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Target Audience: This activity is designed to meet the educational needs of physicians, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Ovarian Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Ovarian Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships: Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

Individuals Who Provided Content Development and/or Authorship Assistance:

Jamie N. Bakkum-Gamez, MD; Lisa Barroilhet, MD; Kian Behbakht, MD; Andrew Berchuck, MD; Heidi J. Gray, MD; Theresa L. Werner, MD; and Emese Zsiros, MD, PhD, (Panel Members) and Jennifer L. Burns (Guidelines Coordinator, NCCN) and Anita M. Engh, PhD (Oncology Scientist/Medical Writer, NCCN) have no conflicts of interest to disclose.

Deborah K. Armstrong, MD, Panel Chair, has disclosed that she receives grant/research support from AstraZeneca Pharamceuticals LP, Advaxis, Clovis Oncology, Syndax, Tesaro, Inc., and Pfizer Inc.

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Mihaela Cristea, MD, Panel Member, has disclosed that she is a scientific advisor for AstraZeneca Pharmaceuticals LP.

Adam C. ElNaggar, MD, Panel Member, has disclosed that he is a scientific advisor for AstraZeneca Pharmaceuticals LP, Clovis Oncology, Tesaro, Inc., and Caris Life Sciences. He also receives grant/research support from Caris Life Sciences.

David M. Gershenson, MD, Panel Member, has disclosed that he has equity interest/stock options in Biogen Iden, Celgene Corporation, and Johnson & Johnson; receives consulting fees/honoraria from Genentech, Inc., and OncLive; receives grant/research support from Novartis Pharmaceuticals Corporation; and receives royalties from Elsevier and UpToDate.

Charles A. Leath III, MD, Panel Member, has disclosed that he is a scientific advisor for AbbVie Inc., and Clovis Oncology.

Joyce Liu, MD, Panel Member, has disclosed that she receives consulting fees/honoraria from Clovis Oncology and Tesaro, Inc.

Haider Mahdi, MD, MPH, Panel Member, has disclosed that he receives grant/research support from Puma Biotechnology, and received consulting fees/honoraria from Tesaro, Inc.

Daniela Matei, MD, Panel Member, has disclosed that she receives consulting fees/honoraria from and is a scientific advisor for Genentech/Roche, AstraZeneca Pharmaceuticals LP, and Radivin.

David M. O'Malley, MD, Panel Member, has disclosed that he receives grant/research support from AbbVie Inc, AstraZeneca Pharmaceuticals LP, Clovis Oncology, Exelixis Inc., Genentech, Inc., GlaxoSmithKline, ImmunoGen, Inc., Janssen Pharmaceutica Products, LP, Novartis Pharmaceuticals Corporation, Novocure, Agenus Inc., Ajinomoto Co, Inc., Array BioPharma Inc., ERGOMED Clinical Research Ltd, INC Research, Inc, Regeneron Pharmaceuticals, Inc., Tesaro, Inc., TRACON Pharmaceuticals, Inc. He receives consulting fees/honoraria from AbbVie Inc., AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, Inc., Ambry Genetics, and Tesaro, Inc. He is a scientific advisor for AbbVie Inc., AstraZeneca Pharmaceuticals LP, Clovis Oncology, Genentech, Inc., ImmunoGen, Inc., Janssen Pharmaceutica Products, LP, Myriad Genetic Laboratories, Inc., Novocure, Agenus Inc., Marker Therapeutics, Inc., OncoQuest Inc., and Regeneron Pharmaceuticals, Inc.

Richard T. Penson, MD, MRCP, Panel Member, has disclosed that he is a scientific advisor for AbbVie, Clovis Oncology, Janssen Oncology, NewLink Genetics, Roche, Inc., and Tesaro Inc.; is a scientific advisor for and received grant/research support from AstraZeneca Pharmaceuticals LP, Eisai Inc., Genentech, Merck & Co., Sutro Biopharma, and Vascular Biogenics Ltd.

Steven W. Remmenga, MD, Panel Member, has disclosed that he is a scientific advisor for TRICARE Humana.

Paul Sabbatini, MD, Panel Member, has disclosed that he receives grant/research support from Bristol-Myers Squibb.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Ovarian Cancer, Version 1.2019

Featured Updates to the NCCN Guidelines

Deborah K. Armstrong, MD[1,*]; Ronald D. Alvarez, MD[2,*]; Jamie N. Bakkum-Gamez, MD[3,*]; Lisa Barroilhet, MD[4,*]; Kian Behbakht, MD[5,*]; Andrew Berchuck, MD[6,*]; Jonathan S. Berek, MD, MMS[7]; Lee-may Chen, MD[8,*]; Mihaela Cristea, MD[9,*]; Marie DeRosa, RN[10]; Adam C. ElNaggar, MD[11,*]; David M. Gershenson, MD[12,*]; Heidi J. Gray, MD[13,*]; Ardeshir Hakam, MD[14]; Angela Jain, MD[15]; Charles A. Leath III, MD[16,*]; Joyce Liu, MD[17,*]; Haider Mahdi, MD, MPH[18,*]; Daniela Matei, MD[19,*]; Michael McHale, MD[20]; Karen McLean, MD, PhD[21]; David M. O'Malley, MD[22,*]; Richard T. Penson, MD, MRCP[23,*]; Sanja Percac-Lima, MD[23]; Elena Ratner, MD[24]; Steven W. Remmenga, MD[25,*]; Paul Sabbatini, MD[26,*]; Theresa L. Werner, MD[27,*]; Emese Zsiros, MD, PhD[28,*]; Jennifer L. Burns[29,*]; and Anita M. Engh, PhD[29,*]

ABSTRACT

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States, with less than half of patients living >5 years from diagnosis. A major challenge in treating ovarian cancer is that most patients have advanced disease at initial diagnosis. The best outcomes are observed in patients whose primary treatment includes complete resection of all visible disease plus combination platinum-based chemotherapy. Research efforts are focused on primary neoadjuvant treatments that may improve resectability, as well as systemic therapies providing improved long-term survival. These NCCN Guidelines Insights focus on recent updates to neoadjuvant chemotherapy recommendations, including the addition of hyperthermic intraperitoneal chemotherapy, and the role of PARP inhibitors and bevacizumab as maintenance therapy options in select patients who have completed primary chemotherapy.

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[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [2]Vanderbilt-Ingram Cancer Center; [3]Mayo Clinic Cancer Center; [4]University of Wisconsin Carbone Cancer Center; [5]University of Colorado Cancer Center; [6]Duke Cancer Institute; [7]Stanford Cancer Institute; [8]UCSF Helen Diller Family Comprehensive Cancer Center; [9]City of Hope National Medical Center; [10]Patient Advocacy; [11]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [12]The University of Texas MD Anderson Cancer Center; [13]University of Washington/Seattle Cancer Care Alliance; [14]Moffitt Cancer Center; [15]Fox Chase Cancer Center; [16]University of Alabama at Birmingham Comprehensive Cancer Center; [17]Dana-Farber/Brigham and Women's Cancer Center; [18]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [19]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [20]UC San Diego Moores Cancer Center; [21]University of Michigan Rogel Cancer Center; [22]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [23]Massachusetts General Hospital Cancer Center; [24]Yale Cancer Center/Smilow Cancer Hospital; [25]Fred & Pamela Buffett Cancer Center; [26]Memorial Sloan Kettering Cancer Center; [27]Huntsman Cancer Institute at the University of Utah; [28]Roswell Park Comprehensive Cancer Center; and [29]National Comprehensive Cancer Network.

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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

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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Overview

For advanced-stage epithelial ovarian cancer, including fallopian tube and primary peritoneal cancers, the best outcomes have been observed in patients whose primary treatment included complete resection of all visible disease and combination chemotherapy.[1] Therefore, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer recommend that primary treatment of presumed advanced-stage ovarian cancer consist of appropriate surgical debulking plus systemic chemotherapy in most patients. For most patients presenting with suspected advanced-stage malignant ovarian cancer, initial surgery should include a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) with comprehensive staging and debulking as indicated.[2–4] Primary debulking surgery (PDS) is the recommended approach for advanced-stage disease if the patient is a surgical candidate, optimal cytoreduction (residual disease <1 cm [R1] and preferably removal of macroscopic disease [R0]) appears feasible, and fertility is not a concern. Neoadjuvant chemotherapy (NACT) with interval debulking surgery (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 disease that is unlikely to be optimally cytoreduced. The anticipated benefit from NACT would be to allow for medical improvement 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. In recent years, new therapies have become available for patients with both newly diagnosed advanced-stage and recurrent ovarian cancer. These NCCN Guidelines Insights focus on recent updates to the recommendations for NACT for advanced-stage ovarian cancer and options for maintenance therapy after completion of primary therapy. These updates to the NCCN Guidelines for Ovarian Cancer are generalized to the more common subtypes and do not necessarily apply to rare ovarian cancer histologies (see full NCCN Guidelines for details).

Neoadjuvant Therapy

Randomized Trials Comparing NACT Versus Conventional Treatment

Several prospective randomized controlled trials have compared a NACT approach (with IDS and postoperative chemotherapy) versus conventional treatment (PDS plus postoperative chemotherapy; Table 1).[5–9] These trials focused on patients with FIGO stage IIIC–IV ovarian cancer that was deemed unlikely to be completely resected. As shown in Table 1, the NACT regimens tested in these trials typically consisted of 3 to 4 cycles of upfront chemotherapy followed by IDS with the goal of maximum cytoreduction, followed by 3 to 4 cycles of postoperative chemotherapy. Several of these trials (EORTC 55971,[5] SCORPION,[7] JCOG0602[8]) allowed IDS in the neoadjuvant arm only for patients experiencing response or stable disease after NACT. The control arms in these trials consisted of PDS (with the goal of maximum cytoreduction) followed by postoperative chemotherapy to a total of 6 to 8 cycles. Specific chemotherapy regimens used in these trials are shown in supplemental eTable 1, available with this article at JNCCN.org.[5–9]

Although there was some variability across these trials, results in general demonstrated that patients treated with NACT had improved surgical outcomes (eg, shorter operative time, less blood loss, fewer high-grade surgical complications or surgery-related adverse events [AEs], shorter hospital stay), less extensive and complicated surgeries needed to achieve optimal cytoreduction, and a lower risk of postoperative death (Table 1).[5–9] Most of these trials found that NACT increased the likelihood of achieving optimal cytoreduction and/or removal of all macroscopic disease (R0).

Although an NACT approach was associated with improved surgical outcomes and less residual disease after surgery, trials that reported progression-free survival (PFS) and overall survival (OS) found no significant differences when compared with the conventional PDS approach (Table 1). For some of these trials, post hoc analyses were conducted to determine whether there are any subgroups of patients for whom NACT may improve PFS or OS. Although analyses of CHORUS did not identify any subgroups with treatment-dependent differences in PFS or OS, analyses of EORTC 55971 and a pooled analysis of the per protocol populations from EORTC 55971 and CHORUS showed that NACT (with IDS and adjuvant chemotherapy) may improve PFS and/or OS in patients with more extensive disease, but conventional treatment (PDS and postoperative chemotherapy) was associated with better PFS and/or OS in patients with less extensive disease.[10,11,13]

Importantly, for some of these trials (EORTC 55971, CHORUS) the median PFS and OS for both treatment arms (Table 1) were inferior to those reported in randomized studies of patients undergoing PDS followed by postoperative intravenous chemotherapy for advanced ovarian cancer (OS mean, ~50 months in the United States).[14,15] Although the median OS in the international trial is 20 months lower than that reported in US trials using the customary sequence of therapeutic interventions (ie, PDS followed by chemotherapy), this difference may have been a result of selection of higher risk patients in the NACT trials (which did not include patients with stage IIIB or earlier stages).

Table 1. Randomized Trials Comparing NACT + IDS Versus PDS

RCT	Patients[a]	Treatment Arms	Arm A vs Arm B: n	Surgical Outcomes	Efficacy	Safety
EORTC 55971 Phase III Vergote et al[5] N=670	FIGO stage IIIC/IV: 76%/24% Poor differentiation: 41%[b] Entry criteria: diagnosis by biopsy; or FNA plus imaging and CA-125:CEA ratio[b]	Arm 1: NACT x 3 cycles →IDS if response/SD →CT x ≥3 cycles →Second look allowed Arm 2: PDS →CT x 3 cycles →IDS option if response/SD & >1 cm after PDS →CT x ≥3 cycles →Second look allowed	334 vs 336	Operative time: median, 180 vs 165 min Residual disease: • R0: 51% vs 19% • ≤1 cm: 81% vs 42% Death <28 d postop: 0.7% vs 2.5%	Median PFS: 12.0 vs 12 mo; NS Median OS: 30 vs 29 mo; *P*=.01[c]	Periop & postop (<28 d) G3–4 AEs (NCI CTC 2.0): • Hemorrhage: 4.1% vs 7.4% • Infections: 1.7% vs 8.1% • Venous complications: 0% vs 2.6%
CHORUS Phase III Kehoe et al[6] N=550	FIGO stage IIIC/IV: 72%/16%[d] Poor differentiation: 77% Entry criteria: diagnosis by imaging, CA-125:CEA >25[d]	Arm 1: NACT x 3 cycles →IDS →CT x 3 cycles Arm 2: PDS →CT x 3 cycles →IDS option for >1 cm residual after PDS →CT x 3 cycles	274 vs 276	Operative time: median, 120 vs 120 min Residual disease: • R0: 39% vs 17%; *P*=.0001 • <1 cm: 73% vs 41%; *P*=.0001 Hospital stay ≤14 d: 93% vs 80%; *P*<.0001 Death <28 d postop: <1% vs 6%; *P*=.001	Median PFS: 12.0 vs 10.7 mo; HR, 0.91 (95% CI, 0.76–1.09) Median OS: 24.1 vs 22.6 mo; HR, 0.87 (95% CI, 0.72–1.05)[e]	G3–4 AEs (CTCAE 3.0): • Postop (<28 d): 14% vs 24%; *P*=.007 • During CT: 40% vs 49%; *P*=.0654
SCORPION Phase III Fagotti et al[7] N=110	FIGO stage IIIC/IV: 89%/11%[f] Poor differentiation: NR[f] Entry criteria: diagnosis and tumor load (predictive index 8–12, no mesenteric retraction) by *S*-LPS[f]	Arm 1: NACT x 3–4 cycles →IDS if response/SD →CT to a total of 6 cycles Arm 2: PDS →CT x 6 cycles	55 vs 55	Operative time: median, 275 vs 451 min; *P*=.0001 Residual disease: • R0: 58% vs 46%; NS • ≤1 cm: 85% vs 91% Hospital stay: median, 6 vs 12 d; *P*=.0001 Death ≤30 d postop: 0% vs 4%; NS PDS associated with more extensive/complex procedures & blood loss[g]	NR	Surgical secondary events G3–4 (MSKCC system): • ≤30 d postop: 6% vs 53%; *P*=.0001 • 1–6 mo postop: 0% vs 15%; *P*=.004 CT-related G3–4 AEs (NCI CTC 2.0): 36% vs 43%; NS
JCOG0602 Phase III Onda et al[8] N=301	FIGO stage III/IV: 68%/32% (IIIC NR) Poor differentiation: NR Entry criteria: diagnosis by imaging plus cytology[h] CA-125 >200 U/mL, CEA <20 ng/mL	Arm 1: NACT x 4 cycles →IDS if response/SD →CT x 4 cycles Arm 2: PDS →CT x 4 cycles →IDS option if residual >1 cm after PDS →CT x 4 cycles	152 vs 149	Operative time: median, 273 vs 341 min; *P*<.001[i] Residual disease: • R0: 55% vs 31% • <1 cm: 71% vs 63%[i] Surgery-related death: 0% vs 0.7%; NS PDS associated with more extensive surgery & blood/ascites loss[i]	NR	G3–4 AEs (CTCAE 3.0): • After surgery: 5% vs 15%; *P*=.005 • First-half CT: 18% vs 20%; NS • Second-half CT: 12% vs 9%; NS
Liu et al[9] N=108	FIGO stage III/IV: 68%/32% G2–3: 55% Entry criteria: diagnosis by imaging, serum CA-125; confirmed by LPS biopsy or laparotomy	Arm 1: NACT IP/IV x 2 cycles →IDS →CT IV x 6 cycles Arm 2: PDS →CT IV x 6–8 cycles	58 vs 50	Operative time: 2.36 vs 3.63 h; *P*<.001 Successful cytoreduction: 74% vs 46%; *P*=.0054 PDS associated with greater blood loss (*P*<.001)	Median PFS: 26 vs 22 mo; NS Median OS: 62 vs 51; NS[j]	CT side effects (degree III–IV): NS

Abbreviations: AE, adverse event; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; CT, chemotherapy; G, grade; HR, hazard ratio; IDS, interval debulking surgery; IP, intraperitoneal; IV, intravenous; LPS, laparoscopic surgery; MSKCC, Memorial Sloan Kettering Cancer Center; NACT, neoadjuvant chemotherapy; NS, not significantly different (between arms); NR, not reported; OS, overall survival; PDS, primary debulking surgery; periop, perioperative; PFS, progression-free survival; postop, postoperative; R0, removal of all macroscopic disease; RCT, randomized controlled trial; SD, stable disease; *S*-LPS; staging laparoscopic surgery.

[a]All trials included patients with ovarian, fallopian tube, or primary peritoneal cancer, including the following histologic types: serous, mucinous, clear cell, endometrioid, undifferentiated, mixed. SCORPION excluded patients with borderline histology.

[b]Histologic grade was unknown for 41% of patients. Stage and cancer type were required to be proven by biopsy (image-guided or during laparoscopy or laparotomy).

[c]OS *P* value was for noninferiority. Post hoc analyses showed no treatment-dependent differences in OS for subgroups based on FIGO stage, WHO performance status, histologic type, or presence/absence of pleural fluid.[5] NACT was associated with better OS in patients with more extensive disease (stage IV, largest metastasis >45 mm diameter; or stage IVB) and PDS was associated with better OS in patients with less extensive disease (stage III, ≤45 mm), and no treatment-dependent difference in OS in patients with an intermediate extent of disease (stage IIIC, <45 mm; or stage IVA).[10,11]

[d]Suspected stage III–IV based on imaging/clinical evidence was confirmed after surgery in 96% of patients; the remaining had stage II or unknown stage. Prior to NACT, diagnosis was confirmed by histology/cytology (laparoscopy in 16%; image-guided biopsy, 42%; or FNA of tumor/effusion, 41%).

[e]Analyses of subgroups showed that residual disease after surgery was prognostic for OS in both treatment groups. Post hoc analyses showed no treatment-dependent differences in OS for subgroups based on age, cancer stage, tumor size (prior to surgery), performance status, or type of CT (single-agent carboplatin vs carboplatin/paclitaxel).

[f]Patients with stage IV were required to have pleural infusion or any resectable disease; 97% of patients had type II histology per Kurman and Shih,[12] which includes conventional high-grade serous carcinoma, undifferentiated carcinoma, and malignant mixed mesodermal tumors (carcinosarcoma).

[g]PDS was associated with a higher rate of upper abdominal procedures (*P*=.0001), surgical complexity (*P*=.0001), blood loss (*P*=.003), and time between surgery and starting postoperative CT (*P*=.0001).

[h]Diagnosis was based on both imaging and cytology of ascites, pleural effusions, or fluids obtained by centesis; histologic confirmation was not required.

[i]Outcomes of surgery in this table include results from all surgeries performed. Patients in the PDS arm had higher rates of para-aortic and pelvic lymphadenectomy (*P*<.001, *P*<.001), resection of abdominal organ and distant metastases (*P*=.012, *P*=.017), and transfusions of albumin or fresh-frozen plasma/plasma protein fraction/albumin (*P*<.001, *P*<.001). They also had higher volumes of blood/ascites loss (*P*<.001).

[j]Subgroup analysis showed that the following factors were prognostic for OS among patients in the NACT arm: stage (III vs IV), histologic grade (1 vs 2 vs 3), residual tumor size (≤1 vs >1 cm), and number of CT cycles.

Selection of Patients for NACT

NCCN recommendations for workup and selection of patients for NACT are aligned with the eligibility criteria and protocols used in the randomized controlled trials shown in Table 1. For these trials, preoperative evaluations and debulking surgeries were performed by gynecologic oncologists; some trials included additional requirements to ensure that the surgeons had sufficient experience performing the procedures.[5–9] The NCCN Ovarian Cancer Panel emphasizes that evaluation by a gynecologic oncologist is important for determining the most appropriate method of obtaining tissue for histologic confirmation and of determining the extent of disease. This recommendation is consistent with those from Society of Gynecologic Oncology and ASCO.[16]

Most of the trials in Table 1 required confirmation of staging and diagnosis based on imaging plus histology of a biopsy specimen or cytology of ascites or pleural effusion. Some trials had additional entry criteria based on serum cancer antigen 125 (CA-125) and carcinoembryonic antigen (CEA) levels, and some required additional diagnostic tests to rule out other types of malignancies. Laparoscopy to evaluate extent of disease and feasibility of resection was required in one of the trials (SCORPION) and also frequently used in the other trials. Reports from several of these trials noted that for some patients, the assignment of histologic type and disease stage was revised after biopsy or laparoscopic evaluation, and sometimes revised after debulking surgery.[5–8] The NCCN Guidelines recommend pathologic confirmation of diagnosis and histologic subtype based on analysis of tumor tissue. If biopsy is not feasible, cytopathology from ascites or pleural effusion combined with a CA-125:CEA ratio of >25 can be used.[6,17–19] Although biopsy can be obtained through a variety of methods, and minimally invasive techniques can be used, laparoscopic evaluation should be considered for determining the feasibility of resection, because it may allow for a more accurate evaluation of whether optimal cytoreduction can be achieved. Because germline and/or somatic *BRCA1* and *BRCA2* mutation status may inform future options for maintenance therapy, all patients with histologically confirmed ovarian cancer should undergo genetic risk evaluation and *BRCA1* and *BRCA2* testing, if not previously performed. However, treatment should not be delayed for genetic counseling referral, because delay in treatment is associated with poorer outcomes.[20,21]

Regimen Options for Patients Treated With NACT

A wide variety of platinum-based regimens have been used in clinical trials testing NACT plus IDS and postoperative chemotherapy. All of the randomized trials in Table 1 used platinum-based combination chemotherapy or monotherapy (supplemental eTable 1). Other chemotherapy regimens that have been tested in prospective trials in patients with ovarian cancer are shown in supplemental eTable 2.[22–27] For most of the trials in supplemental eTables 1 and 2, patients received the same chemotherapy regimen for both NACT and postoperative therapy. For the prospective trials comparing different chemotherapy regimens in patients treated with a NACT approach (PRIMOVAR-1, GEICO 1205/NOVA, ANTHALYA, OV21/PETROC), none has yet demonstrated the superiority of any regimen based on surgical outcomes, PFS, or OS (supplemental eTable 2).[23,25–27] Given that a wide variety of regimens have been successfully used in prospective trials, and in the absence of data indicating that specific regimens should be excluded or favored, the NCCN Guidelines provide a list of options that can be used before and/or after surgery in patients treated with an NACT approach (supplemental eTable 3), including all of the intravenous regimens recommended for conventional treatment of stage II–IV disease (ie, PDS followed by chemotherapy).

Bevacizumab-Containing Regimens for Patients Treated With NACT

Several prospective trials have explored whether adding bevacizumab to platinum-based regimens improves outcomes for patients treated with NACT. Preliminary results from GEICO 1205/NOVA found that adding bevacizumab to a standard carboplatin/paclitaxel regimen did not significantly change the rate of complete response (CR) on NACT (prior to IDS), rate of "optimal surgery", or PFS, but did show a lower rate of grade 3–4 AEs in the arm that included bevacizumab (70% vs 42%, P=.026).[25] The ALTHALYA trial used a similar carboplatin/paclitaxel regimen, but did not find a significant difference in the rate of grade 3–5 AEs for patients treated without versus with bevacizumab (63% vs 62%).[26] Results from ALTHALYA also showed no difference between treatment arms for CR rate prior to IDS, percent of patients with no macroscopic residual disease after IDS, or surgical outcomes (operative time, length of hospital stay, length of stay in intensive care unit, frequency of blood transfusions, and rate of postoperative complications).[26] Taken together, results from these trials indicate that although platinum-based regimens that include bevacizumab have acceptable safety for patients treated with an NACT approach, more data are needed to determine whether the addition of bevacizumab impacts PFS. It is important to note that all of the prospective trials in supplemental eTables 1 and 2 that allowed use of bevacizumab in the NACT setting used a washout period before (and sometimes after) IDS, usually of at least 28 days.[7,24–26] The NCCN Guidelines include 2 bevacizumab-containing regimens as

options for NACT and post-IDS chemotherapy (supplemental eTable 3).

Intraperitoneal/Intravenous Regimens for Patients Treated With NACT

Several trials have explored the use of intraperitoneal/intravenous regimens in patients treated with an NACT approach. Both SWOG S0009 and OV21/PETROC tested postoperative intraperitoneal/intravenous regimens for patients who had platinum-based NACT followed by optimal cytoreduction by IDS.[22,27] In SWOG S0009, among patients with a ≥50% decrease in CA-125 level during NACT, optimal debulking by IDS (<1 cm and malignant pleural effusions resolved), and postoperative intraperitoneal/intravenous chemotherapy, median PFS (29 months) and OS (34 months) compared favorably with results from other trials using intravenous regimens (supplemental eTable 2).[22] To determine whether postoperative intraperitoneal/intravenous chemotherapy improves outcomes compared with intravenous regimens among patients treated with NACT, the OV21/PETROC trial compared 3 different postoperative regimens (supplemental eTable 2) in patients previously treated with platinum-based intravenous NACT (3–4 cycles) and optimal cytoreduction by IDS.[27] Although trends in the rate of progression or death in the first 9 months (from randomization) favored the carboplatin/paclitaxel intraperitoneal/intravenous regimen (Arm 3, 24.5%) over the cisplatin/paclitaxel intraperitoneal/intravenous regimen (Arm 2, 34.7%) or the carboplatin/paclitaxel intravenous regimen (Arm 1, 38.6%), later results (median follow-up 33 months) showed no difference in median PFS between the intraperitoneal/intravenous and the intravenous regimens (supplemental eTable 2). OS rate at 2 years was also not significantly different (74% vs 81% for Arm 1 vs Arm 3).[27] Based on these results, the NCCN Guidelines include both the cisplatin/paclitaxel and carboplatin/paclitaxel intraperitoneal/intravenous regimens as options for postoperative therapy in patients who have received NACT and IDS (supplemental eTable 3). Given the lack of survival improvement in OV21/PETROC, more data are needed to establish whether postoperative intraperitoneal chemotherapy provides clinical benefit in patients who have received intravenous NACT and IDS. Recent results from the phase III randomized controlled GOG-0252 trial have also called into question the value of postoperative intraperitoneal chemotherapy for patients with advanced-stage ovarian cancer treated with PDS.[28] Although earlier trials showed improved PFS and/or OS with intraperitoneal vs intravenous chemotherapy,[1,14,29,30] results from GOG-0252 showed no improvement.[28] However, unlike previous trials, all regimens used in GOG-0252 contained bevacizumab, which may have compensated for the effect of intraperitoneal chemotherapy administration.

Number of Chemotherapy Cycles Before and After IDS

As shown in supplemental eTable 2, results from the PRIMOVAR-1 phase II randomized trial showed that treatment with 3 versus 2 cycles of NACT did not impact response rate, extent of cytoreduction achieved in IDS, operative time, extent of surgery needed, or PFS or OS.[23] Nonetheless, because most of the randomized trials testing NACT protocols used 3 to 4 cycles before IDS (Table 1 and supplemental eTables 1 and 2), the NCCN Guidelines indicate that 3 cycles of NACT before IDS is preferred, although surgery after 4 to 6 cycles may be used based on the clinical judgement of the treating gynecologic oncologist.

After 3 cycles of NACT, patients should be evaluated by a gynecologic oncologist to determine the likelihood of optimal cytoreduction. For patients who responded to NACT and are likely to have optimal cytoreduction, IDS should be performed. Those with stable disease after 3 cycles of NACT can consider IDS, but also should consider either (1) switching to treatment of persistent/recurrent disease or (2) treatment with additional cycles of NACT (to a total of ≥6 cycles) prior to IDS. Patients who experience disease progression during NACT should switch to therapy for persistent/recurrent disease.

Most of the trials testing NACT regimens used at least 3 cycles of chemotherapy after IDS, or indicated that the total number of cycles should be 6 to 8 (Table 1 and supplemental eTables 1 and 2). The NCCN guidelines recommend that regardless of the number of cycles of NACT received, IDS should always be followed by adjuvant chemotherapy. For all patients who undergo NACT plus IDS, a minimum of 6 cycles of treatment is recommended, including at least 3 cycles of adjuvant therapy after IDS.

Interval Debulking Surgery

Analyses of data from multiple prospective trials found that the extent of residual disease after NACT plus IDS was prognostic for PFS and OS.[5,6,9,23] As shown in Table 1 and supplemental eTables 1 and 2, these trials reported optimal cytoreduction in 45% to 91% of patients, with complete removal of all macroscopic disease in 30% to 59%. Therefore, the goal of IDS is to achieve complete removal of macroscopic disease (R0) whenever possible. NCCN-recommended procedures for IDS, described in detail in supplemental eTable 4, are similar to those used in these trials,[5–8,22–24,26] and similar to those recommended for PDS. As mentioned earlier, these trials required experienced gynecologic oncologists for preoperative evaluation and IDS.[5–7,26] Minimally invasive techniques can be used for IDS in select patients. Patients

whose disease is unable to be optimally debulked using minimally invasive techniques should be converted to an open procedure (supplemental eTable 4).

Hyperthermic Intraperitoneal Chemotherapy at the Time of IDS

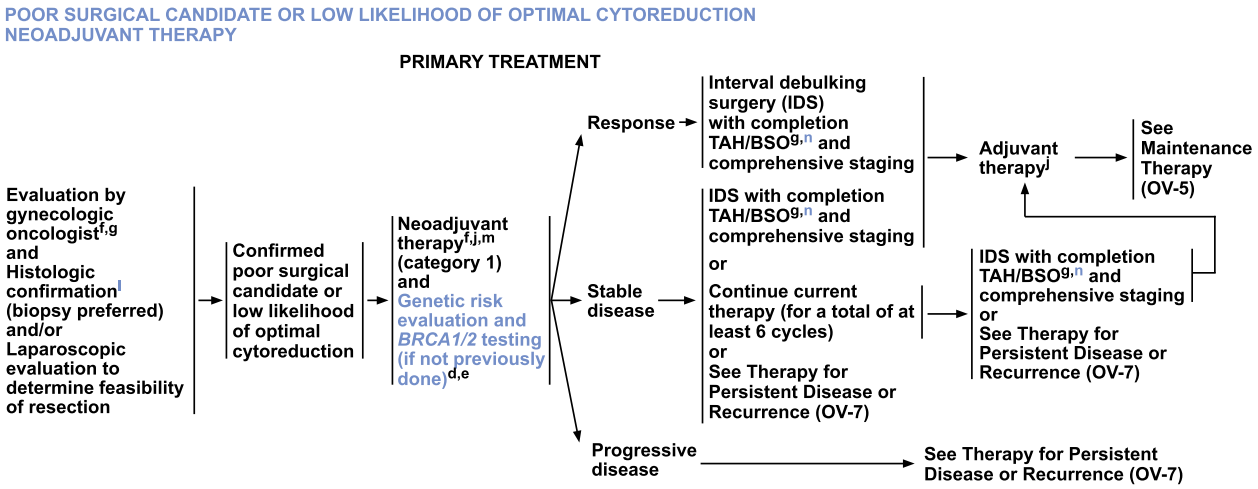
Hyperthermic intraperitoneal chemotherapy (HIPEC) is a technique in which chemotherapy is delivered in a heated solution perfused throughout the peritoneal space. The rationale for hyperthermic delivery is that heat can increase penetration of the chemotherapy at the peritoneal surface and enhance the sensitivity of cancer cells to chemotherapy by inhibiting DNA repair.[31–33] Concerns about the inconvenience of delivery and toxicities associated with postoperative intraperitoneal/intravenous chemotherapy motivated researchers to determine whether HIPEC could improve safety and quality of life. Although raising body temperature carries substantial risks, methods have been developed for raising the temperature of the intraperitoneal space with minimal increase in the temperature of the rest of the body.

Over the past several decades, a few prospective comparative trials (supplemental eTable 5)[34–37] and numerous prospective noncomparative trials (supplemental eTable 6)[38–51] have reported on the use of HIPEC in patients with ovarian cancer. HIPEC methods have evolved over the years to reduce intraoperative and postoperative complications. Both "open" and "closed" abdominal techniques have been developed and tested in prospective studies (supplemental eTables 5 and 6).[34,35,37–51] HIPEC protocols used in prospective studies usually perfused chemotherapy for 60 or 90 minutes (depending on agent and dose used) with solution heated to achieve an intraperitoneal temperature of 41°C to 43°C.[34–51] The duration and safety of cytoreductive surgery plus HIPEC procedures varied across trials, with median procedure time ranging from 300 to 600 minutes and median hospital stay ranging from 8 to 24 days.[34–44,46–51] Excessive blood loss was common, and in some studies, more than half of the patients required transfusions. Intraoperative and postoperative mortality (<30 days from surgery) ranged from 0% to 7%,[38–45,47] although the most recent trials all report no deaths related to the procedure.[49–51] The rate of complications from surgery vary across trials, with major/severe complications (<30 days from surgery) occurring in 9% to 40% of patients.[38–47,49,50] Studies from one center reported that complication rates decreased in more recent years compared with when their center first started performing debulking and HIPEC procedures.[40,52] Common major/severe complications observed across trials include various types of fistulas, abscesses, and infections (wound infection, sepsis, pneumonia, central line–associated infection, intra-abdominal infection), surgical wound dehiscence, bowel perforation, ileus, hemorrhages, venous thromboembolism, myocardial infarction, pleural effusions, pneumothorax, and renal failure/insufficiency.[34,39–43,45,47,48,50,53] Many studies reported that additional procedures were needed to manage complications.[34,40,41,44,46,47,49,50,53,54]

Given the risks associated with HIPEC, prospective studies have focused on using HIPEC immediately after debulking (as part of the same procedure) in patients with high-volume intraperitoneal disease (FIGO stage III–IV at diagnosis or recurrence), particularly those with peritoneal carcinomatosis, who are at risk for widespread residual microscopic disease even after resection to no visible disease. Compared with postoperative intraperitoneal therapy, intraoperative intraperitoneal administration may enable better perfusion of the peritoneal space because adhesions will not yet have formed. Patients with less extensive disease were excluded because they are less likely to have widespread microscopic disease after debulking, and therefore the potential benefit is unlikely to outweigh risks of the procedure. Patients with distant extra-abdominal metastases were often excluded from HIPEC studies because of concerns that intraperitoneal therapy would not be effective treatment of extraperitoneal disease.

Only a few phase III prospective comparative studies have tested whether HIPEC improves outcomes for patients with advanced ovarian cancer (summarized in supplemental eTable 5). The most recent and largest (n=245) of these, M06OVH-OVHIPEC, showed that HIPEC improved recurrence-free survival and OS in patients with FIGO stage III primary epithelial ovarian, fallopian tube, or peritoneal cancer who underwent NACT due to extensive abdominal disease or suboptimal PDS.[37] Although the total procedure time for debulking + HIPEC was longer than for debulking alone, HIPEC did not appear to have any major effects on hospital stay (median, 10 vs 8 days) or administration of postoperative intravenous chemotherapy (ie, time to initiation, rate of completion of all 3 cycles). Most important, no differences in rates of toxicity were seen between arms (grade 3–4 toxicities: 27% vs 25%) or in any of the health-related quality-of-life metrics evaluated.

Because of these positive results, the NCCN Guidelines now include an option to consider HIPEC at the time of IDS in patients with stage III disease treated with NACT (see OV-2 [footnote n], page 903). Similar to the trial, which required patients to have response or stable disease after 3 cycles of NACT and which treated patients with postoperative chemotherapy (3 cycles), the NCCN Guidelines recommend HIPEC as an option for patients who have response or stable disease after NACT (3 cycles preferred, but 4–6 allowed) and that all patients treated with NACT and IDS (± HIPEC) receive



[d]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[e]Primary treatment should not be delayed for a genetic counseling referral. Germline and/or somatic *BRCA1/2* status may inform maintenance therapy.
[f]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.

[g]See Principles of Surgery (OV-A) and Principles of Pathology (OV-B).
[j]See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[l]If biopsy is not feasible, cytopathology from ascites or pleural effusion combined with CA-125:CEA ratio of >25 can be used.
[m]Completion surgery after 3 cycles is preferred; however, surgery may be performed after 4–6 cycles based on the clinical judgment of the gynecologic oncologist.
[n]Hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin (100 mg/m^2) can be considered at the time of IDS for stage III disease.

OV-2

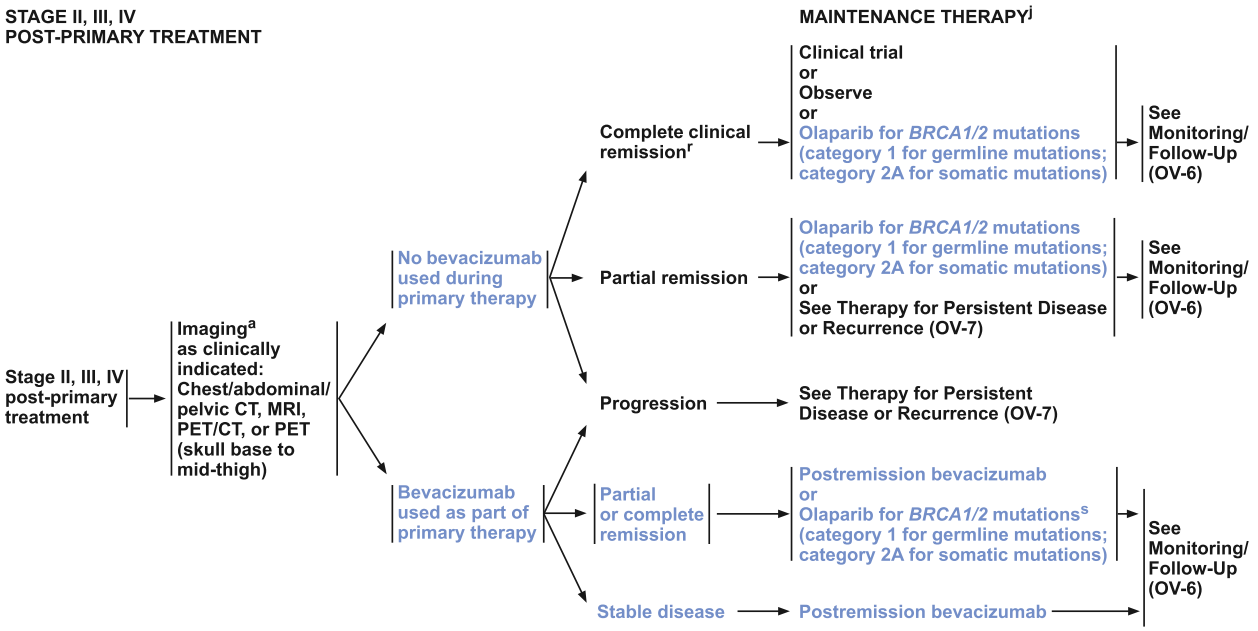
postoperative chemotherapy. Analyses of M06OVH-OVHIPEC showed that the effect of HIPEC was consistent across a wide variety of subgroups (age, histologic type, prior surgery, extent of disease, laparoscopy before surgery). Therefore, the NCCN Guidelines indicate that HIPEC can be considered for all patients with stage III disease for which NACT and IDS is performed, without any further requirements for selection of patients. Importantly, HIPEC is not recommended for patients treated with PDS (no NACT) based on initial results from a randomized controlled trial showing that HIPEC did not improve PFS or OS in a population of patients with optimal cytoreduction (<1 cm residual) after PDS or after NACT + IDS (supplemental eTable 5).[36] In the subset of patients who underwent NACT and IDS, however, long-term follow-up showed a trend toward improved PFS and OS with HIPEC.[36]

In most prospective studies testing HIPEC, the surgery prior to HIPEC was conducted with the goal of maximal cytoreduction (R0 resection) and involved TAH/BSO, omentectomy, and a variety of other procedures, depending on the extent of disease. Optimal cytoreduction (residual disease <1 cm) was achieved in most patients in these trials, and, in some studies, was a requirement for receiving subsequent HIPEC (supplemental eTables 5 and 6). Rates of complete cytoreduction (R0 resection) varied from 50% to 100% in these trials,[38–40,42–48,50,51] and univariable and multivariable analyses showed that residual disease after debulking was the strongest predictor of OS.[38,39,43–45,53,55] Therefore, NCCN recommends maximum effort to achieve complete cytoreduction during IDS, regardless of whether HIPEC is planned.

The NCCN-recommended HIPEC agent is cisplatin, 100 mg/m^2, as was used in M06OVH-OVHIPEC.[37] Although this trial tested only one regimen for NACT and postoperative chemotherapy (carboplatin, area under the curve [AUC] 5–6 + paclitaxel, 175 mg/m^2 body surface area), other studies have used a variety agents, and the optimal pairing of pre/postoperative regimens with HIPEC agent has not been determined. The NCCN Guidelines currently do not restrict the HIPEC recommendation based on the regimen selected for NACT or postoperative chemotherapy.

Options After First-Line Chemotherapy

There are now increasing options for patients with advanced-stage ovarian cancer who have a partial response or a CR after primary therapy (some combination of surgery + chemotherapy; see OV-5, page 904). NCCN recommendations have been revised several



[a]Imaging performed with contrast unless contraindicated.
[j]See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[r]No definitive evidence of disease.
[s]There are limited data on the addition of maintenance olaparib after first-line therapy with bevacizumab. Combination bevacizumab and olaparib maintenance therapy is not recommended at this time.

OV-5

times recently due to emerging data from clinical trials; these recent data and their impact on the recommendations are discussed herein.

Bevacizumab Maintenance Therapy

As described in detail in the complete version of the NCCN Guidelines for Ovarian Cancer (available at NCCN.org), bevacizumab maintenance therapy is recommended for patients with stage II–IV disease who experience response or stable disease after postoperative chemotherapy with one of the recommended carboplatin/paclitaxel/bevacizumab regimens.

Olaparib Maintenance Therapy After Primary Chemotherapy

Olaparib is a PARP inhibitor shown to be active in recurrent ovarian cancer,[56–63] and has been FDA-approved for multiple indications,[64] summarized in Table 2 (the corresponding recommendations can be found on OV-7 and OV-C 6 and 7 of 9 in the NCCN Guidelines at NCCN.org).

More recently, the phase III, double-blind, randomized 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 were in a CR or PR after first-line platinum-based chemotherapy for advanced ovarian cancer (supplemental eTable 7).[68] The risk of progression or death was 70% lower, and whereas the median PFS (from randomization) was 13.8 months for placebo, the median PFS for olaparib had not been reached after a median follow-up of 41 months; OS data are immature. Rates of serious AEs (21% vs 12% for olaparib vs placebo) and study-drug discontinuation due to toxicity were higher in the olaparib arm (supplemental eTable 7). Anemia and neutropenia were among the grade 3–4 AEs that were more frequent with olaparib versus placebo, and sometimes led to study-drug discontinuation. Health-related quality-of-life scores were stable during study treatment with olaparib, and decreased slightly with placebo; this difference was not clinically significant. 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 ovarian cancer, olaparib is currently the only one that is FDA-approved for maintenance treatment after response to first-line chemotherapy in patients with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation (Table 2). The other agents are also being actively studied for this same indication, with results forthcoming.

Table 2. 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 February 2019[65]	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, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 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	
Olaparib December 2018[64]	None	For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated[a] advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy	For the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated[a] 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 complete or partial response to platinum-based chemotherapy
Rucaparib April 2018[66]	None	None	For the treatment of adult patients with deleterious *BRCA* mutation[b] (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥2 chemotherapies	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy
Niraparib March 2017[67]	None	None	None	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy

Abbreviation: USPI, US prescribing information.
[a]Select patients with germline *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer for therapy based on an FDA-approved companion diagnostic for olaparib.
[b]Select patients for therapy based on an FDA-approved companion diagnostic for rucaparib.

Selection of Patients for Olaparib Maintenance Therapy

Disease Type, Histology, and Mutation Status

SOLO-1 enrolled patients with newly diagnosed, histologically confirmed high-grade serous or endometrioid ovarian, primary peritoneal, or fallopian tube cancer, although most had high-grade serous histology (96%) and ovarian cancer (85%).[68] Patients were required to have a deleterious or suspected deleterious *BRCA1* or *BRCA2* mutation. Most patients had germline *BRCA* mutations (n=388/391); only 2 had wild-type germline *BRCA1* and *BRCA2*, and were included in the study based on somatic mutations. For this reason, the recommendation for olaparib maintenance in the first-line setting is category 1 for patients with germline *BRCA1/2* mutations and category 2A for patients with somatic *BRCA1/2* mutations (and wild-type or unknown germline *BRCA1/2* mutation status).

Because *BRCA1/2* mutation status is important for selection of maintenance therapy in patients whose disease responds to primary treatment, the NCCN Guidelines have been updated to 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,[20,69] and olaparib maintenance would not be initiated until completion of platinum-based first-line chemotherapy. The NCCN Guidelines recommend that *BRCA* testing be performed using an FDA-approved test or other validated test performed in a CLIA-approved facility.

Disease Stage and Primary Treatment

SOLO-1 enrolled patients with stage III–IV disease, most with PDS (62%) or IDS (35%).[68] Patients with stage IV

were allowed to have (chemotherapy +) biopsy only, but only a small percentage of the study population had no debulking surgery (2%). At least 75% had no residual macroscopic disease after surgery. After completion of primary chemotherapy, 82% experienced CR (no evidence of disease based on imaging and normal CA-125 level). The NCCN recommendation for maintenance olaparib applies to patients who are in a CR or PR after debulking surgery and chemotherapy, including those treated with PDS + adjuvant chemotherapy, and those treated with NACT, IDS, and adjuvant chemotherapy (OV-2 and OV-5, pages 903 and 904, respectively). Maintenance olaparib is not a recommended option 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 in the complete version of these guidelines at NCCN.org).

In SOLO-1, all patients were required to have had first-line platinum-based chemotherapy, without bevacizumab, for 6 to 9 cycles. Both intravenous regimens and intraperitoneal/intravenous regimens were allowed. Most patients in the trial were treated with carboplatin/paclitaxel or cisplatin/paclitaxel, and most received 6 cycles (supplemental eTable 7).[68] In the NCCN Guidelines, all the intravenous and intraperitoneal/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 (supplemental eTable 3). As discussed earlier, 2 bevacizumab-containing regimens are included among these recommended options. Although SOLO-1 does not provide data to indicate whether maintenance olaparib provides benefit to patients treated with bevacizumab-containing chemotherapy regimens, it is important to note that the effect of maintenance olaparib on PFS (70% improvement; supplemental eTable 7)[68] was far greater than the effects on PFS reported with the addition of bevacizumab to both upfront and maintenance therapy (<30% improvement).[70–72] PFS curves from SOLO-1 show large separation between olaparib versus placebo throughout the time course of the study (median follow-up, 41 months),[68] 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.[71,72] In addition, the exploratory analysis of GOG-0218 based on *BRCA* mutation status suggests that bevacizumab may not improve PFS in patients with *BRCA1/2* mutations.[73] The NCCN panel voted to include olaparib as a maintenance therapy option for patients who were treated with primary chemotherapy regimens containing bevacizumab, provided that they are in a CR or PR after completion of chemotherapy (OV-5, page 904). Combination maintenance therapy with both bevacizumab and olaparib is not currently recommended because of insufficient safety and efficacy data.

NCCN Recommendations

Olaparib has been added to the NCCN Guidelines as an option for maintenance therapy for patients with stage II–IV disease and germline or somatic *BRCA1/2* mutations who are in CR or PR after completing primary treatment with surgery and chemotherapy (OV-5, page 904). When determining whether a patient is a candidate for olaparib maintenance after first-line therapy, it is important to consider the eligibility criteria and characteristics of the patient population enrolled in the SOLO-1 trial.[68]

Options No Longer Recommended

Paclitaxel Maintenance Therapy

Based on results from the randomized GOG-178 trial, paclitaxel used to be a postremission therapy option for patients with stages II–IV and CR after first-line therapy. In patients with CR after initial 5 to 6 cycles of platinum/paclitaxel combination, those receiving 12 versus 3 additional cycles of paclitaxel sustained a PFS advantage (22 vs 14 months; P=.006), although no significant improvement in OS.[74,75] Longer maintenance with paclitaxel was associated with higher rates of grade 2–3 neuropathy and grade 3 pain.[75] More recent results from phase III randomized trials have shown that for patients with CR after first-line platinum/taxane-based chemotherapy, maintenance treatment with paclitaxel (versus observation) did not improve PFS or OS, and was associated with higher rates of gastrointestinal toxicity and neurotoxicity.[76,77] For these reasons, the NCCN Guidelines no longer include paclitaxel as an option for maintenance therapy after primary chemotherapy.

Pazopanib Maintenance Therapy

Pazopanib used to be a recommended postremission therapy option for patients with stages II–IV disease who are in a clinical CR after first-line chemotherapy. This recommendation was based on the AGO-OVAR 16 phase III randomized trial showing improved PFS with pazopanib versus placebo (17.9 vs 12.3 months; HR, 0.77; 95% CI, 0.64–0.91; P=.0021) in patients with FIGO stage II–IV and no evidence of progression or persistent disease (>2 cm) after surgery plus platinum-taxane chemotherapy (≥5 cycles).[78] Pazopanib was a category 2B recommendation for postremission therapy because the FDA has not approved this indication,[79] there was no increase in OS, and the safety profile was concerning. Safety results from AGO-OVAR 16 showed that pazopanib was associated with significantly increased rates of

certain grade 3–4 toxicities, including hypertension, neutropenia, liver-related toxicity, diarrhea, fatigue, thrombocytopenia, and palmar-plantar erythrodysesthesia, and that many of these toxicities were contributing to an increased rate of treatment discontinuation (discontinuation rate due to AEs for pazopanib vs control: 33.3% vs 5.6%).[78] A recent analysis of AGO-OVAR 16 showed that maintenance pazopanib was associated poorer quality of life, often due to persistent diarrhea.[69] At NCCN Member Institutions, pazopanib is rarely or never used for maintenance after primary chemotherapy for ovarian cancer. The NCCN panel consensus supported the removal of postremission pazopanib as an option for maintenance therapy after first-line chemotherapy.

NCCN Recommendations

For patients with advanced disease (stages II–IV) who have completed primary treatment with surgery and a recommended platinum-based chemotherapy regimen (supplemental eTable 3) and have no signs of progression, options depend on the primary chemotherapy regimen used, response to treatment, and *BRCA1/2* mutation status (OV-5, page 904). Patients who are in CR, defined as no evidence of disease, after primary chemotherapy without bevacizumab have several options: (1) maintenance therapy in the context of a clinical trial, (2) observation, or (3) maintenance olaparib for those with a *BRCA1* or *BRCA2* mutation. Patients who are in PR after chemotherapy without bevacizumab can consider options recommended for persistent disease (OV-7, available in the complete version of these guidelines at NCCN.org), and those with a *BRCA1/2* mutation also have maintenance olaparib as an alternative. Patients who are in a CR or PR after a bevacizumab-containing regimen can be treated with maintenance bevacizumab as per the protocol selected for primary therapy (GOG-0218 or ICON7); maintenance with single-agent olaparib is an alternative for those who have *BRCA1/2* mutations. Patients with stable disease after primary treatment with a bevacizumab-containing regimen should receive bevacizumab therapy according to the protocol used for primary treatment (GOG-0218 or ICON7). In each of the above settings in which maintenance olaparib is an option, it is a category 1 option for patients with a germline mutation in *BRCA1/2*, and a category 2A option for those with a somatic mutation in *BRCA1/2*. Further research is needed to determine the effect of maintenance olaparib in patients with somatic *BRCA1/2* mutations (wild-type germline) and in those without *BRCA1* or *BRCA2* mutations.

Summary and Conclusions

These NCCN Guidelines Insights highlight updates to the recommendations for primary treatment of patients diagnosed with advanced ovarian cancer. The NCCN Guidelines are in continuous evolution. They are updated annually, and sometimes more often if new high-quality clinical data become available in the interim. Recommendations in the NCCN Guidelines, with few exceptions, are based on the evidence from clinical trials. Expert medical clinical judgment is required when applying these guidelines in the context of individual clinical circumstances to provide optimal care. The physician and patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

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Deborah K. Armstrong, MD; Ronald D. Alvarez, MD; Jamie N. Bakkum-Gamez, MD; Lisa Barroilhet, MD; Kian Behbakht, MD; Andrew Berchuck, MD; Jonathan S. Berek, MD, MMS; Lee-may Chen, MD; Mihaela Cristea, MD; Marie DeRosa, RN; Adam C. ElNaggar, MD; David M. Gershenson, MD; Heidi J. Gray, MD; Ardeshir Hakam, MD; Angela Jain, MD; Charles A. Leath III, MD; Joyce Liu, MD; Haider Mahdi, MD, MPH; Daniela Matei, MD; Michael McHale, MD; Karen McLean, MD, PhD; David M. O'Malley, MD; Richard T. Penson, MD, MRCP; Sanja Percac-Lima, MD; Elena Ratner, MD; Steven W. Remmenga, MD; Paul Sabbatini, MD; Theresa L. Werner, MD; Emese Zsiros, MD, PhD; Jennifer L. Burns; and Anita M. Engh, PhD

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eTable 1. NACT Regimens Tested in Randomized Prospective Trials Comparing NACT + IDS Versus PDS[a,b]

Trial	Chemotherapy Regimen Options	Route of Administration	Cycle Length (wk)	Patients Treated, n (% of total population)	
				NACT Arm	PDS Arm
EORTC 55971[1]	Platinum-taxane, recommended options: Paclitaxel, 135 mg/m² + cisplatin, 75 mg/m² Paclitaxel, 175 mg/m² + cisplatin, 75 mg/m² Paclitaxel, 175 mg/m² + carboplatin, AUC 5	IV	3	283 (88%)	243 (78%)
	Platinum only: Cisplatin, ≥75 mg/m² Carboplatin, AUC ≥5	IV	3	20 (6%)	25 (8%)
	Other	NR	NR	19 (6%)	21 (7%)
CHORUS[2]	Carboplatin, AUC 5–6 + paclitaxel, 175 mg/m²	NR	3	178 (70%)	138 (61%)
	Alternative carboplatin combination	NR	3	1 (<1%)	0
	Carboplatin, AUC 5–6 monotherapy	NR	3	75 (30%)	89 (39%)
SCORPION[3]	Carboplatin, AUC 5 + paclitaxel, 175 mg/m²	IV	3	29 (56%)	31 (61%)
	Carboplatin, AUC 5 + paclitaxel, 175 mg/m² + bevacizumab	IV	3	20 (39%)	14 (27%)
	Carboplatin + paclitaxel	IV	1	3 (6%)	5 (10%)
	Carboplatin	IV	3	0	1 (2%)
JCOG0602[4]	Paclitaxel, 175 mg/m² + carboplatin, AUC 6	IV	3	150	138
Liu et al[5]	NACT: cisplatin, 75 mg/m² IP + docetaxel, 75 mg/m² IV	IP/IV	3	58	0
	Postoperative: cisplatin, 75 mg/m² IV + docetaxel, 75 mg/m² IV	IV	3	58	50

Abbreviations: AUC, area under the curve; IDS, interval debulking surgery; IP, intraperitoneal; IV, intravenous; NACT, neoadjuvant chemotherapy; NR, not reported; PDS, primary debulking surgery.

[a]Trials shown in Table 1.

[b]All of these trials tested regimens consisting of systemic NACT, followed by IDS (with the goal of maximum cytoreduction), followed by postoperative systemic chemotherapy. Unless otherwise specified, the same regimen was used both as neoadjuvant and postoperatively. In some trials, only patients meeting certain requirements were allowed to have IDS and/or postoperative chemotherapy.

eTable 2. NACT Regimens in Other Prospective Trials

Trial	Stage III/IV (%)	Chemotherapy Regimen[a]	Route of Administration	Cycle Length (wk)	No. of Cycles		Patients Treated (n)	Residual Disease		PFS (mo)	OS (mo)
					Before IDS	After IDS		R0	≤1 cm		
SWOG S0009 Phase II, 1-arm Tiersten et al[6]	74/26[b]	Before IDS: paclitaxel, 175 mg/m^2 + carboplatin, AUC 6	IV	3	3	6	58[c]	NR	45%	21	32
		After IDS: paclitaxel, 175 mg/m^2 IV day 1 + carboplatin, AUC 5 IP day 1 + paclitaxel, 60 mg/m^2 IP day 8	IP/IV	4							
PRIMOVAR-1 Phase II, R Pölcher et al[7]	73/27[d]	Arm 1: carboplatin, AUC 5 IV + docetaxel, 75 mg/m^2	IV	3	3	3	44	30%	75%	12.2	24.1
		Arm 2: carboplatin, AUC 5 IV + docetaxel, 75 mg/m^2	IV	3	2	4	44	44% (NS)	74% (NS)	12.5 (NS)	28.4 (NS)
MITO-16A-MaNGO OV2A Phase IV Post hoc: Daniele et al[8]	75/24[e]	Carboplatin, AUC 5 day 1 + paclitaxel, 175 mg/m^2 day 1 + bevacizumab, 15 mg/kg day 1; then bevacizumab monotherapy (after IDS only)	NR	3	~3	To a total of 6; ≤16	74	64%	87%	NR	NR
GEICO 1205/NOVA Phase II, R, OL Garcia et al[9]	66/34	Arm 1: • Before IDS: carboplatin, AUC 6 + paclitaxel, 175 mg/m^2 • After IDS: carboplatin, AUC 6 + paclitaxel, 175 mg/m^2 + bevacizumab, 15 mg/kg IV; then bevacizumab monotherapy, 15 mg/kg	IV	3	4	3; ≤15 mo	33	NR	64%[g]	20.1	NR
		Arm 2: • Before IDS: carboplatin, AUC 6 + paclitaxel, 175 mg/m^2 + bevacizumab, 15 mg/kg IV • After IDS: carboplatin, AUC 6 + paclitaxel, 175 mg/m^2 + bevacizumab, 15 mg/kg IV; then bevacizumab monotherapy, 15 mg/kg	IV	3	4[f]	3; ≤15 mo	35	NR	66% (NS)	30.4 (NS)	NR

(continued on next page)

Abbreviations: AUC, area under the curve; IDS, interval debulking surgery; IP, intraperitoneal; IV, intravenous; NACT, neoadjuvant chemotherapy; NR, not reported; NS, no significant difference between arms; OL, open-label; OS, overall survival; PFS, progression-free survival; R, randomized; R0, no macroscopic residual disease; RCT, randomized controlled trial.

[a]All of these trials tested regimens consisting of systemic NACT (for indicated number of cycles [No. of cycles before IDS]), followed by IDS (with the goal of maximum cytoreduction), followed by postoperative systemic chemotherapy (for the indicated number of cycles [No. of cycles after IDS]). Unless otherwise specified, the same regimen was used both as neoadjuvant and postoperative . In some trials, only patients meeting certain requirements were allowed to have IDS and/or postoperative chemotherapy.

[b]In SWOG S0009, patients with stage III disease were required to have large pelvic mass and/or bulky abdominal disease and/or malignant pleural effusion; patients with stage IV disease were required to have malignant pleural effusion.

[c]In SWOG S0009, 58 patients were eligible for NACT and 45 completed NACT. Patients were required to have ≥50% decrease in CA-125 to be eligible for IDS, so 36 received IDS. Patients were required to have optimal debulking (<1 cm and malignant pleural effusion resolved) to be eligible for postoperative chemotherapy, so only 26 received postoperative chemotherapy and 18 completed planned treatment. Rate of residual disease and PFS and OS shown in the table is based on total number of patients eligible for NACT. For patients who were optimally debulked by IDS and received postoperative IP/IV chemotherapy, median PFS and OS were 29 and 34 months, respectively.

[d]PRIMOVAR-1 and ANTHALYA: all patients with stage III disease had stage IIIC.

[e]MITO-16A-MaNGO OV2A: all patients with stage III disease had stage IIIB/C.

[f]In the bevacizumab arm of GEICO 1205/NOVA, chemotherapy before IDS included at least 3 cycles of chemotherapy + bevacizumab. In the bevacizumab arm of ANTHALYA, chemotherapy included bevacizumab for cycles 1–3 and 6–8.

[g]For GEICO 1205/NOVA, ASCO abstract reported "optimal surgery rate" without defining optimal surgery.

[h]In OV21/PETROC: <1% and 1% of patients had stage IIB and IIC disease. All patients with stage III disease had stage IIIB/C. All patients with stage IV disease had stage IVA.

[i]In OV21/PETROC, patients were required to have had 3–4 cycles of platinum-based IV NACT (regimen details not reported) followed by optimal IDS (<1 cm); they were randomized after IDS. PFS and OS were measured from randomization. The study was not complete so comparisons of OS were not possible.

eTable 2. NACT Regimens in Other Prospective Trials (cont.)

Trial	Stage III/IV (%)	Chemotherapy Regimen[a]	Route of Administration	Cycle Length (wk)	No. of Cycles		Patients Treated (n)	Residual Disease		PFS (mo)	OS (mo)
					Before IDS	After IDS		R0	≤1 cm		
ANTHALYA Phase II, OL, R Rouzier et al[10]	70 /30[d]	Arm 1: carboplatin, AUC 5 day 1 + paclitaxel, 175 mg/m^2 day 1	IV	3	4	4	37	51%	NR	NR	NR
		Arm 2: carboplatin, AUC 5 day 1 + paclitaxel, 175 mg/m^2 day 1 + bevacizumab, 15 mg/kg day 1; then bevacizumab monotherapy (after IDS only)	IV	3	4[f]	4[f]; 18	58	59%	NR	NR	NR
OV21/PETROC Phase II, RCT Provencher et al[11]	86/13[h]	Before IDS, all arms: platinum-based, details not specified[i]	IV								
		Options after IDS: Arm 1: paclitaxel, 135 mg/m^2 IV day 1 + carboplatin, AUC 5/6 IV day 1 + paclitaxel, 60 mg/m^2 IV day 8	IV	3	3–4	3	95	–[i]	–[i]	11.3[i]	38.1[i]
		Arm 2: paclitaxel, 135 mg/m^2 IV day 1 + cisplatin, 75 mg/m^2 IP day 1 + paclitaxel, 60 mg/m^2 IP day 8	IP/IV	3	3–4	3	72	–[i]	–[i]	NR	NR
		Arm 3: paclitaxel, 135 mg/m^2 IV day 1 + carboplatin, AUC 5/6 IP day 1 + paclitaxel, 60 mg/m^2 IP day 8	IP/IV	3	3–4	3	92	–[i]	–[i]	12.5[i] (NS)	59.3[i]

Abbreviations: AUC, area under the curve; IDS, interval debulking surgery; IP, intraperitoneal; IV, intravenous; NACT, neoadjuvant chemotherapy; NR, not reported; NS, no significant difference between arms; OL, open-label; OS, overall survival; PFS, progression-free survival; R, randomized; R0, no macroscopic residual disease; RCT, randomized controlled trial.

[a]All of these trials tested regimens consisting of systemic NACT (for indicated number of cycles [No. of cycles before IDS]), followed by IDS (with the goal of maximum cytoreduction), followed by postoperative systemic chemotherapy (for the indicated number of cycles [No. of cycles after IDS]). Unless otherwise specified, the same regimen was used both as neoadjuvant and postoperative . In some trials, only patients meeting certain requirements were allowed to have IDS and/or postoperative chemotherapy.

[b]In SWOG S0009, patients with stage III disease were required to have large pelvic mass and/or bulky abdominal disease and/or malignant pleural effusion; patients with stage IV disease were required to have malignant pleural effusion.

[c]In SWOG S0009, 58 patients were eligible for NACT and 45 completed NACT. Patients were required to have ≥50% decrease in CA-125 to be eligible for IDS, so 36 received IDS. Patients were required to have optimal debulking (<1 cm and malignant pleural effusion resolved) to be eligible for postoperative chemotherapy, so only 26 received postoperative chemotherapy and 18 completed planned treatment. Rate of residual disease and PFS and OS shown in the table is based on total number of patients eligible for NACT. For patients who were optimally debulked by IDS and received postoperative IP/IV chemotherapy, median PFS and OS were 29 and 34 months, respectively.

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[i]In OV21/PETROC, patients were required to have had 3–4 cycles of platinum-based IV NACT (regimen details not reported) followed by optimal IDS (<1 cm); they were randomized after IDS. PFS and OS were measured from randomization. The study was not complete so comparisons of OS were not possible.

eTable 3. NCCN Recommended Regimens for Patients Treated With a Neoadjuvant Approach

Options	Cycle Length (wk)	Number of Cycles[a]	
		Before IDS	After IDS
IP/IV regimens[b] (OV-C 3 of 9[c])			
For optimally debulked stage II–III disease: paclitaxel, 135 mg/m^2 IV day 1; cisplatin, 75–100 mg/m^2 IP day 2 after IV paclitaxel; paclitaxel, 60 mg/m^2 IP day 8	3	NR	≥3
Paclitaxel, 135 mg/m^2 IV day 1, carboplatin, AUC 6 IP day 1, paclitaxel, 60 mg/m^2 IP day 8	3	NR	≥3
IV regimens (OV-C 3 of 9[c])			
Paclitaxel, 175 mg/m^2 + carboplatin, AUC 5–6 day 1	3	3–6	≥3
Dose-dense paclitaxel, 80 mg/m^2 days 1, 8, and 15 + carboplatin, AUC 5–6 day 1	3	3–6	≥3
Paclitaxel, 60 mg/m^2 + carboplatin, AUC 2	1	3–6	≥3
Docetaxel, 60–75 mg/m^2 + carboplatin, AUC 5–6 day 1	3	3–6	≥3
Carboplatin, AUC 5 + pegylated liposomal doxorubicin, 30 mg/m^2	4	3–6	≥3
ICON-7: paclitaxel, 175 mg/m^2 + carboplatin, AUC 5–6 + bevacizumab, 7.5 mg/kg day 1	3	3–6[d]	CT: ≥3 Bev: ≤15
GOG-218: paclitaxel, 175 mg/m^2 + carboplatin, AUC 6 day 1. Starting day 1 of cycle 2, bevacizumab, 15 mg/kg	3	3–6[d]	CT: ≥3 Bev: ≤22
IV regimens for elderly patients (age >70 years) and those with comorbidities (OV-C 3 of 9[c])			
Carboplatin, AUC 5	3	NR	≥3
Paclitaxel, 135 mg/m^2 + carboplatin, AUC 5	3	NR	≥3
Paclitaxel, 60 mg/m^2 + carboplatin, AUC 2	1	NR	≥3

Abbreviations: AUC, area under the curve; Bev, bevacizumab; CT, chemotherapy; IDS, interval debulking surgery; IP, intraperitoneal; IV, intravenous; NACT, neoadjuvant chemotherapy; NR, regimen not recommended as an option in that setting.
[a]For all regimens recommended for use before IDS, surgery after 3 cycles of NACT is preferred; however, surgery may be performed after 4–6 cycles based on the clinical judgment of the gynecologic oncologist. A total of ≥6 cycles of treatment is recommended, including at least 3 cycles of adjuvant therapy after IDS.
[b]There are limited data for the use of IP chemotherapy regimens after neoadjuvant therapy and IDS.
[c]See the complete version of the NCCN Guidelines for Ovarian Cancer at NCCN.org.
[d]Bevacizumab-containing regimens should be used with caution before IDS due to potential interference with postoperative healing. Withhold bevacizumab for 6 weeks before IDS.

eTable 4. NCCN Recommendations for Interval Debulking Surgery After Neoadjuvant Therapy

Principles of Surgery: Interval Debulking Surgery After Neoadjuvant Chemotherapy of Invasive Epithelial Ovarian Cancer (OV-A 3 of 4[a])	As with a primary debulking procedure, every effort should be made to achieve maximum cytoreduction during an interval debulking procedure. Maximal effort should be made to remove all gross disease in the abdomen, pelvis, and retroperitoneum. Consultation with a gynecologic oncologist is recommended. • IDS, including completion TAH and BSO with staging, should be performed after ≤4 cycles of neoadjuvant chemotherapy for women with a response to chemotherapy or stable disease. Alternate timing of surgery has not been prospectively evaluated but may be considered based on individual patient-centered factors. • Hyperthermic intraperitoneal chemotherapy with cisplatin (100 mg/m^2) can be considered at the time of IDS for stage III disease. • All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. • An omentectomy should be performed. • Suspicious and/or enlarged nodes should be resected, if possible. Removal of lymph nodes noted to have potential metastasis at the time of initial diagnosis should be considered, even if not currently suspicious or enlarged. • Procedures that may be considered for optimal surgical debulking 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.
Principles of Surgery: General Considerations for IDS[b] (OV-A 1 of 4[a])	• It is recommended that a gynecologic oncologist perform the appropriate surgery. • An open laparotomy including a vertical midline abdominal incision should be used in most patients in whom an interval debulking procedure is planned. ➤ Laparoscopy may be useful to evaluate whether optimal cytoreduction can be achieved in patients with newly diagnosed advanced-stage disease. ➤ Minimally invasive techniques can be used for select patients for interval debulking procedures. Patients who are unable to be optimally debulked using minimally invasive techniques should be converted to an open procedure. • Prior to IDS, counsel patients about port placement if subsequent IP chemotherapy is being considered.

Abbreviations: BSO, bilateral salpingo-oophorectomy; IDS, interval debulking surgery; IP, intraperitoneal; TAH, total abdominal hysterectomy.
[a]See the complete version of the NCCN Guidelines for Ovarian Cancer at NCCN.org.
[b]Recommendations not related to IDS are omitted from this table.

eTable 5. Prospective Comparative Trials Testing HIPEC for Ovarian Cancer

Trial	Patients	Treatment Arms	HIPEC Method & Regimen	Surgical/Safety Outcomes, Arm A vs B	Efficacy Outcomes, Arm A vs B
Phase III nonrandomized Single center Greece 2003–2009 Spiliotis et al[12]	Recurrent after CRS + systemic CT FIGO stage IIIC–IV[a]	Arm A (n=24): Secondary CRS →HIPEC →Postoperative CT Arm B (n=24): Secondary CRS →Postoperative CT	Open technique 90-min perfusion at 42.5°C Cisplatin, 50 mg/m^2	PCI: median, 21.2 vs 19.8; NS CC-0 or CC-1: 83% vs 66%; $P<.01$ Major or minor postoperative complications, grade 2–3[b]: 40% vs 20%; $P<.04$	OS, median (mo)[c]: 19.4 vs 11.2; $P<.05$
Phase III RCT Single center Greece 2006–2013 Spiliotis et al[13]	Recurrent after primary surgery + CT FIGO stage IIIC/IV[d]: 63%/37%	Arm A (n=60): Secondary CRS →HIPEC →Postoperative CT Arm B (n=60): Secondary CRS →Postoperative CT	Open/Closed technique: 66%/33% 60-min perfusion at 42.5°C For platinum-sensitive (n=34): • Cisplatin, 100 mg/m^2 + paclitaxel, 175 mg/m^2 For platinum-resistant (n=26): • Doxorubicin, 35 mg/m^2 + paclitaxel, 175 mg/m^2 • Doxorubicin, 35 mg/m^2 + mitomycin, 15 mg/m^2	Extent of disease: • PCI <5: 12% vs 13% • PCI 5 to <10: 40% vs 37% • PCI ≥10: 48% vs 50% Cytoreduction: • CC-0: 65% vs 55% • CC-1: 20% vs 33% • CC-2: 15% vs 12%	OS, mean (mo): 26.7 vs 13.4; $P=.006$
Phase III RCT Multicenter Korea 2010–2016 Lim et al[14]	Primary Stage III/IV Optimal CRS (<1 cm)	Arm A (n=92): Primary CRS →HIPEC →Postoperative CT Arm B (n=92): Primary CRS →Postoperative CT	90-min perfusion at 41.5°C Cisplatin, 75 mg/m^2	Extent of surgery: NS Residual disease: NS Blood loss, transfusion, neutropenia, thrombocytopenia: NS Hospital stay: NS Operative time: 487 vs 404 min; $P<.001$ Postoperative morbidity/mortality: NS[e]	PFS, 5-y: 21% vs 16%; NS OS, 5-y: 51% vs 49%; NS Patients with NACT: • PFS, 2-y: 37% vs 30% • OS, 5-y: 48% vs 28%
Phase III RCT OL M06OVH-OVHIPEC 8 hospitals Netherlands 2007–2016 van Driel et al[15]	Primary FIGO stage III Extensive abdominal disease (90%) or incomplete primary CRS (>1 cm) (10%)	NACT x 3 cycles[f] →If response ≥SD, then: Arm A (n=122): Interval CRS →Postoperative CT x 3 cycles[f] Arm B (n=123): Interval CRS →HIPEC →Postoperative CT x 3 cycles[f]	Open technique 90-min perfusion at 40°C Cisplatin, 100 mg/m^2	Complete cytoreduction (no macroscopic): 67% vs 69% Operative time: median, 192 vs 338 min Hospital stay: median, 8 vs 10 d Grade 3–4 AEs[g]: 25% vs 27%; NS Postoperative death: 1 vs 0 Time from CRS to start postoperative CT: median, 30 vs 33 d Completed 3 cycles postoperative CT: 90% vs 94%	RFS, median (mo): 10.7 vs 14.2; HR, 0.66 (95% CI, 0.50–0.87); $P=.003$ OS, median (mo): 33.9 vs 45.7; HR, 0.67 (95% CI, 0.48–0.94); $P=.02$

Abbreviations: AE, adverse event; AUC, area under the curve; CC, completeness of cytoreduction score; CC-0, no residual disease; CC-1, residual nodules <2.5 mm; CC-2, residual nodules 0.25–2.5 cm; CC-3, residual nodules >2.5 cm; CRS, cytoreduction surgery; CT, chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; NACT, neoadjuvant chemotherapy; non-R, nonrandomized; NS, no significant difference (between arms); OL, open-label; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; RCT, randomized controlled trial; RFS, recurrence-free survival; SD, stable disease.

[a]Trial excluded patients with metastases outside of peritoneal surfaces (extra-abdominal, parenchymal, bulky retroperitoneal).

[b]Major or minor postoperative complications included both those related to surgery and those related to chemotherapy. Grade 1 was defined as no complications; grade 2, minor complications; grade 3, major complications requiring reoperations or ICR admission; grade 4, in-hospital mortality.

[c]Greater extent of resection and lower PCI were correlated with improved OS.

[d]Excluded patients with pleural disease or lung metastasis, >3 sites of bowel obstruction, bulky disease in retroperitoneal area or mesentry, disease beyond the abdomen, or splanchnic metastasis.

[e]No differences in morbidity or mortality except for anemia (67% vs 50%; $P=.025$) and creatinine elevation (15% vs 4%; $P=.026$).

[f]NACT and postoperative CT regimen: carboplatin (AUC 5–6) + paclitaxel (175 mg/m^2). Randomization was performed after NACT, before interval CRS.

[g]In M06OVH-OVHIPEC, grade 3–4 AEs were reported for the period starting at randomization to 6 weeks after the last cycle of chemotherapy.

eTable 6. Selected[a] Prospective Noncomparative Trials Testing HIPEC for Ovarian Cancer

Trial	Patients	Treatment Arms	n	HIPEC Method	HIPEC Regimen	Operative Time, Median (Range)	Blood Transfusion, n (%)	Hospital Stay, Median (Range), d	Residual Disease After CRS	Postop Morbidity and Mortality	PFS or DFS	OS, mo
Phase II 1990–2004 Cotte et al[16]	Persistent/Recurrent Peritoneal carcinomatosis No extra-abdominal metastases PCI: mean, 11.5 (range, 1–30)	Secondary CRS →HIPEC →Postop CT	81	Closed 90-min 44–46°C	Cisplatin, 20 mg/m²/L	Mean, 4.3[b] h (range, 2.0–8.0 h) [258 min (range, 120–480 min)]	NR	Mean, 17.1 (range, 6–41)	CCR-0/1/2[c]: 56%/25%/20%	Major: 13.5% Death: 2.5%	DFS: median, 19.2 mo	Median, 28.4
Phase II, OL 2000–2007 Di Giorgio et al[17]	Primary/Recurrent FIGO IIIC–IV with peritoneal diffuse carcinomatosis No extra-abdominal metastases Resectable	NACT (n=4) →Primary CRS →HIPEC →Postop CT	22	Closed 60-min 41–43°C	Cisplatin, 75 mg/m²	Mean, 600 min (range, 300–780 min)	Blood loss: 1,638 mL [range, 600–4,900 mL]	Mean, 23.6 (range, 9–90)	CC-0/1/2/3: 68%/23%/5%/5%	G3: 21.3% Death (G4): 4.2%	DFS: median, 27 mo	Median, 25.5
		Secondary CRS →HIPEC →Postop CT	25	Closed 60-min 41–43°C	Cisplatin, 75 mg/m²	Mean, 465 min (range, 180–720 min)	Blood loss: 1,368 mL [range, 100–3,100 mL]	Mean, 20.8 (range, 8–93)	CC-0/1/2/3: 60%/28%/8%/4%		DFS: median, 22.5 mo	Median, 15.5
Pilot 2005–2010 Fagotti et al[18]	Recurrent, platinum-sensitive Exclusively intraperitoneal: 19 (42%) PCI: median, 6 (range, 2–21)	Secondary CRS →HIPEC →Postop CT	41	Closed 30-min 41.5°C	Oxaliplatin, 460 mg/m²	300 min (138–619 min)	19 (44%)	10 (5–30)	CC-0/1: 95%/5% (≥CC-2 not allowed)	Severe[d]: 35% Death: 0%	DFS: median, 24 mo	Median, 38
Phase II 2007–2008 Lim et al[19]	Primary Stage IIIA/IIIC/IV: 3%/80%/17%	NACT (n=14)[e] →Primary CRS (n=30) →HIPEC →Postop CT	30	Closed 90-min 41.5°C	Cisplatin, 75 mg/m²	9.6 h (7.0–13.1 h) [576 min (420–786 min)]	Blood loss: median, 1,500 mL	17 (10–53)	CC-0/1: 83%/14% (<1 cm required)	G3–4: 40% Death: 0%	NR	NR
Phase II 2004–2010 Deraco et al[20]	Primary Stage IIIB/IIIC/IV: 4%/92%/4% No extra-abdominal/hepatic metastases PCI: median, 15.5 (range, 5–26)	CRS →HIPEC (n=26) →Postop CT (n=25)	26	Closed 90-min 42.5°C	Cisplatin, 40 mg/L perfusate + doxorubicin, 15 mg/L perfusate	620 min (280–915 min)	NR	21 (13–67)	CC-0/1: 58%/42% (≥CC-2 not allowed)	G3–5: 15% Death: 4%	PFS: median, 30 mo	5-y: 15.2%

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Abbreviations: CC, complete cytoreduction score; CC-0, no residual disease; CC-1, residual nodules <2.5 mm; CC-2, residual nodules 0.25–2.5 cm; CC-3, residual nodules >2.5 cm; CCR, completeness of cancer resection; CRS, cytoreductive surgery; CT, chemotherapy; DFS, disease-free survival; F/U, follow-up; G, grade; HIPEC, hyperthermic intraperitoneal chemotherapy; IDS, interval debulking surgery; LPS, laparoscopic surgery; NACT, neoadjuvant chemotherapy; NE, not evaluable (not yet reached); NR, not reported; NS, no significant difference; OL, open-label; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; postop, postoperative; R0, no macroscopic residual disease (same as CCR-0).

[a]Selected based on sample size, use of HIPEC intraoperatively with CRS, and to avoid overlapping patient datasets.

[b]Operative time reported did not include time for HIPEC procedure.

[c]CCR-0 was defined as no macroscopic residual disease; CCR-1, ≤5 mm; CCR-2, >5 mm.

[d]Severe postoperative morbidity was defined as an adverse event that occurred <30 days from surgery and resulted in an unplanned admission or in a secondary surgical procedure.

[e]NACT was allowed if optimal cytoreduction was considered difficult. Patients whose disease progressed during NACT were excluded from the trial.

[f]Due to complications, 5 patients did not receive postoperative chemotherapy.

[g]Entry criteria allowed patients with splenic metastases and pleural effusion; patients with liver metastases or supraclavicular metastatic adenopathy were excluded.

[h]Trial excluded patients with extra-abdominal metastases or complete intestinal obstruction.

[i]Maintenance bevacizumab was given at a dose of 15 mg/kg every 3 weeks for 22 cycles.

[j]Postoperative morbidity was reported using Dindo grading.

[k]Trial excluded patients with distant (extra-abdominal) unresectable disease.

[l]Patients with stage IV distant metastases had supradiaphragmatic lymph node metastasis and/or parenchymal liver metastasis. Criteria for treatment with NACT: (1) high tumor dissemination was observed on initial imaging studies and was assumed to occur under the following conditions: (a) multiple and unresectable extra-abdominal metastases, (b) multiple liver parenchymal metastases or pulmonary metastases, and (c) extensive small bowel/mesenteric root involvement; (2) patients had a poor performance status and high operative risk because of medical comorbidities; or (3) optimal debulking surgery (≤1 cm) was unsuitable because of a high tumor burden (Fagotti score ≥8). HIPEC only performed in those who did not have complete response on neoadjuvant therapy and did not have excessive bleeding during IDS.

eTable 6. Selected[a] Prospective Noncomparative Trials Testing HIPEC for Ovarian Cancer (cont.)

Trial	Patients	Treatment Arms	n	HIPEC Method	HIPEC Regimen	Operative Time, Median (Range)	Blood Transfusion, n (%)	Hospital Stay, Median (Range), d	Residual Disease After CRS	Postop Morbidity and Mortality	PFS or DFS	OS, mo
Phase II OL 2005–2009 Ansaloni et al[21]	Primary stage IIIC (n=9) or recurrent with carcinomatosis (n=30) PCI: mean, 11.1 (range, 1–28) PCI <15, >15: 27 (69%) vs 12 (31%)	CRS →HIPEC (n=39) →Postop CT (n=27)	39	Open 90-min 41.5°C	Cisplatin, 100 mg/m² + paclitaxel, 175 mg/m² (n=11) Cisplatin, 100 mg/m² + doxorubicin, 35 mg/m² (n=26) Paclitaxel, 175 mg/m² + doxorubicin, 35 mg/m² (n=1) Doxorubicin, 35 mg/m² (n=1)	Mean, 10 h (range, 7.0–16.3 h) [600 min (range, 420–978 min)]	NR	23.8 (14–39)	CC-0/1/3: 90%/7%/3%	Morbidity: 18% Death: 3%	NR	NR
Phase II 2002–2009 Ceelen et al[22]	Recurrent, heavily pretreated No systemic metastases Potentially resectable Simplified PCI, median, 4 (range, 2–7)	Secondary CRS →HIPEC (n=42) →Postop CT (n=37)[f]	42	40.5–41.0°C Cisplatin: closed 90-min Oxaliplatin: open 30 min	Cisplatin, 100–250 mg/m² (n=25) Oxaliplatin, 460 mg/m² (n=17)	8.3 h (5.1–15.0 h) [498 min (306–900 min)]	NR	16 (10–49)	CC-0/1/2: 50%/36%/14%	Major: 21% Death: 0%	PFS: median, 13 mo	Median, 37
Prospective 2006–2010 Tentes et al[23]	Primary (n=23) or recurrent (n=20) Locally advanced PCI: mean, 15.05 (range, 3–33)	CRS →HIPEC →Postop CT (n=23) if CC1/CC2 or systemic recurrent disease	43	Open 42.5–43°C Cisplatin/ Doxorubicin: 90-min Gemcitabine: 60-min	Cisplatin, 50 mg/m² + doxorubicin, 15 mg/m² (n=15 recurrent, 23 primary) Gemcitabine, 100 mg/m² (n=5 recurrent and platinum-resistant)	NR	NR	NR	CC-0/1/2: 70%/26%/5%	Morbidity (G3): 9% Death (G4): 5%	NR	Mean, 37
Prospective series 2002–2001 Gonzalez-Bayon et al[24]	Primary FIGO stage IIIC–IV No distant metastases[g] PCI: median, 15 (range, 1–36)	NACT x 3–6 cycles →Primary CRS →HIPEC	15	Coliseum (open) 90-min 42–44°C	Cisplatin, 100 mg/m² + doxorubicin, 30 mg/m²	440 min (215–1,000 min)	NR	23 (9–51)	CC-0/1: 73%/27%	G3–4: 27% Death: 7%	DFS: median, 21.1 mo	Median, 77.8
	First recurrence Resectable peritoneal No distant metastases[g] PCI: median, 8 (range, 2–31)	Secondary CRS →HIPEC	19	Coliseum (open) 90-min 42–44°C	Cisplatin, 100 mg/m² + doxorubicin, 30 mg/m²	450 min (225–660 min)	NR	15 (5–24)	CC-0/1: 74%/26%	G3–4: 21% Death: 5%	DFS: median, 18.1 mo	Median, 62.8

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Abbreviations: CC, complete cytoreduction score; CC-0, no residual disease; CC-1, residual nodules <2.5 mm; CC-2, residual nodules 0.25–2.5 cm; CC-3, residual nodules >2.5 cm; CCR, completeness of cancer resection; CRS, cytoreductive surgery; CT, chemotherapy; DFS, disease-free survival; F/U, follow-up; G, grade; HIPEC, hyperthermic intraperitoneal chemotherapy; IDS, interval debulking surgery; LPS, laparoscopic surgery; NACT, neoadjuvant chemotherapy; NE, not evaluable (not yet reached); NR, not reported; NS, no significant difference; OL, open-label; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; postop, postoperative; R0, no macroscopic residual disease (same as CCR-0).

[a]Selected based on sample size, use of HIPEC intraoperatively with CRS, and to avoid overlapping patient datasets.

[b]Operative time reported did not include time for HIPEC procedure.

[c]CCR-0 was defined as no macroscopic residual disease; CCR-1, ≤5 mm; CCR-2, >5 mm.

[d]Severe postoperative morbidity was defined as an adverse event that occurred <30 days from surgery and resulted in an unplanned admission or in a secondary surgical procedure.

[e]NACT was allowed if optimal cytoreduction was considered difficult. Patients whose disease progressed during NACT were excluded from the trial.

[f]Due to complications, 5 patients did not receive postoperative chemotherapy.

[g]Entry criteria allowed patients with splenic metastases and pleural effusion; patients with liver metastases or supraclavicular metastatic adenopathy were excluded.

[h]Trial excluded patients with extra-abdominal metastases or complete intestinal obstruction.

[i]Maintenance bevacizumab was given at a dose of 15 mg/kg every 3 weeks for 22 cycles.

[j]Postoperative morbidity was reported using Dindo grading.

[k]Trial excluded patients with distant (extra-abdominal) unresectable disease.

[l]Patients with stage IV distant metastases had supradiaphragmatic lymph node metastasis and/or parenchymal liver metastasis. Criteria for treatment with NACT: (1) high tumor dissemination was observed on initial imaging studies and was assumed to occur under the following conditions: (a) multiple and unresectable extra-abdominal metastases, (b) multiple liver parenchymal metastases or pulmonary metastases, and (c) extensive small bowel/mesenteric root involvement; (2) patients had a poor performance status and high operative risk because of medical comorbidities; or (3) optimal debulking surgery (≤1 cm) was unsuitable because of a high tumor burden (Fagotti score ≥8). HIPEC only performed in those who did not have complete response on neoadjuvant therapy and did not have excessive bleeding during IDS.

eTable 6. Selected[a] Prospective Noncomparative Trials Testing HIPEC for Ovarian Cancer (cont.)

Trial	Patients	Treatment Arms	n	HIPEC Method	HIPEC Regimen	Operative Time, Median (Range)	Blood Transfusion, n (%)	Hospital Stay, Median (Range), d	Residual Disease After CRS	Postop Morbidity and Mortality	PFS or DFS	OS, mo
Phase II OL 2007–2013 Coccolini et al[25]	Primary FIGO stage IIIC–IV[h] (n=30) or recurrent with peritoneal carcinomatosis (n=24) Resectable PCI: mean, 10.11 (range, 0–28)	Primary CRS →HIPEC	54	Open/Closed: 78%/22% 60/90-min 41.5°C	Cisplatin, 100 mg/m² + paclitaxel, 175 mg/m²	Mean, 8.85 h [531 min]	NR	Mean, 24	CC-0/1: 87%/13% (≥CC-2 not allowed)	G3–4: 35% Death: 5.6%	DFS: median, 12.5 mo	Median, 32.9
CHIPASTIN Phase I dose-finding 2011–2012 Gouy et al[26]	Primary FIGO stage IIIC Unresectable Histologically confirmed	NACT x 6 cycles →Primary CRS →HIPEC →Postop bevacizumab maintenance[i]	30	Open/Closed: 80%/20% 60-min 42°C	Cisplatin, 50/60/70/80 mg/m² (n=4/4/5/13)	410 min (256–780 min)	Blood loss: 950 mL (range, 200–2,720 mL)	18.5 (10–69)	No gross: 100%	Depended on dose	DFS: median, 16.7 mo	2-y: 71%
Prospective cohort 2007–2014 Manzanedo et al[27]	Primary Stage IIIC–IV PCI: mean, 10	NACT →Primary CRS →HIPEC →Postop CT	27	Open 42°C Paclitaxel: 60-min Cisplatin/ Doxorubicin: 90-min	Paclitaxel, 60 mg/m² (n=11) Cisplatin, 100 mg/m² + doxorubicin, 15 mg/m²; (n=15) Oxaliplatin (n=1)	402 min (277–705 min)	NR	12 (6–81)	CC-0–1/2–3: 96%/4%	G3–4[j]: 30% Death: 0%	DFS: median, 12 mo	Median, 40
	Peritoneal recurrence (platinum-resistant/ platinum-sensitive: n=20/10) PCI: mean, 7.5	NACT →Secondary CRS →HIPEC →Postop CT	30	Open 42°C Paclitaxel: 60-min Cisplatin/ Doxorubicin: 90-min	Paclitaxel, 60 mg/m² Cisplatin, 100 mg/m² + doxorubicin, 15 mg/m²	394 min (207–730 min)	NR	13.5 (4–78)	CC-0–1/2–3: 97%/3%	G3–4[j]: 30% Death: 0%	DFS: median, 17 mo	Median, 57
Phase II OL 2015–2016 Paris et al[28]	Primary FIGO stage: IIIB/IIIC[k]: 95%/5% Staging LPS, biopsy	Primary CRS →HIPEC →Postop CT	40	Open/Closed: NR 60-min 41.5°C	Cisplatin, 75 mg/m²	480 min (360–740 min)	17 (42.5)	8 (5–20)	R0 in 100% (required)	G3–4: 20% Death: 0%	PFS: median, 25 mo F/U: 83%	Median, 25 F/U: 92.5%
Pilot 2015–2018 Lee et al[29]	Primary FIGO stage III/IV[l] Histologically confirmed	NACT x 1–4 cycles →IDS →HIPEC (n=27) →Postop CT	27	Open/Closed: 19%/81% 90-min 42°C	Paclitaxel, 175 mg/m²	544 min (277–915 min)	19 (70)	19 (5–131)	NR	G3–4: 19% Death: 0%	PFS: median, 21.3 mo	NE

Abbreviations: CC, complete cytoreduction score; CC-0, no residual disease; CC-1, residual nodules <2.5 mm; CC-2, residual nodules 0.25–2.5 cm; CC-3, residual nodules >2.5 cm; CCR, completeness of cancer resection; CRS, cytoreductive surgery; CT, chemotherapy; DFS, disease-free survival; F/U, follow-up; G, grade; HIPEC, hyperthermic intraperitoneal chemotherapy; IDS, interval debulking surgery; LPS, laparoscopic surgery; NACT, neoadjuvant chemotherapy; NE, not evaluable (not yet reached); NR, not reported; NS, no significant difference; OL, open-label; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; postop, postoperative; R0, no macroscopic residual disease (same as CCR-0).

[a]Selected based on sample size, use of HIPEC intraoperatively with CRS, and to avoid overlapping patient datasets.

[b]Operative time reported did not include time for HIPEC procedure.

[c]CCR-0 was defined as no macroscopic residual disease; CCR-1, ≤5 mm; CCR-2, >5 mm.

[d]Severe postoperative morbidity was defined as an adverse event that occurred <30 days from surgery and resulted in an unplanned admission or in a secondary surgical procedure.

[e]NACT was allowed if optimal cytoreduction was considered difficult. Patients whose disease progressed during NACT were excluded from the trial.

[f]Due to complications, 5 patients did not receive postoperative chemotherapy.

[g]Entry criteria allowed patients with splenic metastases and pleural effusion; patients with liver metastases or supraclavicular metastatic adenopathy were excluded.

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[i]Maintenance bevacizumab was given at a dose of 15 mg/kg every 3 weeks for 22 cycles.

[j]Postoperative morbidity was reported using Dindo grading.

[k]Trial excluded patients with distant (extra-abdominal) unresectable disease.

[l]Patients with stage IV distant metastases had supradiaphragmatic lymph node metastasis and/or parenchymal liver metastasis. Criteria for treatment with NACT: (1) high tumor dissemination was observed on initial imaging studies and was assumed to occur under the following conditions: (a) multiple and unresectable extra-abdominal metastases, (b) multiple liver parenchymal metastases or pulmonary metastases, and (c) extensive small bowel/mesenteric root involvement; (2) patients had a poor performance status and high operative risk because of medical comorbidities; or (3) optimal debulking surgery (≤1 cm) was unsuitable because of a high tumor burden (Fagotti score ≥8). HIPEC only performed in those who did not have complete response on neoadjuvant therapy and did not have excessive bleeding during IDS.

eTable 7. Olaparib Maintenance After First-Line Chemotherapy: SOLO-1 Phase III Randomized Trial[a,30]

Disease & Patient Characteristics	Treatment Prior to Randomization (Surgery + First-Line Chemotherapy)	Study Treatment	Efficacy Outcomes[b] (Arm A vs B)	Safety (Arm A vs B)
Newly diagnosed, histologically confirmed FIGO stage III, IV: 83%, 17% Serous, endometrioid, mixed serous and endometrioid: 96%, 2.3%, 1.5% Ovarian, primary peritoneal, fallopian-tube cancer: 85%, 8%, 6% CA-125 ≤ULN: 95% Mutation in *BRCA1*, *BRCA2*, or both: 72%, 27%, 1% Germline *BRCA* mutation (n=388) or somatic *BRCA* mutation only (n=2)	Surgery: PDS, IDS, no surgery: 62%, 35%, 2% Number cycles of chemotherapy, 4–5, 6, 7–9: 1%, 78%, 21% Chemotherapy agents used: paclitaxel (98%), carboplatin (91%), cisplatin (20%), docetaxel (6%)[c] Response to chemotherapy: 82% CR, 18% PR	Treatment arms: • Arm A: olaparib, 300 mg bid (n=260) • Arm B: placebo (n=131) Completed 2 y of treatment (Arm A vs B): 123 (47%) vs 35 (27%) Treated >2 y (Arm A vs B): 26 (10%) vs 3 (2%) Follow-up duration (Arm A vs B): median, 40.7 vs 41.2 mo	3-y PFS (first progression): 60% vs 27%; HR, 0.30 (95% CI, 0.23–0.41); *P*<.0001 3-y PFS (second progression): 75% vs 60%; HR, 0.50 (95% CI, 0.35–0.72); *P*<.001 3-y OS: 84% vs 80%; HR, 0.95 (95% CI, 0.60–1.53)	Grade 5 AEs: none Grade 3–4 AEs[d]: 39% vs 18% • Anemia: 22% vs 2% • Neutropenia: 9% vs 5% • Thrombocytopenia: 1% vs 2% • Nausea: 1% vs 0% • Fatigue/Asthenia: 4% vs 2% • Diarrhea: 3% vs 0% • Abdominal pain: 2% vs 1% AEs leading to discontinuation: 11.5% vs 2.3%

Abbreviations: AEs, adverse events; CA-125, cancer antigen 125; CR, complete response (defined as NED on imaging and CA-125 ≤ULN); HR, hazard ratio; IDS, interval debulking surgery; NED, no evidence of disease; PDS, primary debulking surgery; PR, partial response (defined as 30% reduction in tumor volume or NED on imaging with CA-125 >ULN); ULN, upper limit of normal.

[a]ClinicalTrials.gov identifier: NCT01844986.

[c]Gemcitabine was used in <1% of patients in each arm. Other agents used in <1% of patients in the olaparib arm only: nab-paclitaxel, doxorubicin, cyclophosphamide, bevacizumab.

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

[d]Toxicities during the trial intervention or up to 30 days after discontinuation of the intervention.

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