National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Ovarian Cancer
Including Fallopian Tube Cancer and Primary Peritoneal Cancer

Version 1.2021 — February 26, 2021

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer

NCCN Guidelines Index
Table of Contents
Discussion

***Deborah K. Armstrong, MD/Chair Ω †**
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

***Ronald D. Alvarez, MD, MBA/Vice Chair Ω**
Vanderbilt-Ingram Cancer Center

Jamie N. Bakkum-Gamez, MD Ω
Mayo Clinic Cancer Center

Lisa Barroilhet, MD Ω
University of Wisconsin Carbone Cancer Center

Kian Behbakht, MD Ω
University of Colorado Cancer Center

Andrew Berchuck, MD Ω
Duke Cancer Institute

Lee-may Chen, MD Ω
UCSF Helen Diller Family Comprehensive Cancer Center

Mihaela Cristea, MD †
City of Hope National Medical Center

Maria DeRosa, RN ¥

Eric L. Eisenhauer, MD Ω
Massachusetts General Hospital Cancer Center

David M. Gershenson, MD Ω
The University of Texas MD Anderson Cancer Center

Heidi J. Gray, MD Ω
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Rachel Grisham, MD †
Memorial Sloan Kettering Cancer Center

Ardeshir Hakam, MD ≠
Moffitt Cancer Center

Angela Jain, MD †
Fox Chase Cancer Center

Amer Karam, MD Ω †
Stanford Cancer Institute

Gottfried E. Konecny, MD Ω
UCLA Jonsson Comprehensive Cancer Center

Charles A. Leath III, MD Ω
O'Neal Comprehensive Cancer Center at UAB

Joyce Liu, MD, MPH † ‡
Dana-Farber/Brigham and Women's Cancer Center

Haider Mahdi, MD, MPH Ω
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Lainie Martin, MD †
Abramson Cancer Center at the University of Pennsylvania

Daniela Matei, MD Ω † ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Michael McHale, MD Ω
UC San Diego Moores Cancer Center

Karen McLean, MD, PhD Ω
University of Michigan Rogel Cancer Center

David S. Miller, MD Ω
UT Southwestern Simmons Comprehensive Cancer Center

David M. O'Malley, MD Ω
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Sanja Percac-Lima, MD, PhD Þ
Massachusetts General Hospital Cancer Center

Elena Ratner, MD Ω
Yale Cancer Center/Smilow Cancer Hospital

Steven W. Remmenga, MD Ω
Fred & Pamela Buffett Cancer Center

Roberto Vargas, MD Ω
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Theresa L. Werner, MD † ‡
Huntsman Cancer Institute at the University of Utah

Emese Zsiros, MD, PhD Ω
Roswell Park Comprehensive Cancer Center

NCCN
Jennifer Burns
Anita Engh, PhD

Ω Gynecology oncology
‡ Hematology/Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
* Discussion writing committee member

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2021 of the NCCN Guidelines for Ovarian Cancer from Version 2.2020 include:

Global
- Changed "Paclitaxel 175/carboplatin" to "paclitaxel/carboplatin q3weeks"
- Changed "homologous recombination deficiency" to "homologous recombination (HR) *status*".

OV-1
- Workup, sixth bullet modified: Evaluate *performance status and* nutritional status
- Footnote a modified: Imaging performed with *oral and IV* contrast unless contraindicated. (Also on OV-3, OV-5, OV-6; footnote t on LCOC-9 and LCOC-12)
- Footnote c added: Chest CT preferred if concern for metastatic or disseminated disease.
- Footnote f modified: Germline and~~/or~~ somatic BRCA1/2 status informs maintenance therapy. (Also on OV-2, OV-3)
- Footnote g modified: In the absence of a BRCA1/2 mutation, homologous recombination *(HR)* ~~deficiency (HRD)~~ status may provide information on the magnitude of benefit of PARP inhibitor (PARPi) therapy ~~(category 2B)~~. *(See OV-B)* (Also on OV-2, OV-3, OV-5)

OV-3
- Findings modified:
  - No evidence of residual disease on workup (suspect stage I ~~A-B)~~
  - No evidence of residual disease on workup (suspect stage ~~IC~~ *II*–IV)
  - Added links to LCOC-2 and LCOC-7 for carcinosarcoma, and ovarian borderline epithelial tumors.
- Primary treatment modified:
  - Suspect stage I: Consider surgical staging *(if not previously done)* if considering observation *or to inform systemic therapy decisions*
  - Suspect stage II–IV, added: Consider surgical staging if not previously done, to inform systemic therapy decisions
- Footnote r added: Although comprehensive surgical staging has not been shown to improve survival in patients with no evidence of residual disease, it can be important for determining the most appropriate postoperative management options, including selection of adjuvant and maintenance therapy.

OV-4
- Primary chemotherapy/primary adjuvant therapy, stage II–IV
  - Bullet removed: Completion surgery as indicated by tumor response and potential resectability in selected patients
- After primary chemotherapy/primary adjuvant therapy, modified: ~~Consider~~ *Provide* symptom management and best supportive care.

OV-5
- "Complete clinical remission" changed to "complete response"; "partial remission" changed to "partial response."
- No bevacizumab used during primary therapy, germline or somatic *BRCA1/2* mutation and CR/PR:
  - Option modified: *Consider* observation *for stage II disease only* ~~(if CR)~~
- Bevacizumab used as part of primary therapy, BRCA1/2 wild-type or unknown and CR/PR:
  - Added branches to differentiate the maintenance therapy options for "HR proficient or status unknown" and "HR deficient."
- Footnote v added: Post-primary treatment recommendations for stage II–IV high-grade serous or grade 2/3 endometrioid carcinoma; consider for clear cell carcinoma or carcinosarcoma with a *BRCA1/2* mutation.

OV-6
- Workup, bullet removed: chest x-ray as indicated

OV-7
- Disease status, added "platinum-resistant disease" and "platinum-sensitive disease" headings. (Also on OV-8)
- Footnote ff added: Definitions of platinum-sensitive and platinum-resistant disease are imprecise; clinical judgment and flexibility should be utilized in determining treatment options. (Also on OV-8)
- Footnote gg added: Data are limited on primary and maintenance therapy for recurrent/persistent LCOC. (Also on OV-8)
- Therapy for platinum-sensitive disease moved to OV-8.

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2021 of the NCCN Guidelines for Ovarian Cancer from Version 2.2020 include:

OV-8
- Maintenance therapy, bullet modified: *PARPi therapy, if not previously used (category 1 for BRCA mutation carriers)* ~~Consider niraparib or olaparib or rucaparib~~
- Footnote mm modified: *PARPi options include niraparib, olaparib, or rucaparib.* For patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy...

Less Common Ovarian Cancers

LCOC-2
- Removed: Consider surgical staging, if not previously done.
- Stage II–IV, after adjuvant treatment added: If known *BRCA1/2* mutation, consider maintenance therapy (post-primary therapy) (see OV-5) (Also on LCOC-3)
- Monitoring/Follow-up modified: Monitoring/Follow-Up *(including tumor testing) and Recurrence therapy* (See OV-6) (Also on LCOC-3 through LCOC-6)
- Footnotes added:
  - g: If not previously done, consider surgical staging and resection of residual disease. (See OV-3) (also on LCOC-3 through LCOC-6)
  - h: If not previously done, consider germline and somatic testing. (See OV-B) (also on LCOC-3 through LCOC-6)
  - i: Germline and somatic *BRCA1/2* status informs maintenance therapy. In the absence of a *BRCA1/2* mutation, (HR) status may provide information on the magnitude of benefit of PARPi therapy. (Also on LCOC-3)
  - j: Data are limited on primary and maintenance therapy for recurrent/persistent LCOC. (Also on LCOC-3 through LCOC-6)

LCOC-5
- Stage IC, adjuvant systemic therapy
  - Following chemotherapy, added: Maintenance hormonal therapy (category 2B) or observe. (Also on LCOC-6)
- Footnotes added:
  - l: MSI/MMR testing is recommended for all patients with endometrioid carcinoma.
  - m: Hormonal therapy options include: aromatase inhibitors (anastrozole, letrozole, exemestane), leuprolide acetate, tamoxifen. (Also on LCOC-6)

LCOC-8
- Modified: Chest/abdomen/pelvic CT with contrast *if not previously done*

LCOC-10
- Footnote v modified: Inhibin levels can be followed ~~if initially elevated~~ for granulosa cell tumors ~~(category 2B)~~.

LCOC-12
- Changed "stem cell transplant (SCT)" to "hematopoietic cell transplant (HCT)". (Also on LCOC-A)

LCOC-A
- Page moved, formerly OV-C (9 of 10).
- Footnote removed: There are limited data on the primary systemic therapy regimens for these LCOC.

LCOC-B
- Page moved, formerly LCOC-13.
- Malignant germ cell tumors, non-dysgerminoma
  - Radiographic imaging modified:
    - ◊ Year 1: ~~Posterioanterior (PA) and lateral chest x-ray and~~ *Chest/* abdominal/pelvic CT (every 3–4 mo)
    - ◊ Year 2: ~~PA and lateral chest x-ray and~~ *Chest/*abdominal/pelvic CT (every 4–6 months)

OV-A (2 of 4)
- First sub-heading modified: Newly Diagnosed Invasive Epithelial Ovarian Cancer Apparently Confined to an Ovary or to the Pelvis *(apparent stage IA-IIA)*
- Second sub-heading modified: Newly Diagnosed Invasive Epithelial Ovarian Cancer Involving the Pelvis and Upper Abdomen *(stage ≥IIB)*
  - Second bullet modified: Suspicious and/or enlarged nodes, *identified on preoperative imaging or during surgical exploration,* should be resected, if possible.
  - Bullet removed: Those patients with tumor nodules outside the pelvis ≤2 cm (presumed stage IIIB) should have bilateral pelvic and para-aortic lymph node dissection as previously described.
  - Reference added: Harter P, Sehouli J, Lorusso D, et al. A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms. N Engl J Med. 2019 Feb 28;380:822-832.

Continued

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Ovarian Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 1.2021 of the NCCN Guidelines for Ovarian Cancer from Version 2.2020 include:

OV-A (4 of 4)
- Special Circumstances
  - First bullet modified: "Fertility-sparing surgery with USO... Comprehensive surgical staging should still be performed to rule out occult higher stage disease but may be omitted in pediatric, adolescent, *and young adult* patients..."
  - Second bullet, line added: If mucinous histology is confirmed by intraoperative frozen section analysis and there are no suspicious lymph nodes, consider omitting lymphadenectomy.
  - Fourth bullet modified: Secondary cytoreduction: A secondary cytoreduction procedure can be considered in patients with recurrent ovarian cancer who ~~recur more than 6–12 months since completion of initial chemotherapy, have an isolated focus (or limited foci) of disease amenable to complete resection, and do not have ascites~~ *develop a recurrence more than 6 months since completion of initial chemotherapy, have a good performance status, have no ascites*, and *have an isolated focus or limited foci of disease amenable to complete resection. In addition to preoperative imaging, laparoscopy may be used to determine if complete resection can be achieved. Secondary cytoreduction can be performed with either open or minimally invasive approaches.*

OV-B (1 of 3)
- Bullets modified:
  - ◊ Next-generation sequencing (NGS) for *BRCA1/2* ~~somatic~~ mutations*, other somatic mutations (eg, NTRK gene fusions) and tumor mutational burden [TMB]*
  - ◊ *Additional testing (particularly for endometrioid carcinomas)*
    - – Immunohistochemistry (IHC) for DNA mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) ~~or~~
    - – Microsatellite instability (MSI) testing ~~via polymerase chain reaction (PCR)~~
  - ◊ ~~Consider evaluation of homologous recombination deficiency.~~ *In addition to BRCA1/2 testing, other methods for evaluating HR* ~~deficiency~~ *status (genomic instability, loss of heterozygosity) can be considered.*

OV-C (1 of 11)
- Newly diagnosed ovarian, Fallopian tube, or primary peritoneal cancer:
  - First bullet modified: If they are eligible for chemotherapy, patients should be informed about the different *primary therapy* options that are available~~—that is~~ such as IV chemotherapy...

OV-C (3 of 11)
- Section added: Principles of Maintenance PARP Inhibitor Therapy

OV-C (4 of 11)
- Third bullet modified: Tumor molecular testing is recommended prior to initiation of therapy for persistent/recurrent disease. *See Principles of Pathology (OV-B).* ~~Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: BRCA1/2, and MSI or dMMR if not previously done. Evaluation of homologous recombination deficiency can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.~~

OV-C (5 of 11)
- Low-Grade Serous (stage IC)/Grade 1 Endometrioid (stage IC)
  - The following hormone therapy options were moved from "other recommended" to "preferred regimens": aromatase inhibitors: anastrozole, letrozole, exemestane (category 2B) (Also on OV-C, 6 of 11 for stage II-IV disease)

OV-C (8 of 11)
- Pembrolizumab indications modified: for microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR] solid tumors, or *patients with tumor mutational burden-high [TMB-H] tumors ≥10 mutations/megabase and no satisfactory alternative treatment options. (Also on OV-C, 9 of 11)*

Continued

Updates in Version 1.2021 of the NCCN Guidelines for Ovarian Cancer from Version 2.2020 include:

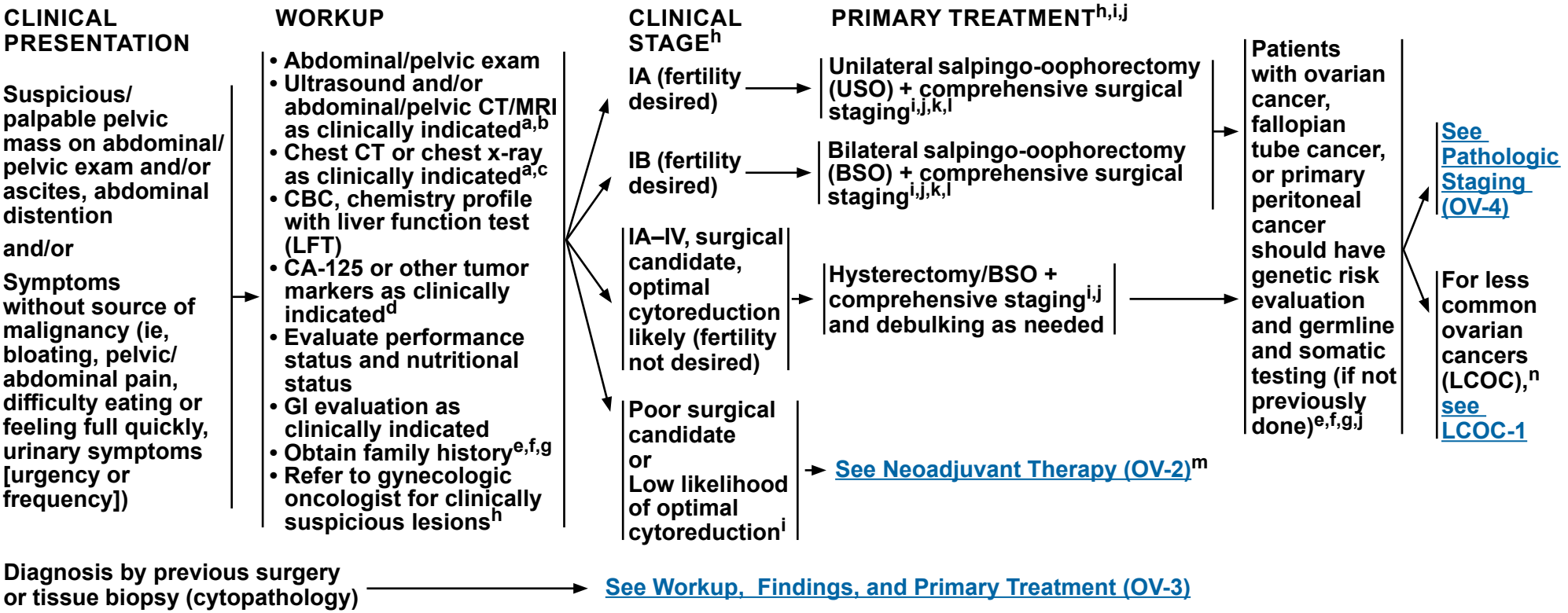
OV-C (10 of 11)

- **References added:**
  - **Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. N Engl J Med 2019;381:2416-2428.**
  - **Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med 2019;381:2391-2402.**
  - **Mirza MR, Monk BJ, Herrstedt J, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154-2164.**
  - **Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. N Engl J Med 2018;379:2495-2505.**
  - **Pujade-Lauraine E, Ledermann JA, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274-1284.**
  - **Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. Br J Cancer 2018;119:1075-1085.**
  - **Coleman RL, Oza AM, Lorusso D, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949-1961.**
  - **Ledermann JA, Oza AM, Lorusso D, et al. Rucaparib for patients with platinum-sensitive, recurrent ovarian carcinoma (ARIEL3): post-progression outcomes and updated safety results from a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:710-722.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
Table of Contents
Discussion



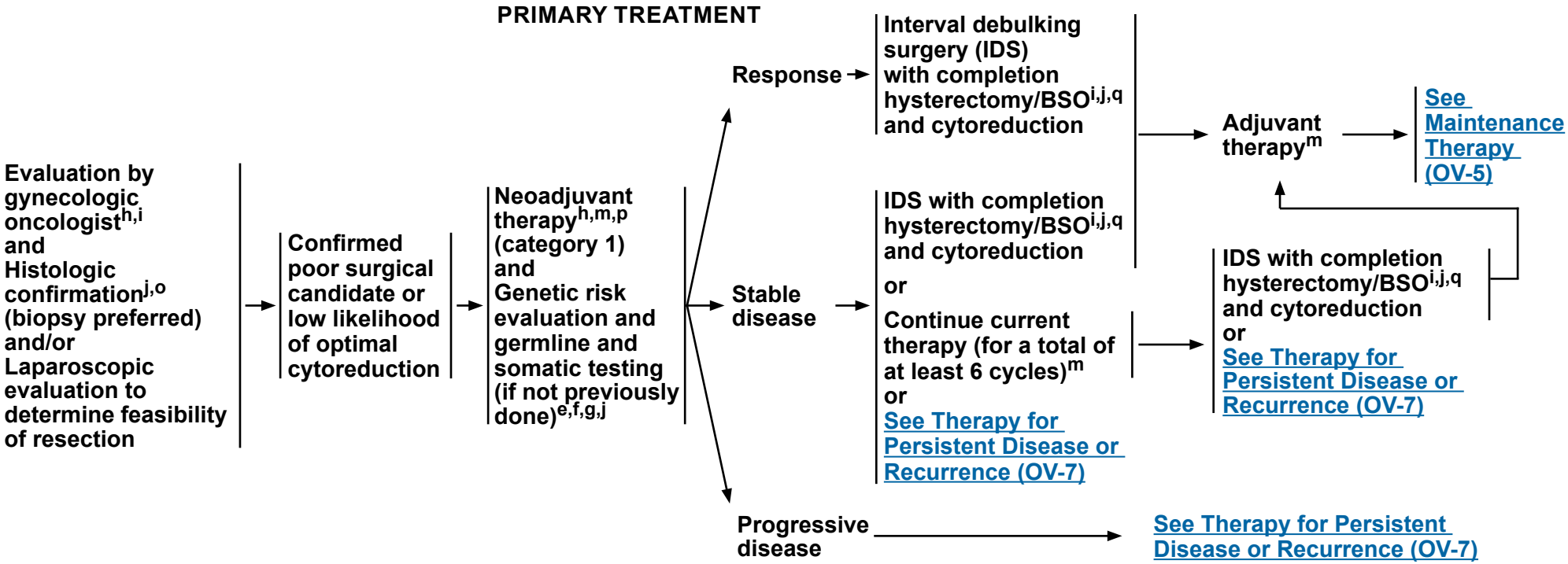
Diagnosis by previous surgery or tissue biopsy (cytopathology) → See Workup, Findings, and Primary Treatment (OV-3)

[a] Imaging performed with oral and IV contrast unless contraindicated.
[b] PET/CT or MRI may be indicated for indeterminate lesions if results will alter management.
[c] Chest CT preferred if concern for metastatic or disseminated disease.
[d] Other tumor markers may include inhibin, beta-human chorionic gonadotropin (β-hCG), alpha-fetoprotein, lactate dehydrogenase (LDH), carcinoembryonic antigen (CEA), and CA 19-9. See Discussion for usefulness of diagnostic tests.
[e] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal.
[f] Germline and somatic *BRCA1/2* status informs maintenance therapy.
[g] In the absence of a *BRCA1/2* mutation, homologous recombination (HR) status may provide information on the magnitude of benefit of PARP inhibitor (PARPi) therapy (See OV-B).
[h] 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.

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

Note: All recommendations are category 2A unless otherwise indicated.
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.

POOR SURGICAL CANDIDATE OR LOW LIKELIHOOD OF OPTIMAL CYTOREDUCTION NEOADJUVANT THERAPY



[e] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
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- Management of occult serous tubal intraepithelial carcinomas.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.

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

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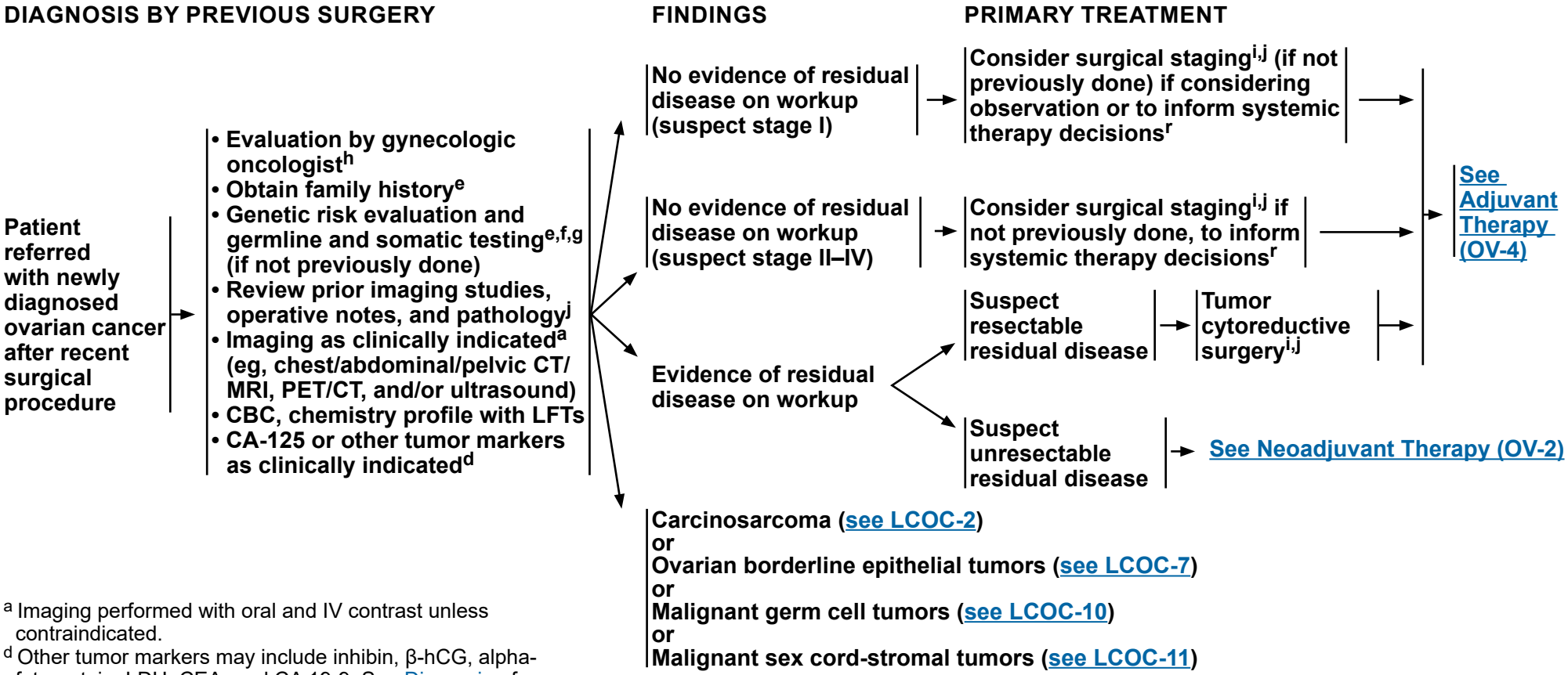

[a] Imaging performed with oral and IV contrast unless contraindicated.

[d] Other tumor markers may include inhibin, β-hCG, alpha-fetoprotein, LDH, CEA, and CA 19-9. See Discussion for usefulness of diagnostic tests.

[e] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[f] Germline and somatic BRCA1/2 status informs maintenance therapy.

[g] In the absence of a BRCA1/2 mutation, homologous recombination (HR) status may provide information on the magnitude of benefit of PARP inhibitor (PARPi) therapy (See OV-B).

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- All patients with suspected ovarian malignancies; published data demonstrate that primary assessment and debulking by a gynecologic oncologist results in a survival advantage.
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- Management of occult serous tubal intraepithelial carcinomas.
- Consideration of laparoscopic evaluation to determine feasibility of debulking surgery in select patients.

[i] See Principles of Surgery (OV-A).

[j] See Principles of Pathology (OV-B).

[r] Although comprehensive surgical staging has not been shown to improve survival in patients with no evidence of residual disease, it can be important for determining the most appropriate postoperative management options, including selection of adjuvant and maintenance therapy.

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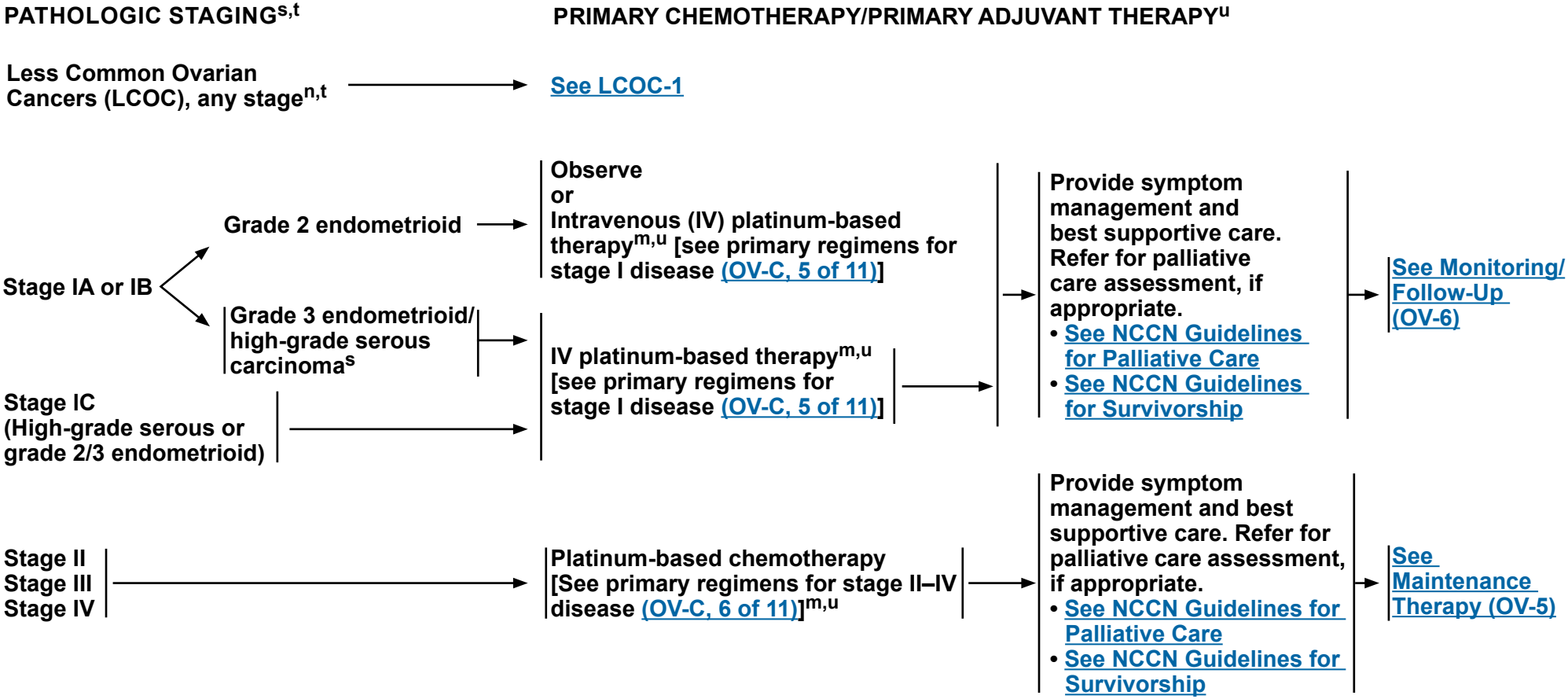
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
Table of Contents
Discussion



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

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

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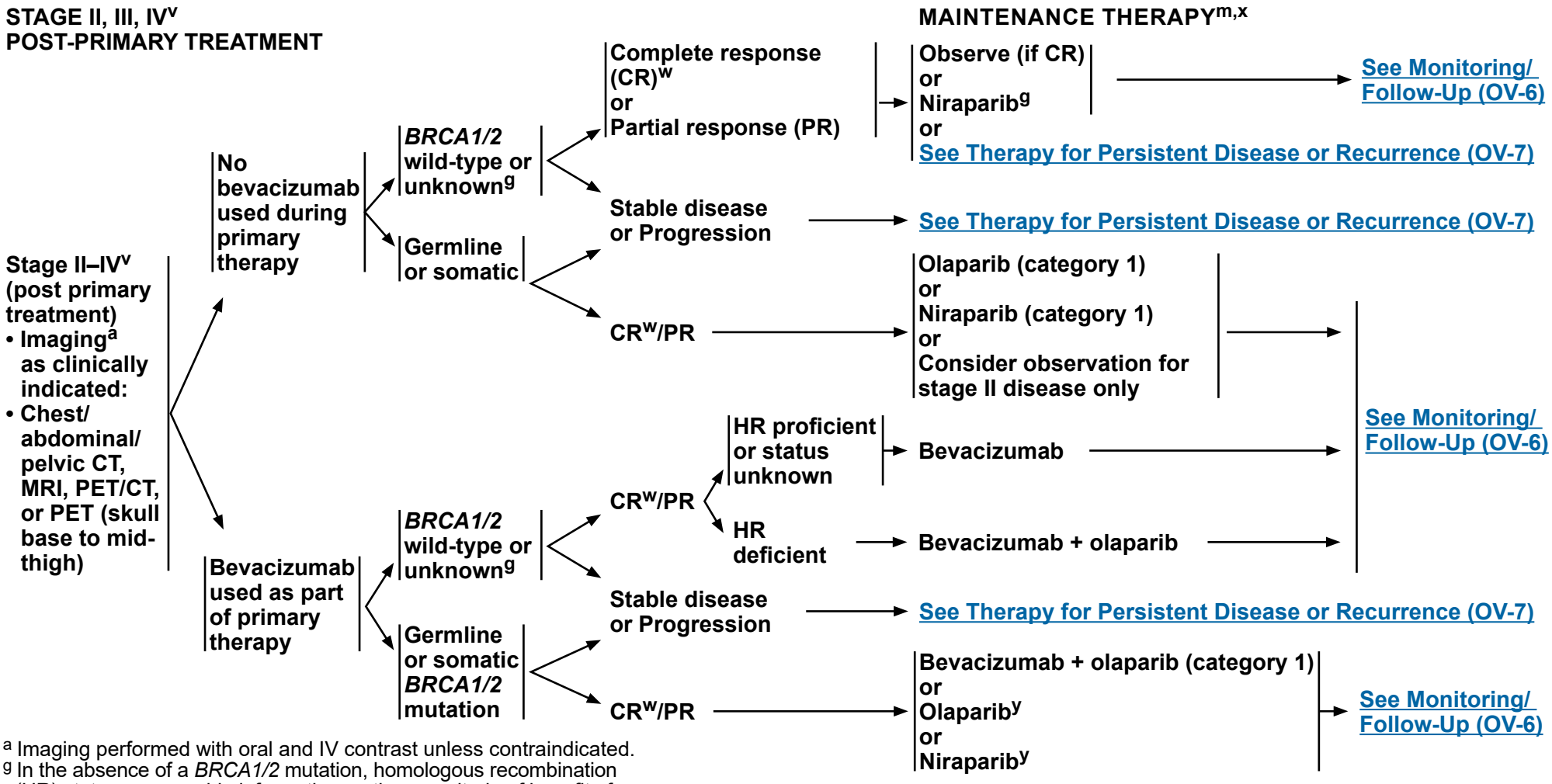
National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Epithelial Ovarian Cancer/Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
Table of Contents
Discussion



[a] Imaging performed with oral and IV contrast unless contraindicated.
[g] In the absence of a *BRCA1/2* mutation, homologous recombination (HR) status may provide information on the magnitude of benefit of PARP inhibitor (PARPi) therapy (See OV-B).
[m] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[v] Post-primary treatment recommendations for stage II–IV high-grade serous or grade 2/3 endometrioid carcinoma; consider for clear cell carcinoma or carcinosarcoma with a *BRCA1/2* mutation.
[w] No definitive evidence of disease.
[x] Data are limited for maintenance therapy with a PARPi for patients with stage II disease.
[y] After first-line therapy with bevacizumab, data are limited on maintenance therapy with a single-agent PARPi (olaparib or niraparib) for patients with a germline or somatic *BRCA1/2* mutation. However, based on the magnitude of benefit of PARPi maintenance therapy for other subgroups, single-agent PARPi can be considered.

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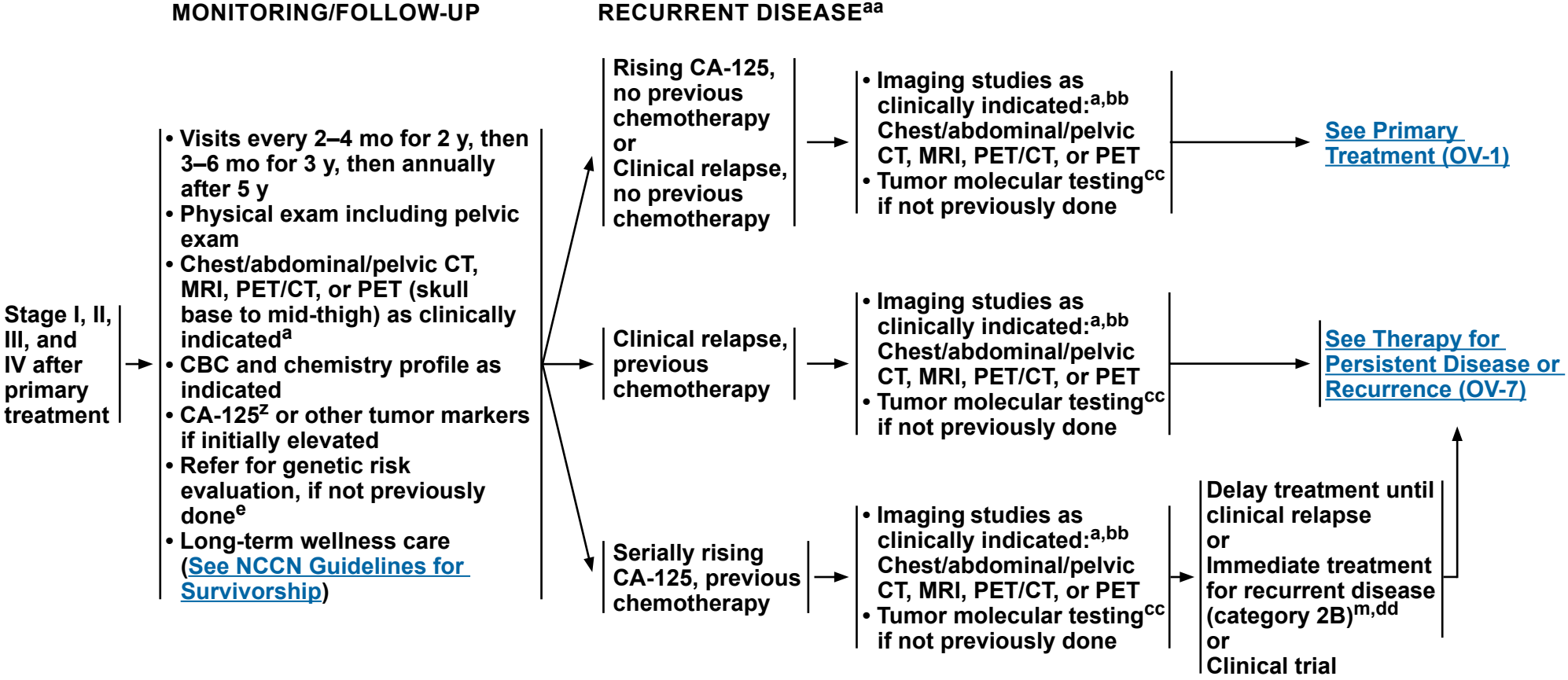

[a] Imaging performed with oral and IV contrast unless contraindicated.

[e] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[m] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

[z] There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See The Society of Gynecologic Oncology (SGO) position statement and Discussion.

[aa] Consider symptom management and best supportive care. See NCCN Guidelines for Palliative Care. Refer for palliative care assessement, if appropriate.

[bb] Surveillance imaging may be indicated when tumor markers are considered unreliable, the physical exam is unreliable, and/or there is a high risk of recurrence.

[cc] Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of HR status can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist (See OV-B).

[dd] See Acceptable Recurrence Therapies (OV-C, 8 of 11).

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DISEASE STATUS[e,cc,ee] | **THERAPY FOR PERSISTENT DISEASE OR RECURRENCE[m,dd,gg,hh,ii]**

Platinum-resistant disease:[ff]
Progression on primary, maintenance or recurrence therapy
or
Stable or persistent disease (if not on maintenance therapy)
or
Complete remission and relapse <6 mo after completing chemotherapy

→ **Clinical trial[jj,kk]**
and/or
Best supportive care (See NCCN Guidelines for Palliative Care)
and/or
Recurrence therapy (see OV-C, 9 of 11)[m,jj,ll]

Platinum-sensitive disease:[ff]
Complete remission and relapse ≥6 mo after completing prior chemotherapy

→ **See OV-8**

e See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

m See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

cc Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of HR status can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist (See OV-B).

dd See Acceptable Recurrence Therapies (OV-C, 8 of 11).

ee Tumor molecular testing prior to initiation of therapy for persistent/recurrent disease, if not previously done.

ff Definitions of platinum-sensitive and platinum-resistant disease are imprecise; clinical judgment and flexibility should be utilized in determining treatment options.

gg Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.

hh During and after treatment for recurrence, patients should be evaluated as indicated with tumor markers and repeat imaging (with modalities previously used) to document response and/or disease status.

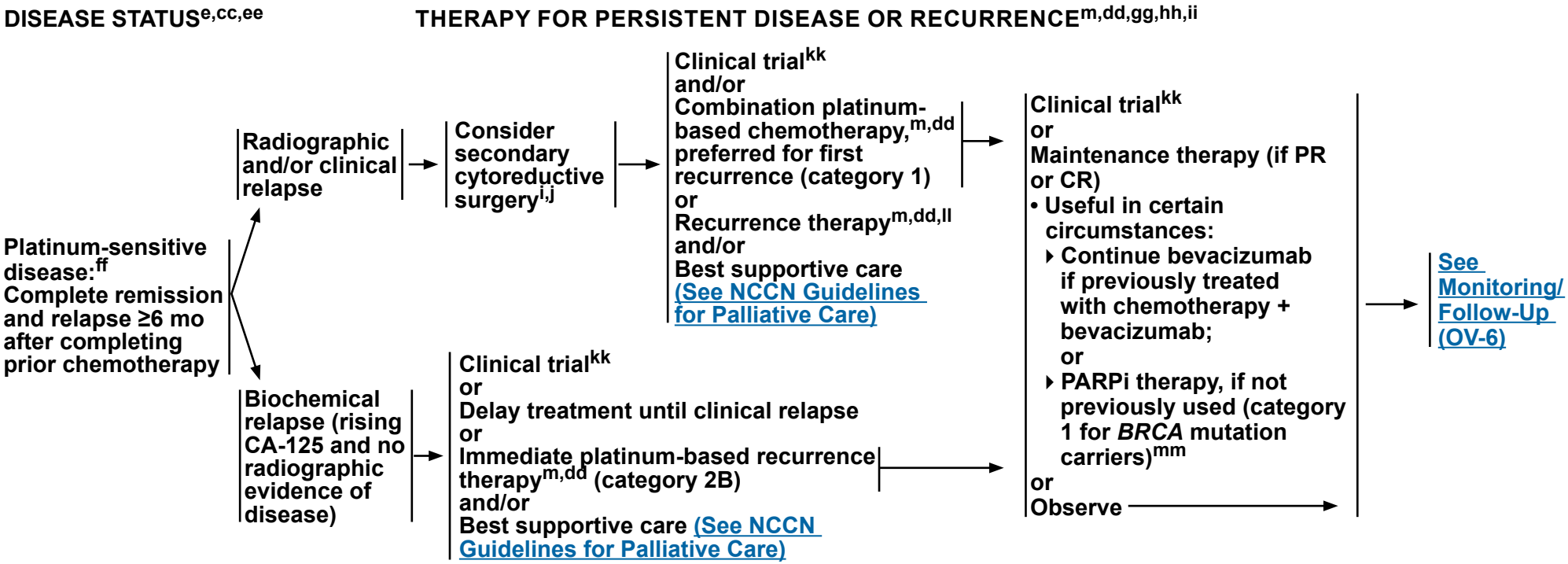
ii See Ancillary Palliative Surgical Procedures (OV-A 4 of 4).

jj Patients who progress on 2 consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. Decisions to offer clinical trials, supportive care only, or additional therapy should be made on a highly individual basis.

kk Clinical trials with newer agents should be strongly considered.

ll Palliative localized RT can be considered.

Note: All recommendations are category 2A unless otherwise indicated.
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.



[e] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal.

[i] See Principles of Surgery (OV-A).

[j] See Principles of Pathology (OV-B).

[m] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

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[hh] During and after treatment for recurrence, patients should be evaluated as indicated with tumor markers and repeat imaging (with modalities previously used) to document response and/or disease status.

[ii] See Ancillary Palliative Surgical Procedures (OV-A 4 of 4).

[kk] Clinical trials with newer agents should be strongly considered.

[ll] Palliative localized RT can be considered.

[mm] PARPi options include niraparib, olaparib, or rucaparib. For patients with platinum-sensitive disease who have completed two or more lines of platinum-based therapy (preferred for those with a *BRCA* mutation). There are limited data on the use of a maintenance PARPi in patients who previously received a PARPi or after recurrence therapy with bevacizumab. Combination bevacizumab/PARPi is not recommended at this time for maintenance after recurrence therapy.

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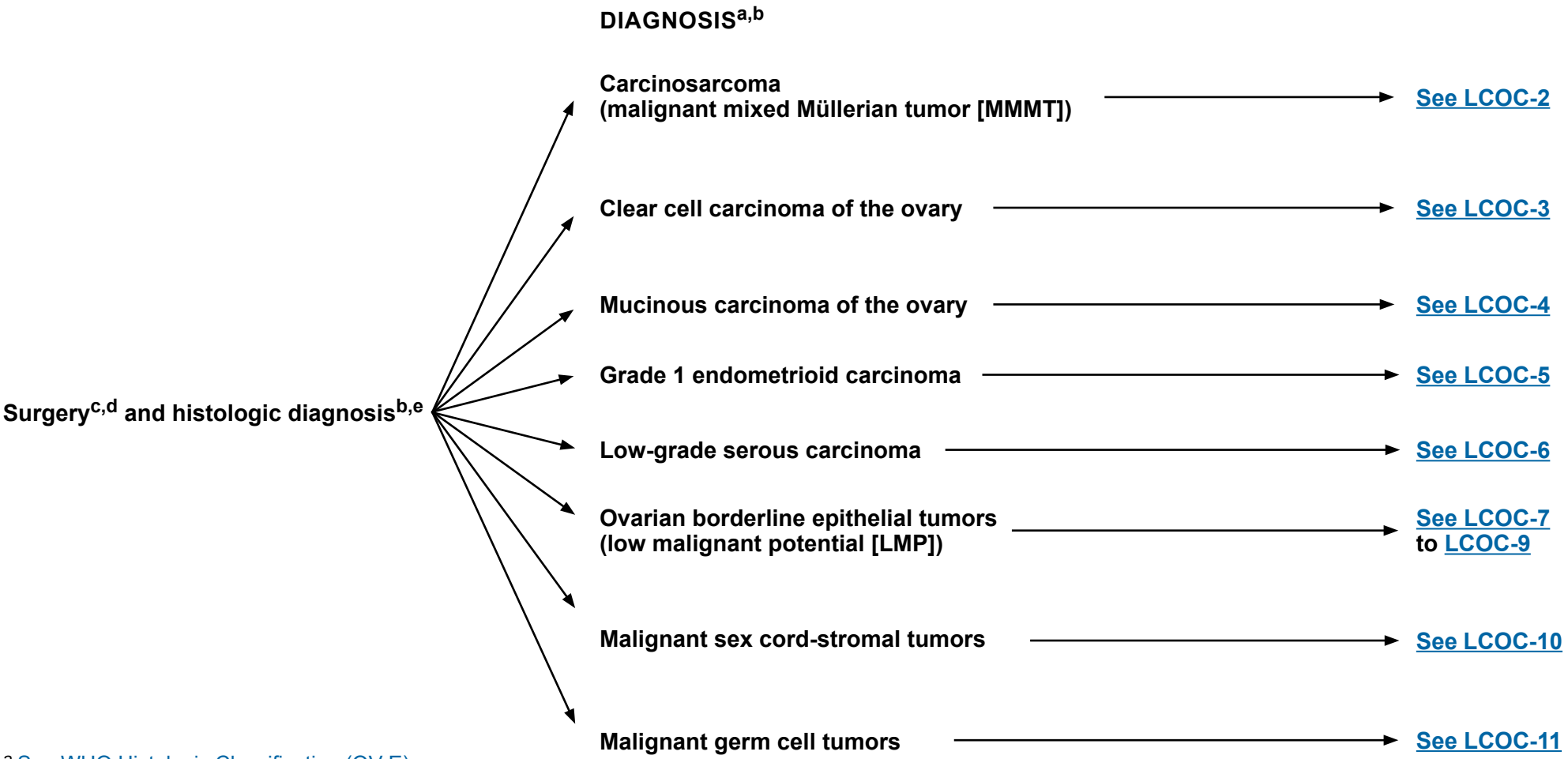

[a] See WHO Histologic Classification (OV-E).

[b] Due to emerging therapeutics for less common ovarian cancers, there is value in identifying potential pathways for rare cancers and it may be useful for clinical trial recruitment. Tumor molecular testing can be considered, if not previously done, as it may help guide treatment. There are limited data in these cancers given their infrequency and it will be difficult to acquire prospective data. Individualized treatment may be the best treatment for these rare tumors. [Committee on the State of the Science in Ovarian Cancer, et al. Ovarian Cancers: Evolving Paradigms in Research and Care. Washington (DC): National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved; 2016.]

[c] See Principles of Surgery (OV-A).

[d] See Principles of Pathology (OV-B).

[e] Less common ovarian cancers are typically diagnosed after surgery. See Workup (OV-1).

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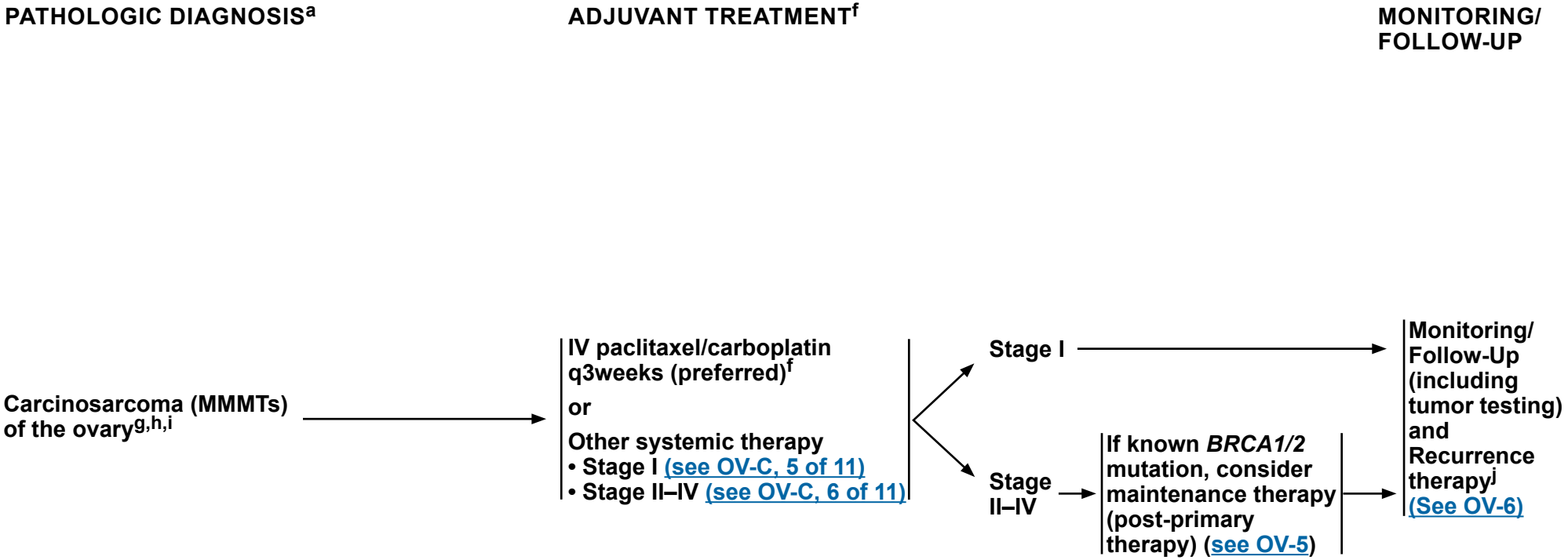

[a] See WHO Histologic Classification (OV-E).
[f] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[g] If not previously done, consider surgical staging and resection of residual disease (See OV-3).
[h] If not previously done, consider germline and somatic testing (See OV-B).
[i] Germline and somatic *BRCA1/2* status informs maintenance therapy. In the absence of a *BRCA1/2* mutation, HR status may provide information on the magnitude of benefit of PARPi therapy.
[j] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.

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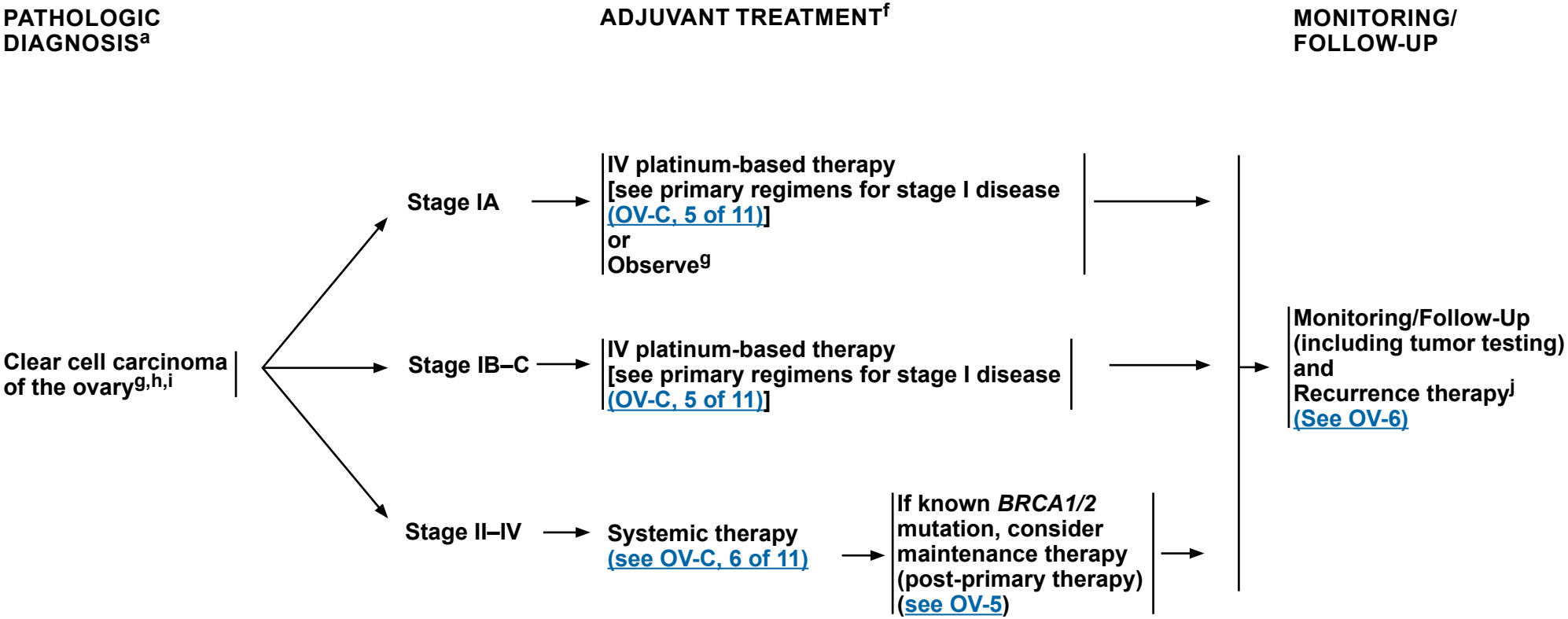

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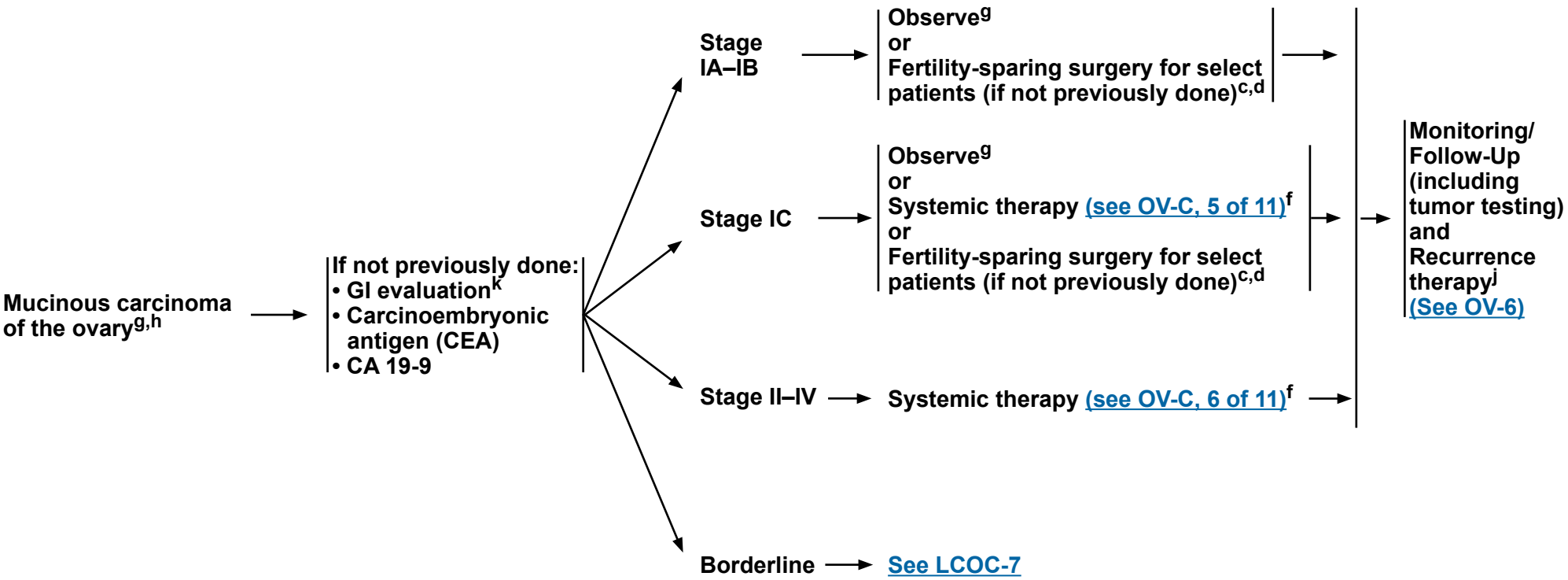

[a] See WHO Histologic Classification (OV-E).
[c] See Principles of Surgery (OV-A).
[d] Principles of Pathology (OV-B).
[f] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[g] If not previously done, consider surgical staging and resection of residual disease (See OV-3).
[h] If not previously done, consider germline and somatic testing (See OV-B).
[j] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.
[k] Consider additional testing, including but not limited to upper and lower endoscopic evaluation, to aid in the identification of metastatic GI malignancies versus primary mucinous ovarian cancer.

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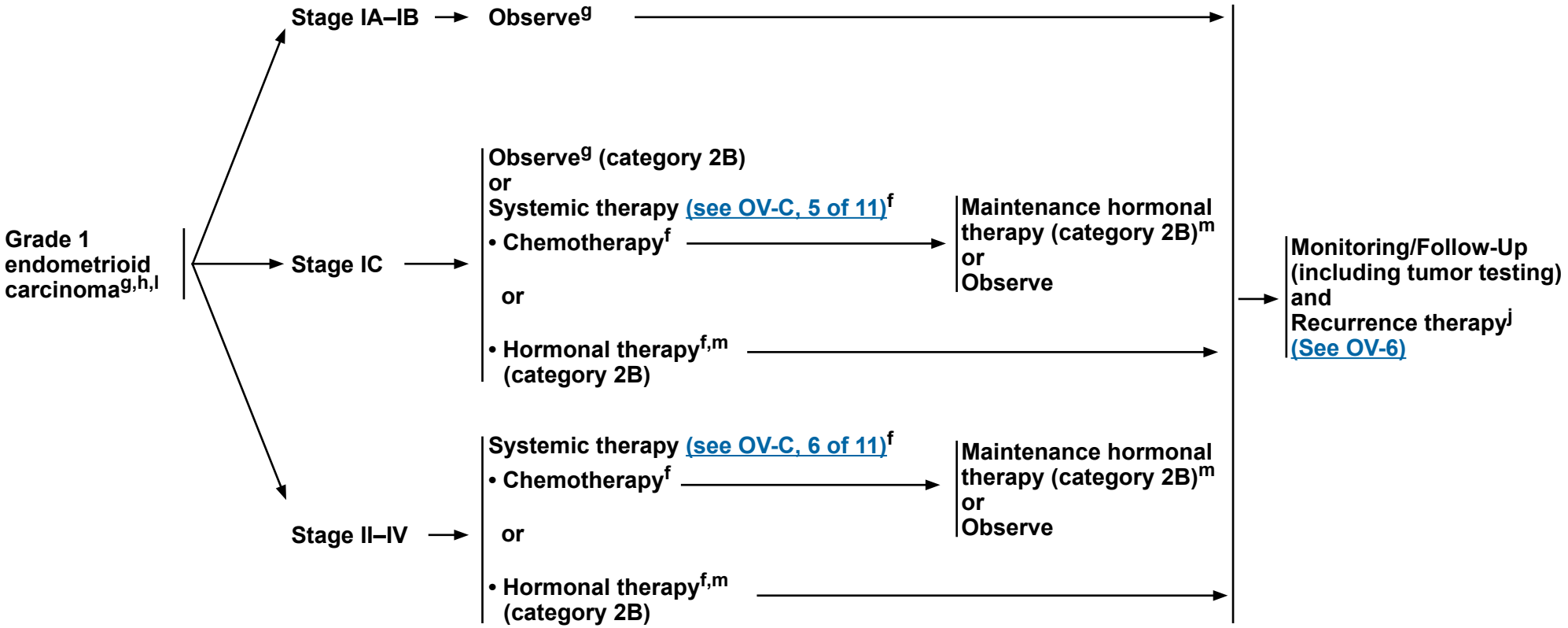
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[a] See WHO Histologic Classification (OV-E).
[f] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[g] If not previously done, consider surgical staging and resection of residual disease (See OV-3).
[h] If not previously done, consider germline and somatic testing (See OV-B).
[j] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.
[l] MSI/MMR testing is recommended for all patients with endometrioid carcinoma.
[m] Hormonal therapy options include: aromatase inhibitors (anastrozole, letrozole, exemestane), leuprolide acetate, tamoxifen.

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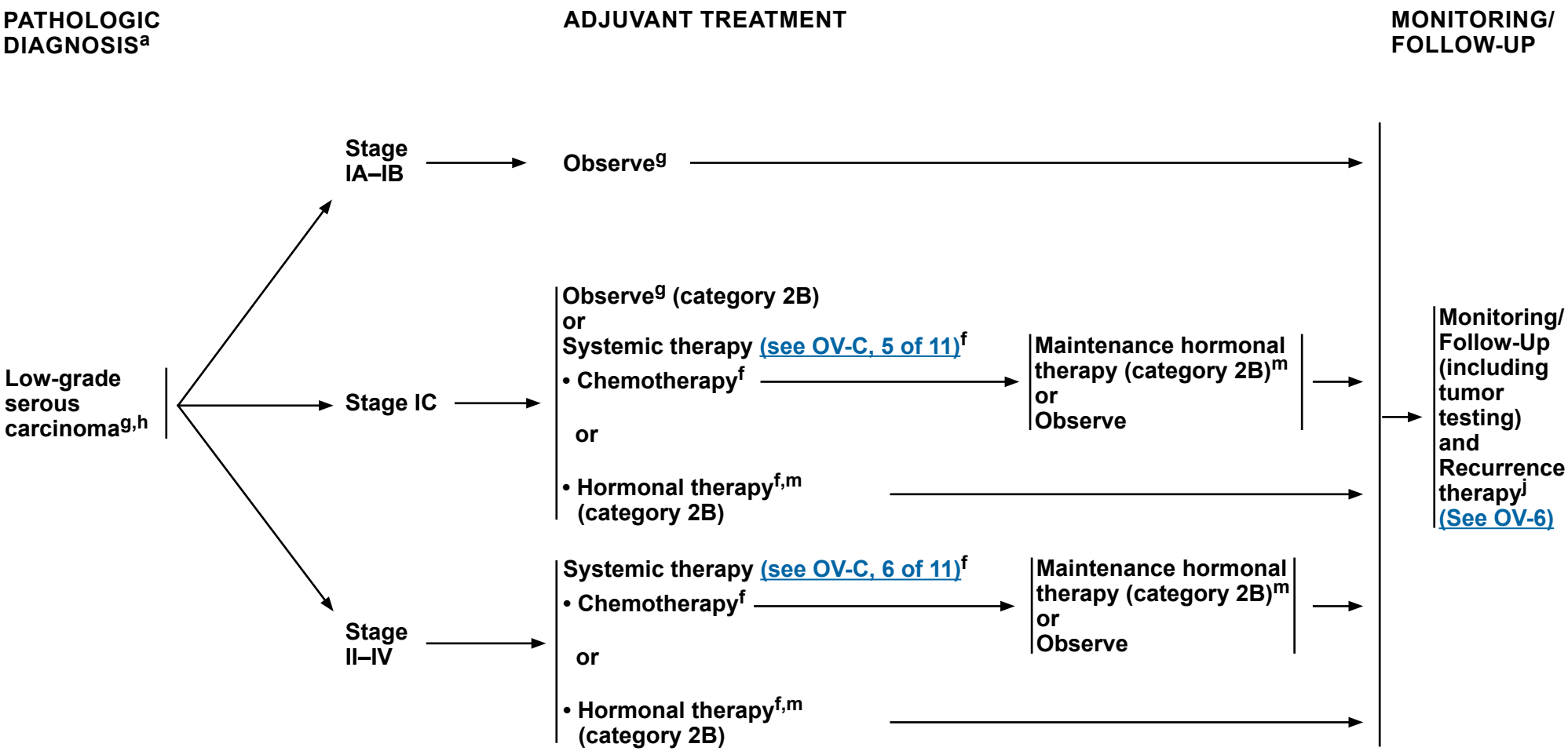
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[a] See WHO Histologic Classification (OV-E).
[f] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[g] If not previously done, consider surgical staging and resection of residual disease (See OV-3).
[h] If not previously done, consider germline and somatic testing (See OV-B).
[j] Data are limited on primary and maintenance therapy for recurrent/persistent LCOC.
[m] Hormonal therapy options include: aromatase inhibitors (anastrozole, letrozole, exemestane), leuprolide acetate, tamoxifen.

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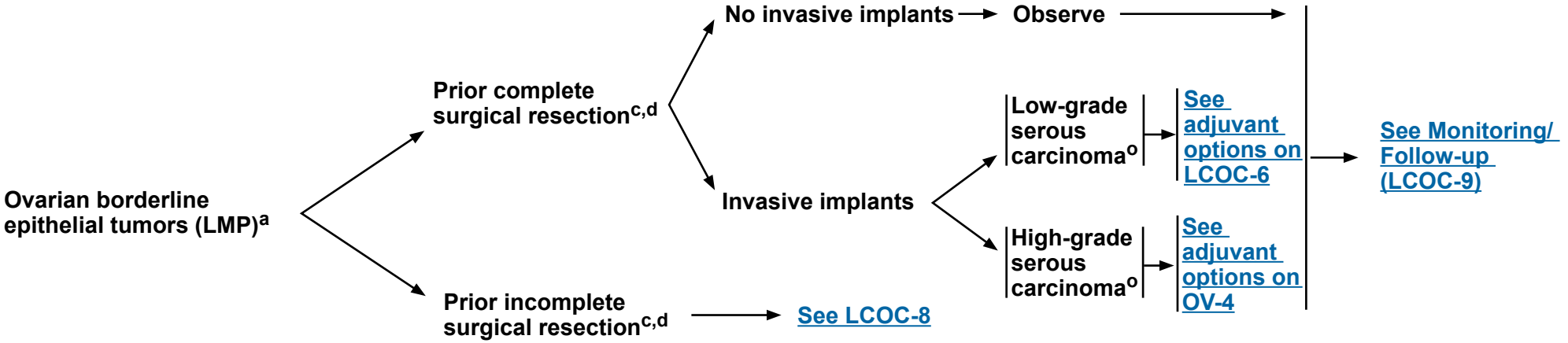
NCCN Guidelines Version 1.2021
Ovarian Borderline Epithelial Tumors (Low Malignant Potential)

NCCN Guidelines Index
Table of Contents
Discussion

PATHOLOGIC DIAGNOSIS[a]

ADJUVANT TREATMENT[n]



[a] See WHO Histologic Classification (OV-E).
[c] See Principles of Surgery (OV-A).
[d] Principles of Pathology (OV-B).
[n] Standard recommendation includes a patient evaluation by a gynecologic oncologist.
[o] Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).

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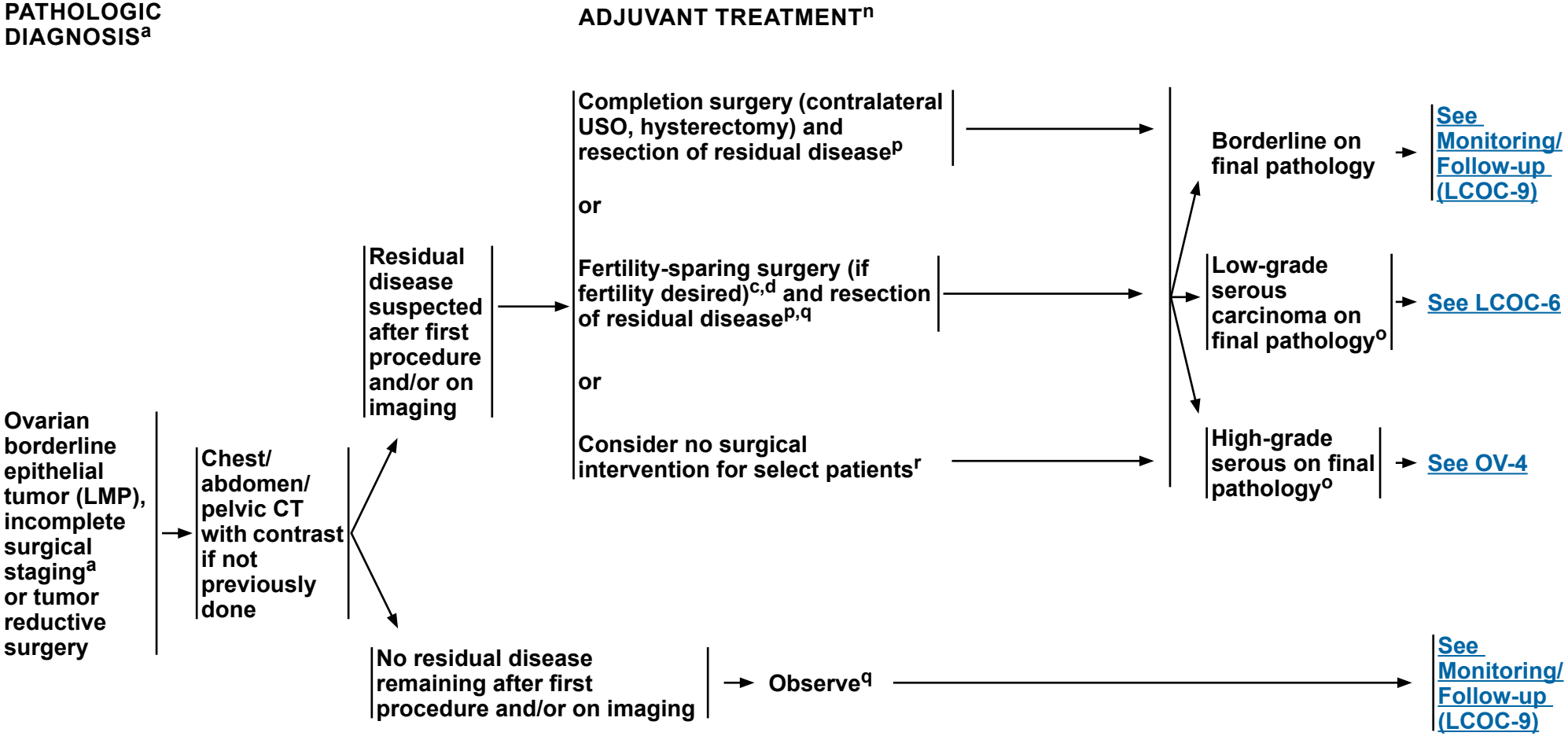
NCCN Guidelines Version 1.2021
Ovarian Borderline Epithelial Tumors (Low Malignant Potential)

NCCN Guidelines Index
Table of Contents
Discussion



[a] See WHO Histologic Classification (OV-E).
[c] See Principles of Surgery (OV-A).
[d] Principles of Pathology (OV-B).
[n] Standard recommendation includes a patient evaluation by a gynecologic oncologist.
[o] Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[p] For pathologically proven ovarian borderline epithelial tumors, lymph node evaluation may be considered on a case-by-case basis.
[q] In patients who underwent USO, consider completion surgery (eg, contralateral USO, hysterectomy) after completion of childbearing (category 2B).
[r] If patient is medically unfit, or for those with unresectable residual disease.

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MONITORING/FOLLOW-UP | **RECURRENT DISEASE** | **RECURRENCE THERAPY**

- Visits every 3–6 mo for up to 5 y, then annually
- Physical exam including pelvic exam
- CA-125[s] or other tumor markers every visit if initially elevated
- CBC, chemistry profile as indicated
- Imaging[t] as clinically indicated: Chest/abdominal/pelvic CT, MRI, PET/CT, or PET (skull base to mid-thigh)
- Ultrasound as indicated for patients with fertility-sparing surgery

→ Clinical relapse → Surgical evaluation + debulking if appropriate

- Noninvasive disease → Observe
- Invasive implants of ovarian borderline epithelial tumors (LMP) or Low-grade invasive carcinoma → See low-grade serous epithelial carcinoma[o] (See LCOC-6)
- Invasive carcinoma (high-grade) → Treatment as epithelial ovarian cancer[o] (See OV-4)

[o] Chemotherapy (IV or IP) has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[s] There are data regarding the utility of CA-125 for monitoring of ovarian cancer after completion of primary therapy. See The Society of Gynecologic Oncology (SGO) position statement and Discussion.
[t] Imaging performed with oral and IV contrast unless contraindicated.

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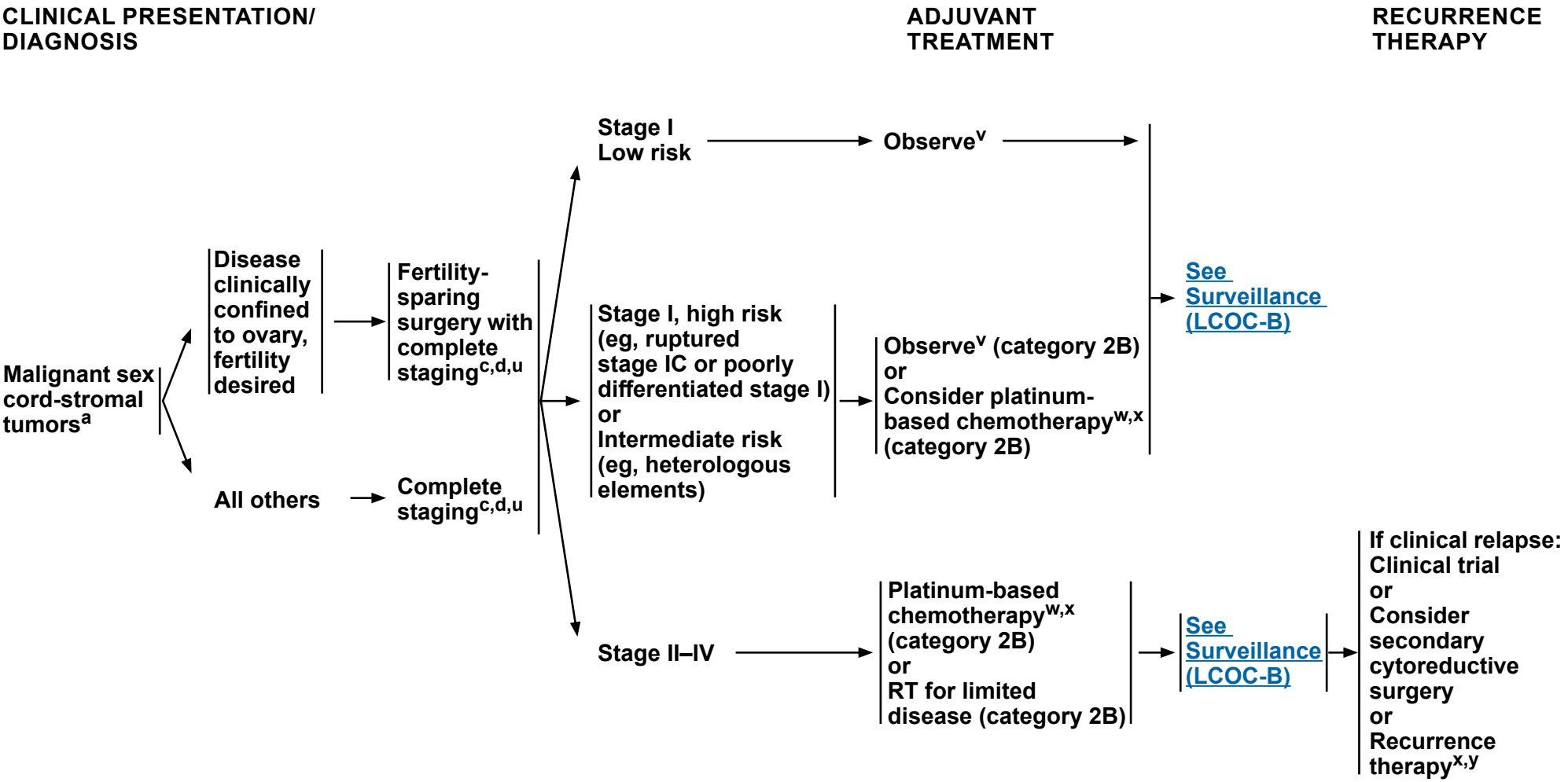

[a] See WHO Histologic Classification (OV-E).
[c] See Principles of Surgery (OV-A).
[d] Principles of Pathology (OV-B).
[u] Lymphadenectomy may be omitted.
[v] Inhibin levels can be followed for granulosa cell tumors.
[w] Acceptable options include paclitaxel/carboplatin (preferred), EP (etoposide, cisplatin), or BEP (bleomycin, etoposide, cisplatin) (category 2B).
[x] See Principles of Systemic Therapy (OV-C) and see Systemic Therapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors (LCOC-A).
[y] Palliative localized RT can be considered.

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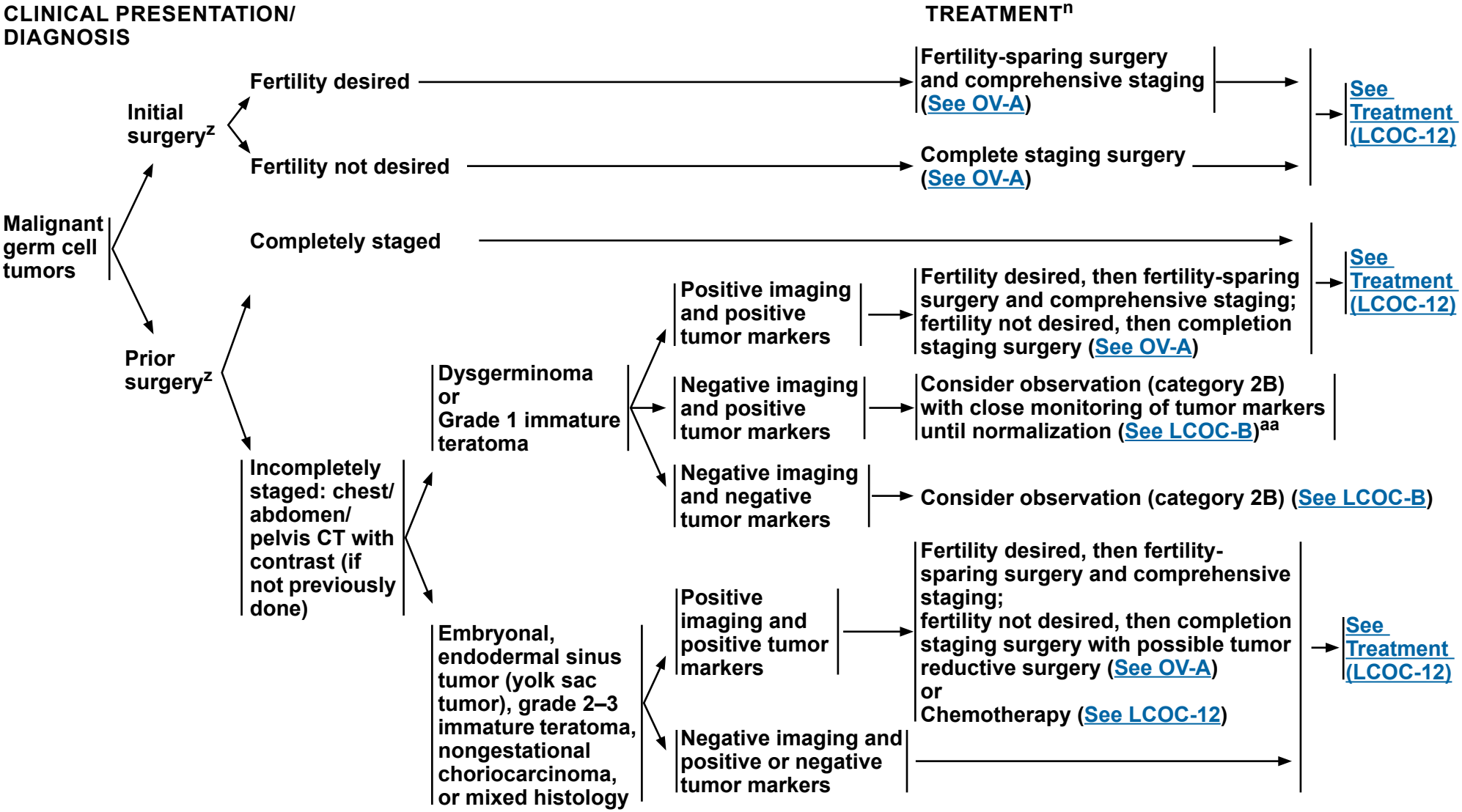
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[n] Standard recommendation includes a patient evaluation by a gynecologic oncologist.
[z] Surgical principles for pediatric/young adult patients may differ from those for adult patients. See Principles of Surgery (OV-A).
[aa] Repeat imaging if tumor markers plateau at significant abnormal level or rise. If imaging positive, follow pathway above for positive imaging and positive tumor markers.

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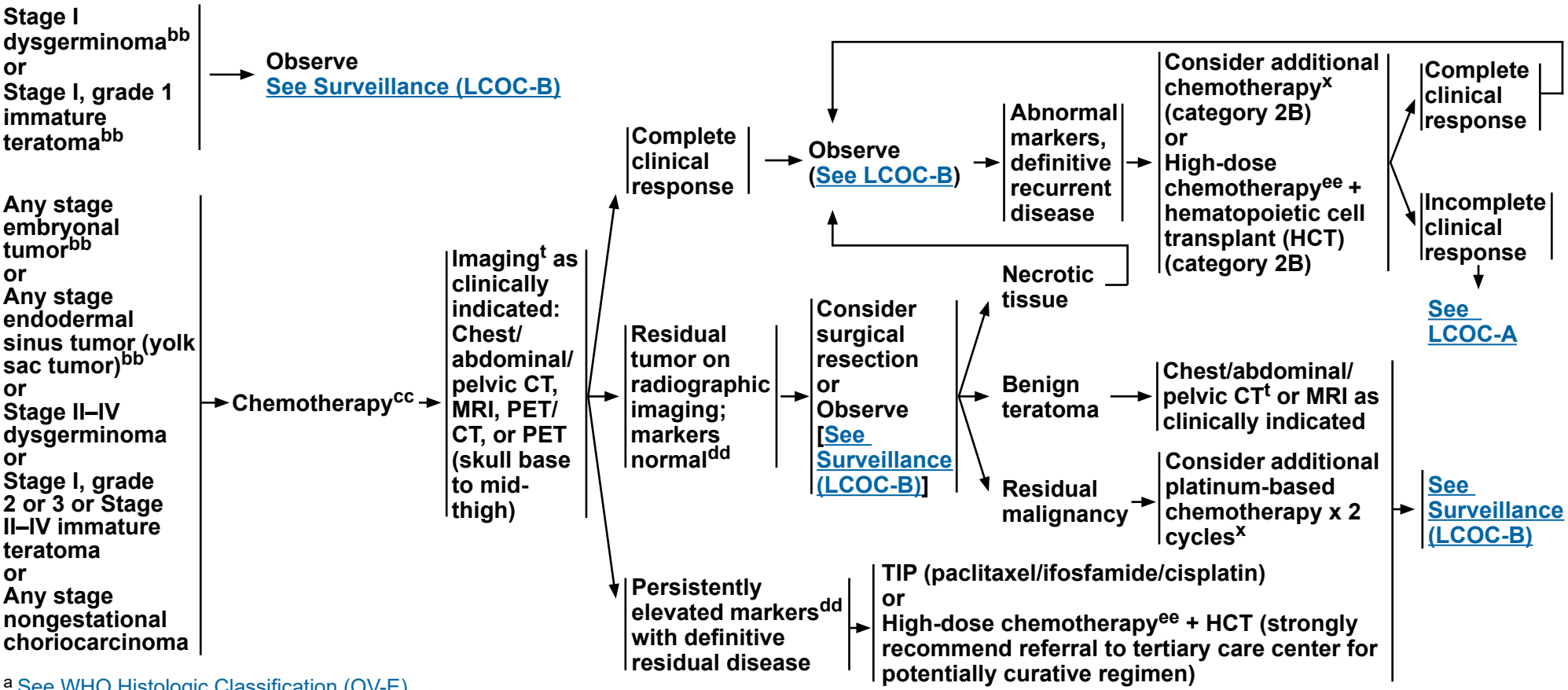
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Malignant Germ Cell Tumors

NCCN Guidelines Index
Table of Contents
Discussion



[a] See WHO Histologic Classification (OV-E).
[t] Imaging performed with oral and IV contrast unless contraindicated.
[x] See Principles of Systemic Therapy (OV-C) and See Systemic Therapy Regimens for Malignant Germ Cell/Sex Cord-Stromal Tumors (LCOC-A).
[y] Palliative localized RT can be considered.
[bb] Pediatric/adolescent patients with the following clinical presentations may consider observation or chemotherapy as treatment options: stage IA, IB dysgerminoma; stage IA, grade 1 immature teratoma; stage IA embryonal tumors; or stage IA yolk sac tumors.
[cc] See Primary Systemic Therapy Regimens for Malignant Germ Cell Tumors (LCOC-A).
[dd] See OV-1 for markers.
[ee] High-dose chemotherapy regimens vary among institutions. Some patients are potentially curable with HCT. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for HCT consultation and potentially curative therapy.

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SYSTEMIC THERAPY REGIMENS[a]
MALIGNANT GERM CELL/SEX CORD-STROMAL TUMORS

MALIGNANT GERM CELL TUMORS[a,b,c]

Primary Therapy

Preferred Regimens
- BEP (bleomycin, etoposide, cisplatin)[d]
  - Bleomycin 30 units IV per week plus etoposide 100 mg/m^2 IV daily on days 1–5 plus cisplatin 20 mg/m^2 IV daily on days 1–5; repeat every 21 days for 3 cycles for good risk (category 2B), or 4 cycles for poor risk.

Other Recommended Regimens
- None

Useful in Certain Circumstances
- Etoposide/carboplatin[a] (for select patients with stage IB–III resected dysgerminoma for whom minimizing toxicity is critical)
  - Carboplatin 400 mg/m^2 IV on day 1 plus etoposide 120 mg/m^2 IV on days 1, 2, and 3 every 28 days for 3 cycles.

Recurrence Therapy

Preferred Regimens (Potentially Curative)
- High-dose chemotherapy[b]
- TIP (paclitaxel, ifosfamide, cisplatin)

Other Recommended Regimens (Palliative Only)
- Cisplatin/etoposide
- Docetaxel
- Docetaxel/carboplatin
- Etoposide/ifosfamide/cisplatin (VIP)
- Paclitaxel
- Paclitaxel/carboplatin
- Paclitaxel/gemcitabine
- Paclitaxel/ifosfamide
- VeIP (vinblastine, ifosfamide, cisplatin)
- VAC (vincristine, dactinomycin, cyclophosphamide)
- TIP
- Supportive care (See NCCN Supportive Care Guidelines)

MALIGNANT SEX CORD-STROMAL TUMORS[a,c]

Primary Therapy

Preferred Regimens
- Paclitaxel/carboplatin

Other Recommended Regimens
- Etoposide/cisplatin (EP)

Useful in Certain Circumstances
- BEP (category 2B)[d]

Recurrence Therapy

Preferred Regimens
- Paclitaxel/carboplatin

Other Recommended Regimens
- EP
- Paclitaxel/ifosfamide
- Docetaxel
- Paclitaxel
- VAC
- Supportive care only (See NCCN Supportive Care Guidelines)
- Targeted therapy
  - Bevacizumab[e] (single agent)

Useful in Certain Circumstances
- Aromatase inhibitors (ie, anastrozole, exemestane, letrozole)
- Leuprolide acetate (for granulosa cell tumors)
- Tamoxifen
- BEP (category 2B)[d]

[a] See Principles of Systemic Therapy (OV-C) and see Discussion for references.
[b] High-dose chemotherapy regimens vary among institutions. Some patients are potentially curable with HCT. Patients with potentially curable recurrent germ cell disease should be referred to a tertiary care institution for HCT consultation and potentially curative therapy.
[c] See WHO Histologic Classification (OV-E).
[d] Recommend pulmonary function test if considering bleomycin.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.

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SURVEILLANCE
MALIGNANT GERM CELL/SEX CORD-STROMAL TUMORS

Malignant Germ Cell Tumors					
	Year 1	Year 2	Year 3	Years 4–5	After 5 Years
Dysgerminoma					
Physical exam and serum tumor markers[a]	Every 2–3 mo	Every 3–4 mo	Every 6 mo	Every 6 mo	Annually
Radiographic imaging	Abdominal/pelvic CT (every 3–4 mo)	Abdominal/pelvic CT (every 6 mo)	Abdominal/pelvic CT (annually)	Abdominal/pelvic CT (annually)	As clinically indicated
Non-dysgerminoma					
Physical exam and serum tumor markers[a]	Every 2 mo	Every 2 mo	Every 4–6 mo	Every 6 mo	Annually
Radiographic imaging	Chest/abdominal/pelvic CT (every 3–4 mo)	Chest/abdominal/pelvic CT (every 4–6 months)	Abdominal/pelvic CT (every 6–12 mo)	Abdominal/pelvic CT (every 6–12 mo)	As clinically indicated

Malignant Sex Cord-Stromal Tumors[c]		
	0–2 Years	After 2 Years
Physical exam	As clinically indicated based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)	As clinically indicated based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)
Serum tumor markers[a]	• Testing as clinically indicated, if applicable • If done, frequency based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)	• Testing as clinically indicated, if applicable • If done, frequency based on stage (ie, 6–12 mo if early-stage, low-risk disease; 4–6 mo if high-risk disease)
Radiographic imaging[b]	Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam	Reserved for patients with symptoms, elevated biomarkers, or suspicious findings on physical exam

[a] See OV-1 for markers.
[b] Chest x-ray, chest/abdominal/pelvic CT, MRI, PET/CT, or PET; with contrast unless contraindicated.
[c] Salani R, Khanna N, Frimer M, et al. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. Gynecol Oncol 2017;146(1):3-10.

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PRINCIPLES OF SURGERY[1]

General Considerations

- 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 with a suspected malignant ovarian/fallopian tube/primary peritoneal neoplasm in whom a surgical staging procedure, a primary debulking procedure, an interval debulking procedure, or secondary cytoreduction is planned.
  - For select patients, a minimally invasive surgical approach may be employed by an experienced surgeon to manage early-stage disease. Laparoscopy may be useful to evaluate whether optimal cytoreduction can be achieved in patients with newly diagnosed advanced stage or recurrent 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.
- Intraoperative pathologic evaluation with frozen sections may assist in management.
- Prior to surgery for ovarian cancer, counsel patients about port placement if intraperitoneal (IP) chemotherapy is being considered.

Operative Reports

- Surgeons should describe the following in the operative report:
  - Extent of initial disease before debulking pelvis, mid-abdomen, or upper abdomen (cutoffs: pelvic brim to lower ribs).
  - Amount of residual disease in the same areas after debulking.
  - Complete or incomplete resection; if incomplete, indicate the size of the major lesion and total number of lesions. Indicate if miliary or small lesions.

[1]Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.

Continued

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PRINCIPLES OF SURGERY[1]

Newly Diagnosed Invasive Epithelial Ovarian Cancer Apparently Confined to an Ovary or to the Pelvis (apparent stage IA-IIA)

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all pelvic disease and to evaluate for occult disease in the upper abdomen or retroperitoneum.

- **On entering the abdomen, aspiration of ascites or peritoneal lavage should be performed for peritoneal cytologic examinations.**
- **All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. In the absence of any suspicious areas, random peritoneal biopsies should be taken from the pelvis, paracolic gutters, and undersurfaces of the diaphragm (diaphragm scraping for Papanicolaou stain is an acceptable alternative).**
- **BSO and hysterectomy should be performed with every effort to keep an encapsulated mass intact during removal.**
- **For selected patients desiring to preserve fertility, USO or BSO with uterine preservation may be considered. Uterine preservation allows for potential future assisted reproductive approaches.**
- **Omentectomy should be performed.**
- **Para-aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels.**
- **The preferred method of dissecting pelvic lymph nodes is bilateral removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve.[2]**

Newly Diagnosed Invasive Epithelial Ovarian Cancer Involving the Pelvis and Upper Abdomen (stage ≥IIB)

In general, every effort should be made during a primary cytoreduction procedure to achieve maximum cytoreduction of all abdominal, pelvic, and retroperitoneal disease. Residual disease <1 cm defines optimal cytoreduction; however, maximal effort should be made to remove all gross disease since this offers superior survival outcomes.[3]

- **Aspiration of ascites (if present) should be performed for peritoneal cytologic examinations. All involved omentum should be removed.**
- **Suspicious and/or enlarged nodes, identified on preoperative imaging or during surgical exploration, should be resected, if possible. Resection of clinically negative nodes is not required.[4]**
- **Procedures that may be considered for optimal surgical cytoreduction (in all stages) include bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.**
- **Select patients with low-volume residual disease after surgical cytoreduction for invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy. In these patients, consideration should be given to placement of IP catheter with initial surgery.**

[1] Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.
[2] Whitney CW, Spirtos N. Gynecologic Oncology Group Surgical Procedures Manual. Philadelphia: Gynecologic Oncology Group; 2010.
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PRINCIPLES OF SURGERY[1]

Interval Debulking Surgery After Neoadjuvant Chemotherapy of Invasive Epithelial Ovarian Cancer

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 hysterectomy and BSO with staging, should be performed after 3–4 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 (HIPEC) 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.**

Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol

- **For information on when RRSO is indicated, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.**
- **Perform minimially invasive laparoscopic surgery.**
- **Survey upper abdomen, bowel surfaces, omentum, appendix (if present), and pelvic organs.**
- **Biopsy any abnormal peritoneal findings.**
- **Obtain pelvic washing for cytology (50 cc normal saline instilled and aspirated immediately).**
- **Perform total BSO, removing 2 cm of proximal ovarian vasculature/IP ligament, all tube up to the cornua, and all peritoneum surrounding the ovaries and tubes, especially peritoneum underlying areas of adhesion between tube and/or ovary and the pelvic sidewall.[4]**
- **Engage in minimal instrument handling of the tubes and ovaries to avoid traumatic exfoliation of cells.[4]**
- **Both ovaries and tubes should be placed in an endobag for retrieval from the pelvis.**
- **Both ovaries and tubes should be processed by sectioning and extensively examining the fimbriated end (SEE-FIM) protocol.[5]**
- **If occult malignancy or serous tubal intraepithelial carcinoma (STIC) is identified, provide referral to gynecologic oncologist.**
- **The prevention benefits of salpingectomy alone are not yet proven. If considered, the fallopian tube from the fimbria to its insertion into the uterus should be removed. In addition, the fallopian tube should be processed and assessed as described above. The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy reduces the risk of developing breast cancer but the magnitude is uncertain. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic.**

[1] Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.
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PRINCIPLES OF SURGERY[1]

Special Circumstances

- **Fertility-sparing surgery:**
  - **Fertility-sparing surgery with USO (preserving the uterus and contralateral ovary) or BSO (preserving the uterus) can be considered for patients with apparent early-stage disease and/or low-risk tumors (early-stage invasive epithelial tumors, LMP lesions, malignant germ cell tumors, mucinous, or malignant sex cord-stromal tumors) who wish to preserve fertility. Refer to reproductive endocrinologist for evaluation and consultation as clinically indicated. Comprehensive surgical staging should still be performed to rule out occult higher stage disease but may be omitted in pediatric, adolescent, and young adult patients with clinically apparent early-stage malignant germ cell tumors based on the pediatric surgical literature.[6]**
- **Mucinous tumors: Primary invasive mucinous tumors of the ovary are uncommon. Thus, the upper and lower GI tract should be carefully evaluated to rule out an occult GI primary with ovarian metastases, and an appendectomy need only be performed in patients with a suspected or confirmed mucinous ovarian neoplasm if it appears to be abnormal. A normal appendix does not require surgical resection in this setting. If mucinous histology is confirmed by intraoperative frozen section analysis and there are no suspicious lymph nodes, consider omitting lymphadenectomy.**
- **Ovarian borderline epithelial (LMP) tumors: Although data show upstaging with lymphadenectomy, other data show that lymphadenectomy does not affect overall survival. However, omentectomy and multiple biopsies of peritoneum (the most common sites of peritoneal implants) may upstage patients in approximately 30% of cases and may affect prognosis.**
- **Secondary cytoreduction: A secondary cytoreduction procedure can be considered in patients with recurrent ovarian cancer who develop a recurrence more than 6 months since completion of initial chemotherapy, have a good performance status, have no ascites, and have an isolated focus or limited foci of disease amenable to complete resection. In addition to preoperative imaging, laparoscopy may be used to determine if complete resection can be achieved. Secondary cytoreduction can be performed with either open or minimally invasive approaches.**

Ancillary Palliative Surgical Procedures[7]

These procedures may be appropriate in select patients:

- **Paracentesis/indwelling peritoneal catheter**
- **Thoracentesis/pleurodesis/video-assisted thoracoscopy/indwelling pleural catheter**
- **Ureteral stents/nephrostomy**
- **Gastrostomy tube/intestinal stents/surgical relief of intestinal obstruction**

[1] Fleming GF, Seidman J, Yemelyanova A, and Lengyl E: Epithelial Ovarian Cancer. In Chi DS, Berchuck A, Dizon D, et al. (eds): Principles and Practice of Gynecologic Oncology, 7th ed, Philadelphia, Lippincott Williams & Wilkins, 2017:611-705.

[6] Billmire D, Vinocur C, Rescorla F, et al. Outcome and staging evaluation in malignant germ cell tumors of the ovary in children and adolescents: an intergroup study. J Pediatr Surg 2004;39:424-429.

[7] Decisions on the use of ancillary procedures should be made in conjunction with a gynecologic oncology surgeon or a practitioner familiar with ovarian cancer patterns of recurrence.

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PRINCIPLES OF PATHOLOGY

General

- The complete histologic classification from the WHO is included in the NCCN Guidelines (see WHO Histologic Classification on OV-E).[1] The WHO pathology manual is also a useful resource.[1,2]
- Most ovarian cancers, including the LCOC, are diagnosed after pathologic analysis of a biopsy or surgical specimen. Fine-needle aspiration (FNA) should be avoided for diagnosis of ovarian cancer in patients with presumed early-stage disease to prevent rupturing the cyst and spilling malignant cells into the peritoneal cavity. However, FNA may be necessary in patients with bulky disease who are not candidates for primary debulking.[3,4]
- Both primary peritoneal and fallopian tube cancers are usually diagnosed postoperatively (if there is no major involvement of the ovary) or preoperatively (if there is a biopsy and the patient has already had a bilateral oophorectomy). Primary peritoneal and fallopian tube cancers are treated in the same manner as epithelial ovarian cancer.
- The CAP protocol is a useful tool for pathology reports.[5,6,7] Pathologic assessment should include:
  - Elements from CAP protocol:[5,6,7]
    - ◊ Tumor site(s) (eg, ovary, fallopian tube, or primary peritoneum)
    - ◊ Tumor size(s)
    - ◊ Other tissue/organ involvement
    - ◊ Ovarian/fallopian tumors: surface involvement (present/absent/cannot determine), specimen integrity (capsule/serosa intact/fractured/ fragmented)
    - ◊ Histologic type and grade
    - ◊ Extension and/or implants (if sampled/identified)
    - ◊ Cytology: peritoneal or ascitic fluid or washings/pleural fluid
    - ◊ Lymph nodes: number and location of nodes examined, size of largest metastatic deposits
    - ◊ STIC, endometriosis (particularly if in continuity with endometrioid or clear cell carcinoma), and/or endosalpingiosis
  - Tumor molecular analyses as clinically indicated:
    - ◊ Next-generation sequencing (NGS) for *BRCA1/2* mutations, other somatic mutations (eg, *NTRK* gene fusions), and tumor mutational burden [TMB]
    - ◊ Additional testing (particularly for endometrioid carcinomas)
      - – Immunohistochemistry (IHC) for DNA mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2)
      - – Microsatellite instability (MSI) testing
    - ◊ In addition to *BRCA1/2* testing, other methods for evaluating HR deficiency status (ie, genomic instability, loss of heterozygosity) can be considered.
    - ◊ Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

References

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PRINCIPLES OF PATHOLOGY

Less Common Ovarian Cancers (LCOC)

- A borderline tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion. The terms for borderline epithelial tumors (also known as LMP tumors or atypical proliferative tumors) have changed over the years.[8] The 2016 and 2017 CAP cancer protocols for ovarian cancer use borderline and do not use LMP.[5,6] Borderline epithelial tumors are typically serous or mucinous; other histologic subtypes can also occur (see WHO Histologic Classification on OV-E).[1,9] The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist.
- Clear cell carcinomas are high-grade tumors that may arise in endometriosis. Most clear cell carcinomas express Napsin A and are negative for WT1 and estrogen receptors.[8]
- It is difficult to distinguish based on histology between primary mucinous ovarian carcinomas and gastrointestinal (GI) metastases.[10,11,12] PAX8 immunostaining is typical of primary ovarian tumors, although the absence of PAX8 does not rule out ovary as the primary site,[13] while SATB2 is consistent with colonic origin.[14] Metastatic colorectal adenocarcinomas also usually are positive for CK20 and CEA.
- Endometrioid carcinomas may be associated with endometriosis.[13,15] Endometrioid adenocarcinomas are usually positive for cytokeratin 7 (CK7), PAX8, CA-125, and estrogen receptors. Endometrioid tumors are also very similar in appearance to sex cord-stromal tumors.[8]
- Most pathologists now consider MMMTs to be a variant of poorly differentiated epithelial ovarian cancer (metaplastic carcinoma).[16]

Special Circumstances

- Other cancers[17,18] that can commonly involve the adnexa include:
  - Uterine
  - Cervical
  - GI (small and large bowel, pancreatic)
  - Lymphoma
- For risk-reducing surgery, pathologic assessment should include:
  - Fallopian tubes should be processed by SEE-FIM of the tubes and then assessed to determine whether any evidence of cancer is present.[19,20]
  - The ovaries should also be carefully sectioned, processed, and assessed.[20] The 2016 and 2017 CAP protocols describe the process for sectioning the fallopian tubes and ovaries.[5,6,21]
- Patients who have equivocal pathologic findings or who are referred to NCCN Member Institutions after having a previous diagnosis of ovarian cancer should have their pathology reviewed by pathologists at NCCN Member Institutions.

References

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PRINCIPLES OF PATHOLOGY
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PRINCIPLES OF SYSTEMIC THERAPY

General Principles

Primary Systemic Therapy Regimens - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

Acceptable Recurrence Therapies- Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

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PRINCIPLES OF SYSTEMIC THERAPY

General

- Patients with ovarian, fallopian tube, or peritoneal cancer should be encouraged to participate in clinical trials during all aspects of their diagnosis and treatment.
- Prior to recommending chemotherapy, requirements for adequate organ function and performance status should be met.
- Prior to the initiation of any therapy:
  - All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy to determine whether they are candidates for primary cytoreductive surgery (PCS).
  - Patients of childbearing potential who desire fertility-sparing procedures should be referred to an appropriate fertility specialist. (See NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology)
  - Goals of systemic therapy should be discussed.
- Consider scalp cooling to reduce incidence of alopecia for patients receiving chemotherapy with high rates of alopecia.
- Patients should be observed closely and treated for any complications during chemotherapy. Appropriate blood chemistry tests should be monitored. Appropriate dose reductions and modifications of chemotherapy should be performed depending on toxicities experienced and goals of therapy.
- After completion of chemotherapy, patients should be assessed for response during and following treatment and monitored for any long-term complications.
- Chemosensitivity/resistance and/or other biomarker assays are being used at some NCCN Member Institutions for decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available. The current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3).

Definitions Used in the NCCN Guidelines for Ovarian Cancer

- Adjuvant therapy: Drugs, radiation, or other forms of supplemental treatment following cancer surgery intended to decrease the risk of disease recurrence or to primarily treat residual disease, whether gross or microscopic, following surgical cytoreduction.
- Neoadjuvant therapy: Drugs, radiation, or other forms of treatment given prior to cancer surgery intended to reduce tumor burden in preparation for surgery.
- Recurrence therapy: Drugs, radiation, or other forms of treatment used to treat recurrent cancer, control symptoms, or increase length and/or quality of life at the time of clinical, biochemical, or radiographic evidence of recurrent cancer following the initial treatment.

For Patients with Newly Diagnosed Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:

- If they are eligible for chemotherapy, patients should be informed about the different primary therapy options that are available—such as IV chemotherapy, a combination of IP and IV chemotherapy, or a clinical trial—so they can decide which is the most appropriate option.
- Prior to the administration of the combined IP and IV regimen, patients must be apprised of the increased toxicities with the combined regimen when compared to using IV chemotherapy alone (increased myelosuppression, renal toxicities, abdominal pain, neuropathy, GI toxicities, metabolic toxicities, and hepatic toxicities).
- Patients considered for the IP cisplatin and IP/IV paclitaxel regimen should have normal renal function prior to starting, a medically appropriate performance status based on the future toxicities of the IP/IV regimen, and no prior evidence of medical problems that could significantly worsen during chemotherapy (eg, pre-existing neuropathy).
- Prior to receiving and after receiving each cycle of IP cisplatin, adequate amounts of IV fluids need to be administered in order to prevent renal toxicity. After each cycle has been completed, patients need to be monitored carefully for myelosuppression, dehydration, electrolyte loss, end-organ toxicities (such as renal and hepatic damage), and all other toxicities. Patients often require IV fluids postchemotherapy in the outpatient setting to prevent or help treat dehydration.
- Refer to the original references (See Discussion) for full toxicity data, doses, schedule, and dose modifications.

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PRINCIPLES OF SYSTEMIC THERAPY

Principles of Neoadjuvant Therapy

- **Consider the histology of the primary tumor and the potential response to primary chemotherapy when evaluating for neoadjuvant chemotherapy.**
- **Any of the primary IV regimens for stage II–IV high-grade serous carcinoma can be used as neoadjuvant therapy before IDS. See OV-C (6 of 11).**
- **Bevacizumab-containing regimens should be used with caution before IDS due to potential interference with postoperative healing. If bevacizumab is being used as part of a neoadjuvant regimen, bevacizumab should be withheld from therapy for at least 6 weeks prior to IDS.**
- **After neoadjuvant therapy and IDS any of the adjuvant therapy options for high-grade serous carcinoma (IV or IP/IV) can be considered. See OV-C (6 of 11).**
- **There are limited data for the use of IP chemotherapy regimens after neoadjuvant therapy and IDS. The following is an additional IP option after IDS: Paclitaxel 135 mg/m^2 IV on Day 1, carboplatin AUC 6 IP Day 1, paclitaxel 60 mg/m^2 IP Day 8.[a]**
- **A minimum of 6 cycles of treatment is recommended, including at least 3 cycles of adjuvant therapy after IDS. Patients with stable disease who are tolerating therapy may continue past 6 cycles.**

[a]Provencher DM, Gallagher CJ, Parulekar WR, et al. OV21/PETROC: A randomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer. Ann Oncol 2018;29:431-438.

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PRINCIPLES OF SYSTEMIC THERAPY

Principles of Maintenance PARP Inhibitor (PARPi) Therapy

- **Post Primary Treatment**
  - **Certain patients with newly diagnosed stage II–IV disease (high-grade serous, grade 2/3 endometrioid, or *BRCA1/2*-mutated clear cell carcinoma or carcinosarcoma) may benefit from maintenance therapy with PARPi if CR or PR is achieved after primary treatment with surgery and platinum-based first-line therapy. See OV-5 for PARPi options and patient selection criteria.**
  - **Data are limited for use of maintenance PARPi post primary treatment in patients with stage II disease and for those with LCOCs.**
- **Post Recurrence Treatment**
  - **Certain patients with recurrent disease may benefit from maintenance therapy with PARPi after recurrence therapy, if in CR or PR after platinum-based recurrence therapy, and if no prior progression on a PARPi. See OV-8 for PARPi options and patient selection criteria.**
- **General Information on PARPi**
  - **For patients receiving PARPi, careful monitoring of blood counts is required.**
  - **Monitoring of renal and hepatic function is recommended**
  - **Monitoring of blood pressure is required for niraparib, and recommended for all other PARPi.**
  - **Appropriate dose holds and modifications should be made depending on the toxicity noted.**
  - **Data are limited on the use of maintenance PARPi in LCOCs.**
  - **Refer to the package insert for more detailed information.**

Regimen	Setting	Dose/Administration	Duration
Olaparib + bevacizumab[1]	Maintenance post primary chemotherapy + bevacizumab	• Olaparib 300 mg PO twice daily • Bevacizumab 15 mg/kg IV every 21 days	• Olaparib: Until disease progression or unacceptable toxicity or up to 24 months • Bevacizumab: Until disease progression or unacceptable toxicity or up to 15 months
Niraparib monotherapy[2,3]	Maintenance post primary chemotherapy	300 mg PO once daily (or 200 mg once daily for patients with a baseline body weight of <77 kg, and/or a platelet count of <150,000/mm^3)	Until disease progression or unacceptable toxicity or up to 36 months
	Maintenance post recurrence chemotherapy	300 mg PO once daily	Until disease progression or unacceptable toxicity
Olaparib monotherapy[4-6]	Maintenance post primary chemotherapy	300 mg PO twice daily[b]	Until disease progression or CR (NED) at 2 yearsb or unacceptable toxicity
	Maintenance post recurrence chemotherapy	300 mg PO twice daily[b]	Until disease progression or unacceptable toxicity
Rucaparib monotherapy[7,8]	Maintenance post recurrence chemotherapy	600 mg PO twice daily	Until disease progression or unacceptable toxicity

[b] In studies, treatment was continued for those with PR at 2 years.

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PRINCIPLES OF SYSTEMIC THERAPY

Recurrent Ovarian, Fallopian Tube, or Primary Peritoneal Cancer:

- Refer to the original references (See Discussion) for full toxicity data, doses, schedule, and dose modifications.
- Patients should be informed about the following:
  1) Availability of clinical trials, including the risks and benefits of various treatments, which will depend on the number of prior lines of chemotherapy the patient has received, and
  2) Performance status, end-organ status, and pre-existing toxicities from prior regimens. If appropriate, palliative care should also be discussed as a possible treatment choice. See NCCN Guidelines for Palliative Care.
- Tumor molecular testing is recommended prior to initiation of therapy for persistent/recurrent disease. See Principles of Pathology (OV-B).
- Because of prior platinum exposure, myelosuppression occurs more frequently with any myelotoxic agent given in the recurrent setting.
- With repeat use of either carboplatin and/or cisplatin, patients are at an increased risk of developing a hypersensitivity reaction (also called an allergic reaction) that could be life-threatening. Thus, patients should be counseled about the risk that a hypersensitivity reaction may occur, educated about the signs and symptoms of hypersensitivity reactions, treated by medical staff who know how to manage hypersensitivity reactions, and treated in a medical setting where appropriate medical equipment is available in case of an allergic reaction. See Management of Drug Reactions (OV-D).
- Before any chemotherapy drug is given in the recurrent setting, the clinician should be familiar with the drug's metabolism (ie, renal, hepatic) and should make certain that the patient is an appropriate candidate for the drug (eg, that the patient has adequate renal or hepatic function).
- Clinicians should be familiar with toxicity management and appropriate dose reduction.
- The schedule, toxicity, and potential benefits of any treatment should be thoroughly discussed with the patient and caregivers. Patient education should also include a discussion of precautions and measures to reduce the severity and duration of complications.

See Acceptable Recurrence Therapies for Platinum-Sensitive Disease (OV-C, 8 of 11)

See Acceptable Recurrence Therapies for Platinum-Resistant Disease (OV-C, 9 of 11)

Continued

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PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[c] - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

Stage I Disease			
• High-grade serous • Endometrioid (grade 2/3) • Clear cell carcinoma[d] • Carcinosarcoma[d]	**Preferred Regimens** • Paclitaxel/carboplatin q3weeks[f]	**Other Recommended Regimens** • Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities) For carcinosarcoma: • Carboplatin/ifosfamide • Cisplatin/ifosfamide • Paclitaxel/ifosfamide (category 2B)
Mucinous carcinoma (stage IC)[d]	**Preferred Regimens** • 5-FU/leucovorin/oxaliplatin • Capecitabine/oxaliplatin • Paclitaxel/carboplatin q3weeks[f]	**Other Recommended Regimens** • Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)
Low-grade serous (stage IC)/Grade I endometrioid (stage IC)[d,e]	**Preferred Regimens** • Paclitaxel/carboplatin q3weeks[f] • Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (category 2B)	**Other Recommended Regimens** • Carboplatin/liposomal doxorubicin • Docetaxel/carboplatin • Hormone therapy (leuprolide acetate, tamoxifen) (category 2B)	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)

Stage II–IV (See OV-C, 6 of 11)

Primary Systemic Therapy Dosing (See OV-C, 7 of 11)

[c] See Discussion for references.
[d] There are limited data on the primary systemic therapy regimens for these LCOC.
[e] Borderline disease with invasive implants may be treated as low-grade serous disease. See LCOC-6 and LCOC-7.
[f] Elderly patients and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing (see OV-C, 7 of 11) may be appropriate for elderly patients with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity. See the NCCN Guidelines for Older Adult Oncology.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[c] - Epithelial Ovarian/Fallopian Tube/Primary Peritoneal

Stage II–IV Disease

• **High-grade serous** • **Endometrioid (grade 2/3)** • **Clear cell carcinoma[d]** • **Carcinosarcoma[d]**	**Preferred Regimens** • Paclitaxel/carboplatin q3weeks[f] • Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[g] (ICON-7 & GOG-218)	**Other Recommended Regimens** • Paclitaxel weekly/carboplatin weekly[f,h] • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks	**Useful in Certain Circumstances** • IP/IV paclitaxel/cisplatin (for optimally debulked stage II–III disease) • For carcinosarcoma: ▸ Carboplatin/ifosfamide ▸ Cisplatin/ifosfamide ▸ Paclitaxel/ifosfamide (category 2B) • Carboplatin (if elderly [age >70] and/or for those with comorbidities)
Mucinous carcinoma[d]	**Preferred Regimens** • 5-FU/leucovorin/oxaliplatin ± bevacizumab[g] (category 2B for bevacizumab) • Capecitabine/oxaliplatin ± bevacizumab[g] (category 2B for bevacizumab) • Paclitaxel/carboplatin q3weeks[f] • Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[g] (ICON-7 & GOG-218)	**Other Recommended Regimens** • Paclitaxel weekly/carboplatin weekly[f,h] • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)
Low-grade serous/Grade I endometrioid[d,e]	**Preferred Regimens** • Paclitaxel/carboplatin q3weeks[f] • Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[g] (ICON-7 & GOG-218) • Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (category 2B)	**Other Recommended Regimens** • Paclitaxel weekly/carboplatin weekly[f,h] • Docetaxel/carboplatin • Carboplatin/liposomal doxorubicin • Paclitaxel weekly/carboplatin q3weeks • Hormone therapy (leuprolide acetate, tamoxifen) (category 2B)	**Useful in Certain Circumstances** • Carboplatin (if elderly [age >70] and/or for those with comorbidities)

Primary Systemic Therapy Dosing (See OV-C, 7 of 11)

[c] See Discussion for references.
[d] There are limited data on the primary systemic therapy regimens for these LCOC.
[e] Borderline disease with invasive implants may be treated as low-grade serous disease. See LCOC-6 and LCOC-7.
[f] Elderly patients and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines. Based on clinical judgment and expected tolerance to therapies, alternate dosing (see OV-C, 7 of 11) may be appropriate for elderly patients with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity. See the NCCN Guidelines for Older Adult Oncology.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[h] Regimen may be considered for those with poor performance status.

Continued

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PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[c] - Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal

Primary Systemic Therapy Recommended Dosing

IV/IP Paclitaxel/cisplatin
- Paclitaxel 135 mg/m^2 IV continuous infusion[i] Day 1; Cisplatin 75–100 mg/m^2 IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m^2 IP Day 8
- Repeat every 21 days x 6 cycles

Paclitaxel/carboplatin q3weeks[j]
- Paclitaxel 175 mg/m^2 IV followed by carboplatin[k] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[j]

Paclitaxel weekly/carboplatin q3weeks
- Dose-dense paclitaxel 80 mg/m^2 IV Days 1, 8, and 15 followed by carboplatin[i] AUC 5–6 IV Day 1
- Repeat every 21 days x 6 cycles

Paclitaxel weekly/carboplatin weekly
- Paclitaxel 60 mg/m^2 IV followed by carboplatin AUC 2 IV
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)[h]

Docetaxel/carboplatin[j]
- Docetaxel 60–75 mg/m^2 IV followed by carboplatin[k] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[j]

Carboplatin/liposomal doxorubicin[j]
- Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m^2 IV
- Repeat every 28 days for 3–6 cycles[j]

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[g] (ICON-7)
- Paclitaxel 175 mg/m^2 IV followed by carboplatin[k] AUC 5–6 IV, and bevacizumab 7.5 mg/kg IV Day 1
- Repeat every 21 days x 5–6 cycles
- Continue bevacizumab for up to 12 additional cycles

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[g] (GOG-218)
- Paclitaxel 175 mg/m^2 IV followed by carboplatin[k] AUC 6 IV Day 1. Repeat every 21 days x 6 cycles
- Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 21 days for up to 22 cycles

Elderly Patients (age >70 years) and/or Those with Comorbidities

Paclitaxel 135/carboplatin[9]
- Paclitaxel 135 mg/m^2 IV + carboplatin AUC 5 IV given every 21 days x 3–6 cycles[j]

Paclitaxel weekly/carboplatin weekly
- Paclitaxel 60 mg/m^2 IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)

Carboplatin[9]
- Carboplatin AUC 5 IV given every 21 days

[c] See Discussion for references.
[g] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[h] Regimen may be considered for those with poor performance status.
[i] The published randomized trial regimen used IV continuous infusion paclitaxel over 24 hours.
[j] For stage I disease: 6 cycles is recommended for high-grade serous; 3–6 cycles for all other ovarian cancer types. For stage II–IV disease: 6 cycles is recommended.
[k] Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. For carboplatin dosing guidelines, see https://www.mskcc.org/clinical-updates/new-guidelines-carboplatin-dosing.

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Continued

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[l]/Fallopian Tube/Primary Peritoneal Cancer[m]

Recurrence Therapy for Platinum-Sensitive Disease[n] (alphabetical order)

Preferred Regimens	Other Recommended Regimens[t]	Useful in Certain Circumstances
Carboplatin/gemcitabine[10] ± bevacizumab[g,o,p,11] Carboplatin/liposomal doxorubicin[12] ± bevacizumab[g,13] Carboplatin/paclitaxel[14] ± bevacizumab[g,o,p,15] Cisplatin/gemcitabine[16] <u>Targeted Therapy (single agents)</u> Bevacizumab[g,o,17,18] Niraparib[q,19] Olaparib[r,20] Rucaparib[s,21]	Carboplatin/docetaxel[22,23] Carboplatin/ paclitaxel (weekly)[24] Capecitabine Carboplatin[u,10] Cisplatin[14] Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Vinorelbine <u>Targeted Therapy</u> Niraparib/bevacizumab[g,25] Pazopanib (category 2B)[26] <u>Hormone Therapy</u> Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	For mucinous carcinoma: • 5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[g,o] • Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)[g,o] Carboplatin/paclitaxel, albumin bound (for confimed taxane hypersensitivity) Carboplatin/paclitaxel[u] (for age >70) Irinotecan/cisplatin (for clear cell carcinoma)[27] <u>Targeted Therapy (single agents)</u> Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[v] Trametinib (for low-grade serous carcinoma)[28] <u>Hormone Therapy</u> Fulvestrant (for low-grade serous carcinoma) <u>Immunotherapy</u> Pembrolizumab (for microsatellite instability-high [MSI-H] or mismatch repair-deficient [dMMR] solid tumors, or patients with tumor mutational burden-high [TMB-H] tumors ≥10 mutations/megabase and no satisfactory alternative treatment options)[v,29]

[g]An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[l]Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[m]Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy (Griffiths RW, et al. Int J Gyn Ca 2011;21:58-65). Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.
[n]In general, the panel would recommend combination, platinum-based regimens for platinum-sensitive recurrent disease based on randomized trial data, especially in first relapses.
[o]Contraindicated for patients at increased risk of GI perforation.
[p]If response after chemotherapy, bevacizumab can be continued as maintenance therapy until disease progression or unacceptable toxicity. Discontinue bevacizumab before initiating maintenance therapy with a PARPi.
[q]For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.
[r]For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[s]For patients with deleterious germline and/or somatic *BRCA* mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[t]Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.
[u]For recommended dosing for elderly patients, see OV-C, 7 of 11.
[v]Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination status can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

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Continued

PRINCIPLES OF SYSTEMIC THERAPY
Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[l]/Fallopian Tube/Primary Peritoneal Cancer[m]

Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy	Cytotoxic Therapy[t]	Immunotherapy
Cyclophosphamide (oral)/bevacizumab[g,30]	Capecitabine	Oxaliplatin	Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/megabase and no satisfactory alternative treatment options)[v,29]
Docetaxel[31]	Cyclophosphamide	Paclitaxel	
Etoposide, oral[32]	Doxorubicin	Paclitaxel, albumin bound	Hormone Therapy
Gemcitabine[33,34]	Ifosfamide	Pemetrexed	Fulvestrant (for low-grade serous carcinoma)
Liposomal doxorubicin[33,34]	Irinotecan	Sorafenib/topotecan[39]	
Liposomal doxorubicin/bevacizumab[g,o,35]	Melphalan	Vinorelbine	Targeted Therapy (single agents)
Paclitaxel (weekly)[36]			Entrectinib or larotrectinib (for *NTRK* gene fusion-positive tumors)[v]
Paclitaxel (weekly)/bevacizumab[g,o,35]			Trametinib (for low-grade serous carcinoma)[28]
Topotecan[37,38]			
Topotecan/bevacizumab[g,o,35]			
Targeted Therapy (single agents)	Targeted Therapy (single agents)	
Bevacizumab[g,o,17,18]	Pazopanib (category 2B)[26]	
Niraparib[q,19]		
Olaparib[r,20]	Hormone Therapy	
Rucaparib[s,21]	Aromatase inhibitors (anastrozole, exemestane, letrozole)	
	Leuprolide acetate	
	Megestrol acetate	
	Tamoxifen	

[g]An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[l]Chemotherapy has not been shown to be beneficial in ovarian borderline epithelial tumors (LMP).
[m]Patients who progress on two consecutive regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy (Griffiths RW, et al. Int J Gyn Ca 2011;21:58-65). Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.
[o]Contraindicated for patients at increased risk of GI perforation.
[q]For patients treated with three or more prior chemotherapy regimens and whose cancer is associated with HRD defined by either: 1) a deleterious or suspected deleterious *BRCA* mutation; or 2) genomic instability and progression >6 months after response to the last platinum-based chemotherapy.
[r]For patients with deleterious germline *BRCA*-mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[s]For patients with deleterious germline and/or somatic *BRCA* mutated (as detected by an FDA-approved test or other validated test performed in a CLIA-approved facility) advanced ovarian cancer who have been treated with two or more lines of chemotherapy.
[t]Many of these single-agent cytotoxic therapy options have not been tested in patients who have been treated with modern chemotherapy regimens.
[v]Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing recommended to include at least: *BRCA1/2*, and microsatellite instability or DNA mismatch repair if not previously done. Evaluation of homologous recombination status can be considered. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist.

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PRINCIPLES OF SYSTEMIC THERAPY
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MANAGEMENT OF DRUG REACTIONS

Overview

- Virtually all drugs used in oncology have the potential to cause adverse drug reactions while being infused, which can be classified as either infusion or allergic reactions.[1]
  - Infusion reactions are often characterized by milder symptoms (eg, hot flushing, rash).
  - Hypersensitivity (allergic) reactions are often characterized by more severe symptoms (eg, shortness of breath, generalized hives/itching, changes in blood pressure).
- Most adverse drug reactions that occur are mild reactions, but more severe reactions can occur.[2,3]
  - Anaphylaxis is a rare type of very severe allergic reaction that can occur with the platinum and taxane agents (and others less commonly), can cause cardiovascular collapse, and can be life-threatening.[4-6]
  - Drug reactions can occur either during the infusion or following completion of the infusion (and can even occur days later).
- In gynecologic oncology treatment, drugs that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel.[1]
  - Adverse reactions associated with taxane drugs (ie, docetaxel, paclitaxel) and biotherapeutic agents tend to be infusion-related often attributed to cremophor in paclitaxel and tend to occur during the first few cycles of treatment (although they can be seen during any infusion regardless of how many previous cycles were administered).
  - Adverse reactions associated with platinum drugs (ie, carboplatin, cisplatin), a true allergy, tend to occur following re-exposure to the inciting drug or less commonly at the completion of initial chemotherapy (ie, cycle 6 of a planned 6 treatments).[3]
- Preparation for a possible drug reaction
  - Patients and their families should be counseled about the possibility of a drug reaction and the signs and symptoms of one. Patients should be told to report any signs and symptoms of a drug reaction, especially after they have left the clinic (ie, delayed rash).
  - Clinicians and nursing staff should be prepared for the possibility of a drug reaction every time a patient is infused with a drug. Standing orders should be written for immediate intervention in case a severe drug reaction occurs and the treatment area should have appropriate medical equipment in case of a life-threatening reaction.[5]
  - Epinephrine (intramuscular 0.3 mL of 1 mg/mL solution/Epipen) should be used for any patient experiencing hypotension (systolic BP of <90 mm Hg) with or without other symptoms of an allergic/hypersensitivity reaction during or shortly after any chemotherapy drug treatment. In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
- Desensitization refers to a process of rendering the patient less likely to react in response to an allergen and can be considered an option for patients who have had drug reactions.[1,7-9]
- If a patient has previously had a very severe life-threatening reaction, the implicated drug should not be used again unless under guidance of an allergist or specialist with desensitization experience.

Continued on OV-D, 2 of 7

References on OV-D, 3 of 7

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MANAGEMENT OF DRUG REACTIONS

Infusion Reactions

- Symptoms include: hot flushing, rash, fever, chest tightness, mild blood pressure changes, back pain, and chills.
- Symptoms usually can be treated by decreasing the infusion rate and resolve quickly after stopping the infusion. However, patients who have had mild reactions to carboplatin, cisplatin, or oxaliplatin may develop more serious reactions even when the platinum drug is slowly infused; therefore, consider consultation with an allergist.[10]
- Infusion reactions are more common with paclitaxel (27% of patients); however, mild reactions can occur with liposomal doxorubicin.[10]
- If an infusion reaction has previously occurred in response to a taxane:
  - For mild infusion reactions (eg, flushing, rash, chills), patients may be rechallenged with the taxane if:
    1) the patient, physician, and nursing staff are all comfortable with this plan;
    2) the patient has been counseled appropriately; and
    3) emergency equipment is available in the clinic area.
  - Typically the taxane infusion can be restarted at a much slower rate, and the rate can be slowly increased as tolerated as per the treating clinician's judgment.[7,11] Note that this slow infusion is different from desensitization.
  - Many institutions have nursing policies that stipulate how to reinfuse the drug if the patient has had a prior infusion reaction.

Allergic Reactions (ie, True Drug Allergies)

- Symptoms include: rash, edema, shortness of breath (bronchospasm), syncope or pre-syncope, chest pain, tachycardia, hives/itching, changes in blood pressure, nausea, vomiting, chills, changes in bowel function, and occasionally feeling of impending doom.
- Symptoms may continue to persist after stopping infusion and/or after treatment interventions.
- Allergic reactions are more common with platinum drugs such as carboplatin (16% of patients), cisplatin, and oxaliplatin.[11] Mild reactions can occur with platinum agents.[11]
- Patients who are at higher risk of developing a hypersensitivity (allergic) reaction include those in the following settings:
  - Re-introduction of the drug after a period of no exposure and following multiple cycles of the drug during the first and subsequent exposures
  - IV administration of the drug rather than oral or IP administration
  - With allergies to other drugs
  - Those who have previously had a reaction
- If an allergic reaction has previously occurred:
  - Consider consultation with an allergist (or qualified medical or gynecologic oncologist) and skin testing for patients who have experienced a platinum reaction (eg, carboplatin-hypersensitivity reaction).[11-13]
  - Patients who have had mild reactions may develop more serious reactions even when the platinum drug is slowly infused.[11]
  - For more severe or life-threatening reactions—such as those involving blood pressure changes, dyspnea, tachycardia, widespread urticaria, anaphylaxis, or hypoxia—the implicated drug should not be used again unless under guidance of a specialist with desensitization experience.
  - If it is appropriate to give the drug again, patients should be desensitized prior to resuming chemotherapy even if the symptoms have resolved. Patients must be desensitized with each infusion if they previously had a drug reaction.[7-9]

References on OV-D, 3 of 7

Note: All recommendations are category 2A unless otherwise indicated.
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.

MANAGEMENT OF DRUG REACTIONS
REFERENCES

[1]Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.
[2]Dizon DS, Sabbatini PJ, Aghajanian C, et al. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. Gynecol Oncol 2002;84:378-382.
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[8]Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: A 6-hour 12 step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. Gynecol Oncol 2004;95:370-376.
[9]Markman M, Hsieh F, Zanotti K, et al. Initial experience with a novel desensitization strategy for carboplatin-associated hypersensitivity reactions. J Cancer Research Clin Oncol 2004;130:25-28.
[10]Gabizon AA. Pegylated liposomal doxorubicin: metamorphosis of an old drug into a new form of chemotherapy. Cancer Invest 2001;19:424-436.
[11]Lenz HJ. Management and preparedness for infusion and hypersensitivity reactions. Oncologist 2007;12:601-609.
[12]Markman M, Zanotti K, Peterson G, et al. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. J Clin Oncol 2003;21:4611-4614.
[13]Zanotti KM, Rybicki LA, Kennedy AW, et al. Carboplatin skin testing: A skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. J Clin Oncol 2001;19:3126-3129.

See Drug Reaction to Platinum Agents on OV-D, 4 of 7

See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-D, 6 of 7

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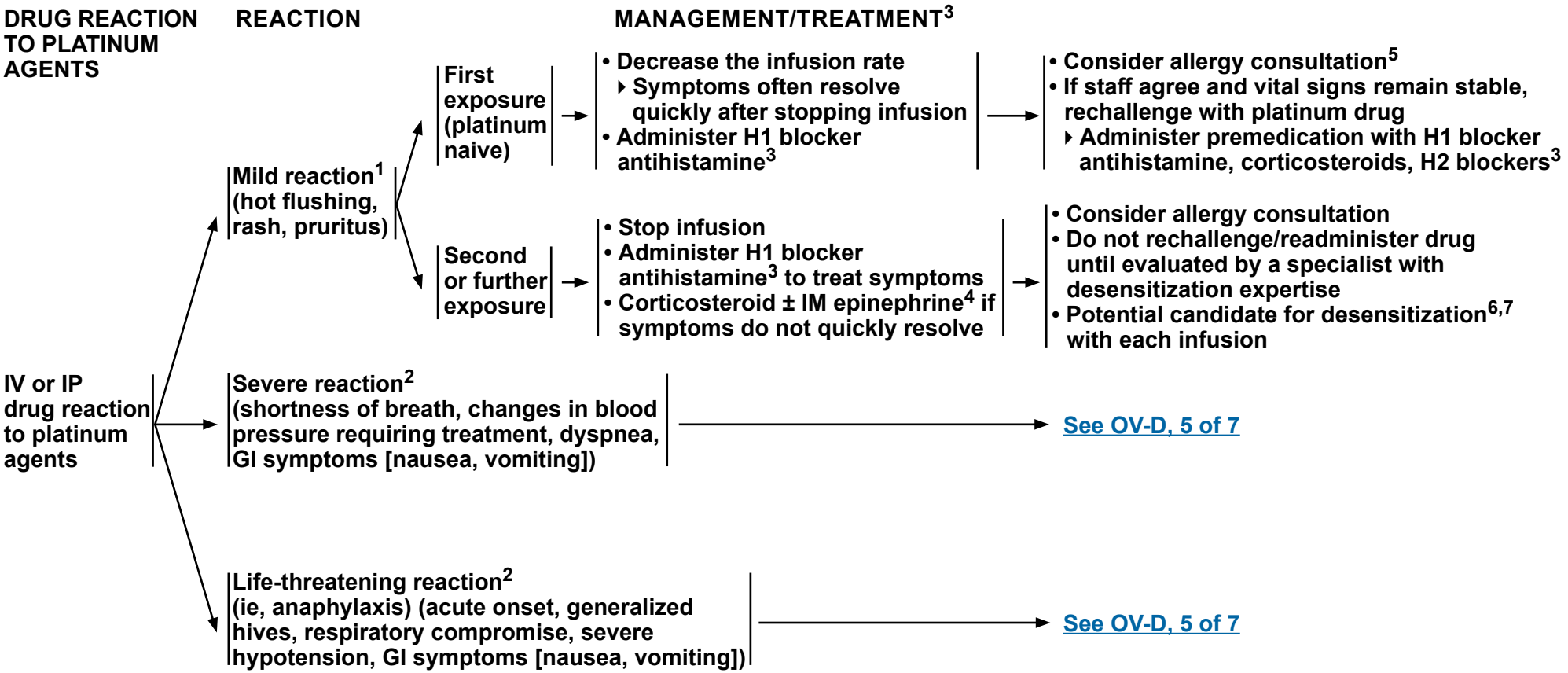
MANAGEMENT OF DRUG REACTIONS



See Drug Reaction to Taxane, Liposomal Doxorubicin, or Biotherapeutic Agents on OV-D, 6 of 7

[1]Most mild reactions are infusion reactions and more commonly are caused by taxanes (ie, docetaxel, paclitaxel), but can also occur with platinum agents (ie, carboplatin, cisplatin).
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[3]H1 blocker antihistamine (eg, diphenhydramine or hydroxyzine); H2 blockers (eg, cimetidine, famotidine); corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone).
[4]In the setting of acute cardiopulmonary arrest, standard resuscitation (ACLS) procedures should be followed.
[5]Mild reactions can progress to severe reactions by re-exposure. An allergy consultation may provide skin testing and evaluate sensitization and the risk for further, more severe reactions.
[6]Referral to academic center with expertise in desensitization is preferred.
[7]Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

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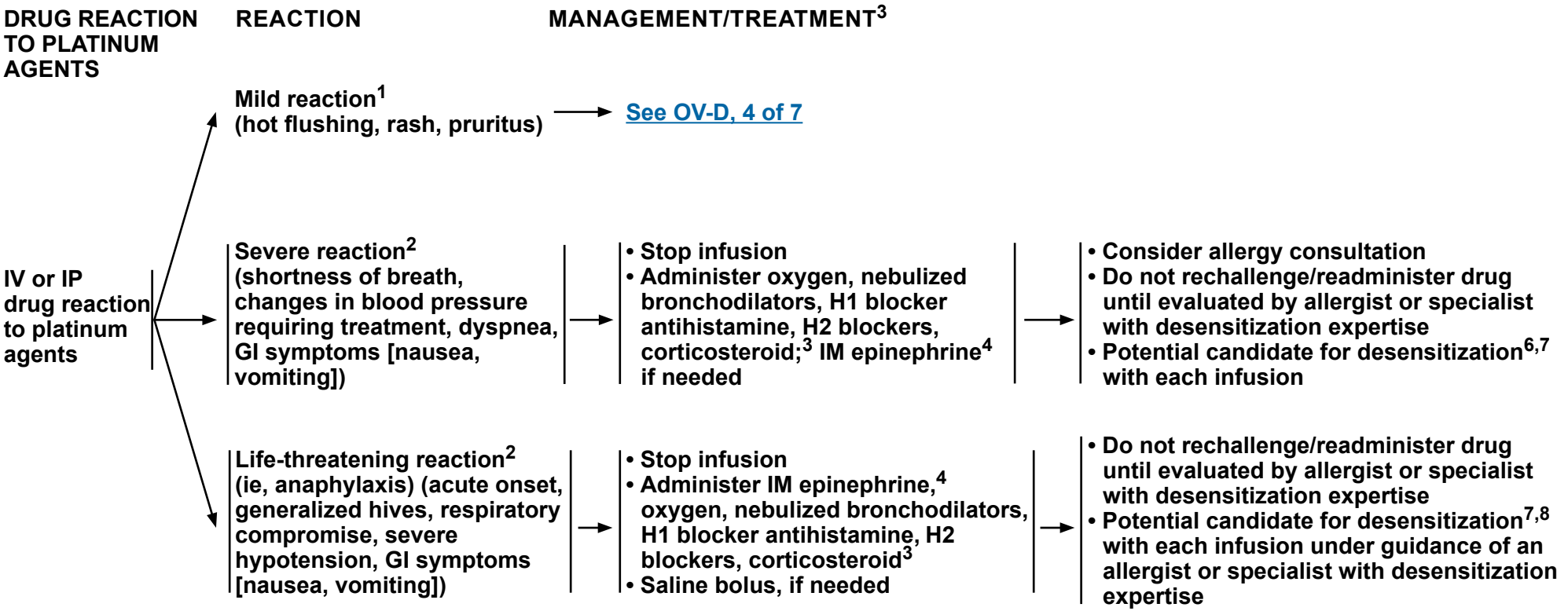
MANAGEMENT OF DRUG REACTIONS



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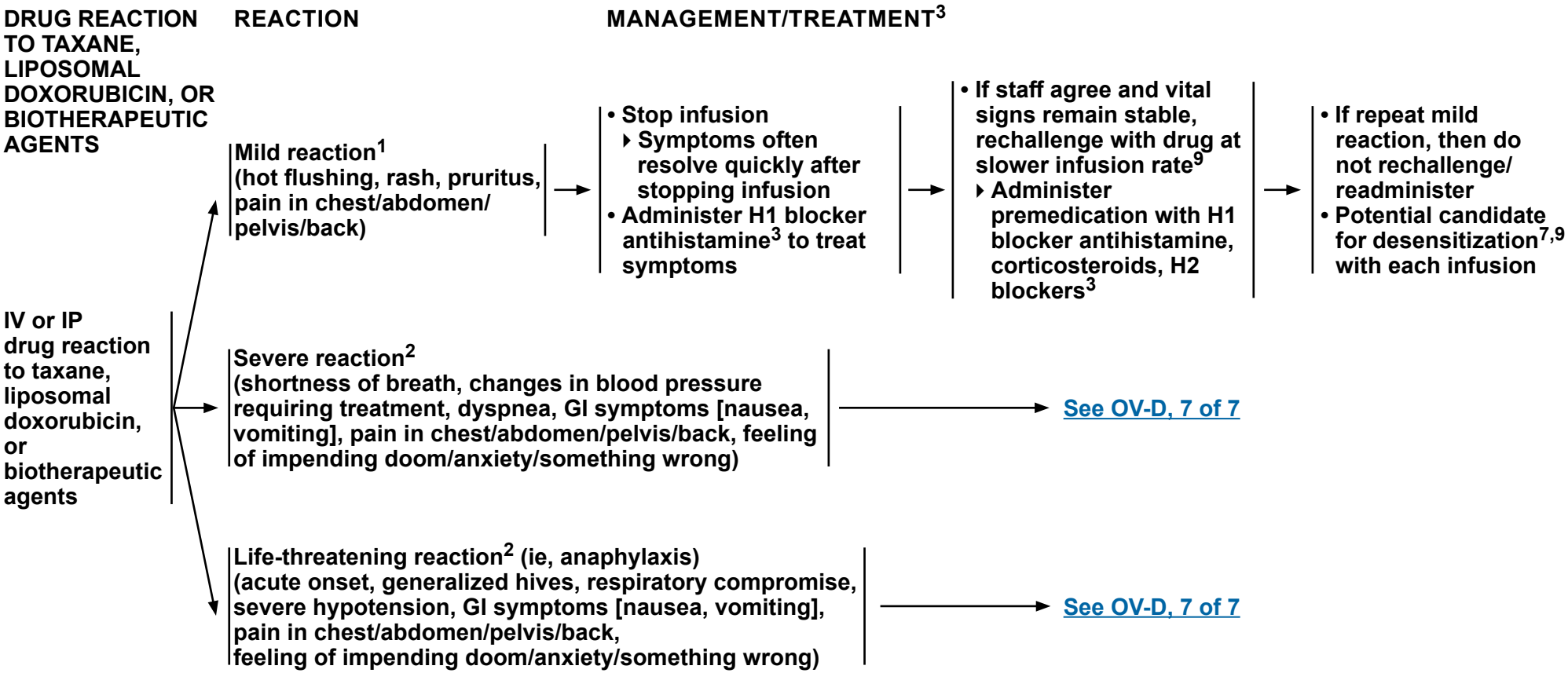
MANAGEMENT OF DRUG REACTIONS



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[7]Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-580.

[9]Consider switching to paclitaxel (albumin-bound) due to medical necessity (ie, hypersensitivity reaction), or consider switching to docetaxel; however, there are no data to support switching taxanes. Cross reactions have occurred and have been life-threatening. Some reactions to paclitaxel may occur because of the diluent.

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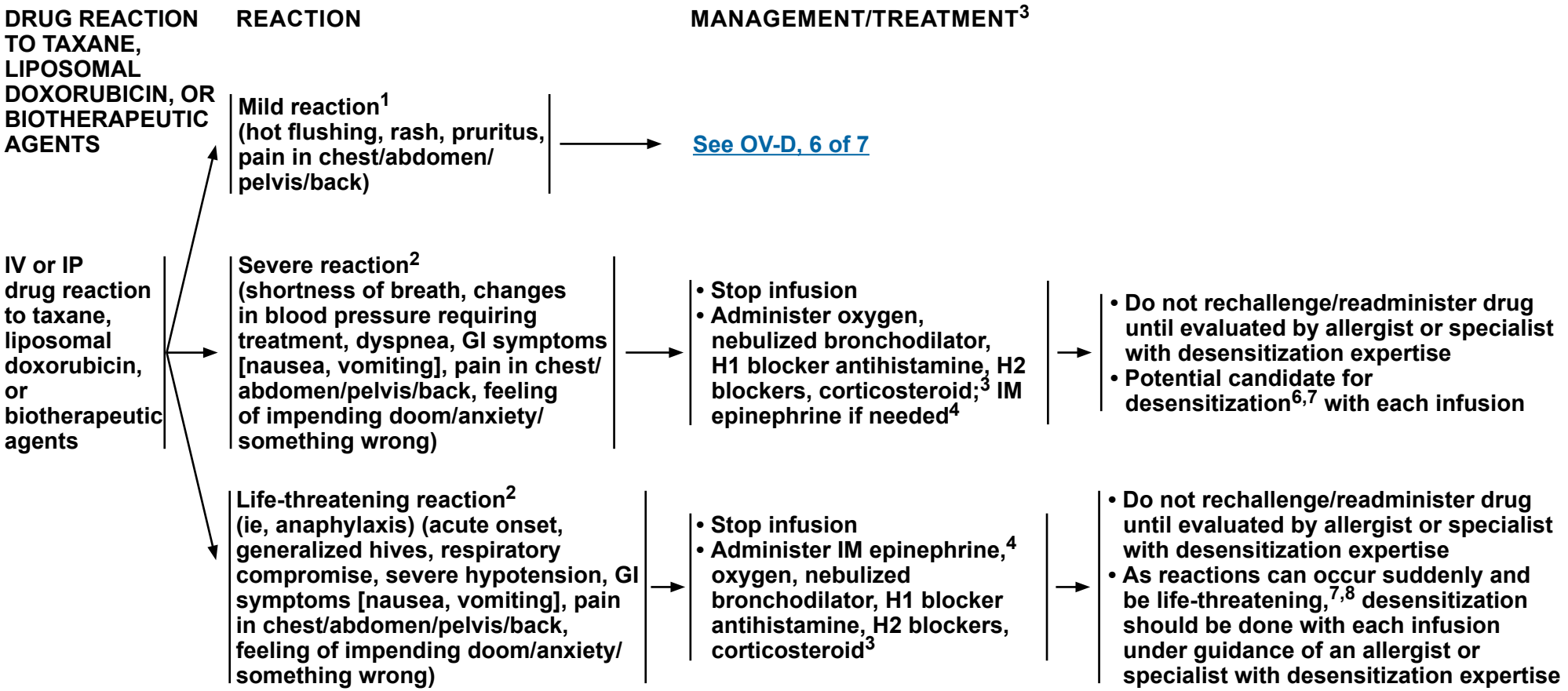
MANAGEMENT OF DRUG REACTIONS



See Drug Reaction to Platinum Agents on OV-D, 4 of 7

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WHO HISTOLOGIC CLASSIFICATION[1,2]

Serous Tumors	
• Serous cystadenoma	Benign
• Serous adenofibroma	Benign
• Serous surface papilloma	Benign
• Serous borderline tumor/atypical proliferative serous tumor	Borderline
• Serous borderline tumor-micropapillary variant/non-invasive low-grade serous carcinoma	Carcinoma in-situ/ grade III intraepithelial neoplasia
• Low-grade serous	Malignant
• High-grade serous	Malignant
Mucinous Tumors	
• Mucinous cystadenoma	Benign
• Mucinous adenofibroma	Benign
• Mucinous borderline tumor/atypical proliferative mucinous tumor	Borderline
• Mucinous carcinoma	Malignant
Endometrioid Tumors	
• Endometriotic cyst	Benign
• Endometriotic cystadenoma	Benign
• Endometriotic adenofibroma	Benign
• Endometrioid borderline tumor/atypical proliferative endometrioid tumor	Borderline
• Endometrioid carcinoma	Malignant
Clear Cell Tumors	
• Clear cell cystadenoma	Benign
• Clear cell adenofibroma	Benign
• Clear cell borderline tumor/atypical proliferative clear cell tumor	Borderline
• Clear cell carcinoma	Malignant

Brenner Tumors	
• Brenner tumor	Benign
• Borderline Brenner tumor/atypical proliferative Brenner tumor	Borderline
• Malignant Brenner tumor	Malignant
Seromucinous Tumors	
• Seromucinous cystadenoma	Benign
• Seromucinous adenofibroma	Benign
• Seromucinous borderline tumor/atypical proliferative seromucinous tumor	Borderline
• Seromucinous carcinoma	Malignant
Undifferentiated carcinoma	Malignant
Mesenchymal Tumors	
• Low-grade endometrioid stromal sarcoma	Malignant
• High-grade endometrioid stromal sarcoma	Malignant
Mixed Epithelial & Mesenchymal Tumors	
• Adenosarcoma	Malignant
• Carcinosarcoma	Malignant

Continued

[1]Reproduced with permission from Kurman RJ, Carcangiu ML, Herrington CS, Young RH. World Health Organization Classification of Tumours of the Female Reproductive Organs. IARC, Lyon, 2014.
[2]Borderline = Unspecified, borderline, or uncertain behavior.

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WHO HISTOLOGIC CLASSIFICATION[1,2]

Sex Cord-Stromal Tumors: Pure Stromal Tumors	
• Fibroma	Benign
• Cellular fibroma	Borderline
• Thecoma	Benign
• Luteinized thecoma associated with sclerosing peritonitis	Benign
• Fibrosarcoma	Malignant
• Sclerosing stromal tumor	Benign
• Signet-ring stromal tumor	Benign
• Microcystic stromal tumor	Benign
• Leydig cell tumor	Benign
• Steroid cell tumor	Benign
• Steroid cell tumor, malignant	Malignant
Sex Cord-Stromal Tumors: Pure Sex Cord Tumors	
• Adult granulosa cell tumor	Malignant
• Juvenile granulosa cell tumor	Borderline
• Sertoli cell tumor	Borderline
• Sex cord tumor with annular tubules	Borderline
Mixed Sex Cord-Stromal Tumors	
• Sertoli-Leydig cell tumors	
▸ Well differentiated	Benign
▸ Moderately differentiated	Borderline
◊ With heterologous elements	Borderline
▸ Poorly differentiated	Malignant
◊ With heterologous elements	Malignant
▸ Retiform	Borderline
◊ With heterologous elements	Borderline
• Sex cord-stromal tumors, NOS	Borderline

Germ Cell Tumors	
• Dysgerminoma	Malignant
• Yolk sac tumor	Malignant
• Embryonal carcinoma	Malignant
• Non-gestational choriocarcinoma	Malignant
• Mature teratoma	Benign
• Immature teratoma	Malignant
• Mixed germ cell tumor	Malignant
Monodermal Teratoma & Somatic-type Tumors from Dermoid Cyst	
• Struma ovarii, benign	Benign
• Struma ovarii, malignant	Malignant
• Carcinoid	Malignant
▸ Strumal carcinoid	Borderline
▸ Mucinous carcinoid	Malignant
• Neuroectodermal-type tumors	
• Sebaceous tumors	
▸ Sebaceous adenoma	Benign
▸ Sebaceous carcinoma	Malignant
• Other rare monodermal teratomas	
• Carcinomas	
▸ Squamous cell carcinoma	Malignant
▸ Others	
Germ Cell- Sex Cord-Stromal Tumors	
• Gonadoblastoma, including gonadoblastoma with malignant germ cell tumor	Borderline
• Mixed germ cell- sex cord-stromal tumor, unclassified	Borderline

Miscellaneous Tumors	
• Adenoma of rete ovarii	Benign
• Adenocarcinoma of rete ovarii	Malignant
• Wolffian tumor	Borderline
• Small cell carcinoma, hypercalcaemic type	Malignant
• Small cell carcinoma, pulmonary type	Malignant
• Wilms tumor	Malignant
• Paraganglioma	Borderline
• Solid pseudopapillary neoplasm	Borderline
Mesothelial Tumors	
• Adenomatoid tumor	Benign
• Mesothelioma	Malignant
Soft Tissue Tumors	
• Myxoma	Benign
• Others	
Tumor-like Lesions	
• Follicle cyst	
• Corpus luteum cyst	
• Large solitary luteinized follicle cyst	
• Hyperreactio luteinalis	
• Pregnancy luteoma	
• Stromal hyperplasia	
• Stromal hyperthecosis	
• Fibromatosis	
• Massive oedema	
• Leydig cell hyperplasia	
• Others	
Lymphoid and Myeloid Tumors	
• Lymphomas	Malignant
• Plasmacytoma	
• Myeloid neoplasms	

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Staging

Table 1
American Joint Committee on Cancer (AJCC)
TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)

Primary Tumor (T)

TNM	FIGO	
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1	**I**	Tumor limited to ovaries (one or both) or fallopian tube(s)
T1a	**IA**	Tumor limited to one ovary (capsule intact) or fallopian tube, no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1b	**IB**	Tumor limited to both ovaries; (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
T1c	**IC**	Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
T1c1	**IC1**	Surgical spill
T1c2	**IC2**	Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c3	**IC3**	Malignant cells in ascites or peritoneal washings
T2	**II**	Tumor involves one or both ovaries or fallopian tubes with pelvic extension below pelvic brim or primary peritoneal cancer
T2a	**IIA**	Extension and/or implants on the uterus and/or fallopian tube(s) and/or ovaries
T2b	**IIB**	Extension to and/or implants on other pelvic tissues
T3	**III**	Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to the retroperitoneal (pelvic and/or para-aortic) lymph nodes
T3a	**IIIA2**	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3b	**IIIB**	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension with or without metastasis to the retroperitoneal lymph nodes
T3c	**IIIC**	Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

Continued

Used with the permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

Staging

Table 1 (Continued)
American Joint Committee on Cancer (AJCC)
TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)

Regional Lymph Nodes (N)

TNM	FIGO	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N0(i+)		Isolated tumor cells in regional lymph node(s) no greater than 0.2 mm
N1	**IIIA1**	Positive retroperitoneal lymph nodes only (histologically confirmed)
N1a	**IIIAi**	Metastasis up to and including 10 mm in greatest dimension
N1b	**IIIAii**	Metastasis more than 10 mm in greatest dimension

Distant Metastasis (M)

TNM	FIGO	
M0		No distant metastasis
M1	**IV**	Distant metastasis, including pleural effusion with positive cytology; liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); and transmural involvement of intestine
M1a	**IVA**	Pleural effusion with positive cytology
M1b	**IVB**	Liver or splenic parenchymal metastases; metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine

Continued

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Staging

Table 2. **AJCC Prognostic Groups**
TNM and FIGO Staging System for Ovarian, Fallopian Tube, and Primary Peritoneal Cancer (8th ed., 2017)

	T	N	M
Stage I	T1	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IC	T1c	N0	M0
Stage II	T2	N0	M0
Stage IIA	T2a	N0	M0
Stage IIB	T2b	N0	M0
Stage IIIA1	T1/T2	N1	M0
Stage IIIA2	T3a	NX/N0/N1	M0
Stage IIIB	T3b	NX/N0/N1	M0
Stage IIIC	T3c	NX/N0/N1	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b

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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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

Table of Contents

This discussion corresponds to the NCCN Guidelines for Ovarian Cancer. MS-1 through MS-82 last updated: January 12, 2021. The remaining text (*Follow-up Recommendations* and subsequent sections) last updated November 11, 2017.

Overview

Ovarian neoplasms consist of several histopathologic entities; treatment depends on the specific tumor type.[1] Epithelial ovarian cancer comprises the majority of malignant ovarian neoplasms (about 90%);[2-4] other less common pathologic subtypes may occur such as malignant germ cell and sex cord-stromal cell tumors. Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women.[5] In 2020 it is estimated that 21,750 new diagnoses and 13,940 deaths from this neoplasm will occur in the United States.[5] Five-year survival is about 48%,[5] although survival is longer for select patients with certain rarer subtypes.[6-8] The incidence of ovarian cancer increases with age and is most prevalent in the sixth and seventh decades of life.[4,7,9,10] The distribution of age at diagnosis varies depending on primary site (ovary, fallopian tube, peritoneum) and cancer subtype.[6,10,11] More than half of patients present with distant disease, although certain uncommon subtypes are more likely to be diagnosed at earlier stages.[5,7,12]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer were originally published in 1996 and have been subsequently updated at least once every year.[13] These NCCN Guidelines® discuss cancers originating in the ovary, fallopian tube, or peritoneum, as fallopian tube and primary peritoneal cancers are managed in a similar manner to ovarian cancer. The NCCN Guidelines include recommendations for epithelial subtypes, including serous, endometrioid, carcinosarcoma (malignant mixed Müllerian tumors [MMMTs] of the ovary), clear cell, mucinous, and borderline epithelial tumors (also known as low malignant potential [LMP] tumors). Recommendations for malignant sex cord-stromal tumors, and malignant germ cell tumors, which are both non-epithelial subtypes, are also discussed. In the NCCN Guidelines, most of the recommendations are based on data from patients with the most common subtypes—high-grade serous and grade 2/3 endometrioid. The NCCN Guidelines also include recommendations specifically for patients with less common ovarian cancers (LCOC), which in the Guidelines include the following: carcinosarcoma, clear cell carcinoma, mucinous carcinoma, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal, and malignant germ cell tumors.

These NCCN Guidelines also include sections on *Principles of Surgery*, *Principles of Pathology*, *Principles of Systemic Therapy*, *Management of Drug Reactions, WHO Histologic Classification,* and *Staging*. Recent additions include: 1) addition of a new section on *Principles of Pathology*; 2) addition of a new page with expanded recommendations for neoadjuvant chemotherapy (NACT); 3) addition of certain PARP (poly ADP ribose polymerase) inhibitors for maintenance therapy in select patients with complete or partial response (CR/PR) after first-line platinum-based chemotherapy, and associated changes to the recommendations for molecular testing; 4) significant revisions to the surveillance recommendations for malignant germ cell tumors, including separate recommendations for dysgerminoma versus non-disgerminoma tumors; and 5) addition of a few more treatment options for persistent, progressive, or recurrent disease. It is important to note that all recommendations are category 2A in the NCCN Guidelines unless otherwise indicated. Category 2A recommendations are based on lower level evidence (such as phase 2 trials) and uniform NCCN consensus (at least 85% of panel members) that the intervention is appropriate.

By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among panel members during the process of developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Ovarian Cancer, an electronic search of the PubMed database was performed to obtain key literature in ovarian cancer published since the previous Guidelines update, using the following search terms: ((ovarian OR fallopian OR (primary and peritoneal) OR ovary OR (sex and cord-stromal) or mullerian) AND (carcinoma OR cancer OR malignancy OR malignancies OR lesion OR tumor). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[14] The search results were narrowed by selecting studies in humans published in English. Articles were also excluded if they: 1) involved investigational agents that have not yet received FDA approval; 2) did not pertain to the disease site; 3) were clinical trial protocols; or 4) were reviews that were not systematic reviews. The search results were further narrowed by selecting publications reporting clinical data, meta-analyses and systematic reviews of clinical studies, and treatment guidelines developed by other organizations.

The potential relevance of the PubMed search results was examined by the oncology scientist and panel chairs, and a list of selected articles was sent to the panel for their review and discussion at the panel meeting. The panel also reviewed and discussed published materials referenced in Institutional Review Comments or provided with Submission Requests. The data from key PubMed articles, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the Development and Update of the NCCN Guidelines are at www.NCCN.org.

Risk Factors for Ovarian Cancer

Reproductive Risk Factors

Epidemiologic studies have identified risk factors in the etiology of ovarian cancer.[4,11,15] A 30% to 60% decreased risk for cancer is associated with 1 or more pregnancies/births, the use of oral contraceptives, and/or breastfeeding.[11,16-29] Conversely, nulliparity confers an increased risk for ovarian cancer. Data suggest that postmenopausal hormone therapy and pelvic inflammatory disease may increase the risk for ovarian cancer,[11,30-40] although results vary across studies.[41-44] The risk for ovarian borderline epithelial tumors (also known as LMP tumors) may be increased after ovarian stimulation for in vitro fertilization.[35,45-49]

Obesity, Smoking, and Lifestyle and Environmental Risk Factors

Studies evaluating obesity as a risk factor for ovarian cancer have yielded inconsistent results,[50] which may be due to associations between obesity and other ovarian cancer risk factors (eg, parity, oral contraceptive use, menopausal status).[26,51,52] The risk associated with obesity may differ across ovarian cancer subtypes, and depend on the timing and reason for weight gain.[42,51-53] Smoking is associated with an increased risk for mucinous carcinomas but a decreased risk for clear cell carcinomas.[11,54-58] Environmental factors have been investigated, such as talc,[59-69] but so far they have not been conclusively associated with the development of this neoplasm.

Family History and Genetic Risk Factors

Family history (primarily patients having two or more first-degree relatives with ovarian cancer)—including linkage with *BRCA1* and *BRCA2* genotypes (hereditary breast and ovarian cancer [HBOC] syndrome) or families affected by Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC] syndrome)—is associated with increased risk of ovarian cancer, particularly early-onset disease.[11,70-91] In addition to mutations in

BRCA1/2 and the genes associated with Lynch syndrome (eg, *MLH1*, *MSH2*, *MSH6*, *PMS2*),[77,89,90,92-95] germline mutations in a variety of other genes have been associated with increased risk of ovarian cancer (eg, *ATM*, *BRIP1*, *NBN*, *PALB2*, *STK11*, *RAD51C*, *RAD51D*).[76,77,92,95-108] Patients with mutations in *BRCA1/2* account for only approximately 15% (range, 7%–21%) of all women who have ovarian cancer.[76,92,98,109-117] Studies testing large panels of genes have found that 3% to 8% of patients with ovarian cancer carry mutations in genes other than *BRCA1* and *BRCA2* known to be associated with ovarian cancer susceptibility.[76,77,98,111,115,116]

Risk-Reducing Surgery for High-Risk Patients

In women at high risk (with either *BRCA1* or *BRCA2* mutations), risk-reducing bilateral salpingo-oophorectomy (BSO) is associated with a reduced risk for breast, ovarian, fallopian tube, and primary peritoneal cancers.[118-122] Prospective studies have shown that among patients at high risk due to *BRCA1* or *BRCA2* mutation, occult ovarian, fallopian tube, or primary peritoneal cancer is found in up to 5% of patients undergoing risk-reducing salpingo-oophorectomy (RRSO),[121,123-128] enabling them to be diagnosed at an earlier and possibly more treatable stage. However, there is a residual risk for primary peritoneal cancer after risk-reducing BSO in these women at high risk for ovarian cancer.[121,124,126,129,130] [131]Additional considerations and recommended procedures for risk reduction surgery are described in the *Risk-Reducing Salpingo-Oophorectomy (RRSO) Protocol* section below.

Serous Tubal Intraepithelial Carcinoma (STIC)

It is now generally accepted that the fallopian tube is the origin of many serous ovarian and primary peritoneal cancers, and that serous intraepithelial carcinoma of the fallopian tube (also known as serous tubal intraepithelial carcinoma [STIC]) is a precursor of most high-grade serous ovarian or peritoneal cancer.[1,130,132-142] A referral to a gynecologic oncologist/comprehensive cancer center is recommended for management of occult STIC. At present, management options consist of: 1) observation alone with or without CA-125 testing when no evidence of invasive cancer is noted; and 2) surgical staging with observation or chemotherapy based on NCCN Guidelines if invasive cancer is noted. For women without prior genetic counseling and/or testing, discovery of a STIC should prompt a genetics evaluation. Nonetheless, it is not clear whether surgical staging and/or adjuvant chemotherapy is beneficial for women with STIC. An ongoing clinical trial (NCT04251052) sponsored by the National Cancer Institute (NCI) will prospectively track the incidence of STIC lesions as well as outcomes in women with pathogenic variants of *BRCA1* that elected to undergo RRSO or risk-reducing salpingectomy with possible delayed oophorectomy.[143]

Screening

Symptoms of Ovarian Cancer

Because of the location of the ovaries and the biology of most epithelial cancers, it has been difficult to diagnose ovarian cancer at an earlier, more curable stage. Evaluations of patients with newly diagnosed ovarian cancer have resulted in consensus guidelines for ovarian cancer symptoms,[142,144-146] which may enable earlier identification of patients who may be at an increased risk of having developed early-stage ovarian cancer.[147,148] Symptoms suggestive of ovarian cancer include: bloating, pelvic or abdominal pain, difficulty eating or feeling full quickly, and urinary symptoms (urgency or frequency), especially if these symptoms are new and frequent (>12 d/mo),[147] and cannot be attributed to any known (previously identified) malignancy or cause. Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility that ovarian pathology may be causing these symptoms.[149,150] Studies testing proposed symptom indices have found that these are not as sensitive or specific as necessary, especially in those with early-stage disease.[148,151-157]

Screening with Ultrasound and/or Serum CA-125

The literature does not support routine screening for ovarian cancer in the (asymptomatic) general population,[158,159] and routine screening is not currently recommended by any professional society.[149,150,158,160-167] Several large prospective randomized trials have evaluated screening for ovarian cancer with serum CA-125 and/or ultrasound (US) compared with "usual care" or no screening in the general population of postmenopausal women with intact ovaries (Table 1). Primary analysis results and meta analyses of data from these randomized studies suggest that screening may increase the likelihood of diagnosis at an early disease stage,[168-170] and may slightly lengthen survival in those diagnosed with ovarian cancer.[159,169,171] However, screening did not improve ovarian cancer-related mortality overall.[159,168,170,171] U.S. Preventative Services Task Force assessment of these randomized trials concluded that in average-risk women aged 45 years or older, ovarian cancer-related mortality was not improved by annual screening with transvaginal US (TVUS) alone, CA-125 alone, or both.[162] Results from these randomized prospective trials and from single-arm prospective trials suggest that the positive predictive value was low (<50%) for the screening methods tested (serum CA-125 and/or US).[172-175] Harms of screening included false positives in up to 44% of patients (over the course of multiple rounds of screening), which may have caused unnecessary stress and resulted in unnecessary surgery in up to 3.2%, with complications in up to 15% of false-positive surgeries.[158,162,168,176-178] A number of analyses have aimed to determine methods to improve the utility of US- and CA-125 based screening in postmenopausal women at average risk.[169,175,179-191] Several have found that compared with a single CA-125 serum concentration threshold for further testing/surgery, using the risk of ovarian cancer algorithm (ROCA) to determine CA-125–based thresholds may enable earlier detection of ovarian cancer and improve the sensitivity of CA-125–based screening.[169,179,181] In the UKCTOCS trial, ROCA was used prospectively in the multimodality screening arm as criteria for further testing (CA-125 at 3 months and/or TVUS), but nonetheless ovarian cancer-related mortality was not significantly different from the unscreened population.[168] Data from large population-based studies have shown that a variety of other conditions not related to cancer may impact CA-125 levels,[192] which may explain the poor positive predictive value of CA-125 screening observed in prospective trials.

Table 1. Prospective Randomized Trials Testing Efficacy of Ovarian Cancer Screening

Trial, Primary Report	Patients	Arms	Follow-up, Median
UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) NCT00058032 Jacobs et al, 2016[168]	• Age: 50–74 years • No prior bilateral oophorectomy • Personal cancer history: no history of ovarian cancer, no active non-ovarian malignancy • Family cancer history of breast or ovarian cancer: 6.4% breast, 1.6%; excluded if elevated risk of familial breast or ovarian cancer	• Annual screening with CA-125, with TVUS as a second-line test (n=50,640) • Annual screening with TVUS (n=50,359) • No screening (n=101,359)	11.1 years
Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial NCT00002540 Pinsky et al, 2016[159]	• Age: 55–74 years • No prior bilateral oophorectomy • Personal cancer history: no prior lung, colorectal, or ovarian; 3.6% had prior breast cancer; no current treatment for other cancer (except nonmelanoma skin cancer) • Family cancer history of breast or ovarian cancer: ~17%	• Screening: annual TVUS and CA-125; bimanual palpitation offered (n=39,105) • Usual care (n=39,111)	14.7 years
UC Pilot Trial Jacobs et al, 1999[171]	• Age: ≥45 years • No prior bilateral oophorectomy • Personal cancer history: no history of ovarian cancer, no active malignancy • Family cancer history: NR	• Screening: offered 3 annual CA-125, with pelvic US as second-line test (n=10,977) • No screening (n=10,958)	6.8 years

CA-125, cancer antigen 125; NR, not reported; TVUS, transvaginal ultrasound; US, ultrasound.

For women with high-risk factors (eg, *BRCA* mutations, family history of breast or ovarian cancer), RRSO is generally preferred over screening as it reduces the likelihood of breast, ovarian, fallopian tube, and primary peritoneal cancers.[118-122] For those who choose to defer or decline RRSO, some physicians use CA-125 monitoring and endovaginal US.[123,160,161,165] Strong supportive evidence for this approach is lacking, however, as several large prospective studies in high-risk patients have shown that these methods have low positive predictive value and do not improve ovarian cancer-related mortality.[193-197] However, prospective studies in high-risk patients have also shown that screening with CA-125 and TVUS may improve the likelihood of diagnosis at an earlier stage,[193,194,196] and may improve survival of the patients who develop ovarian cancer.[195] As in average-risk patients, analyses of data from high-risk patients suggests that interpretation of CA-125 using ROCA rather than a single concentration threshold improves screen sensitivity and the likelihood of ovarian cancer detection at an earlier stage.[193] In high-risk patients the appropriate CA-125 cut-point may depend on menopausal status.[198] Recommendations for screening for ovarian cancer in patients with genetic risk factors can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org).

Screening with Other Biomarker Tests

In addition to CA-125, there are a number of biomarkers that have been explored as possible screening tools for early detection of ovarian cancer.[184,199-212] Data for most of these proposed biomarkers is limited to retrospective analyses comparing biomarker levels in patients with known ovarian cancer versus healthy controls. Very few biomarkers have been tested prospectively to determine whether they can detect ovarian cancer or predict development of ovarian cancer in women who have no other signs or symptoms of cancer. Data show that several markers (including CA-125, HE4, mesothelin, B7-H4, decoy receptor 3 [DcR3], and spondin-2) do not increase early enough to be useful in detecting early-stage ovarian cancer.[185,213,214]

There are a number of biomarker tests and prediction algorithms (based on a variety factors, such as symptoms, imaging results, biomarkers, and patient characteristics) that have been developed for assessing the likelihood of malignancy among patients who have an adnexal mass (and have not yet had surgery). It is important to note that these tests are for preoperative assessment only, and none is suitable for ovarian cancer screening prior to detection of an adnexal mass; they are also not for use as stand-alone diagnostic tests. For example, the OVA1 test is a multivariate index assay (MIA) that uses five markers (including transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125) in preoperative serum to assess the likelihood of malignancy in patients with an adnexal mass for which surgery is planned, with the aim of helping community practitioners determine which patients to refer to a gynecologic oncologist for evaluation and surgery.[215-219] The Society of Gynecologic Oncology (SGO) and the FDA have stated that the OVA1 test should not be used as a screening tool to detect ovarian cancer in patients without any other signs of cancer, or as a stand-alone diagnostic tool.[149,164,220] Moreover, based on data documenting an increased survival, the NCCN Guidelines Panel recommends that all patients with suspected ovarian malignancies (especially those with an adnexal mass) should undergo evaluation by an experienced gynecologic oncologist prior to surgery.[150,221-224] For discussion of preoperative tests recommended by NCCN for patients with an undiagnosed adnexal mass, see the section below entitled *Recommended Workup, Patients Presenting with Clinical Symptoms/Signs*.

Risk-Reducing Salpingo Oophorectomy (RRSO) Protocol

The RRSO protocol is recommended for patients at risk for HBOC and is described in detail in the algorithm (see the *Principles of Surgery* in the algorithm). Selection of patients appropriate for this procedure is described in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org). In addition to reducing the risk of breast, ovarian, fallopian tube, and primary peritoneal cancers in patients at high risk,[118-122] RRSO can also result in early diagnosis of gynecologic cancer. Occult ovarian, fallopian tube, and primary peritoneal cancer is sometimes found by RRSO (in 3.5%–4.6% of patients with *BRCA1/2* mutations),[121,123-128] and in some cases only detected by pathologic examination of specimens.[123,225-230] This emphasizes the need for well-tested protocols that include careful pathologic review of the ovaries and tubes.[126,131]

This protocol recommends minimally invasive laparoscopic surgery. This procedure should include a survey of the upper abdomen, bowel surfaces, omentum, appendix (if present), and pelvic organs. Any abnormal peritoneal findings should be biopsied. Pelvic washing for cytology should be obtained, using approximately 55 cc normal saline instilled and aspirated immediately. The procedure should include total BSO, removing 2 cm of proximal ovarian vasculature or IP ligament, all of the fallopian tube up to the cornua, and all of the peritoneum surrounding the ovaries and fallopian tubes, especially the peritoneum underlying areas of adhesion between the fallopian tube and/or ovary and the pelvic

sidewall.[126] It is recommended to engage in minimal instrument handling of the tubes and ovaries to avoid traumatic exfoliation of cells.[126] Both ovaries and tubes should be placed in an endobag for retrieval from the pelvis. Complete evaluation of the fallopian tubes is important, as prospective studies have found that roughly a half of the cases of occult disease identified by RRSO in *BRCA1/2* mutation carriers were tubal neoplasms.[121,123,125-127] For pathologic assessment, fallopian tubes should be processed by sectioning and extensively examining the fimbriated end (SEE-Fim) of the tubes and then assessed to determine whether any evidence of cancer is present.[131,231,232] The ovaries should also be carefully sectioned, processed, and assessed.[131] The CAP protocol describes the process for sectioning the fallopian tubes and ovaries.[233-235] If occult malignancy or STIC is identified, the patient should be referred to a gynecologic oncologist.

Note that it is controversial whether a hysterectomy should also be done in patients undergoing RRSO. Some patients with elevated risk of ovarian cancer due to genetic risk factors or family history may also have elevated risk of endometrial cancer.[236-240] The relationship between *BRCA* mutations and uterine cancer has been evaluated in multiple studies, with some studies showing that *BRCA* mutation carriers are at higher risk of uterine/endometrial cancer compared with the general population or compared with those without *BRCA* mutations;[241-245] other studies showing no linkage[246,247] or a lower risk of uterine cancer among *BRCA* mutation carriers;[248] and some studies suggesting that increased risk is largely due to tamoxifen exposure.[243,249] In a few studies of *BRCA* mutation carriers who underwent RRSO without hysterectomy and had no evidence of disease at the time of surgery, the post-surgery incidence of uterine cancer was higher compared with the general population,[250-252] but in other studies it was not elevated.[253] Several studies found that *BRCA1* mutations were linked to endometrial or uterine cancer, but *BRCA2* mutations either were not associated with increased risk or were not analyzed.[243-245,250-252] However, there are also studies showing no significant association between uterine cancer and *BRCA1* mutations,[246,248] so further research on this topic is needed.

Certain pathogenic variants associated with Lynch syndrome have been linked to increased risk of endometrial and ovarian cancers, and associated with cases where both types of cancer develop in an individual patient or family.[86,89-91,93,254-258] Certain reproductive factors, such as infertility, parity, and exposure to contraceptives, fertility drugs, and postmenopausal hormone therapy, are known to increase or decrease the risk of both ovarian and endometrial cancers.[18,19,22,33,48,259-261] Among patients with who underwent RRSO due to *BRCA* mutation, diagnosis of breast cancer, or family history of breast/ovarian cancer, and elected to have hysterectomy at the time of RRSO, several studies reported finding occult uterine disease, although the frequency varied.[123,262-265] Based on studies specifically focusing on patients with mutations associated with Lynch syndrome, however, discovery of occult endometrial cancer may be as frequent as occult ovarian/fallopian tube lesions, and the incidence of endometrial cancer may be significantly reduced by prophylactic hysterectomy.[266,267] One large population-based study of women with premenopausal primary breast cancer showed that prophylactic BSO plus hysterectomy reduced the risk of new primary breast cancer and improved breast-cancer associated mortality; neither procedure alone significantly modified these risks, and the effect was not seen in women with postmenopausal breast cancer.[268] See the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org) for further discussion of selection of patients who may benefit from hysterectomy at the time of RRSO.

The prevention benefits of salpingectomy alone are not yet proven.[269-279] If salpingectomy alone is considered, the fallopian tube from the fimbria to its insertion into the uterus should be removed; the fallopian tubes should

also be carefully processed and assessed as described above for BSO.[126,131] The concern for risk-reducing salpingectomy alone is that women are still at risk for developing ovarian cancer. In addition, in premenopausal women, oophorectomy reduces the risk of developing breast cancer but the magnitude is uncertain.[280] For further discussion of residual risks of cancer, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic (available at www.NCCN.org).

The risks of surgery include injury to the bowel, bladder, ureter, and vessels.[125,264,281-283] For both patients who are premenopausal and those who are postmenopausal at time of RRSO, menopause symptoms may emerge, re-emerge, or worsen.[284-290] RRSO may also have long-term impacts on sexual functioning and quality of life (QOL).[284,285,288,289,291-300] Although the existing limited data suggest that management with hormone replacement therapy (HRT) likely does not increase risk of breast cancer in *BRCA* mutation carriers undergoing RRSO,[291,301-306] the efficacy of HRT for symptom management in this population is debated.[284-288,296,297,299,303-305] RRSO in premenopausal women increases risk of certain cardiovascular conditions (eg, coronary heart disease, cardiac arrhythmias, hyperlipidemia), chronic obstructive pulmonary disease, arthritis, asthma, osteoporosis, and mental health conditions (cognitive dysfunction, depression, anxiety).[287,307-313]

Recommended Workup

Patients with ovarian cancer may present in several different ways. Some present with clinical signs and/or symptoms, which upon imaging reveal a pelvic mass and potentially evidence of metastasis. For other patients, ovarian cancer is an incidental finding during a surgery or other procedure. Recommended workup for each of these presentations is described below.

Patients Presenting with Clinical Symptoms/Signs

Clinical symptoms that warrant further workup for possible ovarian cancer include suspicious/palpable pelvic mass found on an abdominal/pelvic exam, ascites, abdominal distention, and/or symptoms (ie, bloating, pelvic/abdominal pain, difficulty eating for feeling full quickly, and urinary symptoms, such as increased urgency or frequency).[147] Clinical signs might include abdominal distension/ascites and a mass noted on abdominal/pelvic examination. Further workup for these patients should include imaging, laboratory studies, evaluation of nutritional status, GI evaluation if indicated, and family history. Each of these elements of workup is described in greater detail below.

Imaging

The primary workup for patients with clinical signs or symptoms of ovarian cancer should include an abdominal/pelvic US and/or abdominal/pelvic CT/MRI scan. US is typically used for initial evaluation, as it has been shown to be effective at triaging the majority of adnexal masses into benign or malignant categories.[314-316] Other imaging modalities may be helpful when the results of US are indeterminate (ie, either the organ of origin or malignant potential is unclear), and may improve assessment of metastases, staging, and preoperative planning.[314,316,317] Abdominal/pelvic MRI may be useful for determining malignant potential of adnexal masses if US is not reliable or results are indeterminate.[314-316,318-322] FDG-PET/CT scan may also be useful for indeterminate lesions.[323-325] The NCCN Panel recommends PET/CT or MRI for indeterminate lesions if they will alter management.

Various imaging methods and algorithms for evaluating imaging results have been proposed for preoperatively distinguishing benign from malignant adnexal masses, with the goal of determining which patients should have surgery and/or be referred to a gynecologic oncologist for further evaluation and surgery. Multiple US-based imaging algorithms for

predicting malignancy have been developed and tested prospective studies comparing preoperative US results to final diagnosis after surgery.[326-330] The most thoroughly tested of these are the International Ovarian Tumor Analysis (IOTA) Simple Rules algorithm, based on five US features;[191,331-340] and the IOTA logistic regression model (LR2), which combines five US variables with age.[189,341-344] A variety of MRI-based approaches for distinguishing benign from malignant masses have been explored in prospective trials comparing preoperative MRI results to final postoperative diagnosis, although these approaches have been less thoroughly tested than the US techniques. Examples include proton MR spectroscopy,[345] diffusion-weighted imaging (DWI),[346-348] apparent diffusion coefficient (ADC) maps,[349] 3.0 Tesla (3T) MRI,[350] and dynamic contrast-enhanced (DCE) MRI.[351] Although both US and MRI are recommended options for preoperative imaging, the NCCN Guidelines are silent regarding the exact techniques used for each, and do not endorse any specific model for preoperative triage.

For assessment of abdominopelvic metastases for preoperative staging, estimation of resectability, and surgical planning, abdominal/pelvic CT or MRI are generally more useful than US.[317,318,321,352-354] Although CT is preferred in some circles, MRI has been shown to provide equivalent accuracy for staging and comparable accuracy for predicting peritoneal tumor volume, and can be useful if CT results are inconclusive.[317] For assessing advanced disease, FDG-PET/CT may also be useful if CT results are indeterminate, and has been shown to have higher accuracy than CT for detection of metastases.[317,324,355-358]

Although there is no direct evidence that chest x-ray or chest CT is necessary, panel members felt that it should be part of the overall evaluation of a patient before surgical staging if clinically indicated. CT of the chest can detect pleural or pulmonary metastases, as well as pleural effusion, which may help with treatment planning.[317] All CT/MRI imaging should be performed with contrast unless contraindicated.

Laboratory Studies and Biomarker Tests

Appropriate laboratory studies for patients presenting with clinical symptoms/signs of ovarian cancer include CBC and chemistry profile with liver function test.

A number of specific biomarkers and algorithms using multiple biomarker test results have been proposed for preoperatively distinguishing benign from malignant tumors in patients who have an undiagnosed adnexal/pelvic mass. Biomarker tests developed and evaluated in prospective trials comparing preoperative serum levels to postoperative final diagnosis include serum HE4 and CA-125, either alone or combined using the Risk of Ovarian Malignancy Algorithm [ROMA] algorithm;[188,190,359-374] the MIA (brand name OVA1) based on serum levels of five markers: transthyretin, apolipoprotein A1, transferrin, beta-2 microglobulin, and CA-125[157,215-219,375]; and the second-generation MIA (MIA2G, branded name OVERA) based on CA-125, transferrin, apolipoprotein A1, follicle-stimulating hormone [FSH], and HE4.[187,376] The FDA has approved the use of ROMA, OVA1, or OVERA for estimating the risk for ovarian cancer in women with an adnexal mass for which surgery is planned, and have not yet been referred to an oncologist.[220,377,378] Although the American Congress of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and OVA1 may be useful for deciding which patients to refer to a gynecologic oncologist,[379] other professional organizations have been non-committal.[164,315,380] Not all studies have found that multi-biomarker assays improve all metrics (ie, sensitivity, specificity, positive predictive value, negative predictive value) for prediction of malignancy compared with other methods (eg, imaging, single-biomarker tests, symptom index/clinical assessment).[188,218,360,381-383] Currently, the NCCN Panel does not recommend the use of these

biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass.

Nonetheless, the NCCN Guidelines do include CA-125 testing as a possible element of preoperative workup, if clinically indicated. This recommendation is based on data showing that serum CA-125 levels correlate with extent of disease, and may have prognostic value, so may help in treatment planning.[384-388] Serum CA-125 levels tend to correlate with the clinical course of disease, especially in those with elevated pretreatment levels, so can be useful for monitoring response to therapy and surveillance for recurrence.[4,385,387-399]

Some evidence suggests that HE4 may be a useful prognostic marker in patients with ovarian cancer, decreases during response to treatment, and may improve early detection of recurrence relative to CA-125 alone.[400-427] NCCN Panel members sometimes test HE4 in patients who do not have elevated CA-125, as HE4 can be useful for future monitoring in such patients. However, because results vary across studies,[428-430] the NCCN Guidelines currently do not recommend routine HE4 as part of preoperative workup.

In addition to CA-125, the NCCN Guidelines mention that other tumor markers may be used as part of preoperative workup, if clinically indicated: inhibin, alpha-fetoprotein [AFP], beta–human chorionic gonadotropin [beta-hCG], lactate dehydrogenase [LDH], carcinoembryonic antigen [CEA], and CA19-9. Serum levels of these markers can be elevated in patients with certain LCOCs, and correlate with disease course in some of these patients. Measurement of these markers prior to surgery can help to assess for LCOC (see *Less Common Ovarian Cancers*), and facilitate future monitoring during surveillance after treatment, especially in patients who do not have elevated serum CA-125 at baseline and/or have tumor types in which CA-125 level is less likely to be informative.[398]

For example, AFP, beta-hCG, and LDH are markers for malignant germ cell tumors that can be helpful in intraoperative diagnosis, preoperative planning, and post-treatment monitoring for recurrence.[379,398,431-439] AFP can be produced by endodermal sinus (yolk sac) tumors, embryonal carcinomas, polyembryomas, and immature teratomas; beta-hCG can be produced by choriocarcinomas, embryonal carcinomas, polyembryomas, and, in low levels, in some dysgerminomas; and LDH can be a marker for dysgerminoma.[431,432] Some studies in young patients presenting with an ovarian mass have found that high levels of AFP and beta-hCG were correlated with higher likelihood of malignancy,[439,440] or linked to specific subtypes,[434,441,442] suggesting that these markers may help with intraoperative diagnosis to determine whether fertility-sparing surgery is an option. High serum AFP levels and poor decline in serum AFP levels after treatment appear to be associated with worse outcomes in patients with germ cell tumors.[435,441-446] High serum beta-CG may also be correlated with poorer prognosis.[435,447] High levels of serum LDH have been correlated with more extensive disease and poor outcomes in some patients with ovarian germ cell tumors.[446,448-450] If a patient with a germ cell tumor or sex chord stromal tumor has elevated levels of one or more of these markers at baseline, and levels decline after treatment, then the marker(s) is more likely to be useful for follow-up for recurrence.[451] AFP and hCG are commonly used to monitor for recurrence in patients with germ cell tumors (GCTs), and have included clinical trials for detection of recurrence.[451-454]

Sex cord-stromal tumors of the ovary, particularly granulosa cell tumors, can produce inhibin, and inhibin expression level in tumor tissue and serum have been proposed as diagnostic markers.[398,455-464] Some studies have shown that serum levels of inhibin A and B, particularly inhibin B, correlate with extent of disease in patients with granulosa cell tumors, decreasing during treatment and then increasing again prior to relapse, leading to the proposal that serum inhibin monitoring may be helpful for

long-term follow-up.[465-470] In some cases of ovarian stromal tumor inhibin levels are not elevated, however, so this marker is not useful for monitoring response to treatment.[471]

Elevated serum CEA is a marker associated with gastrointestinal (GI) primary cancers, but can also occur in patients with ovarian malignancies, particularly mucinous tumors.[4,472-480] Because of its association with GI cancers, some advocate for further GI imaging in patients with high serum CEA.[145,472] A ratio of serum CA-125 to CEA >25 has been proposed for differentiating ovarian cancer from colorectal cancer,[481,482] particularly for confirming ovarian cancer diagnosis in patients considering neoadjuvant therapy (and biopsy results are not available).[472,483] CA-125:CEA ratio has been incorporated into entry criteria in trials testing neoadjuvant therapies.[484-486] For patients with mucinous ovarian cancer, it has been proposed that CEA may be useful for monitoring for recurrent disease.[149,479,487] CA19-9 is another marker that is elevated more often in mucinous tumors compared with other ovarian cancer types.[480,488-495] Results from some studies suggest that serum CA19-9 may be useful for monitoring for recurrence, especially in patients with mucinous ovarian cancers, and in those with high CA19-9 levels prior to treatment.[398,491,496,497]

Evaluation of Nutritional Status and Gastrointestinal (GI) Evaluation

Workup should also include evaluation of the patient's nutritional status, and GI evaluation if clinically indicated. Patients with ovarian cancer often present with bloating, pelvic or abdominal pain, difficulty eating, or feeling full quickly,[147] which can lead to changes in dietary habits that result in poor nutritional status. Poor nutritional status has been linked to higher risk of suboptimal surgery, surgical complications, and poor survival, especially in older patients.[498-504] There are a variety of ways to assess nutritional status, including body weight, body mass index, anthropometrics, serum protein, serum albumin, transferrin, lymphocyte count, bioelectrical impedance analysis, and body composition measures (adipose and lean tissues, skeletal muscle index).[498-501,503,505-519] Two commonly used metrics are the prognostic nutritional index (PNI) and subjective global assessment (SGA).[499,507,520-526] Evaluation of nutritional status is recommended as part of baseline workup as it is important for determining whether a patient is a good surgical candidate, and for preoperative planning.[483,527] For those who are not good surgical candidates, NACT may be a better option versus upfront debulking surgery. However, poor nutritional status in the context of a GI mass may be an indication for prioritizing surgery to remove or reduce the GI mass,[528,529] especially if the patient is otherwise a relatively fit surgical candidate.

Given that GI cancers and primary mucinous carcinoma of the ovary can both cause serum CEA elevation,[4,472-480] and can both present with adnexal masses, GI tract evaluation is especially important in these patients to determine whether patients have metastases to the ovary or primary mucinous carcinoma of the ovary (see *Mucinous Carcinomas*).[530] The presence of a pancreatic mass or widespread abdominal disease should also increase suspicion for primary GI cancer.

Family History and Genetic Testing

Obtaining a family history and referral to a genetic counselor is an important part of workup, as some patients may have hereditary traits that may inform future treatment and determine whether family members should be screened. Primary treatment (surgery and chemotherapy) should not be delayed for a genetic counselling referral, however, as genetic test results are not needed for selection of primary surgery and/or chemotherapy, and delay in treatment is associated with poorer outcomes.[531,532] Recommendations regarding genetic testing can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and the NCCN Guidelines for

Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

Although germline and/or somatic *BRCA1* and *BRCA2* status may inform future options for maintenance therapy, *BRCA* testing for the purpose of informing treatment is not needed until after there is histologic confirmation of ovarian, fallopian tube, or primary peritoneal cancer (eg, after primary surgery or confirmation by biopsy). See *Molecular Testing* section below.

Prediction of Malignancy, Referral to a Gynecologic Oncologist

There are a number of prediction algorithms that combine multiple factors, such as symptoms, imaging results, biomarkers, and patient characteristics, to predict the likelihood of malignancy among patients who have an undiagnosed adnexal mass (ie, a mass detected by clinical exam or imaging that has not yet been resected and definitively diagnosed by pathology).[319,341,354,374,533] These algorithms were developed with the goal of reducing the number and/or extent of unnecessary surgeries by using the likelihood of malignancy to determine which patients are most likely to benefit from surgery, and/or identify cases to be referred to a gynecologic oncologist for further testing and surgery. Many of these algorithms have been tested in prospective trials comparing preoperative prediction to postoperative histologically confirmed diagnosis, including IOTA Assessment of Different NEoplasias in the adneXa (ADNEX), which uses patient age, type of center (oncology referral vs other), serum CA-125, and six US variables;[319,333,534,535] Risk of Malignancy Indexes (RMI-1 through 4), which use US features, patient menopausal status, and serum CA-125;[342,361,362,536-542] combining symptom index (SI) with CA-125 and HE4 results;[156] and the (early) ACOG/SGO referral guidelines based on patient age, CA-125 level, physical findings, imaging results, and family history.[354,374,543] Several prospective studies have compared multiple algorithms or algorithms versus other metrics to determine which most accurately predicts malignancy.[215,217,218,341,360-362,381,382]

Currently the NCCN Guidelines do not endorse any of these methods. Because primary assessment and debulking by a gynecologic oncologist is associated with improved survival, all patients with lesions suspected to be ovarian malignancies (based on clinical evidence) should be referred to an experienced gynecologic oncologist for evaluation—both to assess suitability for different primary surgical options and to select the best method for obtaining the material needed for definitive diagnosis.[150,221-224] A gynecologic oncologist should be involved in assessing whether a patient is a suitable surgical candidate and/or an appropriate candidate for neoadjuvant therapy, and consideration of laparoscopic evaluation to determine feasibility of debulking surgery. A gynecologic oncologist should also be consulted for management of occult STICs.

Workup for Patients Referred with Diagnosis by Previous Surgery

Patients are on occasion referred to NCCN Member Institutions after having a previous diagnosis of ovarian cancer by surgery or tissue biopsy (cytopathology). At times, patients with newly diagnosed ovarian cancer have had cytoreductive surgery and comprehensive staging procedures (ie, having met the standards for surgical staging of the Gynecologic Oncology Group [GOG]).[544] In some instances, referral occurs after incomplete surgery and/or staging (eg, uterus and/or adnexa intact, omentum not removed, incomplete lymph node dissection, residual disease that is potentially resectable, surgical stage not completely documented, occult invasive carcinoma found at time of risk reduction surgery). The components of surgical staging are listed in the algorithm (see *Principles of Surgery* in the algorithm).

Workup procedures are very similar for patients having undiagnosed or diagnosed pelvic masses at the time of referral. In these cases, evaluation by a gynecologic oncologist is important for determining whether the previous surgery was adequate or an additional surgery is needed. Prior imaging studies and operative notes should be reviewed to determine

additional workup needed and to inform treatment approach. Additional imaging may be needed to screen for distant disease and evaluate for residual disease not removed during the previous surgery. Imaging options include chest/abdominal/pelvic CT or MRI, PET/CT, and/or US. All imaging should be performed with contrast unless contraindicated. Pathology review of tissue from the previous surgery is important for confirming diagnosis and cancer type. CBC and chemistry profile with LFTs should be obtained, and CA-125 or other tumor markers should be measured if indicated to corroborate likely diagnosis and to serve as baseline for future follow-up. See section above on *Laboratory Studies and Biomarker Tests*. If not previously done, workup should include obtaining a family history, genetic risk evaluation, and germline and somatic testing, if not previously done. Recommendations regarding genetic testing can be found in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org). As described in the *Molecular Testing* section below, germline and/or somatic *BRCA1/2* testing informs selection of maintenance therapy (after first-line platinum-based chemotherapy). Molecular analysis of tumor tissue from the previous surgery may be warranted. In the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may provide information on the magnitude of benefit of PARP inhibitor maintenance therapy (category 2B).

Diagnosis, Pathology, and Staging

Most ovarian cancers, including the LCOC, are diagnosed after pathologic analysis of a biopsy or surgical specimen, which may occur preoperatively, intraoperatively, or postoperatively. If possible, fine-needle aspiration (FNA) should be avoided for diagnosis of ovarian cancer in patients with presumed early-stage disease to prevent rupturing the cyst and spilling malignant cells into the peritoneal cavity; however, FNA may be necessary in patients who are not candidates for primary debulking, such as those with bulky disease, elderly patients, or patients in poor health.[545,546] Both primary peritoneal and fallopian tube cancers are usually diagnosed postoperatively (if there is no major involvement of the ovary) or preoperatively (if there is a biopsy and the patient has already had a bilateral oophorectomy). Patients who have equivocal pathologic findings or who are referred to NCCN Member Institutions after having a previous diagnosis of ovarian cancer should have their pathology reviewed by pathologists at NCCN Member Institutions.

Primary peritoneal and fallopian tube cancers are treated in the same manner as epithelial ovarian cancer, so distinguishing these three possible primary sites is less crucial than ruling out other cancers that commonly involve the adnexa, such as uterine, cervical, gastro intestinal (small and large bowel, pancreatic) cancers or lymphoma;[547,548] benign ovarian and non-ovarian conditions also need to be ruled out (eg, serous cystadenoma).[549] In addition, metastases to the ovaries need to be ruled out (see *Mucinous Carcinomas*).

The CAP protocol is a useful tool for pathology reports, and has been updated for consistency with the AJCC Cancer Staging Manual, 8th edition.[233,550] Based on the CAP protocol (Version 1.1.1.0; Feb 2020)[233] and panel consensus, the NCCN Guidelines recommend that pathologic assessment should include the following elements: all tumor site(s) (eg, ovary, fallopian tube, pelvic/abdominal peritoneum, uterus, cervix, omentum); all tumor size(s); for ovarian/fallopian tumors, surface involvement (present/absent/cannot determine), specimen integrity (capsule/serosa intact/fractured/fragmented); histologic type and grade; extension and/or implants (if sampled/identified); cytology results from peritoneal/ascitic fluid/washings and pleural fluid; the number and location of lymph nodes examined, and size of largest lymph node metastatic deposits; and evidence of STIC, endometriosis [particularly if in continuity with endometrioid or clear cell carcinoma], and endosalpingiosis.

The complete histologic classification from the WHO is included in the NCCN Guidelines.[1] The WHO pathology manual is also a useful resource.[1,551]

Histologic Subtypes

Epithelial ovarian cancer has four main subtypes, including serous, endometrioid, mucinous, and clear cell; most patients (about 70%) have serous cancers.[3,552-555] Molecular characterization of clear cell, mucinous, or low-grade (grade 1) serous tumors suggests that mutations in these cancer types are different from those in higher grade tumors.[556-558] Ovarian cancer can be divided into Types 1 and 2 based on these molecular alterations. Data suggest that serous tumors can be categorized as either low grade (grade 1) or high grade (grade 2 or 3).[552,559-564]

Ovarian borderline epithelial tumors, also called LMP tumors or atypical proliferative tumors, are another type of primary epithelial lesions. The terms for borderline epithelial tumors have changed over the years, and recent CAP protocols do not use “LMP.”[233,565] Borderline tumors have cytologic characteristics suggesting malignancy, and may grossly resemble an invasive cancer, but microscopic evaluation shows no evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist. The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. Borderline epithelial tumors are typically serous or mucinous; but other histologic subtypes can also occur (see *WHO Histologic Classification* in the algorithm).[1,233]

Carcinosarcomas arising in the ovary, fallopian tubes, or peritoneum, also called carcinomas of Müllerian origin or MMMTs, are biphasic, with both malignant epithelial and sarcomatous elements. Clonality studies suggest that this is a metaplastic carcinoma, with both components arising from an epithelial precursor, and the sarcomatous component resulting from transdifferentiation (epithelial-mesenchymal transition).[566-573]

Germ cell tumors are a non-epithelial subtype, and include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors.[1] Malignant sex cord-stromal tumors, another non-epithelial subtype, are rare and include granulosa cell tumors (most common) and Sertoli-Leydig cell tumors.[1]

In some cases, it can be difficult to distinguish between cancer subtypes. For example, high-grade endometrioid tumors can be difficult to distinguish from high-grade serous tumors.[552] Some endometrioid tumors look similar to clear cell tumors, while others may resemble sex cord-stromal tumors.[552] Immunohistochemistry (IHC) with certain markers may help with differential diagnosis. Whereas most (80%–90%) of serous carcinomas are positive for WT1, endometrioid and clear cell carcinomas are usually negative.[565,574,575] Endometrioid adenocarcinomas are usually positive for cytokeratin 7 (CK7), PAX8, CA-125, and estrogen receptors. The presence of endometriosis can sometimes help to distinguish subtypes, as clear cell carcinomas and endometrioid tumors can be associated with endometriosis, whereas other subtypes are less likely to be.[565] Endometrioid carcinomas are also very similar in appearance to sex cord-stromal tumors.[565] Most clear cell carcinomas express Napsin A, a marker that is specific to this subtype.[576] It is difficult to distinguish based on histology between primary mucinous ovarian carcinomas and GI metastases.[577-579] PAX8 immunostaining is typical of primary tumors,[575] although absence of PAX8 does not rule out ovary as the primary site. SATB2 is consistent with colonic origin.[580] Metastatic colorectal adenocarcinomas also usually are positive for CK20 and CEA.

Stage at diagnosis, prognosis, the typical course of disease, and responsiveness to specific therapies vary across cancer

subtypes.[6,552,554,555,581,582] In the NCCN Guidelines, most of the recommendations are based on data from patients with the most common subtypes—high-grade serous and grade 2/3 endometrioid. The NCCN Guidelines also include recommendations specifically for patients with less common ovarian cancers (LCOC), which in the Guidelines include the following: carcinosarcoma, clear cell carcinoma, mucinous carcinoma, low-grade serous, grade 1 endometrioid, borderline epithelial, malignant sex cord-stromal, and malignant germ cell tumors.

Staging

The NCCN Guidelines for Ovarian Cancer reflect the importance of stage and grade of disease on prognosis and treatment recommendations. Ovarian cancer is classified primarily as stages I to IV using the FIGO (International Federation of Gynecology and Obstetrics) staging system, which was approved by the AJCC and incorporated into the AJCC Cancer Staging Manual 8th Edition staging system, which was published in late 2016 and was effective for all cancer cases recorded on or after January 1, 2018 (see *Staging* section of the algorithm).[550,560] More than half of patients present with distant disease, although certain LCOC are more likely to be diagnosed at earlier stages[5,7,12] Serous ovarian cancer is now often referred to as either low grade (most grade 1 serous tumors) or high grade (most grade 2 or 3 serous tumors).[233,552,559,560,562,563] Pathologists may use histologic grades 1, 2, or 3 for endometrioid carcinomas, mucinous carcinomas, and stage IC tumors.[233] Primary peritoneal adenocarcinoma, fallopian tube carcinoma, and LCOC are also staged using the FIGO/AJCC (8th edition) ovarian cancer staging system.[550,559,560] Except for select women with stage I, grade 1 tumors (in whom survival is greater than 95% after comprehensive laparotomy), patients in all other stages of ovarian cancer are likely to require treatment after surgical staging. All patients with ovarian cancer, particularly those requiring additional treatment, should be encouraged to participate in a relevant clinical trial.

A pathology and staging cancer protocol is available from the College of American Pathologists (CAP) for examination of specimens from patients with primary tumors of the ovary, fallopian tube, or peritoneum, including pTNM requirements from the AJCC Staging Manual 8th edition and FIGO Staging.[233]

Molecular Testing

Upon pathologic confirmation of ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, based on analysis of a biopsy or surgical specimen, patients should be referred for a genetic risk evaluation and germline and somatic testing (if not previously done). This recommendation for germline and somatic testing is intentionally broad so that the genetic counselor and treating oncologist have the latitude to order whatever molecular tests they consider necessary based on evaluation of the individual patient. There is variation across NCCN Member Institutions regarding the breadth and timing of molecular testing for patients with pathologically confirmed ovarian, fallopian tube, or primary peritoneal cancer. Whereas some NCCN Panel members prefer to order individual tests only as needed to inform immediate treatment decisions, others prefer to order a panel of tests early in the course of treatment to avoid having to order more tests later in the course of treatment. Since germline and/or somatic *BRCA1/2* testing informs selection of maintenance therapy for those with stage II–IV disease who are in CR/PR after first-line platinum-based chemotherapy, NCCN Panel members agree that it is important to establish *BRCA1/2* mutation status for patients who may be eligible for maintenance therapy following completion of platinum-based first-line chemotherapy. Next-generation sequencing is an appropriate method for detecting *BRCA1/2* somatic mutations in tumor tissue.

As described in greater detail in the section on *Options After First-Line Chemotherapy*, homologous recombination deficiency status may provide

information on the magnitude of benefit of PARP inhibitor maintenance therapy for those without a *BRCA1/2* mutation. Therefore, there is nonuniform consensus among NCCN Panel members regarding the use of homologous recombination deficiency testing to inform maintenance therapy selection following first-line chemotherapy (category 2B). There are several molecular assays for detecting homologous recombination deficiency in patients without *BRCA1/2* mutations, but the NCCN Panel remains undecided on which specific assays to recommend.

Other tumor tissue molecular markers may inform selection of treatment for persistent or recurrent disease, but testing for these is not needed until the disease has proven to be refractory or at time of relapse. Prior to selection of systemic therapy for refractory or recurrent disease, validated tumor molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Testing is recommended to include at least: *BRCA1/2* and microsatellite instability (MSI) or DNA mismatch repair (MMR) if not previously done, as the results of these tests impact eligibility for certain recurrence therapy options. Polymerase chain reaction (PCR) testing is recommended for testing MSI.[583-591] IHC is recommended for detecting DNA MMR protein (MLH1, MSH2, MSH6, and PMS2).[592-595] Evaluation of homologous recombination deficiency can be considered, as results may help in selection among systemic therapy options for recurrent/refractory disease. Additional somatic tumor testing can be considered at the physician's discretion to identify genetic alterations for which FDA-approved tumor-specific or tumor-agnostic targeted therapy options exist. These additional tests may be particularly useful for patients whose recurrence therapy options are limited. For example, *NTRK* gene fusion testing is needed to determine eligibility for larotrectinib or entrectinib, two targeted agents that may be considered for recurrence therapy.[596-599] Based on results of a phase II study, pembrolizumab has been FDA approved for patients with tumor mutational burden-high (≥10 mutations/megabase; TMB-H) unresectable solid tumors who have progressed following prior treatment and have no satisfactory alternative treatment options.[600-602] Although this trial only included a small number of patients with ovarian cancer (n=15), a retrospective analysis found that TMB-H may be present in approximately 7% of patients with high-grade serous ovarian cancers,[603] so many are curious about the possible role of pembrolizumab for treating these patients, although results from a retrospective analysis showed no association between TMB and response to immune checkpoint inhibitor therapy.[604]

Primary Treatment

Primary treatment for presumed ovarian, fallopian tube, or primary peritoneal cancer usually consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy.[16,145,221,605,606] However, for some patients with early-stage disease, surgery alone (followed by observation) may be sufficient as primary treatment. In addition, for certain histologic subtypes, adjuvant therapy with hormonal agents are options that may be considered. NACT with interval debulking surgery (IDS) should be considered in patients with advanced-stage ovarian cancer who are not good candidates for upfront primary debulking surgery (PDS) due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced.[483,607] Emerging data support an increasing role of PARP inhibitors in the management of ovarian cancer.[608] In the primary treatment setting, PARP inhibitors have been incorporated as NCCN-recommended maintenance therapy options for select patients after first-line chemotherapy. Each of these primary treatment options, including maintenance therapy options after first-line chemotherapy, are described in more detail below. As described above, for all patients with suspected or confirmed ovarian cancer a gynecologic oncologist should be involved in assessing whether a patient is a suitable surgical candidate and/or an appropriate candidate for neoadjuvant therapy, and consideration of laparoscopic evaluation to determine feasibility of debulking surgery. The

NCCN Guidelines recommend symptom management and best supportive care for all patients; women should be referred for palliative care assessment if appropriate (see the NCCN Guidelines for Palliative Care, available at www.NCCN.org).[164,609,610]

Primary Surgery

Based on published improved outcomes, it is recommended that a gynecologic oncologist be the provider to determine the best surgical approach and perform the appropriate primary surgery.[222-224] An open laparotomy is recommended for most patients, but minimally invasive techniques may be appropriate in certain circumstances (See *Open Laparotomy Versus Minimally Invasive Techniques)*. Prior to surgery, patients with advanced disease should be counseled about port placement if intraperitoneal (IP) chemotherapy is being considered. Intraoperative pathologic evaluation with frozen sections may assist in management by providing confirmation of diagnosis and cancer type and providing information about the extent of disease. For all procedures, the surgeon should describe the following in the operative report: 1) the extent of initial disease in the pelvis, mid abdomen, and upper abdomen before debulking; 2) whether a complete or incomplete resection was achieved; and 3) if resection was incomplete, the amount and size of residual disease in the aforementioned areas after debulking.[611]

For most patients presenting with suspected malignant ovarian, fallopian tube, or primary peritoneal neoplasm, initial surgery should include a hysterectomy (if uterus present) and BSO with comprehensive staging and debulking as indicated.[16,612,613] This is the recommended approach for stage IA–IV if optimal cytoreduction appears feasible, the patient is a surgical candidate, and fertility is not a concern. It is described in greater detail below in the section entitled *Debulking Surgery for Newly Diagnosed Disease.*

For patients with early-stage disease who wish to preserve fertility, less extensive surgery may be an option, as described in the section entitled *Fertility-Sparing Options for Stage I Disease.*

NACT with IDS should be considered for patients with advanced-stage ovarian cancer who are not good candidates for PDS due to advanced age, frailty, poor performance status, comorbidities, or who have disease unlikely to be optimally cytoreduced.[483,607] The anticipated benefit from NACT therapy is to allow for medical improvement of the patient and/or clinical response that would increase the likelihood of optimal cytoreduction at IDS. Patients treated with NACT and IDS should also receive postoperative adjuvant chemotherapy. See sections entitled *Neoadjuvant Chemotherapy* and *Interval Debulking Surgery*. As described in the section entitled *Laparoscopic Evaluation Prior to Resection*, for certain patients with bulky disease, a minimally invasive procedure may be appropriate for obtaining biopsy material to confirm diagnosis and/or for molecular testing, and for determining whether optimal cytoreduction is possible.

Open Laparotomy Versus Minimally Invasive Techniques

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

Improvement of minimally invasive methods and selection of appropriate patients are the topics of much study and debate.[614-644] Minimally invasive techniques are commonly used for early-stage disease (or presumed early-stage disease), and some studies have shown no difference in surgical outcomes, recurrence rates, or survival for those who received minimally invasive versus open surgical staging.[615,617-619,622-624,628,635-638,645-

[649] If signs of lymph node metastasis or localized carcinomatosis are found, lymphadenectomy and complete pelvic peritonectomy may be feasible using minimally invasive techniques.[632] The NCCN Guidelines indicate that in early-stage disease, minimally invasive techniques to achieve the surgical goals may be considered in selected patients if performed by an experienced gynecologic oncologist.[318,612,625,650,651]

Studies in patients undergoing PDS for advanced disease have shown that debulking and surgical staging is technically feasible using minimally invasive techniques, and hysterectomy and unilateral salpingo-oophorectomy (USO) or BSO can be achieved using a minimally invasive approach.[621,626] Several studies have reported results for patients who received IDS via minimally invasive techniques, following NACT.[627,630,631,633,643] These studies have shown that for patients undergoing IDS, minimally invasive approaches are safe, technically feasible, and can achieve optimal cytoreduction; cancer-specific survival may be worse (than with laparotomy) if patients are not carefully selected; and patients with extensive disease will likely need to be converted to open lapartomy.[627,630,631,633,643] The NCCN Guidelines recommend that in select patients (who have undergone NACT), minimally invasive procedures may be used for IDS, provided that optimal debulking can be achieved. If the patient cannot be optimally debulked using minimally invasive techniques, either in the PDS or IDS setting, then they should be converted to an open procedure.

Laparoscopic Evaluation Prior To Resection

In select patients with advanced-stage disease, minimally invasive procedures (assessment laparoscopy) may be used to assess whether optimal cytoreduction is likely to be achieved by PDS, in order to determine whether NACT may be a better initial treatment option.[652-663] A randomized trial assessed whether laparoscopy would be useful to predict the ability to achieve optimal cytoreduction (<1 cm residual disease). Optimal cytoreduction was achieved in 90% (92/102) of patients randomized to the assessment laparoscopy arm compared to 61% (60/99) of patients who were randomized to the laparotomy without assessment laparoscopy arm (relative risk [RR], 0.25; 95% CI, 0.13–0.47; $P < .001$).[658] Assessment laparoscopy to evaluate extent of disease and feasibility of resection was used frequently in the large prospective trials validating NACT and IDS and was required in one of these trials (SCORPION).[484-486,663,664]

Fertility-Sparing Options for Stage I Disease

Fertility preservation is an evolving field and area of active research, with many approaches being explored, and many patient- and case-specific factors to consider, especially for those with malignancies.[665-667] Patients who wish to retain fertility options should be referred to a reproductive endocrinologist for preoperative evaluation and consultation. Large retrospective studies and meta-analyses have found that for stage I epithelial ovarian cancer, fertility-sparing surgery did not appear to compromise disease-free survival (DFS) or overall survival (OS) compared with radical surgery.[668-677] Although clear cell histology is associated with increased risk of poor outcomes,[675] some studies have shown that even among patients with stage I clear cell, fertility-sparing surgery does not increase risk of relapse or shorten survival compared with radical surgery.[669,670,673,674,677] Large retrospective studies among patients with stage I borderline ovarian tumors have found that recurrence rate and survival is similar for those treated with fertility-sparing versus radical surgery.[678-681] In retrospective studies, including multivariate analyses, fertility-sparing surgery does not appear to be associated with poorer outcomes (DFS, progression-free survival [PFS], OS) compared with more extensive surgery in patients with stage I germ cell tumors and sex cord-stromal tumors.[682-697] Fertility-sparing surgery may be considered for patients who wish to preserve fertility and have apparent early-stage disease and/or low-risk tumors, such as early-stage invasive epithelial

tumors, LMP lesions, malignant germ cell tumors, or malignant sex cord-stromal tumors. Even if the contralateral ovary cannot be spared, uterine preservation can be considered as it allows for potential future assisted reproductive approaches. A USO (preserving the uterus and contralateral ovary/fallopian tube) and comprehensive surgical staging may be adequate for select patients who wish to preserve fertility and appear to have stage IA unilateral tumors.[698-703] For those with bilateral stage IB tumors who wish to maintain fertility, a BSO (preserving the uterus) and comprehensive surgical staging can be considered. In patients undergoing USO or BSO, comprehensive surgical staging should still be performed in most patients to rule out occult higher-stage disease, because data show that approximately 30% of patients (with presumed early-stage disease) are upstaged after undergoing complete staging surgery.[619,623,624,704-708] Comprehensive surgical staging may be omitted in pediatric/adolescent patients with clinically apparent early-stage malignant germ cell tumors based on the pediatric surgical literature suggesting that incomplete staging does not result in poorer outcomes (OS).[709] For adults with apparent stage I malignant ovarian germ cell tumors, comprehensive staging is recommended based on results from retrospective studies suggesting that incomplete surgical staging may be associated with increased risk of recurrence;[710,711] although others found no relationship between incomplete staging and DFS.[712]

Debulking Surgery for Newly Diagnosed Disease

Debulking surgery is widely accepted as an important component of initial treatment for patients with clinical stage II, III, or IV disease, and multiple retrospective studies have contributed to the understanding of the extent of debulking needed to achieve maximal cytoreduction.[145,221,224,700,704,713-715] Optimal cytoreduction is defined as residual disease less than 1 cm in maximum diameter or thickness;[613,700,716-718] however, maximal effort should be made to remove all gross disease since resection to R0 offers superior survival outcomes.[713,719] Although debulking surgery is the standard of care, this recommendation is based on retrospective data (and thus is not a category 1 recommendation).[718] In general, the procedures described in this section should be part of the surgical management of patients with ovarian, fallopian tube, or primary peritoneal cancer in an effort to fully stage patients and to achieve maximal debulking preferable to resection of all visible disease in appropriate circumstances and at least to less than 1-cm residual disease if complete cytoreduction is not feasible.[720-722] These procedures also apply to many of the LCOC.

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

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

Hysterectomy and BSO should be performed. Although hysterectomy is recommended for most patients, USO or BSO with uterine preservation may be considered for selected patients with apparent stage IA/IB disease desiring to preserve fertility (See *Fertility-Sparing Options for Stage I Disease*). Every effort should be made to keep an encapsulated ovarian

mass intact during removal.[546,622] For young patients who will abruptly enter menopause after surgery, various supportive care measures may be used to help decrease hot flashes and other symptoms, and potentially reduce the risk of other systemic comorbidities that are more likely with surgical menopause.[723-726] HRT has not been shown to worsen survival in premenopausal patients with gynecologic cancers, but limited perspective data exist.[727,728]

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

The use of systematic lymphadenectomy is an area of controversy. For patients with presumed early stage, a randomized trial showed that systematic aortic and pelvic lymphadenectomy improved detection of metastatic nodes compared with node sampling (positive nodes found in 9 vs. 22%; *P* = .007), but was not associated with improved PFS or OS.[729] Operating time and the proportion of patients requiring blood transfusions was significantly higher for those who underwent systematic lymphadenectomy.[729] However, meta-analyses that included retrospective or observational studies have reported that systematic lymphadenectomy improves OS in patients with early-stage disease, even though it does not improve PFS.[730,731] Similar to this randomized controlled trial, other prospective studies using systematic lymphadenectomy have found 3% to 14% of patients had positive lymph nodes.[732-736]

For patients with advanced ovarian cancer, some early prospective studies suggested that systematic lymphadenectomy improved survival.[737,738] An early international randomized trial in patients with stage IIIB–IV (optimally debulked) epithelial ovarian cancer found that systematic lymphadenectomy improved PFS compared with resection of bulky nodes only, although OS was not improved, operating times were longer, and more patients required blood transfusions.[739] A randomized study of patients with stage IA–IV disease undergoing second look surgery found that although systematic lymphadenectomy increased detection of nodal metastases compared with resection of bulky nodes only (positive nodes found in 24% vs. 13%; *P* = .02), this did not translate into improved PFS or OS in the whole population or in subpopulations based on stage or extent of resection.[740] As in other studies, systematic lymphadenectomy was associated with longer operating times, more blood loss and transfusions, and longer hospital stays.[740] More recently, a large randomized trial (LION, NCT00712218) found that in patients with stage IIB–IV ovarian cancer who had macroscopically complete resection and normal nodes both before and during surgery, lymphadenectomy did not improve PFS or OS, and was associated with increased rates of serious postoperative complications and mortality within 60 days after surgery.[741] However, meta-analyses that included data from retrospective and observational studies have found that systematic lymphadenectomy improves OS in patients with advanced disease, even though PFS is not improved.[730,731,742-744]

Pelvic and para-aortic lymph node dissection is recommended for patients with disease confined to affected ovaries or to the pelvis, and for those with more extensive disease who have tumor nodules outside the pelvis that are 2 cm or less (presumed stage IIIB). Para-aortic lymph node dissection should be performed by stripping the nodal tissue from the vena cava and the aorta bilaterally to at least the level of the inferior mesenteric artery and preferably to the level of the renal vessels. The preferred method of dissecting pelvic lymph nodes is removal of lymph nodes overlying and anterolateral to the common iliac vessel, overlying and medial to the external iliac vessel, overlying and medial to the hypogastric vessels, and from the obturator fossa at a minimum anterior to the obturator nerve.[544]

For those with more extensive disease outside of the pelvis (nodules >2 cm), suspicious and/or enlarged nodes should be resected, if possible.[739,745] Systematic lymph node dissection and resection of clinically negative nodes is not required for these patients because results will not change staging and the procedure does not appear to impact OS, based on results from randomized trials (described above).[739-741]

Some surgeons classify debulking based on the number of procedures. Procedures that may be considered for optimal surgical cytoreduction (in all stages) include: bowel resection and/or appendectomy, stripping of the diaphragm or other peritoneal surfaces, splenectomy, partial cystectomy and/or ureteroneocystostomy, partial hepatectomy, partial gastrectomy, cholecystectomy, and/or distal pancreatectomy.[714,719,746]

Extensive resection of upper abdominal metastases is recommended as part of debulking for patients who can tolerate this surgery, as it is associated with improved PFS and OS.[714,719]

Select patients with low-volume residual disease after surgical cytoreduction for stage II or III invasive epithelial ovarian or peritoneal cancer are potential candidates for IP therapy.[747,748] In these patients, consideration should be given to placement of an IP catheter with initial surgery.[612]

Surgical Considerations for Mucinous Tumors

Since primary invasive mucinous tumors of the ovary are uncommon, it is important to establish the primary site in patients with these tumors. Thus, the upper and lower GI tract should be carefully evaluated to rule out an occult GI primary with ovarian metastases, and an appendectomy need only be performed in patients with a suspected or confirmed mucinous ovarian neoplasm if it appears to be abnormal.[749-751] A normal appendix does not require surgical resection in this setting.

Surgical Considerations for Ovarian Borderline Epithelial (LMP) Tumors

Although data show upstaging with lymphadenectomy, other data show that lymphadenectomy does not affect OS.[752-759] However, omentectomy and multiple biopsies of peritoneum (the most common sites of peritoneal implants) may upstage patients and may affect prognosis,[758,760-765] although some retrospective studies did not find association with prognosis.[753,766-768]

Ancillary Palliative Surgical Procedures

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

Analysis of Surgical Specimens

As described in the section entitled *Diagnosis, Pathology, and Staging*, surgical specimens should undergo pathology assessment to determine/confirm diagnosis, determine histologic subtype, and determine stage. Molecular testing is also appropriate for most patients; see *Molecular Testing* section above for detailed recommendations.

Primary Treatment for Patients Referred with Diagnoses by Previous Surgery

For patients referred with newly diagnosed ovarian cancer after a recent surgical procedure, primary treatment depends on the findings noted during the workup and evaluation performed by a gynecologic oncologist,

including the type of cancer, apparent stage, and the extent of residual disease. For those with an epithelial cancer and no evidence of residual disease on workup, further surgical staging is not needed if adjuvant chemotherapy is planned. For select subtypes, observation is an alternative to adjuvant chemotherapy in patients with stage IA/IB (Table 2). For patients with these subtypes and presumed stage IA/IB (and no evidence of residual disease), surgical staging can be considered if the patient would be a candidate for observation or reduced number of cycles of adjuvant chemotherapy. In these cases, observation after complete surgical staging is an option as long as the results confirm stage IA/IB disease. If surgical staging indicates higher-stage disease, however, adjuvant chemotherapy is usually recommended, depending on the specific cancer type. In some cases with presumed stage IA–IC and no signs of residual disease detected by workup, patients may opt for surgical staging to confirm whether they will be eligible for maintenance therapy following adjuvant chemotherapy. As discussed below, bevacizumab and PARP inhibitor maintenance options are only recommended for patients with stage II–IV disease, so those with presumed stage IA–IC disease may be particularly interested in surgical staging to determine whether they should be upstaged and thus eligible and/or needing maintenance therapy.

For patients who have an epithelial cancer and evidence of residual disease on workup, tumor cytoreductive surgery is recommended if the residual disease appears resectable. Following cytoreductive surgery, adjuvant treatment recommendations depend on cancer type and stage. If the residual disease appears unresectable, patients should be treated with NACT and IDS, and postoperative adjuvant chemotherapy could be considered (see sections on *Neoadjuvant Chemotherapy* and *Interval Debulking Surgery*).

Management After Primary Surgery

In the NCCN Guidelines for Ovarian Cancer, adjuvant therapy is defined as drugs or other forms of supplemental treatment following cancer surgery intended to decrease the risk of disease recurrence or to primarily treat residual disease, whether gross or microscopic, following surgical cytoreduction. Most patients with epithelial ovarian, fallopian tube, or primary peritoneal cancer should receive adjuvant systemic chemotherapy after primary surgery. Postoperative observation is an option for select patients with stage I disease, depending on cancer histologic type and substage, as shown in Table 2. Observation is considered an option in these select groups of stage I patients either because survival is greater than 90% with surgical treatment alone, or because for low-risk disease in certain cancer types it has not been demonstrated that adjuvant chemotherapy provides clear clinical benefit compared with observation alone for those who have had complete surgical staging.[769-775] Furthermore, postoperative observation should generally only be considered for patients who have had resection of all disease and complete surgical staging to rule out the possibility of clinically occult disease that would result in upstaging. For some of the less common epithelial cancer types (eg, mucinous, grade 1 endometrioid, low-grade serous), the benefit of adjuvant systemic therapy has not been demonstrated and observation is an option (Table 2). If analysis of a biopsy or surgical specimen shows a non-epithelial cancer type, such as sex cord-stromal or germ cell tumors, a patient should be treated according to separate pathways specific for non-epithelial cancers (see *Less Common Ovarian Cancers: Malignant Sex Cord-Stromal Tumors* and *Malignant Germ Cell Tumors* in the algorithm). See sections below on these less common cancer types.

A large variety of regimens and approaches have been tested in prospective randomized trials as postoperative therapy for patients with newly diagnosed ovarian cancer. Most of these regimens have included

intravenous (IV) chemotherapy, but IP administration of chemotherapy has also been tested, as have targeted agents and drugs from other classes. Recent trials have shown that maintenance therapy after postoperative platinum-based chemotherapy can have a positive impact on PFS in patients with advanced disease, so integration of maintenance therapy as part of postoperative management is increasing in prevalence and importance.[776-779] Selection of immediate postoperative treatment should be informed by eligibility criteria for maintenance therapy. This is discussed in greater detail in the section entitled *Options After First-Line Chemotherapy.*

Based on results of phase III randomized trials, the NCCN Guidelines include several options for postoperative treatment (within 6 weeks) in patients with advanced epithelial cancers: platinum-based IV chemotherapy, platinum-based IV/IP chemotherapy, and platinum-based IP chemotherapy plus bevacizumab, as outlined in Table 3. Specific options and supporting data for each of these categories of treatment are described in greater detail in the sections below. For stage I disease, data are more limited, and while the NCCN Guidelines include some platinum-based IV chemotherapy options, IP/IV chemotherapy and use of bevacizumab are not recommended approaches for stage I disease (Table 2). Specific options for stage I disease are also discussed in a subsequent section. For certain rarer cancer types, there are additional recommended adjuvant treatment options, including additional chemotherapy options, chemotherapy/bevacizumab regimens (stage II–IV only), and hormonal therapies (Table 2 and Table 3). More information on these options can be found in subsequent sections for specific LCOCs.

Table 2: NCCN Recommended Management Options Following Up Front Primary Surgery for Stage I Disease, Epithelial Cancer Types

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

--, not recommended; FU, fluorouracil; IV, intravenous

[a] Stage confirmed by a complete surgical staging procedure and pathologic analysis.

[b] Regimen options for all cancer types include Paclitaxel 175/carboplatin, Docetaxel/carboplatin, Carboplatin/liposomal doxorubicin, as shown in Table 8. Not including options for those who are elderly, have poor performance score, or have comorbidities.
[c] Hormone therapy options include aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, or tamoxifen.

Table 3. NCCN Recommended Management Options Following Up Front Primary Surgery for Stage II-IV[a]

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

FU, fluorouracil; IP, intraperitoneal; IV, intravenous.
[a] Not including options for those who are elderly, have poor performance score, or have comorbidities.
[b] Paclitaxel 175/carboplatin, Paclitaxel weekly/carboplatin weekly, Docetaxel/carboplatin, Carboplatin/liposomal doxorubicin, Paclitaxel weekly/carboplatin every 3 weeks (q3weeks), Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab (ICON-7 & GOG-218), as shown in Table 4 and Table 11.

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

During drug-based therapy, patients should be observed closely and treated for any complications. Appropriate blood chemistry tests should be monitored. Appropriate dose reductions and modifications of chemotherapy should be performed depending on toxicities experienced and goals of therapy. Consider scalp cooling to reduce incidence of alopecia for patients receiving chemotherapy with high rates of alopecia.[780]

Options for IV Chemotherapy

Comparison of IV chemotherapy regimens for postoperative treatment of newly diagnosed ovarian cancer has been the subject of many prospective randomized trials. Most of these trials have failed to show significant differences between regimens in efficacy outcomes (eg, PFS, OS), but many have shown differences in toxicity profile, ability to complete the planned therapy, and QOL. For this reason, the NCCN Guidelines include a number of recommended options for postoperative IV chemotherapy in patients with newly diagnosed epithelial ovarian, fallopian tube, or primary peritoneal cancer. The NCCN-recommended options for platinum-based IV chemotherapy to treat stage II–IV epithelial disease are summarized in Table 4, along with the list of trials that tested these regimens (last column). Table 5, Table 6, and Table 7 summarize the results of randomized trials that tested these recommended regimens. The most commonly used regimen, paclitaxel 175/carboplatin, has been considered the standard postoperative chemotherapy for ovarian cancer for many years, so there are many studies in which it has been tested (Table 5, Table 6, and Table 7).The history supporting these options is summarized below.

Table 4. IV Chemotherapy: NCCN Recommended Options for Stage II–IV, All Epithelial Cancer Types[a,b]

Regimen Short Name	Detailed Dosing per Cycle[c]	Cycle Length, Weeks	# Cycles	Category[d]	Preference Category	Randomized Trials
Paclitaxel 175/ carboplatin	Paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin AUC 5–6[e] IV over 30–60 minutes on Day 1	3	6	2A	Preferred	See Table 5 and 6
Paclitaxel weekly/ carboplatin weekly	Paclitaxel 60 mg/m^2 IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes, weekly	3	6 (18 weeks)	2A	Other Recommended	MITO-7[781] ICON8[782,783]
Paclitaxel weekly/ carboplatin q3weeks	Dose-dense paclitaxel, 80 mg/m^2 IV over 1 hour on days 1, 8, and 15 followed by carboplatin AUC 5–6[e] IV over 30–60 minutes on Day 1	3	6	2A	Other Recommended	ICON8[782,783] JGOG-3016[784-786] GOG-0262[787]
Carboplatin/ liposomal doxorubicin	Carboplatin AUC 5 IV over 30–60 minutes + pegylated liposomal doxorubicin 30 mg/m^2 IV over 1 hour[f]	4	6	2A	Other Recommended	MITO-2[788]
Docetaxel/ carboplatin	Docetaxel 60–75 mg/m^2 IV over 1 hour followed by carboplatin AUC 5–6 IV over 30–60 minutes on Day 1	3	6	2A	Other Recommended	SCOTROC1[789]

AUC, area under the curve; IV, intravenous; q3weeks, every 3 weeks.

[a] Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma; stage IC only for mucinous, low-grade serous, and grade 1 endometrioid.

[b] These options are primarily for patients aged ≤70 years, with good performance status, and without comorbidities. For patients who are elderly, have poor performance score, or have comorbidities, see alternate treatment options discussed in the section entitled *Options for Patients Who Are Elderly or Have Comorbidities or Poor Performance Score.*

[c] Infusion times may need to be adjusted for patients with prior hypersensitivity reaction(s). See *Management of Drug Reactions* in the algorithm.

[d] NCCN Category of Evidence and Consensus.

[e] Note that carboplatin dosing may be revised based on changes in serum creatinine methodology (see FDA carboplatin dosing statement). The AUC of 5 to 6 for carboplatin reflects contemporary treatment.

[f] For the first cycle of pegylated liposomal doxorubicin, infuse at 1 mg/min and make sure that the patient does not have a reaction.

Table 5. IV Chemotherapy: Randomized Trials Comparing Paclitaxel 175/Carboplatin[a] with Other Doublet Combinations[b]

Trial	Stage	N[c]	First-Line Systemic Therapy[d]			Efficacy[e]	Safety/QOL[f]
			Dosing per Cycle	Cycle Length, Weeks	# Cycles		
Dutch/Danish RCT[790,791]	IIB–IV	208	Paclitaxel 175 mg/m^2 D1 + cisplatin 75 mg/m^2 D1	3	6	NS	• More nausea, vomiting, peripheral neurotoxicity • Less granulocytopenia and thrombocytopenia
GOG-158[f, 792]	III	792	Paclitaxel 135 mg/m^2 D1 + cisplatin 75 mg/m^2 D1	3	6	NS	• More GI, renal, and metabolic toxicity; • Less thrombocytopenia
AGO-OVAR-3[793-795]	IIB–IV	798	Paclitaxel 185 mg/m^2 D1[g] + cisplatin 175 mg/m^2 D1	3	6	NS	• More nausea/vomiting, appetite loss, fatigue, and neurotoxicity • Less hematologic toxicity • Worse overall QOL, physical functioning, role functioning, cognitive functioning
ChiCTR-TRC-11001333[796]	II–IV	182	Paclitaxel 175 mg/m^2 D1 + nedaplatin 80 mg/m^2 D1	3	6	ITT: NS Stage III–IV: better PFS (P = .02); NS OS	• Less grade 3–4 leukopenia

D, day (of cycle); GI, gastrointestinal; ITT, intent-to-treat population; NS, no significant difference between arms; QOL, quality of life; RCT, randomized controlled trial.

[a] Each of the trials used the following regimen as comparator: Paclitaxel 175 mg/m^2 + carboplatin AUC 5–6, both D1, every 3 weeks (q3weeks) x 6 cycles.

[b] Doublets not recommended in the NCCN Guidelines.

[c] N shows total number of patients randomized, including those in the Paclitaxel 175/carboplatin control arm.

[d] Test regimen compared with Paclitaxel 175/carboplatin.

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

[f] Toxicity or QOL compared with Paclitaxel 175/carboplatin.

Table 6. IV Chemotherapy: Randomized Trials Comparing Paclitaxel 175/Carboplatin[a] with Triplet/Quadruplet Combinations

Trial	Stage	N[b]	First-Line Systemic Therapy[c]			Efficacy[d]	Safety/QOL[e]
			Dosing per Cycle	Cycle Length, Weeks	# Cycles		
ICON3[797]	IC–IV	653	Cyclophosphamide 500 mg/m^2 D1 + doxorubicin 50 mg/m^2 D1 + cisplatin 50 mg/m^2 D1	3	6	NS	• More nausea/vomiting, fever • Less sensory neuropathy
HeCOG RCT[798]	IIC–IV	247	Paclitaxel 175 mg/m^2 D1 + carboplatin AUC 7 D1 cycles 1, 3, 5[h] + cisplatin at 75 mg/m^2 D1 cycles 2, 4, 6	3	6	NS	• More severe nausea/vomiting

Trial	Stage	N[b]	First-Line Systemic Therapy[c]			Efficacy[d]	Safety/QOL[e]
			Dosing per Cycle	Cycle Length, Weeks	# Cycles		
AGO-OCSG RCT[799]	IIB–IV	1282	Paclitaxel 175 mg/m^2 D1 + carboplatin AUC 5 D1 + epirubicin 60 mg/m^2 D1	3	6	NS	• More nausea/emesis, mucositis, infections, and grade 3–4 hematologic toxicities • Worse QOL
NCT00102375[800]	IIB–IV	1308	Paclitaxel 175 mg/m^2 D1 cycles 1–6 + carboplatin AUC 5 D1 cycles 1–6 + topotecan 1.25 mg/m^2 D1–5 cycles 7–10	3	≤10	NS	• More grade 3–4 hematologic toxicities and grade 3–4 infections
GOG-0182-ICON5[801,802]	III–IV	4312	Paclitaxel 175 mg/m^2 D1 + carboplatin AUC 5 D1 + gemcitabine 800 mg/m^2 D1	3	8[i]	NS	• More neutropenia, thrombocytopenia, anemia, fever/infection, hepatic toxicity, peripheral neuropathy, GI toxicity
			Paclitaxel 175 mg/m^2 D1 + carboplatin AUC 5 D1 + pegylated liposomal doxorubicin 30 mg/m^2 D1 cycles 1, 3, 5, 7	3	8[i]	NS	• More neutropenia, thrombocytopenia, anemia, fever/infection, GI toxicity
			Paclitaxel 175 mg/m^2 D1 cycles 5–8 + carboplatin AUC 5 D3 cycles 1–4, AUC 6 D1 cycles 5–8 + topotecan 125 mg/m^2/d D1–3 cycles 1–4	3	8[i]	NS	• More anemia, hepatic toxicity • Less peripheral neuropathy
			Paclitaxel 175 mg/m^2 D1 cycles 5–8 + carboplatin AUC 6 D8 cycles 1–4, D1 cycles 5–8 + gemcitabine 1000 mg/m^2/d D1,8 cycles 1–4	3	8[i]	NS	• More thrombocytopenia, anemia, hepatic toxicity, pulmonary toxicity • Less peripheral neuropathy
Bolis et al, 2010[803]	III–IV	326	Topotecan 1.0 mg/m^2 D1–3 + paclitaxel 175 mg/m^2 D3 + carboplatin AUC 5 D3	3	6	NS	• More fatigue, anemia, leukopenia, neutropenia
du Bois et al, 2010[804]	I–IV	1742	Paclitaxel 175 mg/m^2 D1 + carboplatin AUC 5 D1 + gemcitabine 800 mg/m^2 D1, D8	3	6	Worse PFS (*P*=.0044) NS OS	• More grade 3–4 hematologic toxicity, fatigue • Worse QOL
OV-16/ EORTC-55012/ GEICO-0101[805]	IIB–IV	819	Cisplatin 50 mg/m^2 D1 cycles 1–4 + topotecan 0.75 mg/m^2 D 1–5 cycles 1–4 + paclitaxel 175 mg/m^2 D1 cycles 5–8 + carboplatin AUC 5 D1 cycles 5–8	3	8[j]	NS	• More hematologic toxicities, thromboembolic events, nausea, vomiting, and hospitalizations • Less neurosensory effects and allergic reactions
NSGO, EORTC GCG and NCIC CTG[806]	IIB–IV	887	Paclitaxel 175 mg/m^2 D1 + carboplatin AUC 5 D1 + epirubicin 75 mg/m^2	3	6–9	NS	• More anemia, febrile neutropenia, use of G-SCF, nausea, vomiting, mucositis • Less allergic reactions, arthralgia, myalgia • Worse QOL

AUC, area under the curve; D, day (of cycle); NS, no significant difference between arms; QOL, quality of life.

[a] Each of the trials used the following regimen as comparator: Paclitaxel 175 mg/m^2 + carboplatin AUC 5–6, both D1, every 3 weeks (q3weeks) x 6 cycles.

[b] N shows total number of patients randomized, including those in the Paclitaxel 175/carboplatin control arm.

[c] Test regimen compared with Paclitaxel 175/carboplatin
[d] Efficacy outcomes compared with Paclitaxel 175/carboplatin; NS indicates no significant difference between regimens for PFS and/or OS.
[e] Toxicity or QOL compared with Paclitaxel 175/carboplatin.
[f] Carboplatin dosing in the control arm of GOG-158 was AUC 7.5 (instead of AUC 5–6).
[g] Paclitaxel dosing in the control arm of AGO-OVAR-3 was 185 mg/m^2 (instead of 175 mg/m^2).
[h] Carboplatin dosing in the control arm of HeCOG was AUC 7 (instead of AUC 5–6).
[i] In GOG-0182-ICON5, 8 cycles was also used for the carboplatin/paclitaxel control arm.
[j] In OV-16, 8 cycles was also used for the paclitaxel/carboplatin control arm.

Table 7. IV Chemotherapy: Randomized Trials Comparing Paclitaxel 175/Carboplatin[a] with Other Recommended Regimens

Trial	Stage	N[b]	First-Line Systemic Therapy[c]			Efficacy[d] HR [95% CI]	Safety/QOL[e]
			Dosing per Cycle	Cycle Length, Weeks	# Cycles		
ICON3[797]	IC–IV	943	Carboplatin AUC ≥5[f] D1	3	6	NS	• Less alopecia grade 3–4, fever grade 3–4, sensory neuropathy grade 2–3, motor neuropathy grade 3–4
SCOTROC1[789]	IC–IV	1077	Docetaxel 75 mg/m^2 D1 + carboplatin AUC 5 D1	3	6[g]	NS	• More GI, peripheral edema, allergic reactions, nail changes • Less neurosensory and neuromotor toxicity, arthralgia, alopecia, abdominal pain • QOL: Global NS
MITO-2 NCT00326456[788]	IC–IV	820	Carboplatin AUC 5 D1 + pegylated liposomal doxorubicin 30 mg/m^2 D1	3	3-6[i]	NS	• More anemia, thrombocytopenia, skin toxicity, stomatitis • Less neuropathy, alopecia, diarrhea • QOL: less diarrhea after 3 cycles and loss of appetite after 3 cycles
MITO-7 NCT00660842[781]	IC–IV	822	Paclitaxel 60 mg/m^2 D1, D8, D15 + carboplatin AUC 2 D1, D8, D15	3	6	NS	• More pulmonary toxicity • Less neutropenia, febrile neutropenia, thrombocytopenia, neuropathy, hair loss, vomiting • Better QOL
JGOG-3016 NCT00226915[784,785]	II–IV	637	Paclitaxel 80 mg/m^2 D1, 8, 15[h] + carboplatin AUC 6 D1	3	6	Better PFS: 0.76 [0.62–0.91]; *P*=.0037 Better OS: 0.79, [0.63–0.99]; *P*=.039	• More grade 3–4 anemia • Global QOL NS; worse QOL on FACT-T subscale
GOG-0262 NCT01167712[787]	II–IV	112	Paclitaxel 80 mg/m^2 D1, 8, 15 + carboplatin AUC 6 D1	3	6	Better PFS: 0.62 [0.40–0.95]; *P*=.03	• More anemia and sensory neuropathy • Less neutropenia • Worse QOL on FACT-O TOI
		580	Paclitaxel 80 mg/m^2 D1, 8, 15 + carboplatin AUC 6 D1 + bevacizumab 15 m/kg D1 cycles 2–6[j]	3	6	NS	
ICON8 NCT01654146[782,783]	IC–IV	1566	Paclitaxel IV 80 mg/m^2 D1, D8, D15 + carboplatin IV AUC 5–6 D1	3	6	NS	• More grade 3–4 AEs, including uncomplicated neutropenia, anemia • Worse Global QOL
			Paclitaxel IV 80 mg/m^2 D1, D8, D15 + carboplatin IV AUC 2 D1, D8, D15	3	6	NS	• More grade 3–4 AEs, including uncomplicated neutropenia, carboplatin hypersensitivity reaction • Worse Global QOL

AE, adverse event; AUC, area under the curve; D, day (of cycle); NS, no significant difference between arms; QOL, quality of life.[a] Unless otherwise noted, each of the trials listed used the following regimen as comparator: Paclitaxel 175 mg/m^2 D1 + carboplatin AUC 5–6 D1, every 3 weeks (q3weeks) x 6 cycles.

[b] N shows total number of patients randomized, including those in the Paclitaxel 175/carboplatin control arm.
[c] Regimen compared with Paclitaxel 175/carboplatin
[d] Efficacy outcomes compared with Paclitaxel 175/carboplatin; NS indicates no significant difference between regimens for PFS and/or OS. Hazard ratio (HR) with 95% confidence interval (CI) and P-value are provided if statistically significant.
[e] Toxicity or QOL compared with paclitaxel 175/carboplatin regimen.
[f] Both arms in ICON3 used carboplatin AUC ≥5.
[g] In SCOTROC1, patients responding after 6 cycles were allowed to continue on carboplatin alone for another 3 cycles.
[h] JGOG-3016, the paclitaxel dosage in the control arm was 180 mg/m^2 (instead of 175 mg/m^2 as in the other trials).
[i] For those with good response after 3 cycles, MITO-2 allowed an additional 3 cycles.
[j] In GOG-0262, those who opted to have bevacizumab and were undergoing NACT (3 cycles) + IDS + adjuvant chemotherapy (3 cycles), bevacizumab was administered for cycles 2, 5, and 6.

Results from multiple early trials suggested that regimens that included a platinum agent resulted in better response rates and PFS (compared with other chemotherapy options).[807,808] Subsequent trials aimed at determining which platinum-based combinations are the most effective and safe.

Selecting a Platinum Agent

Multiple randomized trials compared carboplatin versus cisplatin, either alone or in combination with other agents (examples in Table 5 and 6).[791-794,809-814] All of these trials showed equivalent efficacy, but differences in toxicity profiles and QOL. Cisplatin was associated with higher rates of neurotoxicity, GI toxicities (eg, nausea, emesis), renal toxicity, metabolic toxicities, anemia, and alopecia, while carboplatin was associated with higher rates of thrombocytopenia and granulocytopenia.[791-794,809-814] The AGO-OVAR-3 study found that QOL was significantly better with carboplatin/paclitaxel versus cisplatin/paclitaxel, both in global QOL metrics and on various subscales.[793,794] Several randomized studies tested alternating carboplatin and cisplatin every other course, but found that efficacy was similar and toxicity somewhat worse than using carboplatin for every course.[798,814] Based on results from all these studies carboplatin is the recommended platinum agent for postoperative IV chemotherapy in patients with newly diagnosed ovarian, fallopian tube, and primary peritoneal cancers.

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

Many different chemotherapy agents have been tested in combination with platinum agents as options for IV chemotherapy in newly diagnosed ovarian cancer. Large randomized trials have compared various platinum-based doublet, triplet, and quadruplet combinations with cyclophosphamide, paclitaxel, docetaxel, topotecan, doxorubicin, epirubicin, gemcitabine, topotecan, and melphalan.[788,789,797,799-801,803-806,815-821] Trials that compared platinum-based doublets with cyclophosphamide versus paclitaxel showed that paclitaxel was associated with significantly better response rate, PFS and OS.[815-817] Thus, paclitaxel is preferred over cyclophosphamide for platinum-based combination therapy in the first-line setting. Based on results from randomized trials showing improved safety and QOL with carboplatin/paclitaxel versus cisplatin/paclitaxel (Table 5),[791-794] carboplatin/paclitaxel became the “standard” combination therapy option for postoperative first-line IV chemotherapy in patients with ovarian, fallopian tube, or primary peritoneal cancer. Most subsequent trials used this doublet, usually paclitaxel 175 mg/m^2 plus carboplatin AUC 5–6, given on day 1 of a 21-day cycle, as the control arm (see examples in Table 5, Table 6, and Table 7). This regimen is also a recommended option in the NCCN Guidelines (Table 4).

Two other platinum-based doublets have shown similar efficacy to carboplatin/paclitaxel, but with different safety profiles.[788,789] The SCOTROC1 study found that docetaxel/carboplatin resulted in similar PFS, OS, and global QOL scores as paclitaxel/carboplatin, and was associated with lower rates of neurotoxicity, arthralgia, myalgia, alopecia, and abdominal pain, but higher rates of other adverse events (AEs) (GI, peripheral edema, allergic reactions, and nail changes [Table 7]).[789] The MITO-2 trial found that pegylated liposomal doxorubicin/carboplatin was associated with a higher response rate but similar PFS and OS as paclitaxel/carboplatin (Table 7).[788] pegylated liposomal doxorubicin/carboplatin was associated with higher rates of certain hematologic toxicities, skin toxicity, and stomatitis, but lower rates of neurotoxicity and alopecia than the paclitaxel/carboplatin control.[788] Global QOL and most functional domains and symptom scales were the same across treatment arms, and pegylated liposomal doxorubicin/carboplatin was associated with worse scores for certain patient-reported toxicities.[788] Therefore, this regimen may be useful in select patients at high risk for neurotoxicity or those who would like to avoid alopecia. The docetaxel/carboplatin and liposomal doxorubicin/carboplatin regimens are both recommended options in the NCCN Guidelines (Table 4), and may be considered for patients who are at high risk for neuropathy (eg, patients with diabetes).[822]

Randomized trials testing platinum-based triplet or quadruplet regimens have generally found that these do not improve efficacy but are associated with worse toxicity when compared with platinum-based doublets[797,799-801,803-806] or single-agent platinum regimens.[818,819] Examples of platinum-based triplet and quadruplet regimens that have been compared with the standard paclitaxel/carboplatin regimen are in Table 5 and 6. One study showed that adding gemcitabine to carboplatin/paclitaxel actually resulted in worse PFS compared with carboplatin/paclitaxel alone (Table 5 and 6).[804]

Carboplatin/Paclitaxel Dosing Options

As noted above, for postoperative first-line treatment of ovarian cancer, the most commonly used dosing for IV carboplatin/paclitaxel combination therapy is paclitaxel 175 mg/m^2 + carboplatin AUC 5–6, both given on day 1 of a 3-week cycle. As summarized in Table 7, multiple randomized studies have compared different dosing schedules for IV carboplatin and paclitaxel regimens as first-line postoperative therapy for ovarian cancer.[781-785,787,823,824] Three different randomized trials (JGOG-3016, GOG-0262, and ICON8) tested “dose-dense” weekly paclitaxel dosing of 80 mg/m^2 combined with the standard carboplatin dosing (AUC 6, day 1, every 3 weeks).[782,784,785,787] JGOG-3016 results showed that this regimen improved PFS and OS, GOG-0262 showed that this regimen improved PFS (in the subset of patients who were not receiving concurrent bevacizumab), and ICON8 found no significant improvements in PFS or OS (Table 7). All three trials reported increased rates of neutropenia and signs of worse QOL among patients treated with the dose-dense regimen.

Two randomized trials (MITO-7 and ICON8) compared standard paclitaxel/carboplatin dosing with weekly paclitaxel (60 or 80 mg/m^2) plus weekly carboplatin (AUC 2), and found no significant differences in efficacy outcomes.[781-783] MITO-7, which tested 60 mg/m^2 paclitaxel, showed higher rates of pulmonary toxicity, but lower rates of neutropenia, febrile neutropenia, thrombocytopenia, neuropathy, hair loss, and vomiting, and significant improvement in QOL.[781] ICON8, which tested 80 mg/m^2 paclitaxel, showed higher rates of neutropenia and carboplatin hypersensitivity reaction, and worse global QOL compared with standard carboplatin/paclitaxel dosing.[782,783] Based on these results, if a weekly regimen is used, the paclitaxel weekly/carboplatin weekly regimen using 60 mg/m^2 paclitaxel is the recommended option (for stage II–IV disease; Table 4).

Options for Stage I, Epithelial Cancer Types

Most of the patients had stage III–IV disease in randomized trials testing IV chemotherapy as postoperative first-line treatment for ovarian cancer. More recent trials allowed patients with stage II–IV disease, but only some included patients with select stage I disease (Table 5, Table 6, and Table 7). Therefore, the list of recommended options is much shorter for patients with stage I disease, as summarized in Table 8, which also shows trials that tested the recommended regimens (last column). Patients with stage I disease were included in randomized trials comparing IV paclitaxel/carboplatin (standard dosing) with single-agent carboplatin (ICON3),[797] docetaxel/carboplatin (SCOTROC1),[789] pegylated liposomal doxorubicin/carboplatin (MITO-2),[788] and weekly paclitaxel/weekly carboplatin (MITO-7 and ICON8).[781-783] Of these, the first three are recommended options for stage I disease in epithelial cancer types. Paclitaxel weekly/carboplatin weekly is more logistically challenging to administer and is therefore not often used in the setting of stage I disease, given the lower risk of recurrence (compared with more advanced disease). Patients with stage I disease have also been included in some randomized trials testing triplet or quadruplet regimens,[797,804,819,820] but the added toxicity of these regimens with no clear impact on efficacy makes options inappropriate for stage I.

Table 8. IV Chemotherapy: Regimens Recommended for Stage I, All Epithelial Cancer Types[a, b]

Regimen Short Name	Detailed Dosing per Cycle[c]	Cycle Length, Weeks	# Cycles	Category[d]	Preference Category	Randomized Trials
Paclitaxel 175/ carboplatin	Paclitaxel 175 mg/m^2 IV over 3 hours followed by carboplatin AUC 5–6[e] IV over 30–60 minutes on Day 1	3	High-grade serous: 6 All other: 3	2A	Preferred	ICON3[797] GOG-157[825,826] du Bois, 2010[804] SCOTROC1[789] MITO-2[788] MITO-7[781] ICON8[782,783]
Carboplatin/ liposomal doxorubicin	Carboplatin AUC 5 IV over 30–60 minutes + pegylated liposomal doxorubicin 30 mg/m^2 IV over 1 hour[f]	4	High-grade serous: 6 All other: 3	2A	Other Recommended	MITO-2[788]
Docetaxel/ carboplatin	Docetaxel 60–75 mg/m^2 IV over 1 hour followed by carboplatin AUC 5–6 IV over 30–60 minutes on Day 1	3	High-grade serous: 6 All other: 3	2A	Other Recommended	SCOTROC1[789]

AUC, area under the curve; IV, intravenous.

[a] Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma; stage IC only for mucinous, low-grade serous, and grade 1 endometrioid.

[b] These options are primarily for patients aged ≤70 years, with good performance status, and without comorbidities. For patients who are elderly, have poor performance score, or have comorbidities, see alternate treatment options discussed in the section entitled *Options for Patients Who Are Elderly or Have Comorbidities or Poor Performance Score.*

[c] Infusion times may need to be adjusted for patients with prior hypersensitivity reaction(s). See *Management of Drug Reactions* in the algorithm.

[d] NCCN Category of Evidence and Consensus.

[e] Note that carboplatin dosing may be revised based on changes in serum creatinine methodology (see FDA carboplatin dosing statement). The AUC of 5 to 6 for carboplatin reflects contemporary treatment.
[f] For the first cycle of pegylated liposomal doxorubicin, infuse at 1 mg/min and make sure that the patient does not have a reaction.

Options for Patients Who Are Elderly or Have Comorbidities or Poor Performance Score

Patients with poor PS, comorbidities, or advanced age (>70 years) may be less likely to tolerate the IP/IV regimen or IV combination chemotherapy regimens recommended in the NCCN Guidelines, and this may lead to discontinuation before regimen completion.[795,822,827-829] For example, patients aged 70 years or older undergoing paclitaxel/carboplatin-based therapy may be at higher risk of febrile neutropenia, anemia, diarrhea, asthenia, thromboembolic events, or hypertension (associated with bevacizumab).[795,827] Analyses of data from prospective studies have aimed to identify baseline patient characteristics that are associated with increased risk of severe toxicity and failure to complete adjuvant chemotherapy in patients with newly diagnosed ovarian cancer.[830-835] Results suggest that risk of severe toxicity, discontinuation, and even OS may be correlated with increased age (even among the elderly); performance score; depression at baseline, as quantified by the Hospital Anxiety and Depression Scale (HADS), Activities of Daily Living (ADL) score, Instrumental Activities of Daily Living (IADL) score, and social activities score; lymphopenia, hypoalbuminemia, and a number of comedications.

Based on clinical judgment and expected tolerance to therapies, alternate dosing or single-agent carboplatin may be more appropriate for patients who are elderly, have poor PS, or have comorbidities. As shown in Table 7, the ICON3 trial showed that single-agent carboplatin had similar efficacy but less toxicity than the standard carboplatin/paclitaxel combination.[797] Results from several other early phase III randomized trials also suggest that platinum monotherapy can provide equivalent efficacy but improved safety profile compared with platinum/taxane combination therapies.[808,818,819] ICON2 included analysis of an elderly subgroup that confirmed no differences in OS between single-agent and combination therapy.[819] The phase II EWOT3 study tested single-agent carboplatin (AUC 5, every 3 weeks [q3weeks] x ≤6 cycles) as adjuvant IV chemotherapy in patients aged 70 years or older with stage III–IV newly diagnosed epithelial ovarian cancer.[832] Results showed that overall, 74% of patients completed the planned 6 cycles of therapy. Grade 3–4 hematologic toxicities occurred in 50% of patients, and the most common grade 3–4 nonhematologic toxicities included fatigue (15%), anorexia (12%), infection (9%), and thrombosis (12%).[832,833] The phase II EWOT2 trial tested standard paclitaxel (175 mg/m^2)/carboplatin (AUC 5, both q3weeks) as adjuvant first-line chemotherapy in patients with epithelial ovarian cancer who were elderly (aged ≥70 y), showing 68% completed all 6 cycles.[833] These EWOT trials suggested that neutropenia was more common with paclitaxel/carboplatin, but thrombocytopenia was more common with carboplatin monotherapy.[833] Data from the EWOT studies were used to develop a geriatric vulnerability score (GVS) to help identify elderly patients at risk for worse OS, higher rates of severe AEs and unplanned hospital admissions, and lower rates of treatment completion. This score was based on albuminemia, the IADL score, lymphopenia, and HADS.[832]

GOG-273, a nonrandomized prospective study, evaluated single-agent carboplatin (AUC 5, q3weeks) with and without reduced-dose paclitaxel (135 mg/m^2, q3weeks) as postoperative adjuvant or neoadjuvant therapy in elderly patients (aged ≥70 years) with previously untreated ovarian, primary peritoneal, or fallopian tube cancer.[834] Those who selected

combination therapy versus monotherapy were younger, had better performance score, higher IADL, higher ADL, better QOL, and fewer comorbidities, so outcomes cannot be compared across treatment groups. Nonetheless, results showed that most patients completed 4 cycles of therapy (92% for combination therapy, 75% for monotherapy). Not surprisingly, combination therapy was associated with increased risk of toxicity and greater risk of neurotoxicity, with the most common grade ≥3 side effects being neutropenia, anemia, diarrhea, and dehydration, while for carboplatin monotherapy the most common grade ≥3 side effects were anemia, fatigue, and thrombocytopenia. Paclitaxel hypersensitivity was the major reason for dose reduction in those receiving combination paclitaxel/carboplatin, whereas hematologic toxicity was the primary reason for dose reduction in those receiving carboplatin monotherapy.

As shown in Table 7, the phase 3 randomized trial (MITO-7) showed that weekly paclitaxel 60 mg/m^2 plus weekly carboplatin AUC 2 resulted in similar PFS and OS but improved safety profile and QOL compared with standard paclitaxel (175 mg/m^2)/carboplatin (AUC 6) every 3 weeks in women with chemotherapy-naïve advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer.[781] Median PFS was similar between the two regimens even in the subgroup of patients aged 70 years or older. For example, fewer patients receiving the weekly regimen had higher rates of grade 3 to 4 neutropenia (167 [42%] of 399 patients vs. 200 [50%] of 400 patients).[781] This carboplatin weekly/paclitaxel weekly regimen was also tested in the phase II trial MITO-5 in a population of patients who were elderly (aged ≥70 years) and had high risk of poor outcomes based on frequency of comorbidities, ADL, IADL, and performance score.[836] Results showed that 88.5% of patients were treated without suffering unacceptable toxicity, suggesting that use of this regimen in this population is feasible and has an acceptable safety profile.[836] Therefore, this weekly carboplatin/paclitaxel regimen may be considered for elderly patients or those with poor PS.

EWOC-1 (NCT02001272) is a randomized trial in patients with stage III–IV epithelial ovarian cancer who are elderly (aged ≥70 years) comparing first-line chemotherapy with standard paclitaxel175/carboplatin versus carboplatin monotherapy (AUC 5-6, q3weeks) and versus weekly paclitaxel 60 mg/m^2 plus weekly carboplatin AUC 2.[829] About half of the patients had poor performance score (ECOG ≥2). Results from the preplanned intermediate analysis showed that although the feasibility of all three regimens was not significantly different (65%, 47%, 60%), carboplatin monotherapy was associated with significantly shorter PFS and OS, whereas efficacy results for the two carboplatin/paclitaxel arms were not distinguishable.[829] Based on these survival results the trial is being prematurely terminated.

The recommended IV chemotherapy options for patients who are elderly or have comorbidities are summarized in Table 9, along with the phase II and III trials that tested these regimens (last column). Some NCCN Panel members prefer the paclitaxel/carboplatin combination regimens over carboplatin monotherapy based on the efficacy results of the EWOC-1, but for patients who cannot tolerate toxicities associated with combination therapy, carboplatin monotherapy remains an option. Algorithms are available for predicting chemotherapy toxicity (see the NCCN Guidelines for Older Adult Oncology, available at www.NCCN.org).

Table 9. IV Chemotherapy: NCCN Recommended Options for Patients Who Are Elderly, Have Comorbidities, or Poor Performance Status, All Epithelial Cancer Types[a]

Regimen Short Name	Detailed Dosing per Cycle[b]	Cycle Length, Weeks	# Cycles	Category[c]	Population	Supporting References
Paclitaxel weekly/ carboplatin weekly	Paclitaxel 60 mg/m^2 IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes, weekly	3	Stage I: 6 (18 weeks)[d] Stage II–IV: 6 (18 weeks)	2A	Poor performance status Elderly (aged >70 years) Comorbidities	MITO-7[781] MITO-5[836] EWOC-1[829]
Paclitaxel 135/ carboplatin	Paclitaxel 135 mg/m^2 IV over 3 hours + carboplatin AUC 5 IV over 30–60 minutes	3	Stage I: 3–6[d] Stage II–IV: 6	2A	Elderly (aged >70 years) Comorbidities	GOG-273[834]
Carboplatin	Carboplatin AUC 5 IV over 30–60 minutes	3	Stage I: 3–6[d] Stage II–IV: 6	2A	Elderly (aged >70 years) Comorbidities	ICON2[819] ICON3[797] GOG-273[834] EWOT3[832,833] GOG-273[834] EWOC-1[829]

AUC, area under the curve; IV, intravenous.

[a] Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma; stage IC only for mucinous, low-grade serous, and grade 1 endometrioid.

[b] Infusion times may need to be adjusted for patients with prior hypersensitivity reaction(s). See *Management of Drug Reactions* in the algorithm.

[c] NCCN Category of Evidence and Consensus.

[d] For stage I disease, 6 cycles is recommended for high-grade serous; can consider fewer cycles (as few as 3) for other cancer types.

Number of Cycles

Recommendations for the number of cycles of treatment vary with the stage of the disease. Panel members had an extensive discussion about the number of cycles of chemotherapy that should be recommended for patients with advanced-stage disease. There is no evidence confirming that more than 6 cycles of combination chemotherapy are required for initial chemotherapy. Early randomized studies showed that patients treated with 8 or 10 cycles of adjuvant first-line platinum-based IV chemotherapy had similar survival but experienced worse toxicity than those treated with only 5 cycles.[837,838] For the regimens recommended in the NCCN Guidelines (for postoperative first-line IV chemotherapy), most of the supporting phase III randomized trials tested 6 cycles of therapy (see Table 5, Table 6, and Table 7). Although cross-trial comparisons should be interpreted with caution, the few trials that used greater than 6 cycles,[800,801,805,806] did not appear to show better outcomes than those that used 6 cycles. Also, it has been noted that among the two trials showing improved efficacy with first-line cisplatin/paclitaxel versus cisplatin/cyclophosphamide in patients with advanced ovarian cancer, the later trial that allowed continuation beyond 6 cycles, up to 9 cycles reported a smaller treatment effect (on PFS and OS) and had higher rates of neurotoxicity, suggesting that treatment beyond 6 cycles is unlikely to provide additional clinical benefit.[815,816] One randomized trial (NCT00102375) showed that adding 4 cycles of topotecan after 6 cycles of carboplatin/paclitaxel did not improve PFS or OS, or even response

among those with measurable disease (Table 6).[800] The phase III randomized trial GOG-157 compared 3 versus 6 cycles of paclitaxel/carboplatin as postoperative first-line IV chemotherapy for patients with stage I–II epithelial ovarian cancer at high risk, defined as stage IA/IB with grade 3 or clear cell, or stage IC/II with any grade.[825,826] For the intent-to-treat (ITT) population, the number of cycles did not have a significant impact on relapse-free survival (RFS) or OS, whereas 6 cycles was associated with higher rates of grade 3–4 neurotoxicity, grade 4 granulocytopenia, and grade 2–4 anemia.[825,826] After a median of 91 months of follow-up, exploratory analysis by cancer type showed that 6 cycles (vs. 3) was associated with significant improvement in RFS for patients with serous histology (HR, 0.30; 95% CI, 0.13-0.72; *P* = .007), but this effect was not seen for any other cancer subtypes (ie, endometrioid, clear cell, mucinous), and the number of cycles did not significantly impact OS for any subgroup.[826] Based on these data the NCCN Guidelines recommend 6 cycles adjuvant IV chemotherapy for stage I high-grade serous carcinoma, 3 cycles for other stage I epithelial cancers, and 6 cycles for stage II–IV epithelial disease (regardless of tumor type).

<u>Toxicity</u>

All of these regimens have different toxicity profiles. The docetaxel/carboplatin regimen is associated with increased risk for neutropenia; the IV paclitaxel/carboplatin regimen is associated with increased risk of sensory peripheral neuropathy; and dose-dense paclitaxel is associated with increased risk of anemia and decreased QOL.[784,786,788,789] Note that there are no agents to prevent chemotherapy-induced peripheral neuropathy.[839]

Targeted Agents

<u>Bevacizumab in the First-Line Setting</u>

Two phase 3 randomized trials, GOG-0218 and ICON7, tested the effects of adding bevacizumab during first-line platinum-based combination chemotherapy and as single-agent maintenance therapy after first-line chemotherapy (for patients who had not progressed during initial treatment with chemotherapy + bevacizumab).[840-842] The study design and results from these trials are summarized in Table 10.

Table 10. Bevacizumab in the First-Line Setting: Phase 3 Randomized Controlled Trials

A. Summary of Results

Trial	Patients[a]	First-Line Chemotherapy[b] → Maintenance	n	F/u, mo[c]	PFS Median (months), HR [95% CI], P-value[d]	OS Median (months), HR [95% CI], P-value[d]	AEs G3-4	AEs G5	Dc'd AEs[e]
GOG-0218 NCT00262847 Burger 2011[840]	Stage III incompletely resected (34% ≤1 cm, 40% >1) or stage IV (26%) Residual disease, R0/>0–≤1 cm/>1 cm:[531] 5%/41%/54% Cancer type: 85% serous Tumor grade 3: 73%	Arm 1: carbo/pac/placebo → placebo	625	19.4[f]	10.3	39.3	NR	1.0%	12%
		Arm 2: carbo/pac/bev → placebo	623		11.2 0.908 [0.795–1.040] *P*=.16	38.7 1.036 [0.827–1.297] *P*=.76	NR	1.6%	15%
		Arm 3: carbo/pac/bev → bev	625		14.1 0.717[f] [0.625–0.824] *P*<.001	39.7 0.915[f] [0.727–1.152] *P*=.45	NR	2.2%	17%
GCIG ICON7 Perren 2011[841] Oza 2015[842]	High-risk early stage (I–IIA and clear cell or Grade 3; 9%), IIB–IIIB (21%) or IIIC–IV (70%) Residual disease, R0/>0–≤1 cm/>1 cm: 48%/24%/26% Cancer type: 69% serous Tumor grade 3: 72%	Arm 1: carbo/pac → none	764	48.6	17.5	58.6	54%	1%	NR
		Arm 2: carbo/pac/bev → bev	764	48.8	19.9 0.93[g] [0.83–1.05] *P*=.25	58.0 0.99[g] [0.85–1.14] *P*=.25	65%	1%	NR

B. Treatment Regimens

Trial	Treatments
GOG-0218	Arm 1: Carboplatin AUC 6 + paclitaxel 175 mg/m^2 IV, q3weeks x cycles 1–6 Arm 2: Carboplatin AUC 6 + paclitaxel 175 mg/m^2 IV, q3weeks x cycles 1–6 + bevacizumab 15 mg/kg q3weeks x cycles 2–6 Arm 3[h]: Carboplatin AUC 6 + paclitaxel 175 mg/m^2 IV, q3weeks x cycles 1–6 + bevacizumab 15 mg/kg q3weeks x cycles 2–6 → maintenance bevacizumab 15 mg/kg q3weeks x cycles 7-22
GCIG ICON7	Arm 1: Carboplatin AUC 5–6 + paclitaxel 175 mg/m^2, q3weeks x 6 cycles Arm 2[h]: Carboplatin AUC 5–6 + paclitaxel 175 mg/m^2, q3weeks x 6 cycles + bevacizumab 7.5 m/kg q3weeks x 5–6 cycles (omitted cycle 1 if <4 weeks from surgery) → maintenance bevacizumab 7.5 m/kg q3weeks x 12 cycles

AEs, adverse events; AUC, area under the curve; carbo, carboplatin; bev, bevacizumab; dc'd, discontinued; f/u, follow-up; G, grade; HR, hazard ratio; mo, months; NR, not reported; OS, overall survival; pac, paclitaxel; PFS, progression-free survival; q3weeks, every 3 weeks; R0, no visible residual disease.

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

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

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

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

[e] Patients who discontinued therapy due to AEs.

[f] Multivariate analysis of GOG-0218 results after a median of 73.2 months follow-up confirmed that there was a significant difference in PFS between Arm 1 and Arm 3 (HR [95% CI], 0.74 [0.65–0.84]; *P*<.001) and no significant impact on OS (HR [95% CI], 0.87 [0.75–1.0]; *P*=.053).[843] Long-term follow-up results after a median of 102.9 months confirmed no significant difference in OS between control (median OS, 40.8 mo) and Arm 2 (median OS, 40.8 months; HR, 1.06; 95% CI, 0.94–1.20)

or Arm 3 (median OS, 43.4 months; HR, 0.96; 95% CI, 0.85–1.09).[844] Exploratory analysis of disease-specific survival yielded similar results. Subgroup analysis showed no treatment-dependent differences in OS for patients with stage III disease, but did yield interesting results for patients with stage IV disease. Arm 1 and 2 had no significant difference in OS, but Arm 3 showed significantly longer OS compared with Arm 1 (42.8 mo vs. 32.6 mo; HR, 0.75; 95% CI, 0.59–0.95).[844]

[g] Primary analysis of GCIG ICON7 after a median of 19.4 months follow-up showed improved PFS with bevacizumab (HR [95%CI], 0.81 [0.70–0.94]; *P*=.004). Both PFS and OS showed non-proportionality, with the maximum treatment-dependent differences for PFS and OS between 12–18 mo.[841]

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

Bevacizumab in the First-Line Setting: Efficacy

In GOG-0218, although PFS was similar for patients treated with carboplatin/paclitaxel (Arm 1, control) versus those who also had bevacizumab during initial treatment (Arm 2, carboplatin/paclitaxel/bevacizumab), patients treated with carboplatin/paclitaxel/bevacizumab followed by maintenance with single-agent bevacizumab (Arm 3) had a 3-month improvement in median PFS compared with the control arm (See Table 10A).[840,843] OS was not significantly different across all three arms (Table 10A), even after long-term follow-up.[840,843,844] The effects of treatment on PFS and OS were non-proportional over time, however, with the greatest difference between arms around 15 months, and the Kaplan-Meier curves converging again about 9 months later. Results from ICON7 were similar, with results from the primary analysis (median follow-up 19.4 months) showing longer PFS with carboplatin/paclitaxel/bevacizumab, followed by single-agent bevacizumab maintenance therapy (Arm 2) compared with carboplatin/paclitaxel along (Arm 1).[841] Analyses after longer follow-up (median 48.9 months), however, showed no significant treatment-dependent differences in PFS or OS (Table 10A).[842] Again the effects were non-proportional over time, with the treatment-dependent differences in PFS and OS increasing to a peak between 12–18 months, and the Kaplan-Meier curves subsequently converging.[842]

For both GOG-0218 and ICON7, outcomes with upfront paclitaxel/carboplatin/bevacizumab plus single-agent bevacizumab maintenance (Arm 3 in GOG-0218, Arm 2 in ICON7) were compared with control (paclitaxel/carboplatin alone, Arm 1) for a variety of patient subgroups to determine whether there are particular groups of patients that benefit from bevacizumab. Results across both studies showed that patients with features associated with poor prognosis tend to derive a greater benefit from the addition of bevacizumab.[840] Analyses of data from GOG 0218 showed that bevacizumab improved OS in patients with stage IV disease and in patients with ascites, another high-risk group (more likely to have poor performance score, high-grade serous histology, higher median pre-treatment CA-125 level, and suboptimal surgical cytoreduction).[843-845] For ICON7, although after long-term follow-up (median 48.9 months) there were no significant effects of bevacizumab on PFS or OS for the total population, subgroup analyses identified a high-risk group for which bevacizumab improved both PFS (median PFS for Arm 1 vs. Arm 2: 10.5 vs. 16.0 months; HR, 0.73 [95% CI, 0.61–0.88]; *P* = .001) and OS (median OS for Arm 1 vs. Arm 2: 30.2 vs. 39.7 months; HR, 0.78 [95% CI, 0.63–0.97]; *P* = .03).[842] This high-risk group included those with either stage IV, inoperable stage III, or suboptimally debulked (residual disease >1 cm) stage III. Exploratory analyses suggest that stage may be more important than the extent of residual disease for identifying patients who may benefit from bevacizumab.[846] Although sample sizes were small, analyses found no significant impact of bevacizumab on OS for the following subgroups: clear cell carcinoma, low stage high-grade disease, and low grade serous.[842]

An exploratory analysis of GOG-0218, including 1195 patients with DNA samples that could be sequenced, showed that the presence of mutations in *BRCA1*, *BRCA2*, or non-*BRCA* homologous recombination repair (HRR)

genes was associated with longer PFS and OS relative to patients with no mutations in these genes, even after adjusting for treatment, stage, size of residual disease, and performance status at baseline.[847] For patients without mutations in any of these genes, the addition of bevacizumab (to up-front chemotherapy and as maintenance) was associated with improved PFS (median PFS for Arm 1 vs. Arm 3: 10.6 vs. 15.4 months; HR, 0.71 [95% CI, 0.60–0.85]; *P* = .0001). This treatment effect on PFS was not observed in the group of patients with mutations in *BRCA1/2* or a non-*BRCA* HRR gene. These findings are consistent with those from other exploratory analyses suggesting that patients with poorer prognosis may derive the most benefit from bevacizumab.[847] Nonetheless, mutation status did not significantly modify the effect of bevacizumab on PFS, so these data are insufficient to support using mutation status to identify patients who may benefit from first-line and maintenance bevacizumab.

Bevacizumab Safety and Quality of Life

Based on earlier studies, toxicities that may occur in patients treated with bevacizumab and are of particular concern, may require intervention, and often lead to treatment discontinuation include the following: pain (grade ≥2), neutropenia (grade ≥4), febrile neutropenia, thrombocytopenia, bleeding (grade ≥2; various types), hypertension (grade ≥2), thromboembolism (grade ≥3, various types), GI events (perforations, abscesses, and fistulas), reversible posterior leukoencephalopathy syndrome, renal injury and proteinuria (grade ≥3), and wound disruption. In both GOG-0218 and ICON7, the following types of toxicities were more common in the bevacizumab arm: bleeding, hypertension, proteinuria, thromboembolic events (grade ≥3), GI perforation (grade ≥3), and wound-healing complications.[840,841] For some of these the difference between arms was smaller than expected. Neutropenia occurred with similar rates across arms, and reversible posterior leukoencephalopathy syndrome occurred in GOG-0218 in only the bevacizumab arms.

Data from both GOG-0218 and ICON7 showed that most toxicities developed during the chemotherapy phase of treatment, although there were a few AEs of concern that continued to develop during the bevacizumab maintenance phase, including hypertension, high-grade pain, proteinuria, and thromboembolism.[840] Exploratory analyses tried to identify factors that might be associated with increased risk of bevacizumab-associated AEs.[848,849] Analysis of GI-related AEs in GOG-0218 identified inflammatory bowel disease (IBD), and bowel resection at primary surgery as being associated with increased risk of grade ≥2 perforation, fistula, necrosis, or hemorrhage.[848] Another analysis of GOG-0218 reported that patients treated with bevacizumab had higher rates of readmission, and noted that most readmissions occur within the first 40 days after surgery but after the first cycle of chemotherapy was delivered.[849] Other factors associated with increased rates of readmission (across treatment arms) include baseline CA-125 level, disease stage, surgery involving bowel resection, residual disease, ascites, high body mass index, and poor performance score. Whereas shorter time to start of chemotherapy after surgery was associated with increased rates of readmission,[849] time to initiation longer than 25 days was associated with poorer OS (across treatment arms).[531]

Both GOG-0218 and ICON7 reported some small but statistically significant differences between treatment arms in the global measures of QOL. Analyses of GOG-0218 showed that QOL improved somewhat during the course of the study across all arms (FACT-O TOI scores improved from ~67–68 to ~76–68).[840,850] Results showed slightly worse QOL for patients treated with bevacizumab during the chemotherapy phase (FACT-O TOI scores ≤3 points lower than for placebo; *P* < .001), but this difference did not persist in the maintenance phase.[840,850] There were no statistically significant differences in QOL scores for patients treated with bevacizumab during chemotherapy only (Arm 2) versus bevacizumab during chemotherapy plus maintenance (Arm 3),[850] which

further supports the idea that bevacizumab maintenance did not impact QOL. For FACT-O TOI scores, the threshold for clinically meaningful differences has been suggested to be 5–7 points. Results from ICON7 showed that for both arms QOL improved somewhat over the course of the trial, during both the chemotherapy phase and the maintenance phase.[841,851] However, these increases were smaller in the bevacizumab arm (Arm 2), such that QOL scores were better in the control arm (Arm 1) versus the bevacizumab arm (Arm 2) at the end of chemotherapy (week 18; mean QLQ-C30 score difference of 6.1 points; $P < .0001$) and at the end of the maintenance phase (week 54; 6.4 points; $P < .0001$).[851] Although differences between the two arms (favoring placebo) were consistently present and statistically significant, it is unclear whether they are clinically meaningful, as the threshold for clinical significance is a matter of debate, and some have argued that it should be 10 points.

NCCN Recommendations

Based on results from GOG-0218 and ICON7, the NCCN Guidelines include bevacizumab-containing regimens as options for first-line chemotherapy following cytoreductive surgery (Table 11). The regimens recommended are those used in these trials that consist of upfront carboplatin/paclitaxel/bevacizumab, followed by bevacizumab maintenance (shown in Table 10B, footnote h and Table 11). In both of these trials, treatment was discontinued upon disease progression, so the guidelines recommend single-agent bevacizumab maintenance only for those who have not progressed during the 6 cycles of upfront carboplatin/paclitaxel/bevacizumab (see *Post-Primary Treatment: Maintenance Therapy* in the *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer* section of the algorithm). Given that GOG-0218 found that patients treated with upfront carboplatin/paclitaxel/bevacizumab without single-agent bevacizumab maintenance did not have improved outcomes compared with control (carboplatin/paclitaxel), observation is not a recommended option for patients with response or stable disease following completion of a first-line regimen containing bevacizumab (see bottom two pathways in *Post-Primary Treatment: Maintenance Therapy* in the algorithm). Currently there are no data to support introducing bevacizumab as maintenance therapy if bevacizumab was not included in the initial primary regimens used (see top pathways in *Post-Primary Treatment: Maintenance Therapy* in the algorithm).

Table 11. NCCN Recommended IV Bevacizumab/Chemotherapy Options for Stage II–IV, All Epithelial Cancer Types[a,b]

Regimen Short Name	Detailed Dosing per Cycle	Cycle Length, Weeks	# Cycles[c]	Category[d]	Preference Category	Supporting References
Paclitaxel/ carboplatin/ bevacizumab + maintenance bevacizumab (ICON-7)	Paclitaxel 175 mg/m^2 IV over 3 hours, followed by carboplatin AUC 5–6 IV over 1 hour, and bevacizumab 7.5 mg/kg IV over 30–90 minutes Day 1	3	5–6	2A	Preferred	ICON-7 Perren 2011[841] Oza 2015[842]
	(Maintenance) bevacizumab 7.5 mg/kg IV over 30–90 minutes Day 1	3	≤12	*BRCA1/2* wild-type/unknown: 2A[e] *BRCA1/2* mutation: bevacizumab alone not recommended[f]		
Paclitaxel/ carboplatin/ bevacizumab + maintenance bevacizumab (GOG-218)	Paclitaxel 175 mg/m^2 IV over 3 hours, followed by carboplatin AUC 6 IV over 1 hour, plus bevacizumab (cycles 2–6) 15 mg/kg IV over 30–90 minutes Day 1	3	6	2A	Preferred	GOG-0218 Burger 2011[840] Tewari, 2019[844]
	(Maintenance) bevacizumab 15 mg/kg IV over 30–90 minutes Day 1	3	≤16	*BRCA1/2* wild-type/unknown: 2A[e] *BRCA1/2* mutation: bevacizumab alone not recommended[f]		

AUC, area under the curve; CR, complete response; IV, intravenous; PR, partial response.

[a] Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma; stage IC only for mucinous, low-grade serous, and grade 1 endometrioid.

[b] These options are primarily for patients aged ≤70 years, with good performance status, and without comorbidities. For patients who are elderly, have poor performance score, or have comorbidities, see alternate treatment options discussed in the section entitled *Options for Patients Who Are Elderly or Have Comorbidities or Poor Performance Score.*

[c] NCCN-recommended number of cycles.

[d] NCCN Category of Evidence and Consensus.

[e] For patients with *BRCA1/2* wild-type or unknown mutation status who are in CR/PR after chemotherapy plus bevacizumab, maintenance options include bevacizumab alone (category 2A) or bevacizumab + olaparib (category 2A). See *Options After First-Line Chemotherapy* section for more information.

[f] For patients with a *BRCA1/2* mutation in CR/PR after chemotherapy plus bevacizumab, maintenance therapy options include: bevacizumab + olaparib (category 1), olaparib monotherapy (category 2A), or niraparib monotherapy (category 2A). See *Options After First-Line Chemotherapy* section for more information.

GOG-0218 did not include patients with stage I–II disease, and ICON7 included patients with stage I–IIA disease only if they were considered "high risk" because of poor differentiation (high grade) or clear cell histology (Table 10A). Due to these entry criteria and the results of subgroup analysis suggesting that bevacizumab may only be beneficial in patients with more advanced disease, the NCCN Guidelines do not include the bevacizumab-containing regimens (including bevacizumab maintenance) as options for stage I disease, but only recommend them for patients with stage II or higher.

GOG-0218 and ICON7 included patients primarily with ovarian cancer, but also some with primary peritoneal or fallopian tube cancer.[840,841] These trials mostly included patients with serous histology, but did include patients with other cancer types (ie, mucinous, clear cell, endometrioid). Therefore, the NCCN recommendations regarding use of bevacizumab as part of first-line chemotherapy and maintenance apply to patients with any of these epithelial cancer types.

Bevacizumab Biosimilars

In September 2017 the FDA approved the first bevacizumab biosimilar, ABP-215, as bevacizumab-awwb, for use in certain indications in a number of cancers (ie, colorectal cancer, non-squamous non-small cell lung cancer [NSCLC], glioblastoma, renal cell carcinoma, cervical cancer), but not including any indications in ovarian, fallopian tube, or primary peritoneal cancers due to regulatory exclusivity.[852-854] This approval was based on data demonstrating that the ABP 215 is sufficiently structurally similar to bevacizumab, and functionally similar based on in vitro assays, in vivo assays (cell-based and preclinical models), pharmacokinetic data in healthy adult men, and efficacy and safety data in patients with advanced NSCLC.[852,855-861] Approval in other cancer types was based on extrapolation.[852,862] In 2019 the FDA approved another bevacizumab biosimilar, PF-06439535, as bevacizumab-bvzr, for the same indications as bevacizumab-awwb.[863] This approval was based on demonstration of structural similarity, and data showing functional similarity including in vivo studies, animal studies, pharmacokinetics in healthy subjects and patients with NSCLC, and efficacy and safety data in patients with NSCLC.[864-868] Several other bevacizumab biosimilars are in development.[869-883] Based on a Panel vote, the NCCN Guidelines for Ovarian state that an FDA-approved biosimilar is an appropriate substitute for bevacizumab, wherever bevacizumab is recommended.

Intraperitoneal/Intravenous Regimen

IP chemotherapy has been explored as an option for ovarian cancer based on the idea that localized delivery could improve efficacy, particularly against microscopic spread and peritoneal carcinomatosis, with an acceptable safety profile. Although results from smaller randomized trials (n < 120) suggested no clinical benefit (ie, response rate, PFS, OS) with IP/IV compared with IV regimens,[884,885] three larger randomized trials (n > 400) in newly diagnosed chemotherapy-naïve patients with stage III disease and residual disease 1 cm or less after primary surgery compared IV regimens with IP/IV regimens using similar agents, and found that IP/IV chemotherapy resulted in improved PFS and/or OS, with at least borderline statistical significance (See GOG-104, GOG-114, and GOG-172 in Table 12).[748,886,887] One phase II randomized trial (n = 218) in patients with stage IIIC–IV epithelial ovarian cancer with optimal debulking also showed that IP/IV administration improved PFS and OS compared with IV only.[888,889] Results from these trials suggest that IP/IV administration significantly increases risk of certain high-grade hematologic toxicities (eg, granulocytopenia, leukopenia, neutropenia, thrombocytopenia), and certain non-hematologic toxicities (eg, GI and metabolic toxicities, renal toxicity, abdominal pain, neurologic toxicities, infection, fatigue).[748,886-888,890] The increased risk of toxicity was considered acceptable given the improvement in OS, which was greater than a year (16 months) in one of the trials (Table 12).[748,886,887] Pooled analyses of GOG-114 and GOG-172 data showed that the IP/IV regimen was associated with lower risk of relapse in the peritoneal space,[891] and long-term follow-up (>10 years) showed significant PFS benefit (P = .01) and OS benefit (P = .042), especially after adjusting for other prognostic factors (P = .003 for PFS, P = .002 for OS).[892] This analysis also showed that survival improves with each cycle of IP chemotherapy.[892] Although the extent of residual disease was prognostic for outcome, IP/IV chemotherapy still provided PFS benefit even among those with some gross residual disease (>0–≤1 cm).[892] Based on these results, an IP/IV

option similar to the regimen used in GOG-172 was added to the NCCN Guidelines (Table 13) for patients with optimally debulked (<1 cm residual) stage III disease.[748] Women with optimally debulked stage II disease may also receive IP chemotherapy, as the NCCN Panel has decided that many of the regimens tested in stage III–IV should also be offered to patients with stage II disease. Patients with stage II were allowed in GOG-0252 and another (small) randomized trial, although in both of these studies the IP/IV regimens did not significantly improve PFS or OS compared with IV regimens.[885,893] IP chemotherapy is not recommended for stage I or IV disease.

Table 12. IP/IV Versus IV Platinum-Based Chemotherapy: Randomized Trials

Trial	Patients[a]	First-Line Systemic Therapy[b]	n	Median (months), HR [95% CI], P-value[d]		AEs G5	Dc'd AEs[e]
				PFS	OS		
GOG-0104[886]	Stage III OC/FTC/PPC: 100%, 0, 0 Cancer type, serous/endometrioid/other: 67%/10%/23% Tumor grade, 1/2/3: 12%/30%/58% Residual disease, R0/>0–≤1 cm/>1 cm: 26%/73%/0	IP/IV: Cyclophosphamide 600 mg/m^2 IV + cisplatin 100 mg/m^2 IP, Q3W x 6 cycles	279	NR	49, 0.76 [0.61-0.96], *P*=.02	1%	9%
		IV: Cyclophosphamide 600 mg/m^2 IV + cisplatin 100 mg/m^2 IV, Q3W x 6 cycles	267	NR	41	0	5%
GOG-0114[887]	Stage III OC/FTC/PPC: 100%, 0, 0 Cancer type, serous/endometrioid/other: 67%/12%/21% Tumor grade, 1/2/3: 12%/40%/48% Residual disease, R0/>0–≤1 cm/>1 cm: 35%/65%/0	IP/IV: Carboplatin AUC 9 IV Q4W x 2 cycles; then paclitaxel 135 mg/m^2 IV, then cisplatin 100 mg/m^2 IP, Q3W x 6 cycles	227	18, 0.78, *P*=.01	63; 0.81, *P*=.05	1%	NR
		IV: Paclitaxel 135 mg/m^2 IV + cisplatin 75 mg/m^2 IV, Q3W x 6 cycles	235	22	52	1%	NR
GOG-172 (NCT00003322)[748,890]	Stage III OC/FTC/PPC: 88%, 0, 12% Cancer type, serous/endometrioid/other: 79%/7%/14% Tumor grade, 1/2/3: 10%/37%/51% Residual disease, R0/>0–≤1 cm/>1 cm: 63%/37%/0	IP/IV: Paclitaxel 135 mg/m^2 IV D1 + cisplatin 100 mg/m^2 IP D2 + paclitaxel 60 mg/m^2 IP D8, Q3W x 6 cycles	214	23.8, 0.80 [0.64–1.00], *P*=.05	65.6, 0.75 [0.58–0.97], *P*=.03	2.4%	NR
		IV: Paclitaxel 135 mg/m^2 IV D1 + cisplatin 75 mg/m^2 IV D2, Q3W x 6 cycles	215	18.3	49.7	1.9%	NR
GOG-0252 (NCT00951496)[893]	Stage II/III/IV: 10%/84%/6% OC/FTC/PPC: NR[c] Cancer type, serous/endometrioid/other: 83%/1%/16% Tumor grade, 1/2/3: NR/≥7%/≥72% Residual disease, R0/>0–≤1 cm/>1 cm: 58%/35%/7%	IV/IP pac/carbo bev: paclitaxel 80 mg/m^2 IV D1, D8, D15 + carboplatin AUC 6 IP D1, Q3W x 6 cycles; + bevacizumab 15 mg/kg IV Q3W cycles 2–22	518	27.4, 0.925 [0.802–1.07]	78.9, 0.949 [0.799–1.128]	1.4%	28%
		IV/IP pac/cis/bev: Paclitaxel 135 mg/m^2 IV D1 + cisplatin 75 mg/m^2 IP D2 + paclitaxel 60 mg/m^2 IP D8, Q3W x 6 cycles; + bevacizumab 15 mg/kg IV Q3W cycles 2–22	521	26.2, 0.977 [0.847–1.13]	72.9, 1.05 [0.884–1.24]	2.0%	29%
		IV pac/carbo/bev: Paclitaxel 80 mg/m^2 IV D1, D8, D15 + carboplatin AUC 6 IV D1, Q3W x 6 cycles; + bevacizumab 15 mg/kg IV Q3W cycles 2–22	521	24.9	75.5	1.6%	24%

AE, adverse event; CI, confidence interval; D, day (of cycle); Dc'd, discontinued study treatment; FTC, fallopian tube cancer; G, grade; HR, hazard ratio; IP, intraperitoneal; IV, intravenous; NR, not reported; OC, ovarian cancer; OS, overall survival; PFS, progression-free survival; PPC, primary peritoneal cancer; Q3W, every 3 weeks; R0, removal of all macroscopic disease.

[a] All trials enrolled newly diagnosed, previously untreated/chemotherapy-naïve patients, with an epithelial cancer type.
[b] All patients were treated with surgery followed by chemotherapy.
[c] Percentages for each cancer type were not reported, but trial inclusion criteria allowed OC, FTC, and PPC.
[d] HR and P-values are for comparison with control arm (IV regimen).
[e] Patients who discontinued therapy due to AEs.

Table 13. NCCN Recommended IP/IV Platinum-Based Chemotherapy Option for Optimally Debulked[a] Stage II–III, Selected Epithelial Cancer Types[b]

Regimen Short Name	Detailed Dosing per Cycle	Cycle Length, Weeks	# Cycles	Category[c]	Preference Category	Trials with Supporting Data
IV/IP Paclitaxel/cisplatin	Paclitaxel 135 mg/m^2 IV continuous infusion over 3 or 24 hours Day 1; + Cisplatin 75–100 mg/m^2 IP Day 2 after IV paclitaxel; + Paclitaxel 60 mg/m^2 IP Day 8	3	6	2A	Useful in Certain Circumstances	GOG-0172[748]

IP, intraperitoneal; IV, intravenous.
[a] Optimally debulked is defined as <1 cm residual disease.
[b] Includes high-grade serous, grade 2/3 endometrioid, clear cell carcinoma.
[c] NCCN Category of Evidence and Consensus.

In the large randomized trials that showed that IP/IV benefit, most of the patients had serous or endometrioid disease, and high-grade tumor histology (Table 12), so it is unclear whether patients with LCOCs will benefit from IP/IV chemotherapy. In the NCCN Guidelines, the clear cell carcinoma and carcinosarcoma are the only LCOCs for which IP/IV chemotherapy is a recommended option, as these cancer types are associated with higher risk of poor outcomes.[6,894-896] Patients with carcinosarcoma were not included in the randomized trials testing IP/IV chemotherapy, but 2% to 6% of patients had clear cell carcinoma.[748,886,887,893] These trials included mostly patients with ovarian cancer, but in GOG-172, 12% of patients had primary peritoneal cancer. In the NCCN Guidelines the recommended IP/IV regimen is an option regardless of primary site (ovarian, fallopian, or primary peritoneal). All women should be counseled about the clinical benefit associated with combined IV and IP chemotherapy administration before undergoing surgery.

Enthusiasm for IP/IV chemotherapy has waned considerably due to the results of GOG-0252, a large randomized trial in patients with stage II/III optimally resected (≤1 cm), or stage III/IV suboptimally resected (>1 cm) disease (Table 12).[893] Results showed that for combination therapy with paclitaxel/carboplatin/bevacizumab, IP administration of the carboplatin did not improve PFS or OS compared with IV administration (Table 12).[893] An IV/IP paclitaxel/cisplatin/bevacizumab regimen also did not improve PFS for OS relative to the control IV paclitaxel/carboplatin/bevacizumab regimen (Table 12).[893] These results suggest that given the PFS benefit of adding bevacizumab (during chemotherapy and maintenance), IP administration does not further improve outcomes.

For the recommended IP chemotherapy regimen (Table 13), the IP paclitaxel was infused over 24 hours in the clinical trial (GOG-172).[748] A 3-hour infusion of paclitaxel has not been proven to be equivalent to a 24-hour infusion, although a 3-hour infusion has been reported to be more convenient, easier to tolerate, and less toxic.[897] Note that in all the supporting trials and in the NCCN Guidelines, IP regimens include IV regimens so that systemic disease can also be treated.

The IP paclitaxel/cisplatin regimen is associated with leukopenia, infection, fatigue, renal toxicity, abdominal discomfort, and neurotoxicity.[748,886-888,890] In GOG-172, only 42% of women were able to complete all 6 treatment cycles of the IP regimen;[748] with more experience, this percentage has improved in the major cancer centers.[898] It has been suggested that a lower IP cisplatin dose of 75 mg/m^2 may help to decrease toxicity.[897,898] However, the chemotherapy portion of the IV/IP paclitaxel/cisplatin/bevacizumab regimen used in GOG-0252 was very similar to the IV/IP paclitaxel/cisplatin regimen used in GOG-172, but with a lower dose of cisplatin (75 mg/m^2 vs. 100 mg/m^2), and did not improve PFS/OS relative to control (Table 12).[748,893] Therefore, it is unclear whether the IV/IP chemotherapy regimen with the lower cisplatin dose provides any benefit compared with IV administration.

Prior to the administration of the combined IP and IV regimen, patients must be apprised of the increased toxicities with the combined regimen when compared to using IV chemotherapy alone (increased myelosuppression, renal toxicities, abdominal pain, neuropathy, GI toxicities, metabolic toxicities, and hepatic toxicities). Patients who are candidates for the IP cisplatin and IP/IV paclitaxel regimen should have normal renal function before starting, a medically appropriate PS based on the future toxicities of the IP/IV regimen, and no previous evidence of medical problems that could significantly worsen during chemotherapy, such as preexisting neuropathy. Reasons for discontinuing the IP regimen included catheter complications, nausea/vomiting/dehydration, and abdominal pain.[899] Women unable to complete IP therapy should receive IV therapy. Expert nursing care may help to decrease complications.[900] Giving IV hydration before and after IP chemotherapy is a useful strategy to prevent certain toxicities (nausea, vomiting, electrolyte imbalances, and metabolic toxicities).[898] Prior to receiving and after receiving each cycle of IP cisplatin, adequate amounts of IV fluids need to be administered in order to prevent renal toxicity. After each cycle has been completed, patients need to be monitored carefully for myelosuppression, dehydration, electrolyte loss, end-organ toxicities (such as renal and hepatic damage), and all other toxicities. After chemotherapy, patients often require IV fluids (5–7 days) in the outpatient setting to prevent or help treat dehydration.

Neoadjuvant Chemotherapy

In the NCCN Guidelines for Ovarian Cancer, *neoadjuvant therapy* refers to treatment (eg, drugs and other treatments) that is given to reduce the tumor burden before cancer surgery. The therapeutic benefit of NACT followed by IDS remains controversial (see below).[483,718,901-908]

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.[891] Therefore, the NCCN Guidelines recommend that primary treatment for presumed advanced-stage disease consist of appropriate surgical debulking plus systemic chemotherapy in most patients. For most patients presenting with suspected advanced-stage malignant ovarian, fallopian tube, or primary peritoneal cancer, initial surgery should include a hysterectomy and BSO with comprehensive staging and debulking as indicated.[16,544,612] 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. NACT with IDS should be considered for patients with advanced-stage disease 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.

Randomized Trials Comparing NACT Versus Conventional Treatment

Several prospective randomized trials have compared an NACT approach (with IDS and postoperative chemotherapy) versus conventional treatment (PDS plus postoperative chemotherapy; Table 14).[484-486,663,664] These trials focused on patients with FIGO stage IIIC–IV ovarian, fallopian tube, or primary peritoneal cancer that was deemed unlikely to be completely resected. As shown in Table 14, the NACT regimens tested in these trials typically consisted of 3–4 cycles of upfront chemotherapy, followed by IDS with the goal of maximum cytoreduction, followed by 3–4 cycles of postoperative chemotherapy. Several of these trials (ie, EORTC 55971,[486] SCORPION,[663] JCOG0602[485]) 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 Table 15.[484-486,663,664]

Table 14. Randomized Controlled Trials Comparing NACT + IDS Versus PDS

Trial	Patients[a]	Treatment Arms	Arm A Versus B			
			n	Surgical Outcomes	Median PFS/OS, months	Safety
EORTC 55971 NCIC-CTG OV13 NCT00003636 Phase III Vergote 2010[486] N = 670	FIGO Stage IIIC, IV: 76%, 24% Poor differentiation: 41%[b] Entry criteria: Diagnosis by biopsy[b]	Arm 1: NACT x 3 cycles →IDS if response/SD →Chemo x ≥3 cycles →Second look allowed Arm 2: PDS →Chemo x 3 cycles →IDS option if response/SD and >1 cm after PDS →Chemo x ≥3 cycles →Second look allowed	334 vs. 336	Operative time, minutes: median 180 vs. 165 Residual disease: • R0: 51% vs. 19% • ≤1 cm: 81% vs. 42% Death <28 days postop: 0.7% vs. 2.5%	PFS: 12 vs. 12; NS OS: 30 vs. 29; *P* = .01[c]	Perioperative and postoperative (<28 days) grade 3–4 AEs (NCI CTC 2.0): • Hemorrhage: 4.1% vs. 7.4% • Infections: 1.7% vs. 8.1% • Venous complications: 0 vs. 2.6%
CHORUS ISRCTN74802813 Phase III Kehoe 2015[484] 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 →Chemo x 3 cycles Arm 2: PDS →Chemo x 3 cycles →IDS option for >1 cm residual after PDS →Chemo x 3 cycles	274 vs. 276	Operative time, minutes: median 120 vs. 120 Residual disease: • R0: 39% vs. 17%; *P* = .0001 • <1 cm: 73% vs. 41%; *P* = .0001 Hospital stay ≤14 days: 93% vs. 80%; *P* < .0001 Death <28 days postop: <1% vs. 6%; *P* = .001	PFS: 12.0 vs. 10.7; HR, 0.91 (95% CI, 0.76–1.09) OS: 24.1 vs. 22.6; HR, 0.87 (95% CI, 0.72–1.05)[e]	Grade 3–4 AEs (CTCAE 3.0): • Postop (<28 days): 14% vs. 24%; *P* = .007 • During chemo: 40% vs. 49%; *P* = .0654

Trial	Patients[a]	Treatment Arms	Arm A Versus B			
			n	Surgical Outcomes	Median PFS/OS, months	Safety
SCORPION NCT01461850 Phase III Fagotti 2016[663,909] N = 110	FIGO stage IIIC, IV: 89%, 11%[f] Poor differentiation: NR[f] Entry criteria: diagnosis by S-LPS[f]	Arm 1: NACT x 3–4 cycles →IDS if response/SD →Chemo to a total of 6 cycles Arm 2: PDS →Chemo x 6 cycles	55 vs. 55	Operative time, minutes: median 275 vs. 451; *P* = .0001 Residual disease: • R0: 58% vs. 46%; NS • ≤1 cm: 85% vs. 91% Hospital stay, days: median 6 vs. 12; *P* = .0001 Death ≤30 days postop: 0 vs. 4%; NS PDS associated with more extensive and complex procedures and blood loss[g]	NR	Surgical secondary events grade 3–4 (MSKCC system): • ≤30 days postop: 6% vs. 53%; *P* = .0001 • 1–6 months postop: 0 vs. 15%; *P* = .004 • Chemo-related grade 3–4 AEs (NCI CTC 2.0): 36% vs. 43%; NS
JCOG0602 Phase III Onda 2016[485] 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 →Chemo x 4 cycles Arm 2: PDS →Chemo x 4 cycles →IDS option if residual >1 cm after PDS[i] →Chemo x 4 cycles	152 vs. 149	Operative time, minutes: median 273 vs. 341; *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 and blood/ascites loss[i]	NR	Grade 3–4 AEs (CTCAE 3.0): • After surgery: 5% vs. 15%; *P* = .005 • First-half of chemo: 18% vs. 20%; NS • Second-half of chemo: 12% vs. 9%; NS
Liu 2017[664] N = 108	FIGO stage III, IV: 68%, 32% Grade 2–3: 55% Entry criteria: diagnosis by imaging, serum CA-125; confirmed by LPS biopsy or laparotomy	Arm 1: NACT IP/IV x 2 cycles →IDS →Chemo IV x 6 cycles Arm 2: PDS →Chemo IV x 6–8 cycles	58 vs. 50	Operative time, hours: 2.36 vs. 3.63; *P* < .001 Successful cytoreduction: 74% vs. 46%; *P* = .0054 PDS associated with greater blood loss (*P* < .001)	PFS: 26 vs. 22; NS OS: 62 vs. 51; NS[j]	Chemo side effects (degree III–IV): NS

Abbreviations: AE, adverse event; CA-125, cancer antigen 125; CEA, carcinoembryonic antigen; chemo, chemotherapy; HR, hazard ratio; IP, intraperitoneal; IV, intravenous; IDS, interval debulking surgery; 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; PFS, progression-free survival; postop, postoperative; R0, removal of all macroscopic disease; SD, stable disease; S-LPS; staging laparoscopic surgery

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

[b] In EORTC 55971, 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). If no biopsy specimen, FNA showing adenocarcinoma allowed under certain circumstances: pelvic ovarian mass, metastases outside

of pelvis >2 cm, regional lymph node metastases, proof of stage IV, or CA-125:CEA >25. If serum CA-125:CEA ≤25, barium enema or colonoscopy, gastroscopy, and mammograph had to be negative.

[c] In EORTC 55971, OS *P*-value was for non-inferiority. Post hoc subgroup analyses showed that there was no treatment-dependent difference in OS for any of the subgroups evaluated based on FIGO stage, WHO performance score, histologic type, or presence/absence of pleural fluid.[486] Subgroup analyses showed that NACT was associated with better OS in patients with more extensive disease (stage IV with 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).[607,910]

[d] In CHORUS, patients were included if suspected FIGO stage III–IV based on imaging/clinical evidence, but after surgery only 96% had confirmed III–IV; the remaining had stage II or unknown stage. For those with CA-125:CEA ratio <25 (2%), gastrointestinal carcinoma had to be ruled out by imaging. Only patients in the NACT arm had histologic/cytologic confirmation of diagnosis prior to treatment. Methods used for histologic/cytologic confirmation in NACT arm included: laparoscopy (16%), image-guided biopsy (42%), and FNA cytology of tumor/effusion (41%).

[e] In CHORUS, analyses of subgroups showed that residual disease after surgery was prognostic for OS in both treatment groups. Post-hoc subgroup analyses showed that there was no treatment-dependent difference in OS for any of the subgroups evaluated based on age, cancer stage, tumor size (prior to surgery), performance score, or type of chemotherapy (single-agent carboplatin vs. carboplatin/paclitaxel).

[f] In SCORPION, patients with stage IV required to have pleural infusion or any resectable disease. All patients were required to have a predictive index of 8–12 and no mesenteric retraction. All patients had S-LPS for histologic confirmation and to assess tumor load (predictive index). The proportion of patients with poorly differentiated histology was not reported. However, 97% had type II histology per Kurman and Shih,[911] which includes conventional high-grade serous carcinoma, undifferentiated carcinoma, and malignant mixed mesodermal tumors (carcinosarcoma).

[g] In SCORPION, 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 chemotherapy (*P* = .0001).

[h] JCOG0602 did not require histologic confirmation of diagnoses at trial entry. Diagnosis was based on both imaging and cytology of ascites, pleural effusions, or fluids obtained by centesis.

[i] In JCOG0602, patients in the control arm were allowed to have IDS for residual >1 cm after PDS; and IDS was mandatory if uterus, adnexa, or omentum were not removed at PDS, unless PD was noted. Of 128 patients in the control arm who completed the first 4 cycles of postoperative chemotherapy, 49 had IDS. 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 (FFP)/plasma protein fraction (PPF)/albumin (*P* < .001, *P* < .001). They also had higher volumes of blood/ascites loss (*P* < .001).

[j] In the study reported by Liu et al, 2017[664], subgroup analysis showed that the following factors were prognostic for OS among patients in the NACT arm: tumor stage (III vs. IV), histologic grade (grade 1 vs. 2 vs. 3), residual tumor size (≤1 cm vs. >1 cm), and number of chemotherapy cycles.

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 AEs, shorter hospital stay), less extensive and complicated surgeries needed to achieve optimal cytoreduction, and a lower risk of postoperative death (Table 14).[484-486,663,664] 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 PFS and OS found no significant differences when compared with the conventional PDS approach (Table 14). 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.[607,910,912]

Importantly, for some of these trials (ie, EORTC 55971, CHORUS) the median PFS and OS for both treatment arms (Table 14) were inferior to those reported in randomized studies of patients undergoing PDS followed by postoperative IV chemotherapy for advanced disease (OS mean, ~50 months in the United States).[748,913] 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).

Selection of Patients for NACT

Based on the results from randomized trials shown in Table 14, the NCCN Guidelines recommend considering neoadjuvant therapy for patients with bulky disease that is unlikely to be optimally cytoreduced by up-front surgery. The panel considers the current evidence to be insufficient for justifying NACT as an option for patients who by assessment of a gynecologic oncologist are likely to be optimally cytoreduced by upfront surgery. When selecting patients for NACT with IDS, the cancer type of the primary tumor and potential response to primary chemotherapy should be considered. NACT is not appropriate for patients with non-epithelial cancer types (eg, sex cord-stromal or germ-cell tumors). NACT is not appropriate for patients with disease apparently confined to the ovary. NACT can also be considered for patients who are poor surgical candidates, such as those with poor performance score, in the hopes that tumor load reduction may improve their condition and thereby reduce perioperative risks. At least one of the randomized trials in Table 14 (Liu 2017[664]) showed that among elderly patients with stage III/IV disease, NACT improved the rate of successful cytoreduction and other surgical outcomes (reduced operative time and blood loss), although similar to other randomized trials no improvement in PFS or OS was observed.

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 14. 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.[484-486,663,664] 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 SGO and ASCO.[483]

Most of the trials in Table 14 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 CA-125 and 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 these trials (SCORPION) and also frequently used in the other randomized trials shown in Table 14. 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.[484-486,663] The NCCN Guidelines recommend histologic confirmation of diagnosis and cancer 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.[481,482,484,914] 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* status may inform future options for maintenance therapy, all patients with histologically confirmed ovarian, fallopian tube, or primary peritoneal cancer should undergo genetic risk evaluation and germline and somatic testing, if not previously performed. In the absence of a *BRCA1/2* mutation, homologous recombination deficiency testing may also be considered, as it may provide information about the magnitude of benefit of PARP inhibitor maintenance therapy following first-line chemotherapy (category 2B). However, treatment should not be delayed for genetic counselling referral, because delay in treatment is associated with poorer outcomes.[531,532] See *Molecular Testing* section above.

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 14 used platinum-based combination chemotherapy or monotherapy (Table 15). Other chemotherapy regimens that have been tested in prospective trials in patients with ovarian, fallopian tube, or primary peritoneal cancer are shown in Table 16.[915-920] For most of the trials in Table 15 and Table 16, patients received the same chemotherapy regimen for both NACT and postoperative therapy. For the prospective trials comparing different chemotherapy regimens in patients treated with an NACT approach (ie, PRIMOVAR-1, GEICO 1205/NOVA, ANTHALYA, OV21/PETROC), none has yet demonstrated the superiority of any regimen based on surgical outcomes, PFS, or OS (Table 16).[916,918-920] 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 (Table 17), including all of the IV regimens recommended for conventional treatment of stage II–IV high-grade serous carcinoma (ie, PDS followed by chemotherapy).

Table 15. Neoadjuvant Chemotherapy Regimens Tested in Randomized Prospective Trials Comparing NACT + IDS Versus PDS[a,b]

Trial	Chemotherapy Regimen Options	Route	Cycle Length, Weeks	Patients Treated, n (% of total population)	
				NACT Arm	PDS Arm
EORTC 55971[486]	Platinum-taxane, recommended options: • Paclitaxel 135 mg/m^2 + cisplatin 75 mg/m^2 • Paclitaxel 175 mg/m^2 + cisplatin 75 mg/m^2 • Paclitaxel 175 mg/m^2 + carboplatin AUC 5	IV	3	283 (88%)	243 (78%)
	Platinum only: • Cisplatin ≥75 mg/m^2 • Carboplatin AUC ≥5	IV	3	20 (6%)	25 (8%)
	Other	NR	NR	19 (6%)	21 (7%)
CHORUS[484]	Carboplatin AUC 5–6 + paclitaxel 175 mg/m^2	NR	3	178 (70%)	138 (61%)
	Alternative carboplatin combination	NR	3	1 (<1%)	0
	Carboplatin AUC 5–6	NR	3	75 (30%)	89 (39%)
SCORPION[663]	Carboplatin AUC 5 + paclitaxel 175 mg/m^2	IV	3	29 (56%)	31 (61%)
	Carboplatin AUC 5 + paclitaxel 175 mg/m^2 + bevacizumab	IV	3	20 (39%)	14 (27%)
	Carboplatin + paclitaxel	IV	1	3 (6%)	5 (10%)
	Carboplatin	IV	3	0	1 (2%)
JCOG0602[485]	Paclitaxel 175 mg/m^2 + carboplatin AUC 6	IV	3	150	138
Liu 2017[664]	Before IDS: Cisplatin 75 mg/m^2 IP + docetaxel 75 mg/m^2 IV	IP/IV	3	58	0
	After IDS: Cisplatin 75 mg/m^2 IV + docetaxel 75 mg/m^2 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 14.

[b] All of these trials tested regimens consisting of NACT, followed by IDS (with the goal of maximum cytoreduction), followed by postoperative systemic therapy (for the indicated number of cycles). 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.

Table 16. NACT Regimens in Other Prospective Trials

Trial	Stage III/IV (%)	Chemotherapy Regimen[a]	Route	Cycle Length (wks)	Number of Cycles		Patients Treated (n)	Residual Disease		PFS (mo)	OS (mo)
					Before IDS	After IDS		R0	≤1 cm		
SWOG S0009 (NCT00008138) Phase II, 1-arm Tiersten 2009[915]	74/26[b]	Before IDS: Paclitaxel 175 mg/m^2 + carboplatin AUC 6 After IDS: Paclitaxel 175 mg/m^2 IV day 1 + carboplatin AUC 5 IP day 1 + paclitaxel 60 mg/m^2 IP day 8	IV IP/IV	3 4	3 --	-- 6	58[c]	NR	45%	21	32
PRIMOVAR-1 (NCT00551577) Phase II, R Polcher 2009[916]	73/27[d]	**Arm 1**: Carboplatin AUC 5 + docetaxel 75 mg/m^2 **Arm 2**: Carboplatin AUC 5 + docetaxel 75 mg/m^2	IV IV	3 3	3 2	3 4	44 44	30% 44% (NS)	75% 74% (NS)	12.2 12.5 (NS)	24.1 28.4 (NS)
MITO-16A-MaNGO OV2A (NCT01706120) Phase IV Daniele 2017[917]	75/24[e]	Carboplatin AUC 5 + paclitaxel 175 mg/m^2 + bevacizumab 15 mg/kg; then bevacizumab monotherapy (after IDS only)	NR	3	~3	To a total of 6; ≤16	74	64%	87%	NR	NR
GEICO 1205/NOVA (NCT01847677) Phase II, R, OL Garcia ASCO 2017[918] Garcia, 2019[921]	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; then bevacizumab monotherapy 15 mg/kg **Arm 2**: Before IDS: Carboplatin AUC 6 + paclitaxel 175 mg/m^2 + bevacizumab 15 mg/kg After IDS: Carboplatin AUC 6 + paclitaxel 175 mg/m^2 + bevacizumab 15 mg/kg; then bevacizumab monotherapy 15 mg/kg	IV IV	3 3	4 4[f]	3; ≤15 mo 3; ≤15 mo	33 35	NR NR	64%[g] 66% (NS)	20.1 20.4 (NS)	NR NR
ANTHALYA (NCT01739218) Phase II, OL, R Rouzier 2017[919]	70/30[d]	**Arm 1**: Carboplatin AUC 5 + paclitaxel 175 mg/m^2 **Arm 2**: Carboplatin AUC 5 + paclitaxel 175 mg/m^2 + bevacizumab 15 mg/kg; then bevacizumab monotherapy (after IDS only)	IV IV	3 3	4 4[f]	4 4[f]; 18	37 58	51% 59%	NR NR	NR NR	NR NR
OV21/PETROC (NCT00993655) Phase II, RCT Provencher 2018[920]	86/13[h]	Before IDS, all arms: platinum-based, details not specified[i] After IDS options: **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 **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 **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	IV IV IP/IV	3 3 3	3–4[i] --[i] --[i]	-- 3 3	95 72 92	--[i] --[i] --[i]	--[i] --[i] --[i]	11.3[i] NR 12.5[i] (NS)	38.1[i] NR 59.3[i]

AUC, area under the curve; IDS, interval debulking surgery; IP, intraperitoneal; IV, intravenous; mo, months; 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; wks, weeks.

[a] All of these trials tested regimens consisting of neoadjuvant systemic therapy (for indicated number of cycles [number of cycles before IDS]), followed by IDS (with the goal of maximum cytoreduction), followed by postoperative systemic therapy (for the indicated number of cycles [number or cycles after IDS]). Unless otherwise specified, the same regimen was used both as neoadjuvant and postoperative, and agents were administered on day 1 of each cycle. 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 were required to have large pelvic mass and/or bulky abdominal disease and/or malignant pleural effusion; patients with stage IV 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 with bevacizumab. In the bevacizumab arm of ANTHALYA, chemotherapy included bevacizumab for cycles 1–3 and cycles 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 stage 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.

Table 17. NCCN Guidelines for Ovarian Cancer: Recommended Regimens for NACT and for Adjuvant Chemotherapy After IDS

Options[a]	Cycle Length (weeks)	# Cycles[b]	
		Before IDS	After IDS
IP/IV Regimens[c] (Adjuvant Only)			
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 (Neoadjuvant and Adjuvant)			
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 (aged >70 years) and Those with Comorbidities (Adjuvant Only)			
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

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; post-op, postoperative

[a] All options listed are category 2A.

[b] 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.

[c] There are limited data for the use of IP chemotherapy regimens after neoadjuvant therapy and IDS.

[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.

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 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).[918] 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%).[919] 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).[919] 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. The NCCN Guidelines include two bevacizumab-containing regimens as options for NACT and post-IDS chemotherapy (Table 17). It is important to note that all of the prospective trials in Table 15 and Table 16 that allowed use of bevacizumab in the NACT setting used a washout period before (and sometimes after) IDS, usually of at least 28 days.[663,917-919] Bevacizumab-containing regimens should be used with caution before IDS due to potential interference with postoperative healing. If bevacizumab is being used as part of a neoadjuvant regimen, bevacizumab should be withheld from therapy for at least 6 weeks prior to IDS.

Intraperitoneal/Intravenous Regimens for Patients Treated with NACT

Several trials have explored the use of IP/IV regimens in patients treated with an NACT approach. Both SWOG S0009 and OV21/PETROC tested postoperative IP/IV regimens for patients who had platinum-based NACT followed by optimal cytoreduction by IDS.[915,920] In SWOG S0009, among patients with a 50% or greater decrease in CA-125 level during NACT, optimal debulking by IDS (<1 cm and malignant pleural resolved), and postoperative IP/IV chemotherapy, median PFS (29 months) and OS (34 months) compared favorably with results from other trials using IV regimens (Table 16).[915] To determine whether postoperative IP/IV chemotherapy improves outcomes compared with IV regimens among patients treated with NACT, the OV21/PETROC trial compared three different postoperative regimens (Table 16) in patients previously treated with platinum-based IV NACT (3–4 cycles) and optimal cytoreduction by IDS.[920] Although trends in the rate of progression or death in the first 9 months (from randomization) favored the carboplatin/paclitaxel IP/IV regimen (Arm 3, 24.5%) over the cisplatin/paclitaxel IP/IV regimen (Arm 2, 34.7%) or the carboplatin/paclitaxel IV regimen (Arm 1, 38.6%), later results (median follow-up 33 months) showed no difference in median PFS for the IP/IV regimens versus the IV regimen (Table 16). OS rate at 2 years was also not significantly different (74% vs. 81% for Arm 1 vs. Arm 3).[920]

Based on these results, the NCCN Guidelines include both the cisplatin/paclitaxel IP/IV regimen and the carboplatin/paclitaxel IP/IV regimen as options for postoperative therapy in patients who have received NACT and IDS (Table 17). Given the lack of survival improvement in OV21/PETROC, more data are needed to establish whether postoperative IP chemotherapy provides clinical benefit in patients who have received IV NACT and IDS. Recent results from the phase III randomized controlled GOG-0252 trial have also called into question the value of postoperative IP chemotherapy for patients with advanced-stage disease treated with PDS.[893] Although earlier trials showed improved PFS and/or OS with IP versus IV chemotherapy,[748,886,887,891] results from GOG-0252 showed no improvement.[893] However, unlike previous trials, all regimens used in GOG-0252 contained bevacizumab, which may have compensated for the effect of IP chemotherapy administration.

Number of Chemotherapy Cycles Before and After IDS

As shown in Table 16, 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.[916] Nonetheless, because most of the randomized trials testing NACT protocols used 3 to 4 cycles before IDS (Table 15 and Table 16), the NCCN Guidelines indicate that 3 to 4 cycles of NACT before IDS is preferred, although surgery after 4 to 6 cycles may be used based on the clinical judgment of the treating gynecologic oncologist.

After 3 to 4 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 with completion hysterectomy/BSO and cytoreduction should be performed. Those with stable disease after 3 to 4 cycles of NACT can consider IDS (with completion hysterectomy/BSO, and cytoreduction), but also should consider either 1) switching to treatment for persistent/recurrent disease; or 2) treatment with additional cycles of NACT (to a total of ≥6 cycles), then re-evaluating to determine whether to perform IDS (with completion hysterectomy/BSO, and cytoreduction) or switch to therapy for persistent/recurrent disease. The option to continue on beyond 6 cycles is usually reserved for those who are tolerating therapy and have signs that a response may be achieved, such as those whose CA-125 is continuing to fall. 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 adjuvant chemotherapy after IDS, or indicated that the total number of cycles should be 6 to 8 (Table 14, 15, and 16). 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. Patients with stable disease who are tolerating therapy may continue past 6 cycles.

Interval Debulking Surgery After Neoadjuvant Chemotherapy of Invasive Epithelial Ovarian Cancer

Analyses of data from multiple prospective trials found that the extent of residual disease after NACT plus IDS was prognostic for PFS and OS.[484,486,664,916] As shown in Table 14, 15, and 16, these trials reported optimal cytoreduction in 45% to 91% of patients, with complete removal of all macroscopic disease in 30% to 59%. Therefore, as with a primary debulking procedure, every effort should be made to achieve complete removal of macroscopic disease (R0) during IDS. Maximal effort should be made to remove all gross disease in the abdomen, pelvis, and retroperitoneum. NCCN-recommended procedures for IDS are similar to those used in the trials listed in Table 14, 15, and 16,[484-486,663,915-917,919] and similar to those recommended for PDS. As mentioned earlier, these trials required experienced gynecologic oncologists for preoperative evaluation and IDS.[484,486,663,919] Some NCCN Panel members use online surgical risk calculators to determine whether IDS is safe in a patient who chose NACT (over PDS) due to a medical condition. Examples include the Modified Charlson Comorbidity Index (score <2),[922-926] ASA Physical Classification Status (score <3),[927-929] the Edmonton Frail Scale (score <3),[930] and the ACS NSQIP Surgical Risk Calculator.[931-933] It is recommended that a gynecologic oncologist be consulted and perform the surgery. An open laparotomy including a vertical midline abdominal incision should be used in most patients in whom an interval debulking procedure is planned. 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. Prior to IDS, patients should be counseled about port placement if subsequent IP chemotherapy is being considered.

All interval debulking procedures should include completion hysterectomy and BSO with comprehensive staging. All peritoneal surfaces should be visualized, and any peritoneal surface or adhesion suspicious for harboring metastasis should be selectively excised or biopsied. 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 the nodes are not currently suspicious or enlarged. An omentectomy should be performed, and additional procedures that may be considered 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.

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.[934-936] Concerns about the inconvenience of delivery and toxicities associated with postoperative IP/IV chemotherapy motivated researchers to determine whether HIPEC could improve safety and QOL. Although raising body temperature carries substantial risks, methods have been developed for raising the temperature of the IP space with minimal increase in the temperature of the rest of the body.

Over the past several decades a few randomized trials (Table 18)[937-940] and numerous prospective nonrandomized trials[941-954] 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 these prospective studies.[937,938,940-954] HIPEC protocols used in these prospective studies usually perfused chemotherapy for 60 or 90 minutes (depending on agent and dose used) with solution heated to achieve an IP temperature of 41°C to 43°C.[937-954] 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.[940-947,949-954] 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%,[941-948,950] although the most recent trials all report no deaths related to the procedure.[952-954] The rate of complications from surgery vary across trials, with major/severe complications (<30 days from surgery) occurring in 9% to 40% of patients.[941-950,952,953] 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.[943,955] Common major/severe complications observed across trials include various types of fistulas, abscesses, and infections (eg, 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.[937,942-946,948,950,951,953,956] Many studies reported that additional procedures were needed to manage complications.[937,943,944,947,949,950,952,953,956,957]

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 IP 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 IP therapy, intraoperative IP 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 IP therapy would not be effective treatment for extra-peritoneal disease.

Only a few phase III prospective comparative studies have tested whether HIPEC improves outcomes for patients with advanced ovarian cancer (summarized in Table 18). 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.[940] 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 IV chemotherapy (ie, time to initiation, rate of completion of all 3 cycles). Most important, no differences in rates of toxicity were observed 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. 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 recommend that all patients treated with NACT and IDS (± HIPEC) receive postoperative chemotherapy. Analyses of M06OVH-OVHIPEC showed that the effect of HIPEC was consistent across a wide variety of subgroups (eg, age, cancer 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 (Table 18).[939] 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.[939]

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.[937,938,940-954] Rates of complete cytoreduction (R0 resection) varied from 50% to 100% in these trials,[941-943,945-951,953,954] and univariable and multivariable analyses showed that residual disease after debulking was the strongest predictor of OS.[941,942,946-948,956,958] Therefore, NCCN recommends maximum effort to achieve complete cytoreduction during IDS, regardless of whether or not HIPEC is planned.

The NCCN-recommended HIPEC agent is cisplatin, 100 mg/m^2, as was used in M06OVH-OVHIPEC.[940] 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 [BSA]), other studies have used a variety of 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.

Table 18. 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 non-R Single center Greece 2003–2009 Spiliotis 2011[937]	Recurrent after CRS + systemic chemo FIGO Stage IIIC–IV[a]	Arm A (n = 24): Secondary CRS →HIPEC →Postop chemo Arm B (n = 24): Secondary CRS →Postop chemo	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 (months)[c]: 19.4 vs. 11.2; *P* < .05
Phase III RCT Single center Greece 2006–2013 Spiliotis 2015[938]	Recurrent after primary surgery + chemo FIGO stage IIIC, IV[d]: 63%, 37%	Arm A (n = 60): Secondary CRS →HIPEC →Postop chemo Arm B (n = 60): Secondary CRS →Postop chemo	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 (months): mean 26.7 vs. 13.4; *P* = .006
Phase III RCT Multicenter Korea 2010–2016 Lim ASCO 2017[939]	Primary Stage III/IV Optimal CRS (<1 cm residual)	Arm A (n = 92): Primary CRS →HIPEC →Postop chemo Arm B (n = 92): Primary CRS →Postop chemo	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 (minutes): 487 vs. 404; *P* < .001 Postop morbidity/mortality: NS[e]	PFS, 5-y rate: 21% vs. 16%;NS OS, 5-y rate: 51% vs. 49%;NS Patients with NACT: PFS, 2-y rate: 37% vs. 30% OS, 5-y rate: 48% vs. 28%

Trial	Patients	Treatment Arms	HIPEC Method & Regimen	Surgical/Safety Outcomes, Arm A vs. B	Efficacy Outcomes, Arm A vs. B
Phase III RCT OL M06OVH-OVHIPEC NCT00426257 8 hospitals Netherlands 2007–2016 Van driel 2018[940]	Primary FIGO stage III Extensive abdominal disease (90%) or incomplete primary CRS (>1 cm residual) (10%)	NACT x 3 cycles[f] →if response or stable disease, then: Arm A (n = 122): Interval CRS →Post-op chemo x 3 cycles[f] Arm B (n = 123): Interval CRS →HIPEC →Postop chemo x 3 cycles[f]	Open technique 90-min perfusion at 40°C Cisplatin 100 mg/m^2	CC-0: 67% vs. 69% Operative time (minutes): median 192 vs. 338 Hospital stay (days): median 8 vs. 10 Grade 3–4 AEs:[g] 25% vs. 27%; NS Postop death (n): 1 vs. 0 Time from CRS to start postop chemo (days): median 30 vs. 33 Completed 3 cycles postop chemo: 90% vs. 94%	RFS median (months): 10.7 vs. 14.2; HR, 0.66 (95% CI, 0.50–0.87); *P* = .003 OS median (months): 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; chemo, chemotherapy; CRS, cytoreduction surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; HR, hazard ratio; NACT, neoadjuvant chemotherapy; non-R, non-randomized; NS, no significant difference (between arms); OL, open-label; OS, overall survival; PCI, peritoneal carcinomatosis index; PFS, progression-free survival; postop, postoperative; RCT, randomized controlled trial; RFS, recurrence-free survival; SD, stable disease; y, years.

[a] Trial excluded patients with metastases outside of peritoneal surfaces (eg, 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 post-op chemo 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.

Monitoring Response to Adjuvant Systemic Therapy

After completion of chemotherapy, patients should be assessed for response during and following treatment and monitored for any long-term complications. Consider symptom management and best supportive care, and refer for palliative care assessment, if appropriate. See NCCN Guidelines for Palliative Care and NCCN Guidelines for Survivorship (available at www.NCCN.org).

Patients who have completed primary treatment for stage I disease (surgery alone or with adjuvant systemic therapy) should be monitored for recurrence. See *Follow-up Recommendations* below.

For patients who have completed postoperative chemotherapy as part of primary therapy for stage II–IV disease, imaging is recommended as clinically indicated to determine the extent of disease, if any. Recommended imaging modalities include chest/abdominal/pelvic CT, MRI, PET/CT, or PET (skull base to mid-thigh). All imaging should be performed with contrast unless contraindicated. Patients who have CR, with no evidence of disease, or PR may be eligible for maintenance

therapy as described in the next section (*Options After First-Line Chemotherapy*). Those with stable, persistent, or progressive disease should be managed as described in the section entitled *Therapy for Persistent Disease or Recurrence*.

Options After First-Line Chemotherapy

After initial treatment (eg, surgery followed by chemotherapy), patients should undergo regular clinical re-evaluation. Observation with follow-up is recommended for patients who had stage I disease at presentation and have no signs of new disease. Recommendations for surveillance during observation are in the *Monitoring/Follow-up* section (within the *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer* section in the algorithm).

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

Patients with persistent disease or progression during initial treatment should be treated with second-line approaches (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Therapy for Persistent Disease or Recurrence* in the algorithm and *Recurrent Disease* section below).[959,960]

For patients with advanced-stage (stages II–IV) disease who, after primary therapy (surgery plus chemotherapy), are in complete clinical remission (ie, complete response [CR], defined as no definitive evidence of disease[959,960]), partial remission (ie, partial response [PR]), or stable disease, recommended options depend on the extent of their response and the type of primary chemotherapy they received (see *Post-Primary Treatment: Maintenance Therapy* within the *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer* section of the algorithm). These recommendations have been revised several times recently due to emerging data from clinical trials, summarized in Tables 19, 20, and 21. These recent data and their impact on the recommendations are discussed in the sections below.

Bevacizumab Maintenance Therapy

As described in detail in the previous section entitled *Bevacizumab in the First-Line Setting*, results from the phase III GOG-0218 and ICON7 trials support the use of single-agent bevacizumab maintenance therapy for patients with stage II–IV disease who experience response or stable disease after postoperative chemotherapy with one of the carboplatin/paclitaxel/bevacizumab regimens used in these trials (and recommended by NCCN).[840-842] Based on these results bevacizumab monotherapy was a recommended option for maintenance for patients with stage II–IV disease who were in CR/PR after a primary treatment with surgery and one of the bevacizumab-containing regimens recommended in the first-line setting. However, due to results from subsequent trials showing benefit from PARP inhibitors, as described below, bevacizumab monotherapy is no longer recommended for patients with *BRCA1/2* mutations, but is still recommended as an option for patients who have wild-type or unknown *BRCA1/2* mutation status (in CR/PR after a recommended bevacizumab-containing first-line chemotherapy regimen), as these patients have fewer PARP inhibitor options (See Table 23).

PARP Inhibitor Maintenance Therapy After Primary Chemotherapy

Several PARP inhibitors have been shown to be active in recurrent ovarian cancer,[961-968] and have been FDA approved for multiple indications in ovarian cancer (summarized in Table 22); the corresponding recommendations can be found in the NCCN Guidelines algorithm for *Post-Primary Treatment: Maintenance Therapy* (OV-5), *Therapy for*

Persistent Disease or Recurrence (OV-7) and *Principles of Systemic Therapy: Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer* (OV-C 7 and 8 of 10).

More recently, several phase III double-blind, randomized trials have tested PARP inhibitors as maintenance therapy for patients with newly diagnosed, histologically confirmed, FIGO stage III/IV ovarian, fallopian tube, or primary peritoneal cancer who have completed first-line chemotherapy.[776-779] Characteristics of the patient populations in these trials are summarized in Table 20, and efficacy and safety results are summarized in Table 19 and Table 21.

Table 19. Phase III RCTs Testing PARP Inhibitors for Maintenance After First-Line Chemotherapy: Efficacy

Trial	Maintenance Therapy	Follow-up, Median (mo)	PFS[a] (Arm A versus B)		
SOLO-1 NCT01844986[776]	Arm A (n=260): Olaparib Arm B (n=131): Placebo	40.7 vs. 41.2	Population	3-year	HR [95% CI]
			Overall (all *BRCA1/2* mut)	60% vs. 27%[c]	0.30 [0.23–0.41]
PAOLA-1/ ENGOT-OV25, NCT02477644[777]	Arm A (n=537): Olaparib + bevacizumab Arm B (n=269): Placebo + bevacizumab	22.7 vs. 24.0	Population	Median (mo)	HR [95% CI]
			Overall	22.1 vs. 16.6[d]	0.59 [0.49–0.72]
			BRCA1/2 mut	37.2 vs. 21.7	0.31 [0.20–0.47]
			BRCA1/2-wt/ND	18.9 vs. 16.0	0.71 [0.58–0.88]
			BRCA1/2-wt, HRD[b]	28.1 vs. 16.6	0.43 [0.28–0.66]
			HRP	16.6 vs. 16.2	1.00 [0.75–1.35]
PRIMA/ ENGOT-OV26/ GOG-3012, NCT02655016[778]	Arm A (n=487): Niraparib Arm B (n=246): Placebo	13.8	Population	Median (mo)	HR [95% CI]
			Overall	13.8 vs. 8.2[d]	0.62 [0.50–0.76]
			HRD	21.9 vs. 10.4[d]	0.43 [0.31–0.59]
			BRCA1/2 mut	22.1 vs. 10.9	0.40 [0.27–0.62]
			BRCA1/2 wt, HRD[b]	19.6 vs. 8.2	0.50 [0.31–0.83]
			HRP	8.1 vs. 5.4	0.68 [0.48–0.94]
Trial	**First-Line → Maintenance Therapy[e]**	**Follow-up, Median (mo)**	**PFS (Arm A versus C)**		
VELIA/ GOG-3005 NCT02470585[779]	Arm A (n=375): Carbo/pac/pbo → pbo Arm B (n=383): Carbo/pac/veli → pbo Arm C (n=382): Carbo/pac/veli → veli	28	Population	Median (mo)	HR [95% CI]
			Overall	17.3 vs. 23.5[d]	0.68 [0.56–0.83]
			BRCA1/2 mut	22.0 vs. 34.0[d]	0.44 [0.28–0.68]
			BRCA1/2 wt	15.1 vs. 18.2	0.80 [0.64–1.00]
			HRD[b]	20.5 vs. 31.9[d]	0.57 [0.43–0.76]
			HRP	11.5 vs. 15.0	0.81 [0.69–1.09]

Abbreviations: BID, twice daily; carbo, carboplatin; CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficient; HRP, homologous recombination proficient; mo, months; mut, mutation; ND, not determined (unknown); NR, not reported; pac, paclitaxel; pbo, placebo; RCT, randomized controlled trial; veli, veliparib; wt, wild-type.

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

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

[c] $P < .0001$

[d] $P < .001$

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

Table 20. Phase III RCTs Testing PARP Inhibitors for Maintenance After First-Line Chemotherapy: Patient Characteristics[a]

Trial	SOLO-1[776]	PAOLA-1[777]	PRIMA[778]	VELIA[779]
Maintenance therapy tested	Olaparib vs. placebo	Bevacizumab + olaparib vs. bevacizumab + placebo	Niraparib vs. placebo	Veliparib vs. placebo
Patient characteristics:				
• FIGO stage: III, IV	83%, 17%	70%, 30%	65%, 35%	77%, 23%
• Cancer type: High-grade serous, high-grade endometrioid, other[b]	96%, 2.3%, 1.5%	96%, 2.5%, 1.7%	95%, 2.7%, 2.3%	100%, 0, 0
• Primary cancer site: ovarian, primary peritoneal, fallopian tube	85%, 8%, 6%	86%, 8%, 6%	80%, 6.4%, 13%	NR
• *BRCA1/2* status: mutation, wild-type, unknown	100%, 0, 0	29%, 67%, 4%	30%, NR, NR	26%, 65%, 9%
• Homologous recombination status: deficient, proficient, unknown[c]	100%, 0, 0	48%, 34%, 18%	51%, 34%, 15%	55%, 33%, 12%
Primary treatment and response:				
• Surgery: PDS, IDS, none	62%, 35%, 2%	51%, 42%, 7%	NR, 67%, NR	67%, 28%, 4%
• Macroscopic residual disease after surgery (PDS or IDS): none, some, unknown	76%, 19%, 1%	51%, 33%, 0	NR[d]	64%, 30%, 1%
• Systemic therapy	Platinum-based chemotherapy[e]	Platinum-taxane based chemotherapy[f] + bevacizumab	Platinum-based chemotherapy[f]	Paclitaxel/carboplatin/ placebo vs. paclitaxel/carboplatin/ veliaparib
• Cycles of systemic therapy: 6, 7–9, unknown	78%, 21%, 0[g]	6–9 chemotherapy, 2–3 bevacizumab[g]	69%, 25%, 6%	6[f]
• Response after systemic therapy: CR, PR[h]	82%, 18%	73%, 27%	69%, 31%	NR
• CA-125 ≤ULN after systemic therapy	95%	86%	92%	NR

Abbreviations: CA-125, cancer antigen 125; CR, complete response; HRD, homologous recombination deficient; HRP, homologous recombination proficient; IDS, interval debulking surgery (after neoadjuvant therapy); NED, no evidence of disease; NR, not reported; PDS, upfront primary debulking surgery; PR, partial response; RCT, randomized controlled trial; ULN, upper limit of normal.

[a] All patients had newly diagnosed, histologically confirmed disease. Data show percent of total randomized population (n = 310 for SOLO-1, 806 for PAOLA-1, 733 for PRIMA, 1140 for VELIA).

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

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

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

[e] Chemotherapy agents used in both arms were paclitaxel (98% of patients), carboplatin (91%), cisplatin (20%), docetaxel (6%), and gemcitabine (<1%). Other agents were used in <1% of patients in the olaparib arm only: nab-paclitaxel, doxorubicin, cyclophosphamide, and bevacizumab.

[f] Information is based on entry criteria because data were not reported.
[g] In SOLO-1, 1% of patients had 4 cycles of chemotherapy.
[h] In SOLO-1 and PAOLA-1, CR was defined as NED on imaging (no measurable/assessable disease) and CA-125 ≤ULN. In SOLO-1, PR was defined as 30% reduction in tumor volume or NED on imaging with CA-125 >ULN. In PAOLA-1, PR was defined as radiologic evidence of disease, an abnormal CA-125 level, or both. In PRIMA, CR and PR were judged by "investigator assessment"; more specific criteria were not disclosed. In VELIA, the response rate for the whole population was not reported, and response was not required prior to maintenance therapy.

Olaparib Monotherapy

The SOLO-1 trial demonstrated a remarkable improvement in PFS with single-agent olaparib versus placebo as maintenance therapy for patients with a germline or somatic *BRCA1/2* mutation who had a CR/PR after first-line platinum-based chemotherapy (Table 19).[776] The risk of progression or death was 70% lower, with the median PFS (from randomization) of 13.8 months for placebo, and the median PFS for olaparib had not been reached after a median follow-up of 41 months; OS data are also immature. A subsequent subgroup analysis showed that the PFS benefit was significant regardless of *BRCA* mutation type (*BRCA1* vs. *BRCA2*).[969] Based on results from SOLO-1, the NCCN Guidelines include olaparib monotherapy as a maintenance therapy option for patients who have a *BRCA1/*2 mutation and have a CR or PR after completion of primary therapy including surgery and platinum-based chemotherapy (Table 23).

SOLO-1 excluded patients who received bevacizumab as part of primary systemic therapy, so the efficacy of single-agent olaparib after chemotherapy/bevacizumab primary therapy is unknown. Nonetheless, the benefit from olaparib was sizeable and significant across many subgroups analyzed.[776,969] It is important to note that the effects of maintenance olaparib on PFS (70% improvement; Table 19)[776] are far greater than the effects on PFS reported for the addition of bevacizumab to both upfront and maintenance therapy (<30% improvement).[840,842,843] PFS curves from SOLO-1 show large separation between olaparib versus placebo throughout the time course of the study (median follow-up, 41 months),[776] 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.[842,843] 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.[847] The PAOLA-1 trial (described in the next section) suggested that maintenance olaparib could provide PFS benefit in patients who had bevacizumab during first-line chemotherapy.[777] For these reasons single-agent olaparib is a category 1 option only for patients who did not have bevacizumab as part or primary therapy, but is a category 2A option for patients who received prior bevacizumab, provided that they were in a CR or PR after completion of chemotherapy (Table 23). The NCCN Panel included a footnote to make it clear that data are limited on the use of single-agent olaparib after first-line platinum-based chemotherapy plus bevacizumab, but that evidence from other subgroups suggests that it should be considered as an option for these patients.

Olaparib + Bevacizumab

The phase III double-blind, randomized PAOLA-1 trial demonstrated a remarkable improvement in PFS (HR, 0.59) when olaparib (vs. placebo) was added to maintenance bevacizumab in patients who have a CR or PR after first-line platinum-taxane chemotherapy plus bevacizumab for advanced disease (Table 19).[777] Unlike SOLO-1, PAOLA-1 included both patients with and without *BRCA1/2* mutations. Subgroup analyses showed that similar to the SOLO-1 trial, for patients with *BRCA1/2* mutations, maintenance olaparib reduced the risk of progression or death by approximately 70% (Table 19).[777] A subsequent sub-analysis found that

the PFS benefit of adding olaparib to bevacizumab maintenance was similar and significant regardless of *BRCA* mutation type (*BRCA1* vs. *BRCA2*).[970] Based on these results, maintenance with bevacizumab + olaparib is a category 1 option for patients who have a CR/PR after completing bevacizumab-containing first-line therapy, and single-agent bevacizumab was removed as a maintenance therapy option in this setting.

PAOLA-1 also showed that adding olaparib to maintenance bevacizumab resulted in a smaller but still significant improvement in PFS for those with *BRCA1/2* wild-type or unknown (Table 19).[777] Due to the smaller magnitude of this effect, the NCCN Guidelines include olaparib + bevacizumab combination and bevacizumab monotherapy as category 2A maintenance therapy options for patients with *BRCA1/2* wild-type or unknown mutation status who are in a CR or PR after completion of first-line platinum-based chemotherapy/bevacizumab combination (Table 23).

In PAOLA-1 the population without *BRCA1/2* mutations was further subdivided based on results of MyChoice CDx (Myriad Genetic Laboratories), a proprietary tumor tissue assay that uses multiple molecular tests and combines several metrics (loss of heterozygosity [LOH],[971] telomeric allelic imbalance [TAI],[972] and large-scale state transitions [LST][973] to determine the genomic instability score (GIS), a proxy measure for the presence of homologous recombination deficiency.[974,975] A GIS cutoff of 42 was used to define homologous recombination deficiency status based on a prior analyses of a population of breast and ovarian cancer cases showing that this cutoff identified 95% of patients who had *BRCA1/2* deficiency, defined as either 1) one deleterious mutation in *BRCA1* or *BRCA2*, with LOH in the wild-type copy; 2) two deleterious mutations in the same gene; or 3) promoter methylation of *BRCA1* with LOH in the wild-type copy.[976] Among those without *BRCA1/2* mutations, the PFS benefit of maintenance olaparib was significant for those with homologous recombination deficiency (as defined by the proprietary assay) but was not significant for those who did not have homologous recombination deficiency (Table 19). For this reason, the NCCN Panel included the following footnote relating to the use of maintenance bevacizumab + olaparib: In the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

OS results from PAOLA-1 were not mature.

Niraparib Monotherapy

Similar to the SOLO-1 results for olaparib monotherapy, the PRIMA trial demonstrated a remarkable improvement in PFS with single-agent niraparib (versus placebo) as maintenance therapy for patients with a *BRCA1/2* mutation who were in a CR/PR after first-line platinum-based chemotherapy (Table 19).[778] Based on these results the NCCN Guidelines include single-agent niraparib as a maintenance therapy option for patients with *BRCA1/2* mutations who have completed primary treatment including surgery and platinum-based first-line therapy (Table 23). PRIMA likely did not include many patients who had prior bevacizumab as part of primary systemic therapy, so for patients with a *BRCA1/2* mutation maintenance niraparib is a category 1 option for those who had first-line platinum-based chemotherapy without bevacizumab, and a category 2A option for those who had bevacizumab in conjunction with first-line platinum-based chemotherapy (Table 23).

Unlike SOLO-1, the presence of a *BRCA1/2* mutation was not part of the entry criteria for the PRIMA trial. PRIMA included patients who did not have deleterious mutations in *BRCA1/2*, and results showed significant PFS improvement with niraparib (vs. placebo) for the overall population. Subgroup analyses showed that the effect of maintenance niraparib on PFS was still significant among patients without a *BRCA1/2* mutation (HR,

0.71 [95% CI, 0.58–0.88]), although the size of the effect appears smaller than that seen in patients with *BRCA1/2* mutations (Table 19). Based on these results, the NCCN Guidelines include single-agent niraparib as an option for maintenance therapy for patients with *BRCA1/2* wild-type or unknown, provided they are in a CR or PR after completion of primary platinum-based chemotherapy (without bevacizumab) (Table 23). Given the smaller magnitude of the PFS effect in patients without *BRCA1/2* mutation, and that PRIMA likely included very few patients who had bevacizumab as part of primary therapy, single-agent niraparib is not a recommended maintenance therapy option for those who have *BRCA1/2* wild-type or unknown and received bevacizumab as part of primary therapy (Table 23).

As in PAOLA-1, in PRIMA the patient group without *BRCA1/2* mutation was further subdivided into homologous recombination deficient and proficient based on a GIS cutoff of 42 using the MyChoice CDx (Myriad Genetic Laboratories).[778] Results showed that the PFS effect of niraparib (vs. placebo) remained significant for the smaller subgroup of patients with homologous recombination deficiency but no *BRCA1/2* mutation, and was significant, with a trend toward smaller magnitude, for the homologous recombination-proficient subgroup (Table 19).[778] Because of these results, the NCCN Panel chose to include the following footnote relating to the use of maintenance niraparib: in the absence of a *BRCA1/2* mutation, homologous recombination deficiency status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B).

OS data from the interim analysis was reported (Table 19), but it is premature to draw conclusions from those results.

<u>Veliparib</u>

The phase III VELIA study design was similar to GOG-0218 and ICON7 bevacizumab trials in that it tested the effect of adding veliparib during first-line chemotherapy and as subsequent single-agent maintenance after completion of chemotherapy.[779] VELIA did not require that patients have CR/PR before receiving maintenance therapy; they only needed to have absence of progression during first-line systemic therapy (6 cycles) and no limiting toxicities. Results showed that whereas adding veliparib during first-line chemotherapy did not significantly improve PFS compared with chemotherapy alone, those who received veliparib during first-line chemotherapy and maintenance therapy had significantly improved PFS compared with those who received chemotherapy alone (with placebo during first-line systemic therapy and maintenance; Table 19). Subgroup analyses showed that whereas the PFS benefit from veliparib appeared to be the greatest for those with a *BRCA1/2* mutation, and was significant for those with homologous recombination deficiency (*BRCA1/2* mutation or a GIS ≥33 on myChoice CDx assay), the effect was smaller and not significant for the subgroup without *BRCA1/2* mutation and the subgroup that was homologous recombination-proficient (no *BRCA1/2* mutation and GIS <33; Table 19). OS results were not mature.[779] Veliparib is not recommended in the NCCN Guidelines because it is not FDA approved for any indications. Nonetheless the consistency of the results observed in VELIA support the use of PARP inhibitors as maintenance therapy after first-line platinum-based chemotherapy, and suggest that adding PARP inhibitors during primary chemotherapy may not provide substantial clinical benefit.

<u>PARP Inhibitor Safety</u>

Table 21 summarizes key safety data for the four phase III trials testing PARP inhibitor therapy as maintenance following first-line systemic therapy. Across trials, PARP inhibitor maintenance was associated with higher rates of a number of common non-hematologic AEs, such as fatigue/asthenia, nausea, and vomiting (Table 21). These non-hematologic AEs tended to be low-grade and rarely led to study-drug discontinuation.[776-779] PARP inhibitor therapy was also associated with increased risk for a number of hematologic AEs, such as anemia,

neutropenia, and thrombocytopenia (Table 21). Hematologic AEs were the most common high-grade AEs (grade ≥3), and the most common cause of study drug discontinuation due to toxicity.[776-779] Although rare (≤2%), PARP inhibitor therapy was also associated with risk of myelodysplastic syndrome or acute myeloid leukemia,[776-779] and is mentioned in the FDA labels.[977,978] Bevacizumab is associated with risk of hypertension; in the PAOLA-1 trial, hypertension was a common AE and a common high-grade AE in both arms, although it did not lead to discontinuation.[777] Across trials, rates of high-grade AEs (grade ≥3) were higher for single-agent PARP inhibitor maintenance therapy compared with placebo. In PAOLA-1, however, there was only a small difference between arms in the rate grade ≥3 AEs (Table 21), and serious AEs occurred in 31% in each arm, [777] showing that risk of high-grade/serous AEs was similar for maintenance bevacizumab with versus without olaparib. Rates of study-drug discontinuation due to toxicity were higher with PARP inhibitor maintenance therapy across all trials, including PAOLA-1, largely due to hematologic AEs.

In the SOLO-1, PAOLA-1, PRIMA, and VELIA trials, there were no statistically significant differences between treatment arms in the heath-related QOL metrics evaluated.[776-779]

Table 21. Adverse Events Associated with PARP Inhibitor Maintenance after First-Line Systemic Therapy[a]

Trial	SOLO-1[776]	PAOLA-1[777]	PRIMA[778]	VELIA[779]
Maintenance therapy tested	Olaparib vs. placebo	Bevacizumab + olaparib vs. bevacizumab + placebo	Niraparib vs. placebo	Veliparib vs. placebo[b]
PARP inhibitor maintenance dose	300 mg BID	300 mg BID	300 mg QD[c]	300 mg BID x 2 weeks, then 400 mg BID
AEs Grade 5	none	<1% vs. 1%	0.4% vs. 0.4%	None
AEs Grade ≥3	39% vs. 18%	57% vs. 51%	71% vs. 19%	45% vs. 32%
AEs leading to discontinuation	12% vs. 2%	20% vs. 6%	12.0% vs. 2.5%	17% vs. 1%
Common non-hematologic AEs (>20%), any grade, differing between arms by ≥9%	Nausea: 77% vs. 38% Fatigue/asthenia: 63% vs. 42% Vomiting: 40% vs. 15% Diarrhea: 34% vs. 25% Constipation: 28% vs. 19% Dysgeusia: 26% vs. 4% Decreased appetite: 20% vs. 10%	Nausea: 53% vs. 22% Fatigue/asthenia: 53% vs. 32% Vomiting: 22% vs. 11% Hypertension: 46% vs. 60%	Nausea: 57 vs. 28% Vomiting: 22% vs. 12% Constipation: 39% vs. 19% Headache: 26% vs. 15% Insomnia: 25% vs. 15%	Nausea: 56% vs. 24% Vomiting: 34% vs. 12% Arthralgia: 16% vs. 20%
Common non-hematologic AEs (>5%), grade ≥3	None	Fatigue/asthenia: 5% vs. 1% Hypertension: 19% vs. 30%	Hypertension: 6% vs. 1%	Nausea: 5% vs. 1% Fatigue: 6% vs. 1%
Common hematologic AEs (>20%), any grade, differing between arms by ≥9%	Anemia: 39% vs. 10% Neutropenia: 23% vs. 12%	Anemia: 41% vs. 10% Lymphopenia: 24% vs. 9%	Anemia: 63% vs. 18% Neutropenia: 26% vs. 7% Neutrophil count decreased: 17% vs. 2% Thrombocytopenia: 46% vs. 4% Platelet count decreased: 28% vs. 1%	Thrombocytopenia: 20% vs. 5%
Common hematologic AEs (>5%), grade ≥3	Anemia: 22% vs. 2% Neutropenia: 9% vs. 5%	Anemia: 17 vs. <1% Lymphopenia: 7% vs. 1% Neutropenia: 6% vs. 3%	Anemia: 31% vs. 2% Neutropenia: 13% vs. 1% Neutrophil count decreased: 8% vs. 0 Thrombocytopenia: 29% vs. <1% Platelet count decreased: 13% vs. 0	Anemia: 7% vs. 1% Thrombocytopenia: 7% vs. <1% Neutropenia: 5% vs. 4%

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

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

Although 3 PARP inhibitors (olaparib, rucaparib, and niraparib) are approved for single-agent maintenance therapy in select patients who are in CR or PR after platinum-based chemotherapy for recurrent disease, olaparib, niraparib, and olaparib + bevacizumab are currently the only PARP inhibitor regimens that are FDA approved for maintenance

treatment after response to first-line chemotherapy in patients with newly diagnosed advanced disease (Table 22). The FDA-approved indications are for patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR/PR to first-line platinum-based chemotherapy (Table 22). The FDA indication for single-agent olaparib in this setting is limited to those with a deleterious or suspected deleterious *BRCA* mutation, and the FDA indication for bevacizumab plus olaparib in this setting is limited to those with homologous recombination deficiency, as defined by a deleterious or suspected deleterious *BRCA* mutation and/or genetic instability, as measured using an FDA-approved companion diagnostic. Veliparib is not currently FDA approved.

Maintenance with single-agent bevacizumab is FDA approved in this setting for patients with stage III–IV epithelial ovarian, fallopian tube, or primary peritoneal cancer that has been treated with surgical resection and combination carboplatin/paclitaxel/bevacizumab (Table 22).

Table 22. FDA-Approved Indications for Bevacizumab and PARP Inhibitors in Ovarian Cancer

Agent USPI Date	First-Line Chemotherapy	Maintenance After First-Line Chemotherapy	Recurrence Therapy	Maintenance After Recurrence Therapy
Bevacizumab September 2020[979]	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 ≤2 prior chemotherapy regimens.	
			For epithelial ovarian, fallopian tube, or primary peritoneal cancer, in combination with carboplatin and paclitaxel or carboplatin and gemcitabine, followed by bevacizumab as a single agent, for platinum-sensitive recurrent disease.	
Niraparib April 2020[977]	None	For the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to first-line platinum-based chemotherapy.	For the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥3 prior chemotherapy regimens and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation,[a] or • genomic instability[a] and who have progressed >6 months after response to the last platinum-based chemotherapy.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy.

Agent USPI Date	First-Line Chemotherapy	Maintenance After First-Line Chemotherapy	Recurrence Therapy	Maintenance After Recurrence Therapy
Olaparib May 2020[978]	None	For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated[b] advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy. In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either: • a deleterious or suspected deleterious *BRCA* mutation[b], and/or • genomic instability[b]	For the treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated[b] advanced ovarian cancer who have been treated with ≥3 prior lines of chemotherapy.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in CR or PR to platinum-based chemotherapy.
Rucaparib Oct 2020[980]	None	None	For the treatment of adult patients with deleterious *BRCA* mutation[c] (germline and/or somatic)–associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with ≥2 prior lines of chemotherapies.	For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a CR or PR to platinum-based chemotherapy.

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

NCCN Recommendations for Maintenance After Primary Chemotherapy

For patients who have completed primary surgery and systemic therapy, the NCCN-recommended options for management of patients who have completed primary therapy are summarized in Table 23, including maintenance therapy options. The recommended options depend on disease stage, agents used for primary systemic therapy, response to primary treatment, and *BRCA1/2* mutation status. For the maintenance therapy options, Table 23 also shows which NCCN-recommended options are consistent with an FDA-approved indication, as well as options consistent with an FDA-approved indication that are not recommended in the NCCN Guidelines. Discrepancies between the NCCN recommendations and FDA-approved indications are highlighted in yellow. Table 23 shows the trials that provided data that support the maintenance

therapy options. As illustrated in Table 23, there are several key discrepancies between the FDA labels and NCCN Guidelines recommendations.

1) The FDA-approved indication for maintenance bevacizumab is limited to patients with stage III–IV disease, whereas the NCCN Guidelines include this as an option for stage II disease. The rationale for this is discussed below in the section on *Selecting Patients for Maintenance Therapy, Disease Stage.*

2) The FDA-approved indication for maintenance bevacizumab is not qualified based on *BRCA1/2* mutation status. In contrast, the NCCN Guidelines single-agent bevacizumab maintenance is limited to those without a *BRCA1/2* mutation. The rationale for this is discussed above in the section entitled *Olaparib + Bevacizumab*.

3) The FDA-approved indication for olaparib/bevacizumab combination maintenance therapy does not specify that patients must have had prior bevacizumab, whereas the NCCN Guidelines restrict this option to those with prior bevacizumab, as there are no prospective randomized trial data to suggest that maintenance bevacizumab provides any clinical benefit to those who did not receive prior bevacizumab in combination with platinum-based chemotherapy.

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

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

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

Table 23. NCCN Recommended Options for Maintenance After First-Line Chemotherapy[a]

Pathologic Stage	*BRCA1/2* Status	Primary Systemic Therapy[b]	Response to Primary Therapy	Recommended Options	Category	FDA Indication[e]	Supporting Trial (and citations)
Any	Any	Any	SD/PD	Therapy for persistent disease or recurrence	2A	N/A	N/A
Stage I	Any	Any	CR/PR	Observe	2A	N/A	N/A
Stage II–IV	Mutated	Platinum-based chemotherapy	CR	Observe	2A	N/A	N/A
			CR/PR	Olaparib	1	Yes	SOLO-1[776]
				Bevacizumab + olaparib	NR	Yes	Extrapolation from PAOLA-1[777]
				Niraparib	1	Yes	PRIMA[778]
Stage II–IV	Mutated	Platinum-based chemotherapy + bevacizumab	CR/PR	Bevacizumab	NR	Only for stage III–IV	GOG-0218,[840] ICON7[841,842]
				Olaparib[d]	2A	Yes	Extrapolation from SOLO-1[776] and PAOLA-1[777]
				Bevacizumab + olaparib	1	Yes	PAOLA-1[777]
				Niraparib[d]	2A	Yes	Extrapolation from PRIMA[778]
Stage II–IV	Wild-type or unknown	Platinum-based chemotherapy	CR	Observe	2A	N/A	N/A
			CR/PR	Bevacizumab + olaparib	NR	Yes for patients with genomic instability	Extrapolation from PAOLA-1[777]
				Niraparib[c]	2A	Yes	PRIMA[778]
			PR	Therapy for persistent disease or recurrence	2A	N/A	N/A
Stage II–IV	Wild-type or unknown	Platinum-based chemotherapy + bevacizumab	CR/PR	Bevacizumab	2A	Only for stage III–IV	GOG-0218,[840] ICON7[841,842]
				Bevacizumab + olaparib[c]	2A	Only for patients with genomic instability	PAOLA-1[777]
				Niraparib	NR	Yes	Extrapolation from PRIMA[778]

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

[a] Options shown in this table are for patients with ovarian, fallopian tube, or primary peritoneal cancer who have undergone primary treatment per NCCN Guidelines recommendations with either 1) upfront surgery plus adjuvant systemic therapy; or 2) NACT, IDS, and postoperative adjuvant systemic therapy.

[b] Recommended maintenance therapy options are for those who have undergone primary systemic therapy with an NCCN-recommended regimen. See *Principles of Systemic Therapy: Primary Systemic Therapy Regimens* in the algorithm for options.

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

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

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

Selecting Patients for Maintenance Therapy

Diagnosis and Cancer Type

As shown in Table 20, the trials testing PARP inhibitors as maintenance therapy after first-line systemic therapy enrolled patients with newly diagnosed, histologically confirmed ovarian, primary peritoneal, or fallopian tube cancer. The FDA indications in this setting for olaparib, olaparib + bevacizumab, and niraparib all apply to cancers originating in any of these primary sites (Table 22).

Although most patients in the trials testing PARP inhibitor maintenance after primary therapy had high-grade serous histology (95%–100%), several of these trials (ie, SOLO-1, PAOLA-1, PRIMA), included a small percentage of patients with high-grade endometrioid (2.3%–2.7%), and a small percentage with other cancer types (1.5%–2.3%; Table 20). The NCCN Guidelines recommendations for maintenance options apply to patients with high-grade serous or grade 2/3 endometrioid cancer types. It is not clear whether these maintenance therapies are appropriate for patients with less common epithelial ovarian cancer types (ie, carcinosarcoma, clear cell carcinoma, mucinous carcinoma, grade 1 endometrioid, low grade serous). The FDA indications for PARP inhibitors in this setting are all for “epithelial” cancer (Table 22).

Disease Stage

The trials testing PARP inhibitor maintenance therapy after first-line treatment all required patients to have FIGO stage III–IV, and most patients had stage III disease (65%–83%; see Table 20). Cases of stage II disease at initial diagnosis are rare, especially among patients who have undergone complete surgical staging, so there are little data and low probability of future trials that will address the question of whether it is appropriate to use PARP inhibitors as maintenance after completing primary therapy for stage II disease. For this reason, the NCCN Panel decided that the PARP inhibitor maintenance therapy options (ie, olaparib, niraparib, olaparib + bevacizumab) for patients who have completed first-line chemotherapy are recommended for stage III–IV disease, and should also be considered for patients who have stage II disease, noting that supporting data are limited for stage II. These maintenance therapy options are not recommended for patients with stage I disease (Table 23). The FDA indications for olaparib, olaparib + bevacizumab, and niraparib as maintenance therapy options after first-line chemotherapy are for patients with “advanced” disease, which is not clearly defined (Table 22).

The GOG-0218 and ICON7 regimens for first-line platinum-based chemotherapy with concurrent bevacizumab followed by single-agent maintenance bevacizumab are recommended in the NCCN Guidelines as options for stage III–IV disease, and the NCCN Panel recommends that these can be considered for patients with stage II disease. They are not recommended for stage I disease. Use in stage II should take into consideration that GOG-0218 included only stage III–IV,[840] and although ICON7 included patients with high-risk stage I/II, sub-analyses showed the greatest benefit from bevacizumab among patients with more advanced disease, with no significant impact of bevacizumab on OS for patients with earlier stage disease.[842] The corresponding FDA-approved indication for carboplatin/paclitaxel/bevacizumab followed by single-agent bevacizumab is limited to stage III–IV disease (Table 22).

BRCA1/2 Mutation Status

Because *BRCA1/2* mutation status is important for selection of maintenance therapy in patients with stage II–IV disease that responds to primary treatment, the NCCN Guidelines recommend screening for *BRCA1* and *BRCA2* mutations earlier in the course of workup and primary treatment. Genetic risk evaluation and *BRCA1/2* testing should be initiated as soon as the diagnosis has been confirmed histologically by evaluation of tumor tissue. Primary chemotherapy should not be delayed for a genetic counseling referral, because delay between surgery and start of chemotherapy is associated with poorer outcomes,[531,981] and maintenance would not be initiated until completion of platinum-based first-line chemotherapy, which takes (at least) 18 weeks. The NCCN Guidelines recommend that *BRCA* testing be performed using an FDA-approved test or other validated test performed in a CLIA-approved facility.

Homologous Recombination Deficiency

There is consensus that the presence of a deleterious germline or somatic mutation in *BRCA1* or *BRCA2* confers a level of homologous recombination deficiency that is clinically relevant to the selection of therapy for patients with ovarian cancer. However, for patients with ovarian cancer who do ***not*** have a deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2*, various molecular markers and metrics have been proposed to determine whether the cancer is associated with a clinically relevant level of homologous recombination deficiency. Different methods and cutoffs were used in the PAOLA-1, PRIMA, and VELIA trials.[777-779] Because in PRIMA the study regimen being tested improved PFS (compared with control) even among the homologous recombination "proficient" subgroups, but the same was not true in PAOLA-1 or VELIA (Table 19), it is not clear whether the assays and cutoffs used to assign homologous recombination deficiency in those studies should be used to inform selection of maintenance therapy after first-line treatment. This is an area of ongoing investigation and as such, the NCCN Panel is not ready to recommend any particular approach for determining homologous recombination deficiency in patients with ovarian cancer who do not have a *BRCA1/2* mutation.

Primary Treatment

All four trials testing PARP inhibitor maintenance after primary treatment included both patients who had received upfront PDS followed by adjuvant chemotherapy, as well as patients who had received NACT with IDS and adjuvant chemotherapy (Table 20). For trials with reported data regarding the types of primary surgery received (ie, SOLO-1, PAOLA-1, VELIA), more than half of the patients had upfront PDS, most of the remainder had NACT and IDS, and very few did not have any primary surgery (≤7%; Table 20). In these three trials, more than half of the population had surgery resulting in no macroscopic residual disease after surgery (Table 20). In SOLO-1 and PAOLA-1, subgroup analyses showed significant PFS benefit from PARP inhibitor maintenance regardless of the type of primary surgery (PDS vs. IDS) and presence versus absence of macroscopic residual disease after primary surgery.[777,969] Subgroup analyses of VELIA showed PFS benefit from veliparib regardless of the type of primary surgery (PDS vs. IDS).[779]

In contrast to the other three trials, the PRIMA trial required that patients with stage III have either unresectable disease or visible residual disease after primary surgery, and likely included more patients treated with IDS (vs. PDS), such that a much smaller proportion of the population had a surgery that resulted in no macroscopic disease. For PRIMA the data on primary surgeries received and extent of residual disease after surgery were not reported clearly. The PRIMA report did not include subgroup analyses based on type of surgery or residual disease after surgery, but did show that the PFS benefit associated with maintenance niraparib was significant for both those with and those without prior NACT.[778]

In SOLO-1, PAOLA-1, and PRIMA, most patients had at least 6 cycles of platinum-based chemotherapy as part of primary treatment (Table 20). Both IV regimens and IP/IV regimens were allowed in SOLO-1 and PAOLA-1.[776,777] In the NCCN Guidelines, all the IV and IP/IV regimens recommended for neoadjuvant/adjuvant primary chemotherapy in patients with stage II–IV high-grade serous or endometrioid disease include 6 cycles of platinum-based combination chemotherapy (See *Principles of Systemic Therapy*: *Primary Systemic Therapy Regimens* in the algorithm).

SOLO-1, PAOLA-1, and PRIMA required patients to have CR or PR before initiation of maintenance therapy, and most had CR after primary systemic therapy, although the definitions of CR and PR varied (Table 20). Subgroup analyses in SOLO-1 and PRIMA showed that PFS benefit from single-agent PARP inhibitor maintenance was significant regardless of depth of response (CR vs. PR) after first-line systemic therapy.[776,778] VELIA did not require that patients have CR or PR after primary chemotherapy as a criterion for receiving veliparib maintenance therapy, and did not report response rate for the overall population.[779]

The NCCN recommendations for maintenance bevacizumab and PARP inhibitors apply to patients with a CR (no evidence of disease) or PR after debulking surgery and chemotherapy, including those treated with PDS followed by adjuvant chemotherapy, and those treated with NACT, IDS, and adjuvant chemotherapy. Maintenance therapy is not recommended for patients who have progressive or stable disease on primary treatment; these patients should be treated with recurrence therapy options as shown in *Therapy for Persistent Disease or Recurrence* in the *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer* section of the algorithm.

Maintenance Therapies No Longer Recommended

Paclitaxel Maintenance Therapy

Based on results from the randomized GOG-178 trial, paclitaxel used to be a post-remission therapy option for patients with stages II–IV and CR after first-line therapy. In patients with CR after initial 5–6 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.[982,983] Longer maintenance with paclitaxel was associated with higher rates of grade 2–3 neuropathy and grade 3 pain.[983] 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 (vs. observation) did not improve PFS or OS, and was associated with higher rates of GI toxicity and neurotoxicity.[984,985] 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 post-remission therapy option for patients with stages II–IV disease in 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).[986,987] Pazopanib was a category 2B recommendation for post-remission therapy because the FDA has not approved this indication,[988] there was no increase in OS, and the safety profile was concerning.[987] 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%).[986] A recent analysis of AGO-OVAR 16 showed that maintenance pazopanib was associated with poorer QOL, often due to persistent diarrhea.[981] 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 post-remission pazopanib as an option for maintenance therapy after first-line chemotherapy.

Drug Reactions

Virtually all drugs have the potential to cause adverse reactions while being infused, which can be classified as infusion reactions or allergic reactions, and can occur either during the infusion or following completion of the infusion (even days later).[989-993] Drugs used in gynecologic oncology treatment that more commonly cause adverse reactions include carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, and paclitaxel.[993] Drug reactions can occur with either IV or IP administration of these drugs.[994] Most of these drug reactions are mild infusion reactions, but more severe hypersensitivity (allergic) reactions and life-threatening anaphylaxis can occur.[994-997]

Symptoms of (mild) infusion reactions include hot flushing, rash, fever, chest tightness, mild blood pressure changes, back pain, and chills (Table 24). Adverse reactions associated with taxane drugs (ie, docetaxel, paclitaxel) and biotherapeutic agents tend to be mild infusion-related reactions, are often attributed to cremophor in paclitaxel, and tend to occur during the first few cycles of treatment (although they can be seen during any infusion regardless of how many previous cycles were administered).

Mild infusion reactions are common with paclitaxel (27% of patients),[998] but mild reactions can also occur with liposomal doxorubicin,[999] docetaxel, or even platinum agents (ie, carboplatin, cisplatin).

Allergic reactions (ie, true drug allergies) are more common with platinum agents such as carboplatin (16% of patients), cisplatin, and oxaliplatin,[998,1000] and tend to occur following re-exposure to the inciting drug or less commonly at the completion of initial chemotherapy (ie, cycle 6 of a planned 6 treatments).[997] Symptoms of allergic reactions include rash, edema, shortness of breath (bronchospasm), syncope or pre-syncope, chest pain, tachycardia, generalized hives/itching, changes in blood pressure, nausea, vomiting, chills, changes in bowel function, and occasionally feeling of impending doom (Table 24). Symptoms of allergic reactions may continue to persist after stopping infusion and/or after treatment interventions. Patients who are at higher risk of developing a hypersensitivity (allergic) reaction include those undergoing re-introduction of the drug after a period of no exposure and following multiple cycles of the drug during the first and subsequent exposures;[1001,1002] those undergoing IV administration of the drug rather than oral or IP administration; those with allergies to other drugs; and those who have previously had a reaction. Severe allergic reactions include those that cause shortness of breath, changes in blood pressure requiring treatment, and GI symptoms (eg, nausea, vomiting). Anaphylaxis is a rare type of very severe allergic reaction that can occur with the platinum and taxane agents (and others less commonly), can cause cardiovascular collapse, and can be life-threatening.[995,996,1003] Life-threatening allergic reactions such as anaphylaxis are distinguished from other severe reactions by acute onset, generalized hives, respiratory compromise, and severe hypotension (Table 24).

Table 24. Drug Reactions: Symptoms

Severity of Reaction	Mild (infusion)		Severe (allergic)		Life-Threatening (allergic)	
Drug causing reaction	Platinum	Non-platinum[a]	Platinum	Non-platinum[a]	Platinum	Non-platinum[a]
Symptoms						
Hot flushing	x	x				
Dermatologic						
Rash	x	x				
Pruritus	x	x				
Generalized hives					x	x
Pain in chest, abdomen, pelvis, or back		x		x		x
Respiratory						
Shortness of breath, dyspnea			x	x		
Respiratory compromise					x	x
Cardiovascular						
Changes in BP requiring Tx			x	x		
Severe hypotension					x	x
GI symptoms [eg, nausea, vomiting]			x	x	x	x
Acute onset					x	x
Feeling of impending doom, anxiety, or something wrong				x		x
Symptoms often resolve quickly after stopping infusion	x	x				

BP, blood pressure; GI, gastrointestinal; Tx, treatment.
[a] Taxane, liposomal doxorubicin, or biotherapeutic agents.

Preparation for a Possible Drug Reaction

Patients and their families should be counseled about the possibility of a drug reaction and the signs and symptoms of one. Patients should be told to report any signs and symptoms of a drug reaction, especially after they have left the clinic (ie, delayed rash). Clinicians and nursing staff should be prepared for the possibility of a drug reaction every time a patient is infused with a drug. Standing orders should be written for immediate intervention in case a severe drug reaction occurs and the treatment area should have appropriate medical equipment in case of a life-threatening reaction.[1003] Epinephrine (intramuscular 0.3 mL of 1 mg/mL solution/EpiPen) should be used for any patient experiencing hypotension (systolic BP of <90 mm Hg) with or without other symptoms of an allergic/hypersensitivity reaction during or shortly after any chemotherapy drug treatment. In the setting of acute cardiopulmonary arrest, standard resuscitation (advanced cardiovascular life support [ACLS]) procedures should be followed.

Management of Drug Reactions

Algorithms are provided for management of mild, severe, and life-threatening reactions (summarized in Table 25).[1004] These drug reaction algorithms are also useful for patients with other gynecologic cancers (eg, cervical, vulvar, and uterine cancers) who are receiving carboplatin, cisplatin, docetaxel, liposomal doxorubicin, oxaliplatin, or

paclitaxel. The management recommendations depend on the severity of the reaction and the type of drug that caused the reaction (platinum vs. non-platinum [taxane, liposomal doxorubicin, or biotherapeutic agents]; see Table 25). Typically, the infusion should be stopped for patients having a reaction. The one exception to this rule is that mild infusion reactions occurring during first exposure to a platinum agent may be managed by decreasing the infusion rate and administering an H1 blocker antihistamine (eg, diphenhydramine or hydroxyzine), and usually resolve after stopping the infusion. Whereas H1 blocker antihistamine such as diphenhydramine or hydroxyzine is recommended for managing drug reactions, regardless of severity, H2 blockers such as cimetidine and famotidine are reserved for severe or life-threatening reactions.

Corticosteroids are also generally reserved for severe or life-threatening reactions, but may be needed for mild reactions to platinum agents in patients with prior exposure, if symptoms do not quickly resolve after administering an H1 blocker. IM epinephrine is recommended for life-threatening reactions, but may sometimes be needed for severe (but not life threatening) reactions, or for mild reactions to platinum agents if symptoms are not responding to other interventions. Life-threatening reactions require oxygen and nebulized bronchodilators, and saline bolus may also be needed for life-threatening reactions to platinum agents. Standard resuscitation procedures (ie, ACLS) should be followed for patients with acute cardiopulmonary arrest.[1005-1008]

Table 25: Drug Reactions: Management

Severity of Reaction	**Mild (infusion)**			**Severe (allergic)**		**Life-Threatening (allergic)**	
Drug causing reaction	Platinum		Non-platinum[a]	Platinum	Non-platinum[a]	Platinum	Non-platinum[a]
Prior exposure	0	≥1	≥0	≥0	≥0	≥0	≥0
Infusion recommendation							
Decrease infusion rate	x						
Stop infusion		x	x	x	x	x	x
Recommended therapy							
H1 blocker antihistamine (eg, diphenhydramine or hydroxyzine)	x	x	x	x	x	x	x
H2 blockers (eg, cimetidine, famotidine)				x	x	x	x
Corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone)		If needed		x	x	x	x
IM epinephrine		If needed		If needed	If needed	x	x
Oxygen				x	x	x	x
Nebulized bronchodilators				x	x	x	x
Saline bolus						If needed	

IM, intramuscular.
[a] Taxane, liposomal doxorubicin, or biotherapeutic agents.

Rechallenge and Desensitization

Recommendations for rechallenge and desensitization depend on the number and severity of the previous reactions. Patients who have had mild reactions to a drug may develop more serious reactions upon re-exposure even when the drug is slowly infused.[998] Therefore, for patients who have experienced a reaction to a platinum agent, consider consultation with an allergist (or qualified medical or gynecologic oncologist) for skin testing and to evaluate sensitization and the risk for further, more severe reactions.[998,1004,1009,1010] Skin testing is associated with false-negative results.[1011,1012] In cases of prior mild infusion reaction to the first exposure of a platinum or non-platinum agent, rechallenge may be attempted if the patient, physician, and nursing staff are all comfortable with this plan, the patient has been counseled appropriately, vital signs remain stable, emergency equipment is available in the clinic area, and the patients has received premedication with H1 blocker antihistamine, corticosteroids (eg, methylprednisolone, hydrocortisone, dexamethasone), and H2 blockers (eg, cimetidine, famotidine).[1013-1016] For rechallenge with non-platinum agents after mild reaction to first exposure, slower infusion rate should be used. Typically, a taxane infusion can be re-started at a much slower rate, and the rate can be slowly increased as tolerated as per the treating clinician's judgment.[998,1017] Many institutions have policies that stipulate how to reinfuse the drug if the patient has had a prior infusion reaction.

Note that this rechallenge with slow infusion is different from desensitization. Desensitization refers to a process of rendering the patient less likely to react in response to an allergen, and can be considered an option for patients who have had drug reactions.[993,1017-1019] For patients with allergic reactions, various desensitization protocols have been published.[990,993,1010,1017,1018,1020-1024] To maximize safety, patients may be desensitized in an intensive care unit.[993,1021] Almost all patients complete the desensitization protocol with only mild breakthrough reactions (about 90%).[993,1022,1024-1026] For patients with more than one prior mild reaction or any severe or life-threatening reactions—such as those involving blood pressure changes, dyspnea, tachycardia, widespread urticaria, anaphylaxis, or hypoxia— the implicated agent should not be used again unless under the supervision and guidance of an allergist or specialist with desensitization experience. For those with more than one mild reaction to a non-platinum agent, consider switching to paclitaxel (albumin-bound) due to medical necessity (ie, hypersensitivity reaction),[1027,1028] or consider switching to docetaxel; however, there are no data to support switching taxanes. Cross reactions have occurred and have been life-threatening. Some reactions to paclitaxel may occur because of the diluent, in which case switching to albumin-bound paclitaxel could diminish future risks. For patients with hypersensitivity to platinum-reagents, data suggest that re-administration of platinum-based treatment resulted in hypersensitivity reactions in approximately one third of patients, although none were severe (grade ≥3), and survival was improved compared with patients who were switched to non-platinum agents.[1029]

If a mild allergic reaction is suspected, and it is appropriate to administer the drug again, patients should be desensitized prior to resuming chemotherapy even if the symptoms have resolved.[991] Patients must be desensitized with each infusion if they previously had a drug reaction.[1017-1019] Data suggest that an extended infusion schedule and use of premedication may decrease the number of hypersensitivity reactions to carboplatin.[1001,1030]

Radiation Therapy

Whole abdominal radiation therapy is rarely used for epithelial ovarian, primary peritoneal, and fallopian tube cancers at NCCN Member Institutions. It is not included as a treatment recommendation in the NCCN Guidelines for Ovarian Cancer. Palliative localized RT is an option for symptom control in patients with recurrent disease (see *Epithelial Ovarian*

Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Therapy for Persistent Disease or Recurrence in the algorithm).[1031-1035] Patients who receive pelvic radiation are prone to developing vaginal stenosis, which can impair sexual function.[1036] Vaginal dilators can be used to prevent or treat vaginal stenosis. Dilator use can start 2 to 4 weeks after RT is completed and can be done indefinitely.[1037]

Follow-up Recommendations

Recurrent disease may be identified clinically (eg, pelvic pain, weight loss), biochemically (ie, elevated CA-125 levels), and/or with imaging. After the completion of primary surgery and chemotherapy in patients with all stages of ovarian cancer (or Fallopian tube cancer or primary peritoneal cancer) who have had a CR, the standard recommendation is observation with follow-up to monitor for recurrent disease. Recommendations for monitoring are described in the algorithm and also apply to some of the LCOC (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Monitoring/Follow-up* in the algorithm). Chest/abdominal/pelvic CT, MRI, FDG-PET/CT, FDG-PET scans (skull base to mid-thigh), and chest x-ray may be ordered if clinically indicated; imaging is done with contrast unless contraindicated.[1038-1041] Patients should be educated about the signs and symptoms suggestive of recurrence (eg, pelvic pain, bloating, early satiety, obstruction, weight loss, fatigue). Patients who have had fertility-sparing surgery should be monitored by US examinations of the abdomen and pelvis if indicated; completion surgery should be considered (category 2B) after they finish childbearing. For the 2017 update (Version 1), the NCCN Panel added a recommendation for long-term wellness care (see the NCCN Guidelines for Survivorship, available at www.NCCN.org).

If the CA-125 level was initially elevated, then measurement of a CA-125 level or other tumor markers is recommended. A multi-institutional European trial assessed the use of CA-125 for monitoring for ovarian cancer recurrence after primary therapy.[1042,1043] The data suggest that treating recurrences early (based on detectable CA-125 levels in patients who are asymptomatic) is not associated with an increase in survival and is associated with a decrease in QOL.[1044] Recommendations from the SGO state that use of CA-125 levels for surveillance is optional.[1040] The NCCN Panel feels that the European trial has limitations and patients should discuss the pros and cons of CA-125 monitoring with their physicians. In addition, patients seem reluctant to give up monitoring.[1045] Others have discussed this study in greater detail.[388,1046,1047]

Management of an Increasing CA-125 Level

The management of patients in a clinical complete remission is somewhat controversial; this includes patients who are found to have an increasing CA-125 level (during routine monitoring and follow-up) but no signs or symptoms of recurrent disease (eg, pelvic pain, bloating, obstruction), following an evaluation including a negative pelvic examination and negative chest/abdominal/pelvic CT scans.[1048] Patients who have never received chemotherapy (ie, naïve to chemotherapy) should be managed using recommendations for newly diagnosed patients, should undergo clinically appropriate imaging studies and surgical debulking, and should be treated as previously described (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Primary Treatment* in the algorithm).

Recurrence therapy refers to drugs, radiation, or other treatment that is given to decrease tumor burden, control symptoms, or increase length and/or QOL for patients with recurrent disease. After the documentation of an increased CA-125 level (ie, biochemical relapse), the median time for a clinical relapse is 2 to 6 months. Data suggest that immediate treatment for biochemical relapse is not beneficial; therefore, immediate treatment is a category 2B recommendation in the NCCN Guidelines.[1042] After biochemical relapse, recommended options include enrollment in a clinical

trial, delaying treatment (ie, observation) until clinical symptoms arise, or immediate treatment (category 2B) (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Therapy for Persistent Disease or Recurrence* in the algorithm). Because tamoxifen and other hormonally active agents have a defined response rate for patients with recurrent disease who have progressed after platinum-based chemotherapy,[1049] these agents are frequently administered to patients who have only a rising CA-125 level[1050] as evidence of tumor progression.[1051] Tamoxifen, other hormonal agents, or other recurrence therapy are acceptable recommendations for this clinical situation (category 2B for all).

Recurrent Disease

The prognosis is poor either 1) for patients who progress after 2 consecutive chemotherapy regimens without ever sustaining a clinical benefit (refractory);[1052] or 2) for those whose disease recurs in less than 6 months (platinum resistant). Note that progression is typically defined using RECIST (Response Evaluation Criteria in Solid Tumor) criteria.[959,960] Panel members emphasized the importance of clinical trials to identify agents active in this group of patients.[1053,1054] Because their disease was resistant to the primary induction regimen, retreatment with a platinum compound or paclitaxel is not generally recommended. Although panel members do not recommend retreatment with platinum agents, they recognize that altering the schedule of paclitaxel may produce secondary responses.[1055,1056] Before any drug is given in the recurrent setting, the clinician should be familiar with the drug's metabolism and should make certain that the patient is an appropriate candidate for the drug (eg, that the patient has adequate renal or hepatic function). Clinical judgment must be used when selecting postoperative chemotherapy.

Options for patients with platinum-resistant disease or for those with stages II to IV disease who have a PR include clinical trial, recurrence therapy (see *Principles of Systemic Therapy: Acceptable Recurrence Therapies for Epithelial Ovarian Cancer [including LCOC]/Fallopian Tube/Primary Peritoneal Cancer* in the algorithm),[1057] and/or best supportive care (see NCCN Guidelines for Palliative Care, available at www.NCCN.org). Although palliative care is appropriate at many stages during the disease course, an assessment for palliative care is especially appropriate for women with platinum-resistant disease who may be receiving continuous systemic therapy. Patients who relapse 6 months or more after initial chemotherapy are termed *platinum sensitive*.[1058,1059] Combination platinum-based chemotherapy for a total of 6 cycles is preferred for first recurrence (category 1) in patients with platinum-sensitive disease (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Therapy for Persistent Disease or Recurrence* in the algorithm); other recurrence therapies are also an option.[1059,1060] Possible regimens are discussed in the following section (see *Acceptable Recurrence Modalities* in this Discussion).

Patients with ovarian cancer will often be retreated with multiple courses of recurrence therapy. Caution should be used in patients who receive multiple sequential courses of chemotherapy, because they may experience excessive toxicity and may not be able to tolerate doses used for first-line recurrence therapy; thus, clinical judgment should be used when selecting doses (see *Principles of Systemic Therapy* in the algorithm). Potential ancillary palliative, surgical, and/or supportive care procedures for selected patients are summarized in the algorithm (see *Principles of Surgery* in the algorithm).[1061-1066] Secondary cytoreductive surgery can be considered for patients who recur (ie, radiographic and/or clinical relapse) after a long disease-free interval (6 months or more).[718,1067-1072] A meta-analysis suggests that survival increases for patients with recurrent disease who have complete debulking.[720] The duration of the disease-free interval has not been established, although

panel members agreed that it should be at least 6 months before surgery is considered.[612,1073]

Although chemotherapy/resistance assays and/or other biomarker assays are being used in some NCCN Member Institutions to aid in selecting chemotherapy in situations where multiple equivalent chemotherapy options are available; the current level of evidence (category 3) is not sufficient to supplant standard-of-care chemotherapy.[1074,1075] The NCCN Panel feels that in vitro chemosensitivity testing to choose a chemotherapy regimen for recurrent disease situations should not be recommended (category 3), owing to the lack of demonstrable efficacy for such an approach. ASCO also does not recommend use of chemotherapy sensitivity and resistance assays, unless in a clinical trial setting.[1076] Note that a category 3 recommendation reflects strong disagreement about the intervention. At least 3 different NCCN Member Institutions must agree to include the category 3 intervention in the guideline, otherwise it is deleted.

Regardless of which regimen is selected initially, reevaluation should follow after 2 to 4 cycles of chemotherapy (depending on the agent) to determine if patients benefited from chemotherapy. Patients who primarily progress on 2 consecutive chemotherapy regimens without evidence of clinical benefit may not benefit from additional therapy.[1052] Decisions to offer supportive care, additional therapy, or clinical trials should be made on a highly individual basis. Localized RT can also provide effective palliation when radiation ports are tailored to specific symptomatic disease sites.[1031,1032]

Acceptable Recurrence Modalities

The NCCN Panel feels that no single therapeutic agent should be currently recommended as the treatment of choice for recurrent ovarian carcinoma. Some regimens and agents are preferred based on expert opinion primarily for reasons of decreased toxicity and/or marginally increased effectiveness (see *Principles of Systemic Therapy*: *Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer* in the algorithm).[900] A meta-analysis of chemotherapy for recurrent ovarian cancer was published in 2007.[1058] Recurrence therapy refers to therapy (eg, drugs, radiation, or other treatment) that is given for recurrent cancer to control symptoms and increase length or QOL for clinical, biochemical, or radiographic evidence of recurrent cancer following initial treatment.

Preferred Therapies

The consensus of the NCCN Panel for the treatment of recurrent disease is summarized in the algorithm (see *Principles of Systemic Therapy*: *Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer* in the algorithm). Platinum-based combination chemotherapy is recommended (category 1) for a total of 6 cycles for platinum-sensitive recurrence (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Therapy for Persistent Disease or Recurrence* in the algorithm).[1058,1059] For patients with platinum-sensitive disease who cannot tolerate combination therapy, the preferred single agent is carboplatin or cisplatin.[1059,1077,1078] Preferred combinations for platinum-sensitive recurrent disease include carboplatin/paclitaxel (category 1),[1059] carboplatin/liposomal doxorubicin (category 1),[1079-1081] carboplatin/weekly paclitaxel,[784] carboplatin/albumin-bound paclitaxel (for taxane hypersensitivity), carboplatin/docetaxel,[1082,1083] carboplatin/gemcitabine (which has been shown to improve PFS),[1059,1077,1078] cisplatin/gemcitabine, or carboplatin/gemcitabine/bevacizumab.[1077]

The category 1 recommendation for carboplatin/liposomal doxorubicin is based on recent data and uniform consensus from the panel.[1079,1080,1084-1087] Carboplatin/liposomal doxorubicin is equivalent to carboplatin/paclitaxel but has a different toxicity profile.

Carboplatin/liposomal doxorubicin is easier to tolerate; women tend to discontinue therapy with carboplatin/paclitaxel more often than they do with carboplatin/liposomal doxorubicin. Other combination regimens, including those with bevacizumab, are discussed in the following paragraphs. For the 2017 update (Version 1), the NCCN Panel added a recommendation (category 2A) for carboplatin/albumin-bound paclitaxel as recurrence therapy for women with platinum-sensitive disease and confirmed taxane hypersensitivity. Preliminary data from a phase 2 study of carboplatin/nab-paclitaxel in platinum-sensitive patients indicated that the overall response rate was 79%; 39% (15/38) of patients had a CR rate.[1088] A recent study of carboplatin/albumin-bound paclitaxel in patients with gynecologic tumors included 22 patients with ovarian cancer; the regimen was well tolerated and no patients had hypersensitivity reactions.[1028]

For platinum-resistant disease, non-platinum–based agents or regimens are preferred (ie, docetaxel, oral etoposide, gemcitabine, weekly paclitaxel with or without pazopanib, liposomal doxorubicin with or without bevacizumab, weekly paclitaxel/bevacizumab, topotecan with or without bevacizumab); sequential therapy using single agents is typically used.[966,1089] A phase 2 trial (MITO-11) assessed weekly paclitaxel with (or without) pazopanib in patients with platinum-resistant or refractory advanced ovarian cancer.[1089] The data show that PFS was increased in the paclitaxel/pazopanib arm when compared with paclitaxel alone (median 6.35 months [95% CI, 5.36–11.02] vs. 3.49 months [2.01–5.66]; HR, 0.42 [95% CI, 0.25–0.69]; *P* = .0002). Combination regimens with bevacizumab (AURELIA trial) are described later in this section (see *Bevacizumab* in this Discussion). Combination therapy is not preferred over single-agent therapy for platinum-resistant disease. For the 2017 update (Version 2), the NCCN Panel clarified this point by adding a footnote stating that the panel recommends combination, platinum-based regimens for platinum-sensitive recurrent disease, especially first relapses.

The response rate of the following agents appears to be similar: topotecan, 20%;[1090] gemcitabine, 19%;[1091,1092] liposomal doxorubicin, 26%;[1091-1093] and oral etoposide, 27%.[1094] In patients with platinum-resistant disease, the response rate for docetaxel is 22% and for weekly paclitaxel is 21%.[1055,1095,1096] Reports suggest that weekly topotecan is less toxic than the daily regimen.[1097,1098] Palliative chemotherapy has been shown to reduce symptoms in patients with platinum-resistant disease.[1099]

Other Potentially Active Agents

Other potentially active agents include altretamine, capecitabine, cyclophosphamide, doxorubicin, ifosfamide, irinotecan, melphalan, oxaliplatin, paclitaxel, nanoparticle albumin-bound paclitaxel (nab-paclitaxel), pemetrexed, and vinorelbine (see *Principles of Systemic Therapy*: *Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer* in the algorithm).[1096,1100-1104] Nab-paclitaxel has an overall response rate of 64%.[1105] Vinorelbine has a response rate of 20%.[1106,1107] Altretamine has a 14% response rate[1108] and ifosfamide has a 12% response rate,[1109] although less information is available regarding their use in patients with paclitaxel-refractory disease. In women with platinum-resistant disease, the response rate for pemetrexed is 21%.[1055,1095,1096] Single-agent paclitaxel, nab-paclitaxel, and oxaliplatin can be used in appropriate patients.[982,1059,1095,1110] Capecitabine has activity if disease was resistant to platinum and taxanes.[1111] Other alkylating agents, including cyclophosphamide and melphalan, can also be used.[807,815] In addition, hormonal therapy with tamoxifen or other agents including aromatase inhibitors (such as anastrozole and letrozole), leuprolide acetate, or megestrol acetate continues to be a viable therapeutic option for patients who cannot tolerate or have not responded to cytotoxic regimens.[1112-1118] Studies are ongoing for new agents to treat platinum-resistant disease.[1119] The NCCN Panel also recommends (category 2B) single-agent pazopanib

as a potentially active targeted recurrence therapy in patients who had a CR to initial therapy.[1120] In a phase 2 trial in 36 patients, the overall response rate was 18% with grade 3 elevations in ALT and AST in a few patients (8%).

Bevacizumab

Based on phase 2 trials, panel members feel that single-agent bevacizumab is a preferred option in patients who have recurrent disease (especially those with ascites), which is reflected in the category 2A recommendation for bevacizumab alone for women with either platinum-sensitive or platinum-resistant disease.[545,966,1121,1122] The response rate for single-agent bevacizumab is about 20%;[545,1121,1123-1126] it may cause hypertension, arterial thrombosis, or intestinal perforation. Bevacizumab combination regimens, or single-agent bevacizumab, are contraindicated in patients at increased risk of GI perforation.[848,1127] For the 2017 update (Version 2), the NCCN Panel added a footnote that there are limited data about the efficacy of bevacizumab as recurrence therapy (either single-agent or combination therapy) for patients previously treated with bevacizumab. The NCCN Panel added another footnote to clarify that bevacizumab can be continued as single-agent maintenance therapy until disease progression or unacceptable toxicity if patients respond to the initial recurrence chemotherapy/bevacizumab regimens described in the following paragraphs (see *Principles of Systemic Therapy*: *Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal Cancer* in the algorithm).

Several phase 3 randomized trials have assessed combination therapy with bevacizumab for recurrent ovarian cancer (ie, AURELIA, OCEANS).[1127,1128] The AURELIA trial assessed bevacizumab combined with chemotherapy—either liposomal doxorubicin, weekly paclitaxel, or topotecan—versus chemotherapy alone in patients with advanced platinum-resistant ovarian cancer. For patients receiving bevacizumab/chemotherapy, the primary endpoint of PFS was 6.7 months versus 3.4 months with chemotherapy alone. The median OS was 16.6 months for the bevacizumab/chemotherapy arm versus 13.3 months for chemotherapy alone; the OS HR was 0.85 (95% CI, 0.66–1.08; $P < .174$). Hypertension and proteinuria (≥ grade 2) were more common with bevacizumab. GI perforation occurred in 2.2% of patients on the bevacizumab arm. Based on the results of the AURELIA trial, the NCCN Panel recommends the following combination regimens for patients with platinum-resistant recurrent ovarian cancer: weekly paclitaxel/bevacizumab, liposomal doxorubicin/bevacizumab, and topotecan/bevacizumab.[1127,1129]

A phase 3 randomized trial (OCEANS) assessed carboplatin/gemcitabine with and without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer who had not previously received bevacizumab. In the OCEANS trial, PFS was increased in patients receiving the chemotherapy/bevacizumab arm when compared with chemotherapy alone (12.4 vs. 8.4 months, $P < .0001$).[1128] The final survival analysis did not show an increase in OS with the chemotherapy/bevacizumab arm when compared with chemotherapy alone (bevacizumab/chemotherapy: 33.6 months; chemotherapy alone: 32.9 months; HR, 0.95; $P = .65$).[1130] GI perforation occurred in 2 patients in the chemotherapy/bevacizumab arm. One patient died from intracranial hemorrhage in the chemotherapy/bevacizumab arm. For the 2017 update, the NCCN Panel revised the recommendation for carboplatin/gemcitabine/bevacizumab to category 2A (from category 2B) based on clinical experience. However, category 1 combination regimens are recommended over this bevacizumab regimen. The carboplatin/gemcitabine/bevacizumab regimen is not recommended in patients who are at risk for GI perforation.

A recent phase 3 randomized trial (GOG-0213) assessed recurrence combination therapy with carboplatin/paclitaxel/bevacizumab in patients

with platinum-sensitive recurrent ovarian cancer.[1131] Women receiving chemotherapy/bevacizumab had slightly increased median OS when compared with chemotherapy alone (42.2 months [95% CI, 37.7–46.2) versus 37.3 months (32.6–39.7) (HR, 0.829; 95% CI, 0.683–1.005; *P*=.056). Most patients in both arms had at least one grade 3 or worse AE; 96% (317/325) of patients in the chemotherapy/bevacizumab group versus 86% (282/332) with chemotherapy alone; the most common of these AEs were hypertension, fatigue, and proteinuria. Nine (3%) treatment-related deaths occurred in the bevacizumab arm versus 2 (1%) deaths in the chemotherapy alone arm. For the 2017 update, the NCCN panel added carboplatin/paclitaxel/bevacizumab as a potentially active regimen based on this trial.

PARP Inhibitors

Olaparib

Data suggest that olaparib (AZD2281), which is a PARP inhibitor, is active in select patients (those with *BRCA1* and *BRCA2* mutations have higher response rates than those who are *BRCA* negative), especially those with platinum-sensitive disease.[961-966] If disease is resistant or refractory to platinum, then a lower response rate to olaparib is observed.[962,964] A trial assessed olaparib in women with recurrent advanced ovarian cancer; the overall response rate was 34% (CR, 2%; and PR, 32%).[1132,1133] The FDA approved olaparib for patients with advanced ovarian cancer who have received treatment with 3 or more lines of chemotherapy and who have a germline *BRCA* mutation.[1133,1134] The NCCN Panel recommends single-agent olaparib as recurrence therapy for patients with advanced ovarian cancer (platinum sensitive or resistant) who have received 3 or more lines of chemotherapy and who have a germline *BRCA* mutation (detected using an FDA-approved test or other validated test performed in a CLIA-approved facility) based on this trial and the FDA approval.[1135]

A recent phase 3 randomized trial (SOLO2/ENGOT-Ov21) assessed olaparib (tablets) as maintenance therapy for women (n=295) with platinum-sensitive high-grade serous ovarian cancer and BRCA mutations who had received 2 or more lines of chemotherapy; the trial also included patients with high-grade endometrioid cancer, primary peritoneal, or fallopian tube cancer.[967] Data show that the median PFS was significantly longer in women receiving olaparib (19.1 months [95% CI, 16.3–25.7]) than in those receiving placebo (5.5 months [5.2–5.8]; HR, 0.30 [95% CI, 0.22–0.41], *P*<.0001). More patients receiving olaparib maintenance therapy had serious AEs (18% [35/195]) compared with placebo (8% [8/99]). The most common serious (grade 3 or worse) AEs included anemia (19% [38/195] in the olaparib group vs. 2% [2/99] in the placebo group), fatigue or asthenia (4% [8/195] vs. 2% [2/99]), and neutropenia (5% [10/195] vs. 4% [4/99]). In the olaparib group, one (1%) patient died from a treatment-related AE (acute myeloid leukemia). The FDA recently approved olaparib (tablets) as maintenance therapy for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had complete or PRs to platinum-based chemotherapy.

For the 2017 update (Version 3), the NCCN Panel recommends that olaparib (tablets) be considered as maintenance therapy for women with ovarian cancer who have received 2 or more lines of chemotherapy based on this trial (SOLO2/ENGOT-Ov21) and the FDA approval.[967] Note that olaparib is transitioning from capsules (original FDA approval) to tablets for the maintenance and recurrence therapy indications. Olaparib tablets (100 mg and 150 mg) should not be substituted with olaparib capsules (50 mg) because of differences in the dosing and bioavailability of each formulation.

Rucaparib

Rucaparib is also an oral PARP inhibitor.[1136] A recent phase 2 trial (ARIEL2) assessed rucaparib as recurrence therapy for patients with

platinum-sensitive ovarian cancer.[1137] PFS was increased in patients (n = 40) with *BRCA* mutations (12.8 months [95% CI, 9.0–14.7]) when compared with wild type (n = 70) (5.2 months [95% CI, 3.6–5.5]) (HR, 0.27; 95% CI, 0.16–0.44, *P*<.0001). For women taking rucaparib, serious AEs were small intestinal obstruction (10 [5%] of 204 patients), malignant neoplasm progression (10 [5%]), and anemia (9 [4%]). During the trial, 3 patients died (2 with disease progression; one with sepsis and disease progression); deaths were not reported as related to treatment. Based on this trial and the FDA approval, the NCCN Panel recommends single-agent rucaparib as recurrence therapy for patients with platinum-sensitive or platinum-resistant ovarian cancer who have been treated with 2 or more lines of chemotherapy and have BRCA mutations (detected as previously described).[1137,1138] The NCCN Panel feels that rucaparib is preferred for patients with platinum-resistant disease, because there are fewer good options for this setting. In a pooled analysis, the overall response rate with rucaparib was reported as 66% (52/79; 95% CI, 54–76) for platinum-sensitive disease and 25% (5/20; 95% CI [9–49]) for platinum-resistant disease.[1136] A recent phase 1 to 2 study reported a response rate of 59.5% in patients with platinum-sensitive disease and BRCA mutations who had received 2 to 4 courses of therapy.[1136]

Niraparib

Niraparib is another oral PARP 1/2 inhibitor.[1139] A phase 3 trial (NOVA) assessed niraparib as maintenance therapy for patients with platinum-sensitive ovarian cancer who responded to recurrence therapy.[1139] For the 2017 update (Version 1), the NCCN Panel added a recommendation to repeat the prior imaging to assess response. Data showed that niraparib increased PFS regardless of whether patients had a BRCA mutation when compared with placebo. Patients receiving niraparib without a germline BRCA mutation had increased PFS (12.9 months vs. 3.8 months). Women with a germline BRCA mutation had a much greater increase in PFS (21.0 vs. 5.5 months) (HR, 0.27; 95% CI, 0.17–0.41). For those taking niraparib, grade 3 or 4 AEs that were commonly reported included thrombocytopenia (33.8%), anemia (25.3%), and neutropenia (19.6%). For the 2017 update (Version 1), the NCCN Panel recommends niraparib as maintenance therapy for patients with platinum-sensitive disease who have had 2 or more lines of platinum-based therapy and a CR or PR to the most recent line of recurrence therapy based on this trial and the FDA approval.[1139,1140]

Less Common Ovarian Cancers

The LCOC include carcinosarcomas (MMMTs), clear cell carcinoma, mucinous carcinoma, low-grade (grade 1) serous/endometrioid epithelial carcinoma, borderline epithelial tumors, malignant sex cord-stromal tumors, and malignant germ cell tumors.[142] The complete histologic classification for ovarian cancer from the WHO describes the different types of LCOC (see *WHO Histologic Classification* in the algorithm).[1] The AJCC/FIGO staging system for ovarian cancer is also used to stage the LCOC (see *Staging: Table 1* and other staging tables in the algorithm). Panel members believe there is value in identifying pathways that may serve as therapeutic targets for the LCOC because of the promise of new and novel approaches to treatment.[142] However, there are limited data for these rare histologies because of their infrequency and it will be difficult to acquire prospective data. Clinical trials for eligible patients and individualized treatment plans, for those who are ineligible for trials, may be the most suitable approaches to treatment in these patients at this time. The different IV and IV/IP chemotherapy regimens used for high-grade serous ovarian cancer may also be recommended for patients with LCOC; however, the recommendations are only category 2A for LCOC because of the limited data.

Recommended Workup

Patients may obtain consultation at an NCCN Member Institution for recommendations and treatment of an undiagnosed pelvic mass, or for

management of a previously biopsied malignant ovarian tumor. Many such patients come to NCCN Member Institutions after having had previous surgery at other institutions. Patients having a histologically undiagnosed pelvic mass should undergo evaluation and staging as described in the algorithm (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Workup* in the algorithm). The diagnosis of LCOC is often not made until after surgery for a suspicious pelvic mass (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Primary Treatment* in the algorithm). Therefore, the workup for LCOC is the same as for other types of ovarian cancer except that tumor markers are measured and other testing is done to determine the specific histopathology (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Workup* in the algorithm). Tumor markers may include CA-125, inhibin, beta-hCG, alfa-fetoprotein, and carcinoembryonic antigen (CEA). Women younger than 35 years with a pelvic mass should have AFP levels measured to assess for germ cell tumors and to rule out pregnancy.[436-438] A GI tract evaluation is recommended for mucinous histology to determine whether an occult GI primary has metastasized to the ovaries.[530] An intraoperative frozen section evaluation is recommended for women who would like to maintain their fertility (see next section).

Surgery

In contrast to high-grade serous epithelial ovarian cancer or MMMTs, many patients with other LCOC present at an early stage. Some of the tumors may be confined to one ovary. Thus, some of these patients are candidates for fertility-sparing surgery, which may be done laparoscopically (see *Principles of Surgery* in the algorithm).[699,700,703,1141-1145] Fertility-sparing surgery may be performed (if technically feasible) if the intraoperative frozen section results are positive for apparent early-stage tumors and/or low-risk tumors (ie, malignant germ cell tumors, borderline epithelial tumors, clinical stage I epithelial ovarian tumors, clinical stage I mucinous tumors, or clinical stage I sex cord-stromal tumors).[699,700,703,1142-1145] Patients who do not desire fertility preservation; those who have a clinical stage II, III, or IV epithelial ovarian cancer; those with a clinical stage II, III, or IV sex cord-stromal tumor; or those with MMMT should undergo comprehensive surgical staging as per the ovarian cancer guidelines (see *Principles of Surgery* in the algorithm).

Patients may have been referred to an NCCN Member Institution after receiving a diagnosis of an LCOC tumor. The recommended initial surgical recommendation depends on the specific histologic diagnosis. Often, patients have been comprehensively staged (having met the standards for surgical staging of the GOG) and have undergone cytoreductive surgery. In some instances, they are referred after having had *incomplete* staging (ie, uterus and/or adnexa intact, omentum not removed, surgical stage not documented).

Clear Cell Carcinoma

Clear cell carcinomas are considered high-grade tumors; they are more common than the other LCOC.[565] Most clear cell carcinomas are negative for WT1 and estrogen receptors.[565] The NCCN Guidelines provide an algorithm for clear cell carcinomas (see *Less Common Ovarian Cancers: Clear Cell Carcinoma of the Ovary* and *WHO Histologic Classification* in the algorithm).[1] Because patients are typically diagnosed with clear cell carcinoma after pathologic analysis of a surgical specimen, the workup for suspicious or palpable pelvic masses is done before surgery as described in the algorithm (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Workup* in the algorithm).

Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy (see *Less Common Ovarian Cancers: Clear Cell Carcinoma of the Ovary* in the algorithm).[1146] Fertility-sparing surgery is not recommended for stage IA to

C clear cell carcinomas. Lymphadenectomy has been shown to improve survival.[1147] The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for clear cell carcinomas (see *Staging: Table 1* in the algorithm).[550] Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and papillary serous carcinomas.[1148-1150] For patients with stage IA to IC disease, recommended postoperative treatment is the standard IV taxane-carboplatin regimens (with paclitaxel or docetaxel) used for high-grade serous ovarian cancer.[1147] Fertility-sparing surgery and/or observation/monitoring are an option for patients with unilateral clear cell borderline tumors (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm). For patients with stage II to IV clear cell carcinoma, postoperative treatment is standard regimens used for epithelial ovarian cancer (eg, IV carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin). Patients with advanced clear cell carcinoma have a poor prognosis.[1146,1147] Data suggest that 6 or 3 cycles of postoperative chemotherapy are equivalent for patients with clear cell carcinoma.[826,1151]

Mucinous Carcinomas

Mucinous tumors are unusual because they may be very large cystic masses that may fill the abdomen and pelvis; this presentation often suggests mucinous histology. Patients with mucinous carcinoma of the ovary are often diagnosed with early-stage disease and have a good prognosis; the 5-year DFS is about 80% to 90%.[530,1152] Women with mucinous tumors typically present at a younger age (20–40 years) than those with high-grade serous ovarian cancer. The NCCN Guidelines provide an algorithm for mucinous carcinoma (see *Less Common Ovarian Cancers: Mucinous Carcinoma of the Ovary* and the *WHO Histologic Classification* in the algorithm).[1] For the 2017 update (Version 1), the NCCN Panel added a recommendation for fertility-sparing surgery, if not previously done, for select patients with stage IA to C disease.

Patients are typically diagnosed with mucinous carcinoma after surgery for a suspicious pelvic mass (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Primary Treatment* in the algorithm). Therefore, the initial workup is the same as for other types of ovarian cancer (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Workup* in the algorithm). Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy or observation (see *Less Common Ovarian Cancers: Mucinous Carcinoma of the Ovary* in the algorithm).[530] An appendectomy is also recommended at primary surgery in patients with suspected or confirmed mucinous ovarian tumors. Fertility-sparing surgery is an option for select patients with stage I mucinous tumors (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).The staging system for high-grade serous epithelial ovarian cancer and primary peritoneal cancer is also used for mucinous carcinomas (see *Staging: Table 1* in the algorithm).[550]

The additional workup includes a GI tract evaluation and CEA level for patients with mucinous histology to determine whether patients have either occult GI primary that has metastasized to the ovaries or primary mucinous carcinoma of the ovaries (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Workup* in the algorithm).[530] Metastases to the ovaries are more common, and primary mucinous tumors of the ovaries are uncommon; it is difficult to distinguish between metastatic adenocarcinomas to the ovaries and primary mucinous carcinomas.[577-579] PAX8 immunostaining may be useful.[577]

Postoperative observation and monitoring are recommended for patients with stage IA or IB mucinous tumors because most of these tumors are benign or borderline.[530,565] For patients with stage IC mucinous carcinomas, postoperative options include: 1) observation; 2) IV carboplatin with either paclitaxel or docetaxel; 3)

5-FU/leucovorin/oxaliplatin GI regimen); or 4) capecitabine/oxaliplatin (GI regimen).[530] Some clinicians feel the GI regimens are appropriate because mucinous carcinomas of the ovary are similar to GI tumors.[1153] For patients with stages II to IV mucinous carcinomas, postoperative options include: 1) chemotherapy using the regimens for epithelial ovarian cancer (eg, IV carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin); 2) 5-FU/leucovorin/oxaliplatin (GI regimen); or 3) capecitabine/oxaliplatin (GI regimen). For the 2017 update (Version 1), the NCCN Panel added recommendations for recurrence therapy for mucinous carcinomas: 1) 5-FU/leucovorin/oxaliplatin with or without bevacizumab (category 2B for bevacizumab); or 2) capecitabine/oxaliplatin.

Low-Grade (Grade 1) Serous/Endometrioid Epithelial Carcinomas

The NCCN Guidelines provide an algorithm for grade 1 (low-grade) serous carcinomas/endometrioid epithelial carcinomas (see *Low-Grade Serous Carcinoma* and *Grade 1 Endometrioid Carcinoma* and the *WHO Histologic Classification* in the algorithm).[1] Endometrioid carcinomas may be associated with endometriosis.[575,581] Endometrioid adenocarcinomas are usually positive for cytokeratin 7 (CK7), PAX8, CA-125, and estrogen receptors; metastatic colorectal adenocarcinomas are usually positive for CK20, CEA, and CDX2.[565] Endometrioid tumors are also very similar in appearance to sex cord-stromal tumors.[565] Lynch syndrome is associated with risk for endometrioid carcinomas, clear cell carcinomas, and serous carcinomas.[1148-1150]

Patients with low-grade (grade 1) serous carcinomas often have more indolent disease and present at a younger age than those with high-grade serous carcinomas; however, they may also present with more advanced disease.[582,1154] Low-grade serous carcinomas do not typically progress to high-grade serous carcinomas; the 2 types of tumors are quite different.[142] Serous carcinomas are usually positive for WT1 and estrogen receptors.[565]

Primary treatment for these patients includes completion surgery with comprehensive staging followed by postoperative therapy or observation; patients are typically diagnosed after surgery (see *Low-Grade Serous Carcinoma* and *Grade 1 Endometrioid Carcinoma* within the *Less Common Ovarian Cancers section* in the algorithm).[582] The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for low-grade (grade 1) serous/endometrioid carcinomas (see *Staging: Table 1* in the algorithm).[550] Fertility-sparing surgery is an option for patients with serous and endometrioid borderline tumors (see *Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* and the *WHO Histologic Classification* in the algorithm).[1] Some clinicians feel that neoadjuvant therapy should not be recommended for patients with low-grade (grade 1) serous carcinomas, because they often respond poorly to chemotherapy.[582]

Postoperative observation and monitoring are recommended for patients with stage IA or IB disease. For patients with stage IC to II disease, postoperative options include: 1) IV carboplatin with either paclitaxel or docetaxel; 2) observation (category 2B); or 3) hormone therapy including anastrozole, letrozole, leuprolide, or tamoxifen (category 2B for all hormone therapy). Postoperative options for patients with stage III to IV disease include: 1) first-line chemotherapy regimens used for epithelial ovarian cancer (eg, IV carboplatin with paclitaxel, docetaxel, or liposomal doxorubicin); or 2) hormone therapy (category 2B) as previously described (see *Principles of Systemic Therapy: Primary Systemic Therapy Regimens* in the algorithm).[582,816,1155,1156] A recent study suggested that hormone maintenance therapy may be useful for women with stage II to IV low-grade serous ovarian carcinomas after surgery and platinum-based chemotherapy, although OS was not significantly improved when compared with observation (102.7 vs. 115.7 months, respectively).[582,1157]

Malignant Germ Cell Tumors

These malignant tumors include dysgerminomas, immature teratomas, embryonal tumors, and endodermal sinus (yolk sac) tumors (see the *Less Common Ovarian Cancers: Malignant Germ Cell Tumors* and the *WHO Histologic Classification* in the algorithm).[1] They mainly occur in girls, adolescents, and younger women who are often diagnosed with stage I disease; the median age at diagnosis is 16 to 20 years.[431,1158] Germ cell tumors are the predominant ovarian tumor in this age group.[473] The recommended workup may include pulmonary function studies if bleomycin is being considered (see *Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer: Workup* in the algorithm).[436,1159] In young women (<35 years) with a pelvic mass, AFP levels can indicate the presence of germ cell tumors.[436-438] However, pregnancy should also be ruled out. Gonadal dysgenesis is a risk factor for germ cell tumors.[473] Malignant germ cell tumors have an excellent prognosis.[1160] After appropriate treatment, 5-year survival is more than 85%.[1158,1161,1162]

Treatment

Fertility-sparing surgery is recommended for those desiring fertility preservation, regardless of stage (see *Less Common Ovarian Cancers: Malignant Germ Cell Tumors* in the algorithm).[431,703,1162-1165] Surgery for children or adolescents may differ from that for adult women (see *Principles of Surgery* in the algorithm). In children or adolescents with early-stage germ cell tumors, comprehensive staging may be omitted.[709,1166] Completion surgery with comprehensive staging is recommended as initial surgery for patients who do not desire fertility preservation (see *Less Common Ovarian Cancers: Malignant Germ Cell Tumors* in the algorithm).[473] The staging system for high-grade serous ovarian and primary peritoneal cancer is also used for malignant germ cell tumors (see *Staging: Table 1* in the algorithm).[550] After comprehensive surgical staging, observation with monitoring is recommended for patients with stage I dysgerminoma or stage I, grade 1 immature teratoma.[1167] If patients have had incomplete surgical staging, recommended options depend on the type of tumor, the results of imaging and tumor marker testing (eg, AFP, beta-HCG), the age of the patient, and whether the patient desires fertility preservation (see *Less Common Ovarian Cancers: Malignant Germ Cell Tumors* in the algorithm). Patients who chose fertility-sparing surgery should be monitored by US examinations if necessary; completion surgery (category 2B) should be considered after finishing childbearing.

After surgery, observation with surveillance is the recommended option for patients with stage I dysgerminoma or stage I, grade I immature teratoma based on European and pediatric reports.[451,453,454,1168] Observation or chemotherapy may be considered for children or adolescents with select stage IA or IB tumors (see *Less Common Ovarian Cancers: Malignant Germ Cell Tumors* in the algorithm).[431,451,1168-1171] For patients with stage II to IV malignant dysgerminomas or immature teratomas, postoperative chemotherapy is recommended (see *Principles of Systemic Therapy: Systemic Therapy Regimens - Malignant Germ Cell/Sex Cord-Stromal Tumors* in the algorithm).

Postoperative chemotherapy for 3 to 4 cycles with bleomycin/etoposide/cisplatin (BEP) (category 2B for 3 vs. 4 cycles) is recommended for: 1) any stage embryonal tumors or endodermal sinus tumors; 2) stages II to V dysgerminoma; or 3) stage I, grade 2 to 3, or stage II to IV immature teratoma (see the *Principles of Systemic Therapy*: *Systemic therapy Regimens - Malignant Germ Cell/Sex Cord-Stromal Tumors* in the algorithm).[1159,1172-1174] If considering the use of bleomycin, pulmonary function tests are recommended.[1159,1161] The 4-cycle BEP regimen is recommended (category 2A) as the standard regimen. Although most clinicians avoid a 3-week BEP regimen, some feel that a 3-week BEP regimen (3 cycles) may be useful in patients with low-risk or stage 1 disease, although this is a category 2B recommendation; the

Memorial Sloan Kettering Cancer Center criteria can be used to identify tumors that are low risk.[447,451,1175-1181] In select patients with stage IB to III dysgerminoma for whom minimizing toxicity is critical, 3 courses of etoposide/carboplatin can be used (carboplatin 400 mg/m^2 [AUC =~5–6] on day 1 plus etoposide 120 mg/m^2 on days 1–3 every 4 weeks for 3 courses).[1182] Dose reductions or delays are not recommended even in the setting of neutropenia.

Surveillance recommendations for germ cell tumors are described in the algorithm (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the algorithm).[1040] Patients achieving a complete clinical response after chemotherapy should be observed clinically every 2 to 4 months with AFP and beta-HCG levels (if initially elevated) for 2 years. For those with abnormal markers and definitive recurrent disease, options (category 2B) include: 1) high-dose chemotherapy;[1183] or 2) consider additional chemotherapy (see *Principles of Systemic Therapy: Systemic Therapy Regimens – Malignant Germ Cell/Sex Cord-Stromal Tumors* in the algorithm). Referral of these patients to a tertiary care center for stem-cell transplant consultation and potentially curative therapy is strongly recommended. Several case reports suggest that patients who have received chemotherapy for germ cell tumors may later present with growing teratoma syndrome.[1184-1187]

Residual or Recurrent Disease

For patients having radiographic evidence of residual tumor (after surgery and chemotherapy) but with normal AFP and beta-HCG, consider surgical resection of the tumor; observation with monitoring is also an option. Clinical judgment should be used regarding the frequency of imaging.[1188] Further options depend on which findings are present: residual malignancy, benign teratoma, or necrotic tissue (see *Therapy for Recurrent/Persistent Disease* for *Malignant Germ Cell Tumors* in the algorithm). For patients with definitive residual disease and with persistently elevated AFP and/or beta-HCG after first-line chemotherapy, recommendations include TIP (paclitaxel, ifosfamide, cisplatin)[1189] or high-dose chemotherapy. Referral to a tertiary care center for potentially curative treatment is strongly recommended.[1190] There are small series but no major trials in adult patients.

Patients with recurrent or residual malignancy after multiple chemotherapeutic regimens may be treated with a recurrence modality (see *Principles of Systemic Therapy: Acceptable Systemic Therapy Regimens - Malignant Germ Cell/Sex Cord-Stromal Tumors* in the algorithm), including potentially curative high-dose chemotherapy or TIP. Other regimens include VAC (vincristine, dactinomycin, cyclophosphamide), VeIP (vinblastine, ifosfamide, cisplatin), VIP (etoposide, ifosfamide, cisplatin), cisplatin/etoposide, docetaxel/carboplatin, paclitaxel/carboplatin, paclitaxel/gemcitabine, paclitaxel/ifosfamide, docetaxel, paclitaxel, RT, or supportive care only.[1177,1190-1194] These recurrence regimens (see *Principles of Systemic Therapy: Systemic Therapy Regimens - Malignant Germ Cell/Sex Cord-Stromal Tumors* in the algorithm) are not generalizable for all of the uncommon histology tumors; therefore, patients should be referred to tertiary care institutions for treatment.

Malignant Sex Cord-Stromal Tumors

Malignant sex cord-stromal tumors are rare and include granulosa cell tumors (most common) and Sertoli-Leydig cell tumors; they are typically associated with a good prognosis.[684,1195] Most patients with granulosa tumors present with early-stage disease; the disease is typically indolent.[683] The complete histologic classification for ovarian cancer from the WHO includes the different types of sex cord-stromal tumors; it is important to determine whether the sex cord-stromal tumor is benign or malignant (see *WHO Histologic Classification: Sex Cord-Stromal Tumors* in the algorithm).[1] The staging system for high-grade serous ovarian and

primary peritoneal cancer is also used for sex cord-stromal tumors (see *Staging: Table 1* in the algorithm).[550]

Patients with stage IA or IC sex cord-stromal tumors desiring to preserve their fertility should be treated with fertility-sparing surgery (see *Less Common Ovarian Cancers: Malignant Sex Cord-Stromal Tumors* in the algorithm).[682,683,1196,1197] Although complete staging is recommended for all other patients, lymphadenectomy may be omitted for tumors grossly confined to the ovary.[1198] For patients who choose fertility-sparing surgery, completion surgery (category 2B) should be considered after childbearing is finished. Postoperative options in the NCCN Guidelines have category 2B recommendations (see *Less Common Ovarian Cancers: Malignant Sex Cord-Stromal Tumors* in the algorithm).[1196] For patients with high-risk stage I tumors (tumor rupture, stage 1C, poorly differentiated tumor, and tumor size >10–15 cm[470]), postoperative recommendations (all are category 2B) include observation or consideration of platinum-based chemotherapy.[1199] Observation is recommended for those with surgical findings of low-risk stage I tumor (ie, without high-risk features) (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the algorithm). For patients with granulosa cell tumors who are being observed, inhibin levels can be followed if they were initially elevated (category 2B). For patients with stage II to IV tumors, recommended options (all are category 2B) include RT for limited disease or platinum-based chemotherapy (BEP or paclitaxel/carboplatin regimens are preferred).[1200-1203]

Surveillance recommendations for malignant sex cord-stromal tumors are provided in the algorithm, which are based on the SGO recommendations (see *Surveillance for Malignant Germ Cell and Sex Cord-Stromal Tumors* in the algorithm).[1040] Prolonged surveillance is recommended for granulosa cell tumors, because they can recur years later (eg, 30 years).[684,1164,1195,1204] For patients with stage II to IV tumors who subsequently have a clinical relapse, options include a clinical trial or recurrence therapy (see *Principles of Systemic Therapy: Systemic Therapy Regimens - Malignant Germ Cell/Sex Cord-Stromal Tumors* in the algorithm).[1195,1204-1207] Cytotoxic recurrence therapy includes: docetaxel, paclitaxel, paclitaxel/ifosfamide, paclitaxel/carboplatin, and VAC. Hormone recurrence therapy includes: aromatase inhibitors, leuprolide, and tamoxifen. Note that single-agent bevacizumab or leuprolide is an option for patients with recurrent granulosa cell tumors.[1207,1208] Secondary cytoreductive surgery may also be considered. Palliative localized RT may also be useful.

Carcinosarcomas (Malignant Mixed Müllerian Tumors)

MMMTs are rare tumors with a poor prognosis; they are the most aggressive tumors in the algorithm.[1209-1212] Most pathologists now consider MMMTs to be a variant of poorly differentiated epithelial ovarian cancer (metaplastic carcinoma).[569] Patients with MMMTs are not candidates for fertility-sparing surgery regardless of age or stage. The staging system for ovarian and primary peritoneal cancer is also used for MMMTs (see *Staging: Table 1* in the algorithm).[550,1211]

Optimal surgical debulking is recommended for patients with MMMTs (see *Principles of Surgery* in the algorithm).[1211,1213-1215] After complete surgical staging, several postoperative chemotherapy regimens are recommended for patients with stage I to IV MMMT. Patients with stage I to IV MMMT or recurrence may be treated using the same primary chemotherapy regimens that are recommended for epithelial ovarian cancer; for the 2017 update (Version 1), the panel decided these chemotherapy regimens are preferred options (see *Principles of Systemic Therapy: Primary Systemic Therapy Regimens* in the algorithm).[569,1216-1221] For example, IV carboplatin with either paclitaxel, docetaxel, or liposomal doxorubicin are recommended for patients with stage I-IV MMMT. The IP chemotherapy regimen described for ovarian cancer can be used for select patients with

MMMT. Other recommended postoperative chemotherapy options include cisplatin/ifosfamide (category 2A), carboplatin/ifosfamide (category 2A), and ifosfamide/paclitaxel (category 2B).[569,1209,1216,1222] After treatment, the surveillance and follow-up recommendations for epithelial ovarian cancer are also used for MMMTs.

Borderline Epithelial Tumors (Low Malignant Potential)

Diagnosis

Borderline epithelial tumors are rare tumors and are managed differently than high-grade carcinomas (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).[1141,1223] Five-year survival exceeds 80%.[1224] In contrast to patients with frankly invasive ovarian carcinoma, women with borderline epithelial tumors tend to be younger, are often diagnosed with stage I disease, and are candidates for fertility-sparing surgery.[1225,1226] A borderline tumor is a primary epithelial lesion with cytologic characteristics suggesting malignancy but without frank invasion and with a clinically indolent course and good prognosis.[1227,1228]

The terms for borderline epithelial tumors (also known as LMP tumors or atypical proliferative tumors) have changed over the years.[565] The 2016 and 2017 CAP cancer protocols for ovarian cancer use borderline and do not use LMP.[1229,1230] Borderline epithelial tumors are typically serous or mucinous; other histologic subtypes can also occur (see *WHO Histologic Classification* in the algorithm).[1,1141]

The characteristic pathologic hallmark of typical epithelial ovarian cancer is the identification of peritoneal implants, which microscopically and/or macroscopically invade the peritoneum. A borderline epithelial tumor may grossly resemble an invasive cancer. However, microscopic evaluation fails to reveal evidence of frank invasion by the tumor nodules, although rarely invasive implants (which continue to be consistent with the diagnosis of borderline epithelial lesions) can be identified microscopically by the pathologist.

Treatment

Surgery is the primary treatment for borderline epithelial tumors, including standard ovarian cancer debulking surgery or fertility-sparing surgery depending on the surgical evaluation and other factors (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).[1231] Treatment guidelines for borderline epithelial tumors depend on the histologic and clinical characteristics, the age of the patient,[1226] and whether invasive implants are present. Patients should be evaluated by a gynecologic oncologist. At NCCN Member Institutions, patients may be initially evaluated with an undiagnosed pelvic mass or with an established diagnosis of borderline epithelial tumor. NCCN Panel Members are less likely to recommend aggressive treatment after surgery; observation is one of several possible approaches.[1141,1232] Although the staging system for epithelial ovarian cancer is used for borderline epithelial tumors, the NCCN Guidelines use the presence or absence of invasive implants to determine the need for postoperative therapy (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).

Patients with a borderline epithelial tumor who desire to maintain their fertility may undergo surgery limited to a USO (preserving the uterus, contralateral ovary, and contralateral Fallopian tube) with resection of residual disease.[699,700,1233] BSO and preserving the uterus is an option for select patients. If the patient does not desire fertility-sparing surgery, standard ovarian cancer surgery (TAH, BSO, and debulking as needed) and resection of residual disease are recommended. Data do not show increased survival with lymphadenectomy and omentectomy for borderline epithelial tumor, although upstaging does occur.[752,1234] Lymph node evaluation may be considered on a case-by-case basis.

For patients with known borderline epithelial tumors who had incomplete previous surgery and/or were incompletely staged at the time of their initial laparotomy, recommendations depend on whether invasive implants are present and whether fertility preservation is desired (see the prior incomplete surgical resection pathway in *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm). Patients who want to preserve their fertility should have fertility-sparing surgery and resection of residual disease. Some clinicians feel that the appearance of invasive implants on the peritoneal surfaces in patients with borderline epithelial tumors portends a less favorable prognosis; therefore, postoperative chemotherapy with the same regimens used for low-grade (grade 1) serous epithelial ovarian cancer can be considered for these patients (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).[1225,1226,1235] Postoperative IV carboplatin with either docetaxel or paclitaxel is recommended. The benefit of chemotherapy, either IP or IV, is controversial in patients with borderline epithelial tumors. The significance of invasive implants remains under investigation.[1141,1236] The benefit of postoperative chemotherapy has not been demonstrated for patients who have no microscopically demonstrable invasive implants.[1237] Although observation is an option for all patients, it is a category 3 recommendation for patients with invasive implants and a category 2B recommendation for patients without invasive implants (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).

Follow-up

Treatment recommendations after surgery depend on the presence or absence of invasive implants. The initial therapeutic approach for patients having invasive implants may include treatment with the same chemotherapeutic regimens used for low-grade (grade 1) serous epithelial ovarian cancer or observation (category 3) (see *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).[1236] Patients with no invasive implants may be observed (category 2B) and monitored (see *Monitoring/Follow-Up* in *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm).[1225,1238] Patients who chose fertility-sparing surgery should be monitored by US examinations if necessary. After childbearing is completed, completion surgery should be considered (category 2B).[1141]

Relapse

At the time of clinical relapse, surgical evaluation and debulking are recommended if appropriate. Patients who have low-grade invasive carcinoma or invasive implants from borderline epithelial tumors may be treated using the same recommendations as for low-grade (grade 1) serous epithelial ovarian cancer; those with high-grade invasive implants may be treated using the same recommendations as for epithelial ovarian cancer (see *Recurrence Therapy* in *Less Common Ovarian Cancers: Ovarian Borderline Epithelial Tumors [Low Malignant Potential]* in the algorithm). Observation is recommended for those with noninvasive disease.

Summary

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in women. More than 70% of patients present with advanced disease. The literature does not support routine screening for ovarian cancer in the general population, and routine screening is not currently recommended by any professional society. These NCCN Guidelines discuss epithelial ovarian cancer and LCOC, including carcinosarcomas (MMMTs of the ovary), clear cell carcinomas, mucinous carcinomas, low-grade serous carcinomas/endometrioid epithelial carcinomas, borderline epithelial tumors (also known as LMP tumors),

malignant sex cord-stromal tumors, and malignant germ cell tumors. Primary peritoneal and Fallopian tube cancers are treated in the same manner as epithelial ovarian cancer.

The complete histologic classification for ovarian cancer from the WHO describes the different types of LCOC. Panel members believe there is value in identifying pathways that may serve as therapeutic targets for the LCOC because of the promise of new and novel approaches to treatment. However, there are limited data for these rare histologies because of their infrequency and it will be difficult to acquire prospective data. Clinical trials for eligible patients, and individualized treatment plans for those who are not eligible for trials, may be the most suitable approaches to treatment in these patients at this time.

Most ovarian cancers, including the LCOC, are diagnosed after pathologic analysis of a biopsy or surgical specimen. Based on published improved outcomes, it is recommended (category 1) that a gynecologic oncologist perform the primary surgery. Primary treatment for presumed ovarian cancer consists of appropriate surgical staging and debulking surgery, followed in most (but not all) patients by systemic chemotherapy. Debulking surgery is the initial treatment recommendation for patients with clinical stage II, III, or IV disease. For most patients, initial surgery should include hysterectomy, BSO, and debulking as needed. Procedures that may be considered for optimal surgical debulking include: radical pelvic dissection, bowel resection and/or appendectomy, lymphadenectomy, diaphragm or other peritoneal surface stripping, splenectomy, partial hepatectomy, partial gastrectomy, or partial cystectomy and/or ureteroneocystostomy, cholecystectomy, and/or distal pancreatectomy. Most patients have a hysterectomy with BSO, omentectomy, and lymphadenectomy of suspicious/enlarged nodes. Patients with low-volume residual disease after surgical debulking for stage II or III invasive epithelial ovarian or peritoneal cancer are candidates for IP therapy. In these patients, consideration should be given to placement of an IP catheter with initial surgery. In women with optimally debulked stage III cancer, the IP regimen has yielded median survival of 65.6 months. In women receiving a dose-dense weekly paclitaxel/carboplatin regimen, median OS was 100.5 months.

For a young patient who wishes to maintain fertility, a USO (preserving the uterus and contralateral ovary) and comprehensive surgical staging may be adequate for select unilateral stage I tumors (stage 1A and 1C, but not stage 1B) and/or low-risk ovarian tumors (ie, early-stage, grade 1 tumors; borderline tumors). For those with stage IB tumors who wish to maintain fertility, a BSO (preserving the uterus) and comprehensive surgical staging are recommended.

Most patients with epithelial ovarian cancer receive postoperative systemic chemotherapy. Consideration of palliative care interventions is appropriate at several stages during the disease course. Recommendations regarding initial primary systemic therapy include IV with [or without] IP options. All of the regimens (including the combined IV/IP chemotherapy) may be used for epithelial ovarian, primary peritoneal, and Fallopian tube cancers; some of these regimens are recommended for some of the LCOC. NACT may be considered (category 1) for patients with bulky stage III to IV disease or high-risk surgical candidates; a gynecologic oncologist should make this assessment before NACT is administered.

For all patients, the NCCN Guidelines recommend symptom management, best supportive care, and long-term wellness care; patients should be referred for palliative care assessment if appropriate. Patients should be educated about signs and symptoms suggestive of recurrence such as pelvic pain, bloating, early satiety, obstruction, weight loss, and fatigue. Recurrent disease may be identified clinically (eg, pelvic pain, weight loss), biochemically (ie, elevated CA-125 levels), and/or with imaging. The NCCN Guidelines recommend a number of different regimens and agents

for recurrence therapy; some of them are designated as preferred regimens. Patients with ovarian cancer will often be retreated with multiple courses of recurrence therapy. Patients who relapse 6 months or more after initial chemotherapy are termed *platinum sensitive*. Those who relapse after less than 6 months are termed *platinum resistant*. Platinum-based combination chemotherapy is preferred in patients with platinum-sensitive disease, especially for first recurrence. For platinum-resistant disease, non-platinum–based agents or regimens are preferred. Some of the new additions for 2017 include: 1) carboplatin/liposomal doxorubicin for first-line therapy; 2) niraparib and olaparib for maintenance therapy; and 3) rucaparib, carboplatin/albumin-bound paclitaxel, and carboplatin/paclitaxel/bevacizumab for recurrence therapy.

Recommended Readings

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