these results, the NCCN Panel chose to include the following footnote relating to the use of maintenance niraparib: in the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

OS data from the interim analysis was reported (Table 10), but it is premature to draw conclusions from those results.

Veliparib

The phase III VELIA study design was similar to GOG-0218 and ICON7 bevacizumab trials in that it tested the effect of adding veliparib during first-line chemotherapy and as subsequent single-agent maintenance after completion of chemotherapy.[169] VELIA did not require that patients have CR/PR before receiving maintenance therapy; they only needed to have absence of progression during first-line systemic therapy (6 cycles) and no limiting toxicities. Results showed that whereas adding veliparib during first-line chemotherapy did not significantly improve PFS compared with chemotherapy alone, those who received veliparib during first-line chemotherapy and maintenance therapy had significantly improved PFS compared with those who received chemotherapy alone (with placebo during first-line systemic therapy and maintenance; Table 10). Subgroup analyses showed that whereas the PFS benefit from veliparib appeared to be the greatest for those with a *BRCA1/2* mutation, and was significant for those with homologous recombination deficiency (*BRCA1/2* mutation or a GIS ≥33 on myChoice CDx assay), the effect was smaller and not significant for the subgroup without *BRCA1/2* mutation and the subgroup that was homologous recombination proficient (no *BRCA1/2* mutation and GIS <33; Table 10). OS results were not mature.[169] Veliparib is not recommended in the NCCN Guidelines because it is not FDA approved for any indications. Nonetheless the consistency of the results observed in VELIA support the use of PARP inhibitors as maintenance therapy after first-line platinum-based chemotherapy, and suggest that adding PARP inhibitors during primary chemotherapy may not provide substantial clinical benefit.

PARP Inhibitor Safety

Table 12 summarizes key safety data for the four phase III trials testing PARP inhibitor therapy as maintenance following first-line systemic therapy. Across trials, PARP inhibitor maintenance was associated with higher rates of a number of common nonhematologic AEs, such as fatigue/asthenia, nausea and vomiting (Table 12). These

nonhematologic AEs tended to be low-grade and rarely led to study-drug discontinuation.[166–169] PARP inhibitor therapy was also associated with increased risk for a number of hematologic AEs, such as anemia, neutropenia, and thrombocytopenia (Table 12). Hematologic AEs were the most common high grade AEs (grade ≥3), and the most common cause of study drug discontinuation due to toxicity.[166–169] Although rare (≤2%), PARP inhibitor therapy was also associated with risk of myelodysplastic syndrome or acute myeloid leukemia,[166–169] and is mentioned in the FDA labels.[261,262] Bevacizumab is associated with risk of hypertension; in the PAOLA-1 trial, hypertension was a common AE and a common high-grade AE in both arms, although it did not lead to discontinuation.[167] Across trials, rates of high-grade AEs (grade ≥3) were higher for single-agent PARP inhibitor maintenance therapy compared with placebo. In PAOLA-1, however, there was only a small difference between arms in the rate grade ≥3 adverse events (Table 12), and serious AEs occurred in 31% in each arm,[167] showing that risk of high-grade/serous AEs was similar for maintenance bevacizumab with versus without olaparib. Rates of study-drug discontinuation due to toxicity were higher with PARP inhibitor maintenance therapy across all trials, including PAOLA-1, largely due to hematologic AEs.

In the SOLO-1, PAOLA-1, PRIMA, and VELIA trials, there were no statistically significant differences between treatment arms in the heath-related QOL metrics evaluated.[166–169]

FDA-Approved Indications for Maintenance Therapy After First-line Systemic Therapy

Although 3 PARP inhibitors (olaparib, rucaparib, and niraparib) are approved for single-agent maintenance therapy in select patients who are in CR or PR after platinum-based chemotherapy for recurrent disease, olaparib, niraparib, and olaparib + bevacizumab are currently the only PARP inhibitor regimens that are FDA approved for maintenance treatment after response to first-line chemotherapy in patients with newly diagnosed advanced disease (Table 13). The FDA approved indications are for patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy (Table 13). The FDA indication for single-agent olaparib in this setting is limited to those with a deleterious or suspected deleterious *BRCA* mutation, and the FDA indication for bevacizumab plus olaparib in this setting is limited to those with homologous recombination deficiency, as defined by a deleterious or suspected deleterious *BRCA* mutation and/or genetic instability, as measured using an FDA-approved companion diagnostic. Veliparib is not currently FDA approved.

Maintenance with single-agent bevacizumab is FDA approved in this setting for patients with stage III–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer that has been treated with surgical resection and combination carboplatin/paclitaxel/bevacizumab (Table 13).

NCCN Recommendations for Maintenance After Primary Chemotherapy

For patients who have completed primary surgery and systemic therapy, the NCCN recommended options for management of patients who have completed primary therapy are summarized in Table 14, including maintenance therapy options. The recommended options depend on disease stage, agents used for primary systemic therapy, response to primary treatment, and *BRCA1/2* mutation status. For the maintenance therapy options, Table 14 also shows which NCCN recommended options are consistent with an FDA-approved indication, as well as options consistent with an FDA-approved indication that are not recommended in the NCCN Guidelines. Discrepancies between the NCCN recommendations and FDA-approved indications are highlighted in yellow. Table 14 shows the trials that provided data that supports the maintenance therapy options. As illustrated in Table 14, there are several key discrepancies between the FDA labels and NCCN Guidelines recommendations.

1. The FDA-approved indication for maintenance bevacizumab is limited to patients with stage III-IV disease, whereas the NCCN Guidelines include this as an option for stage II disease. The rationale for this is discussed in "Selecting Patients for Maintenance Therapy, Disease Stage"(page 217).
2. The FDA-approved indication for maintenance bevacizumab is not qualified based on *BRCA1/2* mutation status. In contrast, the NCCN Guidelines single-agent bevacizumab maintenance is limited to those without a *BRCA1/2* mutation. The rationale for this is discussed in "Olaparib + Bevacizumab" (page 212).
3. The FDA-approved indication for olaparib/bevacizumab combination maintenance therapy does not specify that patients must have had prior bevacizumab, whereas the NCCN Guidelines restrict this option to those with prior bevacizumab, as there are no prospective randomized trial data to suggest that maintenance bevacizumab provides any clinical benefit to those who did not receive prior bevacizumab in combination with platinum-based chemotherapy.
4. The FDA-approved indication for olaparib/bevacizumab combination maintenance therapy is restricted to

patients with *BRCA1/2* mutations or genomic instability, presumably based on the results of the subgroup analysis in PAOLA-1 showing no PFS benefit for those without homologous recombination deficiency. The NCCN Guidelines include olaparib/bevacizumab combination maintenance therapy as an option regardless of homologous recombination deficiency status, choosing instead to focus on the PFS benefit observed for the larger subgroup of patients without *BRCA1/2* mutation (not further subdivided by homologous recombination deficiency status).

5. The FDA approved indication for niraparib maintenance is not restricted by *BRCA1/2* mutation status or whether bevacizumab was given in combination with platinum-based chemotherapy. In the NCCN Guidelines, however, for patients who received bevacizumab as part of primary therapy, niraparib is a maintenance option only for those with a *BRCA1/2* mutation. The rationale for this is described in "Niraparib Monotherapy" (page 214).

When determining whether a patient is a candidate for maintenance after first-line therapy, and selecting among recommended maintenance therapy options, it is important to consider the eligibility criteria and characteristics of the patient population enrolled in the trials supporting the maintenance therapy options. The following sections describe considerations for selecting maintenance therapy.

Selecting Patients for Maintenance Therapy

Diagnosis and Cancer Type

As shown in Table 11, the trials testing PARP inhibitors as maintenance therapy after first-line systemic therapy enrolled patients with newly-diagnosed, histologically confirmed ovarian, primary peritoneal, or fallopian tube cancer. The FDA indications in this setting for olaparib, olaparib + bevacizumab, and niraparib all apply to cancers originating in any of these primary sites (Table 13).

Although most patients in the trials testing PARP inhibitor maintenance after primary therapy had high-grade serous histology (95%–100%), several of these trials (SOLO-1, PAOLA-1, PRIMA), included a small percentage of patients with high-grade endometrioid (2.3%–2.7%), and a small percentage with other cancer types (1.5%–2.3%; Table 11). The NCCN Guidelines recommendations for maintenance options apply to patients with high-grade serous or grade 2/3 endometrioid cancer types. It is not clear whether these maintenance therapies are appropriate for patients with less common epithelial ovarian cancer types (carcinosarcoma, clear cell carcinoma, mucinous carcinoma, grade 1 endometrioid, low grade serous). The FDA indications for PARP inhibitors in this setting are all for "epithelial" cancer (Table 13).

Disease Stage

The trials testing PARP inhibitor maintenance therapy after first-line treatment all required patients to have FIGO stage III-IV, and most patients had stage III disease (65%–83%; see Table 11). Cases of stage II disease at initial diagnosis are rare, especially among patients who have undergone complete surgical staging, so there is little data and low probability of future trials that will address the question of whether it is appropriate to use PARP inhibitors as maintenance after completing primary therapy for stage II disease. For this reason, the NCCN Panel decided that the PARP inhibitor maintenance therapy options (olaparib, niraparib, olaparib + bevacizumab) for patients who have completed first-line chemotherapy are recommended for stage III-IV disease, and should also be considered for patients who have stage II disease, noting that supporting data are limited for stage II. These maintenance therapy options are not recommended for patients with stage I disease (Table 14). The FDA indications for olaparib, olaparib + bevacizumab, and niraparib as maintenance therapy options after first-line chemotherapy are for patients with "advanced" disease, which is not clearly defined (Table 13).

The GOG-0218 and ICON7 regimens for first-line platinum-based chemotherapy with concurrent bevacizumab followed by single-agent maintenance bevacizumab are recommended in the NCCN Guidelines as options for stage III-IV disease, and the NCCN panel recommends that these can be considered for patients with stage II disease. They are not recommended for stage I disease. Use in stage II should take into consideration that GOG-0218 included only stage III-IV,[219] and although ICON7 included patients with high-risk stage I/II, subanalyses showed that the greatest benefit from bevacizumab among patients with more advanced disease, with no significant impact of bevacizumab on OS for patients with earlier stage disease.[221] The corresponding FDA-approved indication for carboplatin/paclitaxel/bevacizumab followed by single-agent bevacizumab is limited to stage III-IV disease (Table 13).

BRCA1/2 Mutation Status

Because *BRCA1/2* mutation status is important for selection of maintenance therapy in patients with stage II-IV disease that responds to primary treatment, the NCCN Guidelines recommend screening for *BRCA1* and *BRCA2* mutations earlier in the course of workup and primary treatment. Genetic risk evaluation and *BRCA1/2* testing should be initiated as soon as the diagnosis has been confirmed histologically by evaluation of tumor tissue. Primary chemotherapy should not be delayed for a genetic counseling referral, because

delay between surgery and start of chemotherapy is associated with poorer outcomes,[230,272] and maintenance would not be initiated until completion of platinum-based first-line chemotherapy, which takes (at least) 18 weeks. The NCCN Guidelines recommend that *BRCA* testing be performed using an FDA-approved test or other validated test performed in a CLIA-approved facility.

Homologous Recombination Deficiency

There is consensus that the presence of a deleterious germline or somatic mutation in *BRCA1* or *BRCA2* confers a level of homologous recombination deficiency that is clinically relevant to the selection of therapy for patients with ovarian cancer. However, for patients with ovarian cancer who do *not* have a deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2*, various molecular markers and metrics have been proposed to determine whether the cancer is associated with a clinically relevant level of homologous recombination deficiency. Different methods and cutoffs were used in the PAOLA-1, PRIMA, and VELIA trials.[167–169] Because in PRIMA the study regimen being tested improved PFS (compared with control) even among the homologous recombination "proficient" subgroups, but the same was not true in PAOLA-1 or VELIA (Table 10), it is not clear whether the assays and cutoffs used to assign homologous recombination deficiency in those studies should be used to inform selection of maintenance therapy after first-line treatment. This is an area of ongoing investigation and as such, the NCCN Panel is not ready to recommend any particular approach for determining homologous recombination deficiency in patients with ovarian cancer who do not have a *BRCA1/2* mutation.

Primary Treatment

All four trials testing PARP inhibitor maintenance after primary treatment included both patients who had received upfront PDS followed by adjuvant chemotherapy, as well as patients who had received NACT with IDS and adjuvant chemotherapy (Table 11). For trials with reported data regarding the types of primary surgery received (SOLO-1, PAOLA-1, VELIA), more than half of the patients had upfront PDS, most of the remainder had NACT and IDS, and very few did not have any primary surgery (≤7%; Table 11). In these three trials, more than half of the population had surgery resulting in no macroscopic residual disease after surgery (Table 11). In SOLO-1 and PAOLA-1, subgroup analyses showed significant PFS benefit from PARP inhibitor maintenance regardless of the type of primary surgery (PDS vs IDS) and presence vs absence of macroscopic residual disease after primary surgery.[167,264] Subgroup analyses of VELIA showed PFS benefit from veliparib regardless of the type of primary surgery (PDS vs IDS).[169]

In contrast to the other 3 trials, the PRIMA trial required that patients with stage III have either unresectable disease or visible residual disease after primary surgery, and likely included more patients treated with IDS (versus PDS), such that a much smaller proportion of the population had a surgery that resulted in no macroscopic disease. For PRIMA the data on primary surgeries received and extent of residual disease after surgery were not reported clearly. The PRIMA report did not include subgroup analyses based on type of surgery or residual disease after surgery, but did show that the PFS benefit associated with maintenance niraparib was significant for both those with and those without prior NACT.[168]

In SOLO-1, PAOLA-1 and PRIMA, most patients had at least 6 cycles of platinum-based chemotherapy as part of primary treatment (Table 11). Both intravenous regimens and IP/intravenous regimens were allowed in SOLO-1 and PAOLA-1.[166,167] In the NCCN Guidelines, all the intravenous and IP/intravenous regimens recommended for neoadjuvant/adjuvant primary chemotherapy in patients with stage II–IV high-grade serous or endometrioid disease include 6 cycles of platinum-based combination chemotherapy (see Table 3 and "Principles of Systemic Therapy, Primary Systemic Therapy Regimens," OV-C 4 of 10, available at NCCN.org).

SOLO-1, PAOLA-1 and PRIMA required patients to have CR or PR before initiation of maintenance therapy, and most had complete response after primary systemic therapy, although the definitions of CR and PR varied (Table 11). Subgroup analyses in SOLO-1 and PRIMA showed that PFS benefit from single agent PARP inhibitor maintenance was significant regardless of depth of response (CR vs PR) after first-line systemic therapy.[166,168] VELIA did not require that patients have CR or PR after primary chemotherapy as a criteria for receiving veliparib maintenance therapy, and did not report response rate for the overall population.[169]

The NCCN recommendations for maintenance bevacizumab and PARP inhibitors apply to patients with a CR (no evidence of disease) or PR after debulking surgery and chemotherapy, including those treated with PDS followed by adjuvant chemotherapy, and those treated with NACT, IDS, and adjuvant chemotherapy (see OV-2 [available at NCCN.org] and OV-5 [page 194]). Maintenance therapy is not recommended for patients who have progressive or stable disease on primary treatment; these patients should be treated with recurrence therapy options as shown on OV-7 (available at NCCN.org).

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eTable 1. IV Chemotherapy: Randomized Trials Comparing Paclitaxel 175/Carboplatin[a] With Other Doublet Combinations[b]

			First-Line Systemic Therapy[d]				
Trial	Stage	N[c]	Dosing per Cycle	Cycle Length, wk	No. of Cycles	Efficacy[e]	Safety/QoL[f]
Dutch/Danish RCT[1,2]	IIB–IV	208	Paclitaxel, 175 mg/m^2 D1+ cisplatin, 75 mg/m^2 D1	3	6	NS	• More nausea, vomiting, peripheral neurotoxicity • Less granulocytopenia and thrombocytopenia
GOG-158[f,3]	III	792	Paclitaxel, 135 mg/m^2 D1+ cisplatin, 75 mg/m^2 D1	3	6	NS	• More GI, renal, and metabolic toxicity • Less thrombocytopenia
AGO-OVAR-3[4–6]	IIB–IV	798	Paclitaxel, 185 mg/m^2 D1[g]+ cisplatin, 175 mg/m^2 D1	3	6	NS	• More nausea/vomiting, appetite loss, fatigue, and neurotoxicity • Less hematologic toxicity • Worse overall QoL, physical functioning, role functioning, cognitive functioning
ChiCTR-TRC-11001333[7]	II–IV	182	Paclitaxel, 175 mg/m^2 D1+ nedaplatin, 80 mg/m^2 D1	3	6	ITT: NS Stage III–IV: better PFS (P=.02); NS OS	• Less grade 3/4 leukopenia

Abbreviations: AUC, area under the curve; D, day of cycle; GI, gastrointestinal; ITT, intention to treat; NS, no significant difference between arms; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial.
[a]Each of the trials used the following regimen as comparator: paclitaxel, 175 mg/m^2 + carboplatin, AUC 5–6, both D1, q3wk x 6 cycles.
[b]Doublets not recommended in the NCCN Guidelines.
[c]Total number of patients randomized, including those in the paclitaxel 175/carboplatin control arm.
[d]Test regimen compared with paclitaxel 175/carboplatin.
[e]Efficacy outcomes compared with paclitaxel 175/carboplatin; NS indicates no significant difference between regimens for PFS and/or OS.
[f]Toxicity or QoL compared with paclitaxel 175/carboplatin.

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eTable 2. IV Chemotherapy: Randomized Trials Comparing Paclitaxel 175/Carboplatin[a] With Triplet/Quadruplet Combinations

Trial	Stage	N[b]	First-Line Systemic Therapy[c] Dosing per Cycle	Cycle Length, wk	No. of Cycles	Efficacy[d]	Safety/QoL[e]
ICON3[1]	IC–IV	653	Cyclophosphamide, 500 mg/m² D1+ doxorubicin, 50 mg/m² D1+ cisplatin, 50 mg/m² D1	3	6	NS	• More nausea/vomiting, fever • Less sensory neuropathy
HeCOG RCT[2]	IIC–IV	247	Paclitaxel, 175 mg/m² D1+ carboplatin, AUC 7 D1 cycles 1, 3, 5[h]+ cisplatin, 75 mg/m² D1 cycles 2, 4, 6	3	6	NS	• More severe nausea/vomiting
AGO-OCSG RCT[3]	IIB–IV	1,282	Paclitaxel, 175 mg/m² D1+ carboplatin, AUC 5 D1+ epirubicin, 60 mg/m² D1	3	6	NS	• More nausea/emesis, mucositis, infections, and grade 3/4 hematologic toxicities • Worse QoL
NCT00102375[4]	IIB–IV	1,308	Paclitaxel, 175 mg/m² D1 cycles 1–6+ carboplatin, AUC 5 D1 cycles 1–6+ topotecan, 1.25 mg/m² D1–5 cycles 7–10	3	≤10	NS	• More grade 3/4 hematologic toxicities and grade 3/4 infections
GOG-0182-ICON5[5,6]	III–IV	4,312	Paclitaxel, 175 mg/m² D1+ carboplatin, AUC 5 D1+ gemcitabine, 800 mg/m² D1	3	8[i]	NS	• More neutropenia, thrombocytopenia, anemia, fever/infection, hepatic toxicity, peripheral neuropathy, GI toxicity
			Paclitaxel, 175 mg/m² D1+ carboplatin, AUC 5 D1+ PLD, 30 mg/m² D1 cycles 1, 3, 5, 7	3	8[i]	NS	• More neutropenia, thrombocytopenia, anemia, fever/infection, GI toxicity
			Paclitaxel, 175 mg/m² D1 cycles 5–8+ carboplatin, AUC 5 D3 cycles 1–4, AUC 6 D1 cycles 5–8+ topotecan, 1.25 mg/m²/d D1–3 cycles 1–4	3	8[i]	NS	• More anemia, hepatic toxicity • Less peripheral neuropathy
			Paclitaxel, 175 mg/m² D1 cycles 5–8+ carboplatin, AUC 6 D8 cycles 1–4, D1 cycles 5–8+ gemcitabine, 1,000 mg/m²/d D1 and 8 cycles 1–4	3	8[i]	NS	• More thrombocytopenia, anemia, hepatic toxicity, pulmonary toxicity • Less peripheral neuropathy
Bolis et al, 2010[7]	III–IV	326	Topotecan, 1.0 mg/m² D1–3+ paclitaxel, 175 mg/m² D3+ carboplatin, AUC 5 D3	3	6	NS	• More fatigue, anemia, leukopenia, neutropenia
du Bois et al, 2010[8]	I–IV	1,742	Paclitaxel, 175 mg/m² D1+ carboplatin, AUC 5 D1+ gemcitabine, 800 mg/m² D1 and 8	3	6	Worse PFS (P=.0044) NS OS	• More grade 3/4 hematologic toxicity, fatigue • Worse QoL
OV-16/EORTC-55012/GEICO-0101[9]	IIB–IV	819	Cisplatin, 50 mg/m² D1 cycles 1–4+ topotecan, 0.75 mg/m² D1–5 cycles 1–4+ paclitaxel, 175 mg/m² D1 cycles 5–8+ carboplatin, AUC 5 D1 cycles 5–8	3	8[j]	NS	• More hematologic toxicities, thromboembolic events, nausea, vomiting, and hospitalizations • Less neurosensory effects and allergic reactions
NSGO, EORTC GCG, and NCIC CTG[10]	IIB–IV	887	Paclitaxel, 175 mg/m² D1 + carboplatin, AUC 5 D1 + epirubicin, 75 mg/m²	3	6–9	NS	• More anemia, febrile neutropenia, use of G-CSF, nausea, vomiting, mucositis • Less allergic reactions, arthralgia, myalgia • Worse QoL

Abbreviations: AUC, area under the curve; D, day of cycle; G-CSF, granulocyte colony-stimulating factor; GI, gastrointestinal; NS, no significant difference between arms; OS, overall survival; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; QoL, quality of life.

[a]Each of the trials used the following regimen as comparator: paclitaxel, 175 mg/m² + carboplatin, AUC 5–6, both D1, q3wk x 6 cycles

[b]Total number of patients randomized, including those in the paclitaxel 175/carboplatin control arm.

[c]Test regimen compared with paclitaxel 175/carboplatin

[d]Efficacy outcomes compared with paclitaxel 175/carboplatin; NS indicates no significant difference between regimens for PFS and/or OS.

[e]Toxicity or QoL compared with paclitaxel 175/carboplatin.

[f]Carboplatin dosing in the control arm of GOG-158 was AUC 7.5 (instead of AUC 5–6).

[g]Paclitaxel dosing in the control arm of AGO-OVAR-3 was 185 mg/m² (instead of 175 mg/m²).

[h]Carboplatin dosing in the control arm of HeCOG was AUC 7 (instead of AUC 5–6).

[i]In GOG-0182-ICON5, 8 cycles was also used for the carboplatin/paclitaxel control arm.

[j]In OV-16, 8 cycles was also used for the paclitaxel/carboplatin control arm.

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