NCCN: Continuing Education

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

Accreditation Statements

In support of improving patient care, National Comprehensive Cancer Network (NCCN) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians: NCCN designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses: NCCN designates this educational activity for a maximum of 1.0 contact hour.

Pharmacists: NCCN designates this knowledge-based continuing education activity for 1.0 contact hour (0.1 CEUs) of continuing education credit. UAN: JA4008196-0000-22-010-H01-P

Physician Assistants: NCCN has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 1.0 AAPA Category 1 CME credit. Approval is valid until September 10, 2023. PAs should only claim credit commensurate with the extent of their participation.

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: (1) review the educational content; (2) take the posttest with a 66% minimum passing score and complete the evaluation at **https://education.nccn.org/node/91110**; and (3) view/print certificate.

Pharmacists: You must complete the posttest and evaluation within 30 days of the activity. Continuing pharmacy education credit is reported to the CPE Monitor once you have completed the posttest and evaluation and claimed your credits. Before completing these requirements, be sure your NCCN profile has been updated with your NAPB e-profile ID and date of birth. Your credit cannot be reported without this information. If you have any questions, please email education@nccn.org.

Release date: September 10, 2022; Expiration date: September 10, 2023

Learning Objectives:

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

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

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients.

Individuals Who Provided Content Development and/or Authorship Assistance:

The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.
Lee-may Chen, MD, Panel Member
Heidi G. Gray, MD, Panel Member
Steven W. Remmenga, MD, Panel Member
Emese Zsiros, MD, PhD, Panel Member
Mary A. Dwyer, MS, CGC, Senior Director, Guidelines Operations, NCCN
Lisa Hang, PhD, Oncology Scientist/Medical Writer, NCCN

The faculty listed below have the following relevant financial relationship(s) with ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

Deborah K. Armstrong, MD, Panel Chair, has disclosed receiving grant/research support from AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc., Pfizer Inc., and Syndax Pharmaceuticals Inc.; and serving as a scientific advisor for AstraZeneca Pharmaceuticals LP and Johnson & Johnson.

Ronald D. Alvarez, MD, MBA, Panel Vice Chair, has disclosed serving as a scientific advisor for AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, and Myriad Genetic Laboratories, Inc.

Floor J. Backes, MD, Panel Member, has disclosed receiving grant/research support from AstraZeneca Pharmaceuticals LP, BeiGene, Clovis Oncology, Eisai Inc., ImmunoGen, Inc., Merck & Co., Inc., and Natera, Inc.; and serving as a scientific advisor for Agenus Inc., AstraZeneca Pharmaceuticals LP, Clovis Onocology, Eisai Inc., GlaxoSmithKline, ImmunoGen, Inc., and Merck & Co., Inc.

Eric L. Eisenhauer, MD, Panel Member, has disclosed receiving consulting fees from Seagen Inc.

David M. Gershenson, MD, Panel Member, has disclosed serving as a scientific advisor for Genentech, Inc., Onconova Therapeutics, and Verastem Oncology; owning equity interest/stock options in Bristol-Myers Squibb Company, Johnson & Johnson, and Procter & Gamble Company; receiving grant/research support from the Novartis Pharmaceuticals Corporation; and receiving royalty income from Elsevier.

Amer Karam, MD, Panel Member, has disclosed serving in a product/speakers' bureau for AstraZeneca Pharmaceuticals LP and GlaxoSmithKline; and receiving consulting fees from Clovis Oncology.

Charles Leath III, MD, MSPH, Panel Member, has disclosed receiving consulting fees from AbbVie Inc., Celsion Corporation, Clovis Oncology, Eisai Inc., GlaxoSmithKline, ImmunoGen, Inc., Merck & Co., Inc., Natera, Inc., PAREXEL International Corporation, and Seattle Genetics, Inc.; and receiving grant/research support from AbbVie, Inc., Agenus Inc., Celsion Corporation, GlaxoSmithKline, ImmunoGen, Inc., Merck & Co., Inc., and Seattle Genetics, Inc.

Joyce Liu, MD, MPH, Panel Member, has disclosed receiving consulting fees from AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc., EpsilaBio, Genentech, Inc., GlaxoSmithKline, and Regeneron Pharmaceuticals, Inc.

Daniela Matei, MD, Panel Member, has disclosed receiving consulting fees from AstraZeneca Pharmaceuticals LP, Eisai Inc., GlaxoSmithKline, and Seagen Inc.; receiving grant/research support from AbbVie, Inc. and PinotBio Inc.; and serving as a scientific advisor for GlaxoSmithKline and KIYATEC Inc.

David S. Miller, MD, Panel Member, has disclosed receiving grant/research support from Advaxis Inc., Advenchen Laboratories, LLC, Aeterna Zentaris Inc., Agenus Inc., Akesobio, Aprea Therapeutics AB, AstraZeneca Pharmaceuticals LP, EMD Serono Research & Development Institute, ImmunoGen, Inc., Incyte Corporation, Janssen Pharmaceutica Products, LP, Karyopharm Therapeutics, Leap Therapeutics, Inc., Mateon Therapeutics, Inc., Merck & Co., Inc., Millennium Pharmaceuticals, Inc., Novartis Pharmaceuticals Corporation, NVISION, Pfizer Inc., Regeneron Pharmaceuticals, Inc., Syros Pharmaceuticals, TESARO, Inc., TRACON Pharmaceuticals, Inc., US Biotest, Inc., and Xenetic Biosciences, Inc.; serving as a consultant/advisor for AbbVie, Inc., Agenus Inc., AstraZeneca Pharmaceuticals LP, Asymmetric Therapeutics, LLC, Eisai Inc., Eisai Europe Limited, EMD Serono Inc., GlaxoSmithKline, ImmunoGen, Inc., Incyte Corporation, iTeos Belgium SA, Karyopharm Therapeutics, Merck & Co., Inc., Myriad Genetic Laboratories, Inc., Novartis Pharmaceuticals Corporation, Novocure, Seagen Inc., and Tarveda Therapeutics; and serving on a speaker/product bureau for Clovis Oncology and Genentech Inc.

Premal H. Thaker, MD, Panel Member, has disclosed serving as a scientific advisor for Agenus Inc., AstraZeneca Pharmaceuticals LP, Clovis Oncology, Eisai Inc., GlaxoSmithKline, Merck & Co., Inc., Mersana Therapeutics Inc., Novartis Pharmaceuticals Corporation, Novocure, and Seagen Inc.; receiving grant/research support from GlaxoSmithKline and Merck serving on a data safety monitoring board for and receiving consulting fees from Celsion Corporation; and serving on a steering committee for Novocure.

Andrea Wahner Hendrickson, MD, Panel Member, has disclosed receiving grant/research support from Amgen Inc., Aravive, Inc., AstraZeneca Pharmaceuticals LP, Harpoon Therapeutics, Inc., ProLynx, and TESARO, Inc.; and serving as a scientific advisor for Oxcia AB.

Theresa L. Werner, MD, Panel Member, has disclosed serving as a scientific advisor for Mersana Therapeutics Inc.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

This activity is supported by educational grants from AstraZeneca; BeiGene; Exact Sciences; Gilead Sciences, Inc.; GlaxoSmithKline; Lantheus Medical Imaging Inc.; Novartis; Pharmacyclics LLC, an AbbVie Company and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Taiho Oncology, Inc. This activity is supported by an independent educational grant from Astellas. This activity is supported by an education grant from Astellas and Seagen Inc. This activity is supported by a medical education grant from Karyopharm® Therapeutics. This activity is supported through an Independent Medical Education grant from Merck & Co., Inc.

Ovarian Cancer, Version 3.2022

Featured Updates to the NCCN Guidelines

Deborah K. Armstrong, MD[1,*]; Ronald D. Alvarez, MD, MBA[2,*]; Floor J. Backes, MD[3,*]; Jamie N. Bakkum-Gamez, MD[4]; Lisa Barroilhet, MD[5]; Kian Behbakht, MD[6]; Andrew Berchuck, MD[7]; Lee-may Chen, MD[8,*]; Viola C. Chitiyo, BSN, RN[9]; Mihaela Cristea, MD[10]; Maria DeRosa, RN[11]; Eric L. Eisenhauer, MD[12,*]; David M. Gershenson, MD[13,*]; Heidi J. Gray, MD[14,*]; Rachel Grisham, MD[9]; Ardeshir Hakam, MD[15]; Angela Jain, MD[16]; Amer Karam, MD[17,*]; Gottfried E. Konecny, MD[18]; Charles A. Leath III, MD, MSPH[19,*]; Gary Leiserowitz, MD[20]; Joyce Liu, MD, MPH[21,*]; Lainie Martin, MD[22]; Daniela Matei, MD[23,*]; Michael McHale, MD[24]; Karen McLean, MD, PhD[25]; David S. Miller, MD[26,*]; Sanja Percac-Lima, MD, PhD[12]; Steven W. Remmenga, MD[27,*]; John Schorge, MD[28]; Daphne Stewart, MD, MS[10]; Premal H. Thaker, MD[29,*]; Roberto Vargas, MD[30]; Andrea Wahner Hendrickson, MD[4,*]; Theresa L. Werner, MD[31,*]; Emese Zsiros, MD, PhD[32,*]; Mary A. Dwyer, MS, CGC[33,*]; and Lisa Hang, PhD[33,*]

ABSTRACT

Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States, with less than half of patients living >5 years following diagnosis. The NCCN Guidelines for Ovarian Cancer provide recommendations for the diagnosis, evaluation, treatment, and follow-up for patients with ovarian, fallopian tube, and primary peritoneal cancers. These NCCN Guidelines Insights summarize the panel discussion behind recent important updates to the guidelines, including revised guidance on alternative chemotherapy regimens for patients with advanced age and/or comorbidities, a new algorithm for recurrent low-grade serous carcinoma based on developing research and novel therapeutic agents, and updated language regarding tumor molecular analysis applications in ovarian cancer.

J Natl Compr Canc Netw 2022;20(9):972–980
doi: 10.6004/jnccn.2022.0047

[1]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [2]Vanderbilt-Ingram Cancer Center; [3]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [4]Mayo Clinic Cancer Center; [5]University of Wisconsin Carbone Cancer Center; [6]University of Colorado Cancer Center; [7]Duke Cancer Institute; [8]UCSF Helen Diller Family Comprehensive Cancer Center; [9]Memorial Sloan Kettering Cancer Center; [10]City of Hope National Medical Center; [11]Patient advocate; [12]Massachusetts General Hospital Cancer Center; [13]The University of Texas MD Anderson Cancer Center; [14]University of Washington/Seattle Cancer Care Alliance; [15]Moffitt Cancer Center; [16]Fox Chase Cancer Center; [17]Stanford Cancer Institute; [18]UCLA Jonsson Comprehensive Cancer Center; [19]O'Neal Comprehensive Cancer Center at UAB; [20]UC Davis Comprehensive Cancer Center; [21]Dana-Farber/Brigham and Women's Cancer Center; [22]Abramson Cancer Center at the University of Pennsylvania; [23]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [24]UC San Diego Moores Cancer Center; [25]University of Michigan Rogel Cancer Center; [26]UT Southwestern Simmons Comprehensive Cancer Center; [27]Fred & Pamela Buffett Cancer Center; [28]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [29]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [30]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [31]Huntsman Cancer Institute at the University of Utah; [32]Roswell Park Comprehensive Cancer Center; and [33]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

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

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

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

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

All recommendations are category 2A unless otherwise noted.

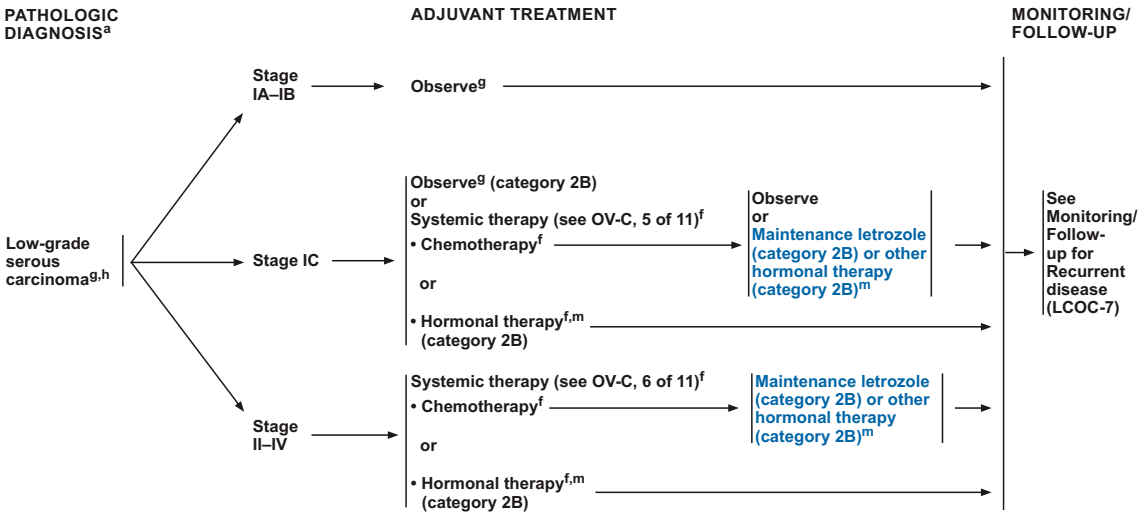
Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

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

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

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



[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).
[m] Other hormonal therapy options include: aromatase inhibitors (anastrozole, exemestane), leuprolide acetate, tamoxifen.

LCOC-6

Overview

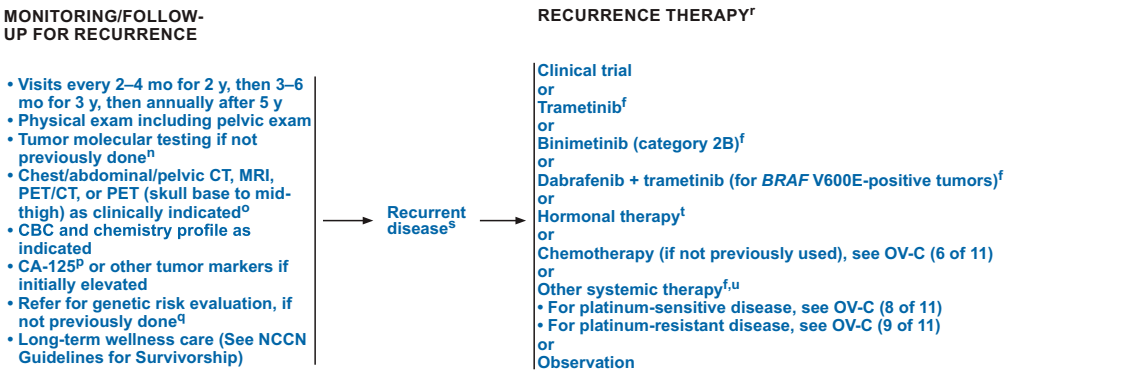
Ovarian neoplasms consist of several histopathologic entities, with epithelial ovarian cancer accounting for the majority of malignant ovarian neoplasms (~90%).[1–4] Epithelial ovarian cancer is the leading cause of death from gynecologic cancer in the United States and is the country's fifth most common cause of cancer mortality in females.[5] In 2022 it is estimated that 19,880 new diagnoses and 12,810 deaths from this malignancy will occur in the United States.[5] Five-year survival is approximately 49%, although survival is longer for select patients with early-stage disease and certain histologic subtypes.[5–8] Approximately half of patients present with distant disease; however, certain uncommon subtypes, such as clear cell and endometrioid cancer, are more likely to be diagnosed at earlier stages.[5–7,9]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Ovarian Cancer discuss cancers originating in the ovary, fallopian tube, or peritoneum, and include recommendations for epithelial subtypes, including serous, endometrioid, carcinosarcoma (malignant mixed Müllerian tumors of the ovary), clear cell, mucinous, and borderline epithelial tumors (also known as *low malignant potential tumors*). The recommendations are based primarily on data from patients with the most common subtypes—high-grade serous and grade 2 and 3 endometrioid carcinoma. Also included in the guidelines are recommendations for less common ovarian cancers (LCOCs), specifically carcinosarcoma, clear cell carcinoma, mucinous carcinoma, low-grade serous carcinoma (LGSC), grade 1 endometrioid carcinoma, borderline epithelial tumors, and nonepithelial subtypes including malignant sex cord-stromal tumors and germ cell tumors.

These NCCN Guidelines Insights summarize the panel discussion behind recent updates to the guidelines, including revised guidance on adjuvant chemotherapy regimens for patients with advanced age and/or comorbidities, an updated algorithm for LGSC based on emerging research and novel therapeutic agents, and revised language regarding tumor molecular analysis applications in ovarian cancer.

Adjuvant Chemotherapy Options for Patients With Advanced Age and/or Comorbidities

Adjuvant systemic chemotherapy is considered an essential component of care for patients with ovarian, fallopian tube, or primary peritoneal cancers. For most patients with epithelial cancer types and stage I disease, first-line systemic therapy generally consists of intravenous platinum-based chemotherapy, with the guidelines recommending paclitaxel at 175 mg/m^2 + carboplatin at an



[f] See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).
[n] Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, BRCA1/2, HR status, MSI, TMB, NTRK if prior testing did not include these markers. More comprehensive testing may be particularly important in LCOC with limited approved therapeutic options (See OV-B).
[o] Imaging performed with oral and IV contrast (unless contraindicated) and rectal contrast as needed.
[p] 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.
[q] See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[r] There is no standard sequencing of drugs for recurrent disease. Considerations include prior therapies, disease burden, relative efficacy, and relative toxicity profile.
[s] Consider secondary cytoreduction in patients with long disease-free interval, isolated masses rather than diffuse carcinomatosis on imaging, and/or bowel obstruction.
[t] An aromatase inhibitor (ie, letrozole, anastrozole, exemestane) is preferred if not used previously. Fulvestrant, tamoxifen, or leuprolide acetate is recommended if an aromatase inhibitor was given previously.
[u] Data are limited on maintenance therapy for recurrent/resistant LCOC. See OV-8 for maintenance options after platinum-based therapy, and patient selection criteria.

LCOC-7

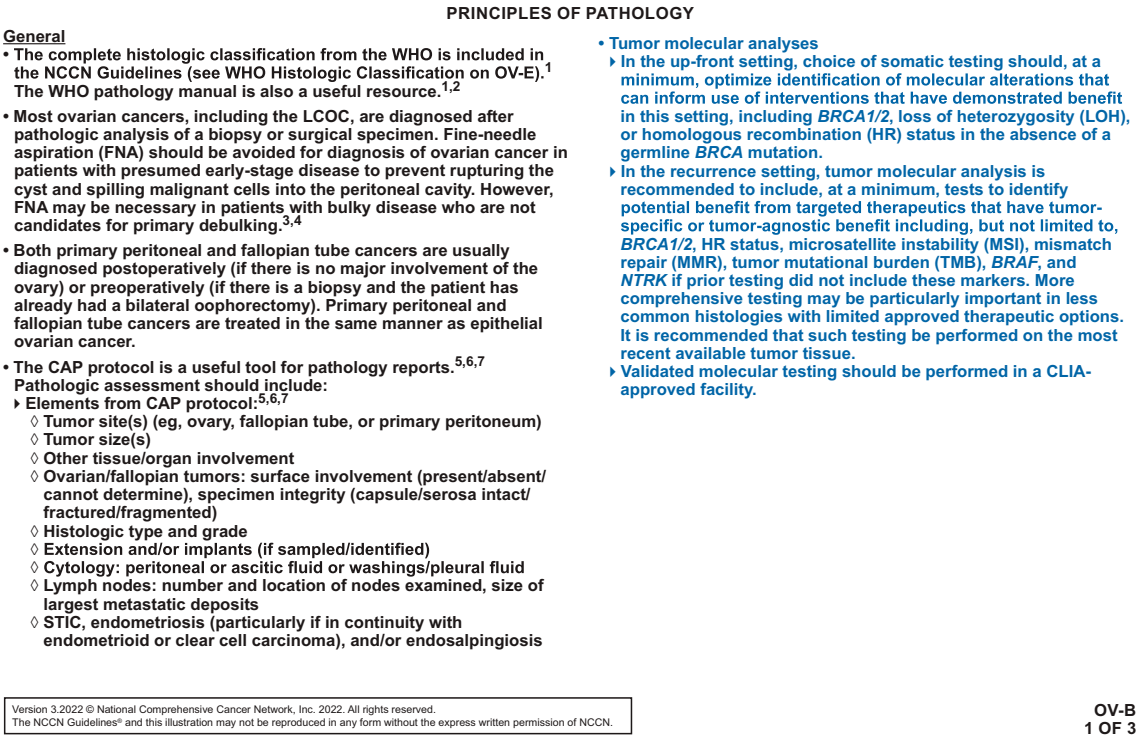
area under the curve (AUC) of 5 to 6 every 3 weeks (q3wk) as a preferred regimen. Intravenous platinum-based chemotherapy ± bevacizumab is also a recommended option for first-line systemic therapy for those with stage II–IV disease. Additionally, alternate regimens (such as platinum-based intravenous/intraperitoneal [IP] chemotherapy or hormone therapy) are recommended as options, depending on cancer subtype, completeness of the initial surgery, and stage of disease. The "Principles of Systemic Therapy" section of the full guidelines (OV-C 5–7 of 11; available at NCCN.org) provides a complete list of primary systemic therapy options recommended for epithelial ovarian, fallopian tube, and primary peritoneal cancers.

Unfortunately, patients with advanced age (≥70 years) and/or comorbidities may be less likely to tolerate certain combination chemotherapy regimens, leading to discontinuation before the regimen is completed.[10–14] For example, patients aged ≥70 years undergoing paclitaxel/carboplatin-based therapy may be at higher risk of febrile neutropenia, anemia, diarrhea, asthenia, thromboembolic events, or hypertension (associated with bevacizumab).[10,11] Studies have suggested that risk of severe toxicity, discontinuation of adjuvant chemotherapy, and even worse overall survival (OS) may be correlated with increased age (even among the elderly), functional status or depression at baseline (as quantified by the Hospital Anxiety and Depression Scale, Activities of Daily Living score, Instrumental Activities of Daily Living score, and social activities score), lymphopenia, hypoalbuminemia, and a number of comedications.[15–20]

Because elderly patients and individuals with comorbidities may be intolerant to the combination chemotherapy regimens, alternate combination therapy dosing (see OV-C 7 of 11, page 977) may be appropriate for these patients. For example, the dose of paclitaxel and carboplatin can be reduced. Guidance on how potential chemotherapy toxicity can be assessed can be found in the NCCN Guidelines for Older Adult Oncology (available at NCCN.org).

Prior versions of the NCCN Guidelines for Ovarian Cancer recommended carboplatin monotherapy as an option for elderly patients and/or those with comorbidities. Although this recommendation was based on clinical evidence from several studies,[17–19,21,22] none of the studies were randomized trials specifically designed to evaluate single-agent carboplatin in elderly patients and/or patients with comorbidities.

More recently, the open-label, phase II, randomized EWOC-1 trial evaluated carboplatin monotherapy (AUC 5–6 q3wk) alongside 2 other carboplatin combination regimens (weekly paclitaxel, 60 mg/m^2/carboplatin, AUC 2, or paclitaxel, 175 mg/m^2/carboplatin, AUC 5 q3wk) in 120 patients aged ≥70 years with stage III/IV epithelial



ovarian, fallopian tube, or primary peritoneal cancer.[23] A Geriatric Vulnerability Score (GVS) of ≥3 was also required for eligibility in this study. The GVS was developed to identify vulnerable elderly patients with advanced ovarian cancer[17]; those with a score ≥3 are likely to experience worse survival, lower treatment completion, and toxicity.

Data from this study suggested that carboplatin monotherapy was associated with significantly worse outcomes than the carboplatin combination therapy regimens in this patient population.[23] Median OS was 7.4 months (95% CI, 5.3–32.2 months) in the carboplatin monotherapy group compared with 17.3 months (95% CI, 10.8–32.2 months) in the weekly paclitaxel/carboplatin group and not reached in the paclitaxel/carboplatin q3wk group. The hazard ratio (HR) for inferior OS of the carboplatin monotherapy group versus the paclitaxel/carboplatin q3wk group was 2.79 (95% CI, 1.57–4.96; $P<.001$). Higher incidences of grade ≥3 thrombocytopenia and anemia were reported in the carboplatin monotherapy group than the carboplatin combination therapy groups. In contrast, higher rates of low-grade gastrointestinal adverse events, neuropathy, and alopecia were reported in the 2 carboplatin combination groups.

Due to the worse survival outcomes associated with carboplatin monotherapy compared with the carboplatin combination regimens, the trial was prematurely terminated on the recommendation of the independent data monitoring committee.[23] Therefore, based on these data, the NCCN panel no longer recommends carboplatin monotherapy as an option for patients who are elderly and/or those with comorbidities, because carboplatin combination therapy is now considered the standard-of-care first-line chemotherapy regimen for this population.

The following regimens are recommended in the guidelines as options for elderly patients (age >70 years) and/or those with comorbidities (OV-C 7 of 11, page 977): (1) intravenous paclitaxel, 135 mg/m^2 + intravenous carboplatin, AUC 5 given every 21 days for 3 to 6 cycles, depending on stage and cancer subtype,[19] or (2) intravenous paclitaxel, 60 mg/m^2, followed by intravenous carboplatin, AUC 2 on days 1, 8, and 15, repeated every 21 days for 6 cycles.[23–25]

The latter option can also be considered for patients with poor performance status. The "Principles of Systemic Therapy" section in the full version of these guidelines (available at NCCN.org) provides a complete list of recommended primary therapy regimens and dosing recommendations for ovarian, fallopian tube, and primary peritoneal cancers.

Management of LGSC

LGSC is a subtype of serous carcinoma that is considered pathologically distinct from the more commonly diagnosed high-grade serous carcinoma (HGSC), and represents <5% of epithelial ovarian cancers.[26,27] LGSC is characterized by

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/m² IV continuous infusion[k] Day 1; Cisplatin 75–100 mg/m² IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m² IP Day 8
- Repeat every 21 days x 6 cycles

Paclitaxel/carboplatin q3weeks[f,l]
- Paclitaxel 175 mg/m² IV followed by carboplatin[m] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[l]

Paclitaxel weekly/carboplatin q3weeks[f]
- Dose-dense paclitaxel 80 mg/m² IV Days 1, 8, and 15 followed by carboplatin[k] AUC 5–6 IV Day 1
- Repeat every 21 days x 6 cycles

Paclitaxel weekly/carboplatin weekly[f]
- Paclitaxel 60 mg/m² IV followed by carboplatin AUC 2 IV
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)[j]

Docetaxel/carboplatin[l]
- Docetaxel 60–75 mg/m² IV followed by carboplatin[m] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[j]

Carboplatin/liposomal doxorubicin[l]
- Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m² IV
- Repeat every 28 days for 3–6 cycles[l]

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[f,i] (ICON-7)
- Paclitaxel 175 mg/m² IV followed by carboplatin[m] 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[f,i] (GOG-218)
- Paclitaxel 175 mg/m² IV followed by carboplatin[m] 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[f,g]
- Paclitaxel 135 mg/m² IV + carboplatin AUC 5 IV given every 21 days x 3–6 cycles[l]

Paclitaxel weekly/carboplatin weekly[f]
- Paclitaxel 60 mg/m² 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)

[c] See Discussion for references.
[f] Albumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.
[i] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[j] Regimen may be considered for those with poor performance status.
[k] The published randomized trial regimen used IV continuous infusion paclitaxel over 24 hours.
[l] 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.
[m] 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.

OV-C
7 OF 11

mild to moderate nuclear atypia, and up to 12 mitoses per 10 high-powered fields (HPF), whereas HGSC is characterized by marked nuclear atypia and >12 mitoses per 10 HPF.[27–29] Additionally, activating mutations in the MAPK pathway are frequently identified in LGSC, but not HGSC; in contrast, *TP53* mutations are generally associated with HGSC, but not LGSC.[30–35] LGSCs is associated with more indolent disease and presents at a younger age than HGSCs; however, they are also often advanced at diagnosis.[28,29,36,37] Approximately 60% of LGSCs (vs 2% of HGSCs) are also associated with serous borderline tumors (low malignant potential).[29] Due to these distinctions, patients with LGSCs are generally managed differently from those with HGSCs, as described in the following section.

Primary Treatment

Primary treatment for LGSCs consists of completion surgery with comprehensive staging, followed by adjuvant therapy or observation.[36] Typically the diagnosis of LGSC is made via comprehensive pathology review after initial surgery. The staging system for high-grade serous ovarian, fallopian tube, and primary peritoneal cancers is also used for those that are low-grade serous.[38] LGSCs often respond poorly to chemotherapy compared with HGSCs[39]; therefore, neoadjuvant chemotherapy is less favored for patients with LGSC.[36]

Recommendations for adjuvant treatment are stratified by stage in the guidelines (see LCOC-6, page 974). Postoperative observation is a category 2A recommendation for stage IA and IB disease and a category 2B recommendation for IC disease. Several adjuvant systemic therapy options, including paclitaxel/platinum-containing regimens, are recommended for stage IC or stage II–IV disease, although there are limited data on systemic therapy regimens in patients with LGSC in general.

Patients with LGSCs may also benefit from maintenance hormone therapy following adjuvant chemotherapy. One database study observed that patients with stage II–IV LGSC who received maintenance hormone therapy after completing primary cytoreductive surgery and first-line platinum-based chemotherapy experienced longer progression-free survival (PFS) than those who did not receive maintenance hormone therapy (median PFS, 64.9 vs 26.4 months; $P<.001$).[40] Most patients in the study received letrozole (54.3%), with a lower proportion receiving tamoxifen (28.6%). Based on these data, maintenance hormone therapy (letrozole, anastrozole, exemestane, leuprolide acetate, or tamoxifen) is a category 2B recommendation in the guidelines.

Adjuvant hormone therapy as a substitute for adjuvant chemotherapy is another potential option for these patients.[41] However, because there are no supporting prospective data,

this is a category 2B recommended option in the guidelines. A randomized trial of paclitaxel/carboplatin chemotherapy followed by maintenance hormonal therapy versus hormonal therapy alone in patients with LGSC is currently underway (NRG identifier: NRG-GY019).

Monitoring/Follow-up for Recurrent Disease

Unfortunately, patients with LGSC, particularly those with advanced-stage disease, may experience disease relapse; therefore, continued monitoring of these patients is essential. The guidelines recommend monitoring for potential recurrence of LGSC through follow-up visits every 2 to 4 months for 2 years, followed by 3 to 6 months for 3 years, and then annually after 5 years (see LCOC-7, page 975). These visits should consist of a physical examination, including a pelvic examination. Tumor molecular testing is recommended, if not previously done; more comprehensive somatic genetic testing may be particularly important in LGSC, which has limited approved therapeutic options. Imaging and CBC count/chemistry profile are also recommended, as clinically indicated. CA-125 or other tumor markers should be assessed if initially elevated. Refer patients for a genetic risk evaluation, if not previously done. For guidance on long-term wellness care for patients who have been treated for LGSC, please refer to the NCCN Guidelines for Survivorship (available at NCCN.org).

Recurrence Therapy

The NCCN Guidelines recommend several options for patients with recurrent LGSC (see LCOC-7, page 975). Secondary cytoreduction can be considered for patients with a long disease-free interval, isolated masses rather than diffuse carcinomatosis on imaging, and/or bowel obstruction. Systemic therapy is another option for this patient population; however, the guidelines emphasize that there is no standard sequencing of drugs for recurrent disease. Therefore, each patient should be evaluated on an individual basis, taking into consideration prior therapies, disease burden, molecular profile, and the relative efficacy and toxicity profile before initiating systemic therapy. Recommended systemic therapies for this patient population in this setting include chemotherapy (if not previously used) and hormonal therapy.[36,42]

However, it has been reported that LGSC may be more chemoresistant than HGSC in the recurrent setting.[43] Thus, effective systemic options for recurrent LGSC have remained an unmet need. Importantly, recent studies have suggested that MEK inhibitors have activity in recurrent LGSC. A phase II/III, open-label, randomized study evaluated the efficacy and safety of trametinib, a MEK1/2 inhibitor, compared with 5 standard-of-care (SoC) options (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, or tamoxifen) in 260 patients with recurrent LGSC.[44] The median PFS was 13.0 months in the trametinib arm compared with 7.2 months in the SoC group (HR, 0.48; 95% CI, 0.36–0.64; $P<.0001$). The overall response rate (ORR) of the trametinib group was 26%, which was significantly higher than the 6% ORR of the SoC group ($P<.0001$). The most common grade 3 or 4 adverse events reported in the trametinib group were skin rash, anemia, hypertension, diarrhea, nausea, and fatigue. Due to the superior outcomes reported in this trial, the NCCN panel recommends trametinib as a category 2A option for patients with recurrent LGSC.

The efficacy and safety of another MEK1/2 inhibitor, binimetinib, was evaluated in a phase III open-label study in 303 patients with recurrent LGSC.[45] Patients were randomized to receive either binimetinib or physician's choice chemotherapy (PCC; pegylated liposomal doxorubicin, paclitaxel, or topotecan). Median PFS was 9.1 months in the binimetinib group versus 10.6 months in the PCC group (HR, 1.21; 95% CI, 0.79–1.86; $P=.807$); therefore, the primary endpoint of PFS by blinded independent central review (BICR) was not met in this study. However, binimetinib was numerically superior to PCC across certain endpoints, such as PFS by local investigator assessment (12.5 vs 11.6 months, respectively) and ORR by BICR (16% vs 13%, respectively). Additionally, PFS and ORR data from a post hoc analysis suggested that a response to binimetinib may be associated with the presence of a *KRAS* mutation. Based on these data, the NCCN panel recommends binimetinib as a category 2B option for patients with recurrent LGSC.

Recently, a new option became available for patients with recurrent LGSC with a *BRAF* V600E mutation. In June 2022, the FDA granted accelerated approval to selective BRAF inhibitor dabrafenib in combination with trametinib for the treatment of adult and pediatric patients (aged ≥6 years) with unresectable or metastatic solid tumors with *BRAF* V600E mutation who have experienced disease progression following prior treatment and have no satisfactory alternative treatment options.[46–48] This approval was based on several studies; one of these was the phase II, open-label, single-arm NCI-MATCH trial (subprotocol H), in which dabrafenib in combination with trametinib was evaluated in patients with solid tumors, lymphoma, or multiple myeloma whose disease progressed on at least one standard therapy.[49] Of the 29 patients included in the primary analysis, 5 had LGSC and 1 had mucinous-papillary serous adenocarcinoma of peritoneum. The ORR of the overall population was 38%, with a PFS of 11.4 months. Notably, a clinical benefit was observed in all 6 patients with primary gynecologic cancer; 5 achieved a partial response (>12 months for 3 patients) and 1 had stable disease for 8 months following treatment. Based on the results, the combination of dabrafenib and trametinib has been added to the guidelines as a category 2A recurrence therapy option for patients with *BRAF* V600E–positive tumors (including LGSC).

In addition to the options described earlier, other acceptable systemic recurrence therapies listed in the

"Principles of Systemic Therapy" section in the full version of these guidelines (pages OV-C 8 and 9 of 11, available at NCCN.org) can be considered. Clinical trial enrollment and observation are other recommended options for patients with recurrent LGSC.

In response to the availability of novel treatment options for recurrent LGSC, the NCCN panel has developed a new algorithm page with recommendations for management of these patients (see LCOC-7, page 975).

Tumor Molecular Analysis in Ovarian Cancer

Upon pathologic confirmation of ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, 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 whichever molecular tests they consider necessary based on evaluation of the individual patient and their cancer family history. Because germline and/or somatic *BRCA1/2* testing informs selection of maintenance therapy for patients with stage II–IV disease experiencing complete or partial response 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. Homologous recombination status (eg, homologous recombination–deficient vs homologous recombination–proficient) may provide information on the magnitude of benefit of PARP inhibitor maintenance therapy for those without a *BRCA1/2* mutation. For additional recommendations on workup, staging, and primary treatment of ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, refer to page OV-1 in the full version of these guidelines (available at NCCN.org).

With the availability of next-generation sequencing technology, the panel discussed whether comprehensive tumor molecular analysis should be recommended for all patients. Some panel members stated that comprehensive tumor testing may not be necessary for certain patients in the up-front setting, specifically those with a germline mutation in *BRCA1/2* or other homologous recombination/DNA repair pathway genes. On the other hand, some patients (such as those who lack a *BRCA1/2* mutation or experience disease recurrence) may benefit from a more thorough tumor molecular analysis to inform additional targeted therapy options. The panel agreed that tumor testing may be beneficial at multiple points throughout the evolution of the disease.

Therefore, the current guidelines now recommend tumor molecular analysis both in the up-front setting and upon recurrence (OV-B 1 of 3, page 976). The goal of tumor testing in the up-front setting is to optimize identification of molecular alterations that can inform the use of interventions with demonstrated benefit in this setting, such as PARP inhibitors. Molecular alterations that should be probed for in this setting include *BRCA1/2* status, loss of heterozygosity, or homologous recombination status, in the absence of a germline *BRCA* mutation.

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. The panel recommends that tumor molecular analysis in the recurrence setting should include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit. These include (but are not limited to): *BRCA1/2*, hormone receptor status, microsatellite instability, mismatch repair, tumor mutational burden, *BRAF*, and *NTRK*, if prior testing did not include these markers. The panel emphasizes that more comprehensive tumor analysis may be particularly important for less common histologies with limited approved treatment options. 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.

Summary

The NCCN panel recommends carboplatin combination regimens as first-line chemotherapy treatment options for elderly patients and/or those with comorbidities; single-agent carboplatin is no longer recommended for this patient population based on data from the EWOC-1 study. In addition, the guidelines now include updated recommendations for the management of recurrent LGSC, due to emerging data on novel therapeutics. Finally, recommendations for tumor molecular analysis in patients with ovarian, fallopian tube, or primary peritoneal cancers have been revised to clarify that tumor testing in the up-front and recurrence settings is recommended for select biomarkers.

To participate in this journal CE activity, go to https://education.nccn.org/node/91110

References

1. Kurman RJ, Carcangiu ML, Harrington CS, et al, eds. WHO Classification of Tumours of Female Reproductive Organs, 4th ed. Lyon, France: IARC Publications; 2014.
2. Chan JK, Cheung MK, Husain A, et al. Patterns and progress in ovarian cancer over 14 years. Obstet Gynecol 2006;108: 521–528.

3. Prat J. New insights into ovarian cancer pathology. Ann Oncol 2012; 23(Suppl 10):X111–117.
4. Jelovac D, Armstrong DK. Recent progress in the diagnosis and treatment of ovarian cancer. CA Cancer J Clin 2011;61:183–203.
5. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7–33.
6. Peres LC, Cushing-Haugen KL, Köbel M, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. J Natl Cancer Inst 2019;111:60–68.
7. Park HK, Ruterbusch JJ, Cote ML. Recent trends in ovarian cancer incidence and relative survival in the United States by race/ethnicity and histologic subtypes. Cancer Epidemiol Biomarkers Prev 2017;26:1511–1518.
8. Howlader N, Noone A, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD. Based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Accessed July 6, 2022. Available at: https://seer.cancer.gov/csr/1975_2014/
9. Stewart SL, Harewood R, Matz M, et al. Disparities in ovarian cancer survival in the United States (2001-2009): findings from the CONCORD-2 study. Cancer 2017;123(Suppl 24):5138–5159.
10. Hilpert F, du Bois A, Greimel ER, et al. Feasibility, toxicity and quality of life of first-line chemotherapy with platinum/paclitaxel in elderly patients aged ≥70 years with advanced ovarian cancer—a study by the AGO OVAR Germany. Ann Oncol 2007;18:282–287.
11. Selle F, Colombo N, Korach J, et al. Safety and efficacy of extended bevacizumab therapy in elderly (≥70 years) versus younger patients treated for newly diagnosed ovarian cancer in the international ROSiA study. Int J Gynecol Cancer 2018;28:729–737.
12. Fairfield KM, Murray K, Lucas FL, et al. Completion of adjuvant chemotherapy and use of health services for older women with epithelial ovarian cancer. J Clin Oncol 2011;29:3921–3926.
13. Falandry C, Savoye AM, Stefani L, et al. EWOC-1: a randomized trial to evaluate the feasibility of three different first-line chemotherapy regimens for vulnerable elderly women with ovarian cancer (OC): a GCIG-ENGOT-GINECO study [abstract]. J Clin Oncol 2019;37:Abstract 5508.
14. Hershman DL, Till C, Wright JD, et al. Comorbidities and risk of chemotherapy-induced peripheral neuropathy among participants 65 years or older in Southwest Oncology Group clinical trials. J Clin Oncol 2016;34:3014–3022.
15. Freyer G, Geay JF, Touzet S, et al. Comprehensive geriatric assessment predicts tolerance to chemotherapy and survival in elderly patients with advanced ovarian carcinoma: a GINECO study. Ann Oncol 2005;16:1795–1800.
16. Trédan O, Geay JF, Touzet S, et al. Carboplatin/cyclophosphamide or carboplatin/paclitaxel in elderly patients with advanced ovarian cancer? Analysis of two consecutive trials from the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. Ann Oncol 2007;18:256–262.
17. Falandry C, Weber B, Savoye AM, et al. Development of a geriatric vulnerability score in elderly patients with advanced ovarian cancer treated with first-line carboplatin: a GINECO prospective trial. Ann Oncol 2013;24:2808–2813.
18. Tinquaut F, Freyer G, Chauvin F, et al. Prognostic factors for overall survival in elderly patients with advanced ovarian cancer treated with chemotherapy: results of a pooled analysis of three GINECO phase II trials. Gynecol Oncol 2016;143:22–26.
19. von Gruenigen VE, Huang HQ, Beumer JH, et al. Chemotherapy completion in elderly women with ovarian, primary peritoneal or fallopian tube cancer – an NRG oncology/Gynecologic Oncology Group study. Gynecol Oncol 2017;144:459–467.
20. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. J Clin Oncol 2011;29:3457–3465.
21. International Collaborative Ovarian Neoplasm Group. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 2002;360:505–515.
22. ICON Collaborators. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. Lancet 1998;352:1571–1576.
23. Falandry C, Rousseau F, Mouret-Reynier MA, et al. Efficacy and safety of first-line single-agent carboplatin vs carboplatin plus paclitaxel for vulnerable older adult women with ovarian cancer: a GINECO/GCIG randomized clinical trial. JAMA Oncol 2021;7:853–861.
24. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2014;15:396–405.
25. Pignata S, Breda E, Scambia G, et al. A phase II study of weekly carboplatin and paclitaxel as first-line treatment of elderly patients with advanced ovarian cancer: a Multicentre Italian Trial in Ovarian cancer (MITO-5) study. Crit Rev Oncol Hematol 2008;66:229–236.
26. Committee on the State of the Science in Ovarian Cancer Research. Ovarian Cancers: Evolving Paradigms in Research and Care. Washington, DC: National Academies Press; 2016.
27. Prat J, D'Angelo E, Espinosa I. Ovarian carcinomas: at least five different diseases with distinct histological features and molecular genetics. Hum Pathol 2018;80:11–27.
28. Bodurka DC, Deavers MT, Tian C, et al. Reclassification of serous ovarian carcinoma by a 2-tier system: a Gynecologic Oncology Group study. Cancer 2012;118:3087–3094.
29. Malpica A, Deavers MT, Lu K, et al. Grading ovarian serous carcinoma using a two-tier system. Am J Surg Pathol 2004;28:496–504.
30. Jones S, Wang TL, Kurman RJ, et al. Low-grade serous carcinomas of the ovary contain very few point mutations. J Pathol 2012;226:413–420.
31. Wong KK, Tsang YT, Deavers MT, et al. BRAF mutation is rare in advanced-stage low-grade ovarian serous carcinomas. Am J Pathol 2010; 177:1611–1617.
32. Cheasley D, Nigam A, Zethoven M, et al. Genomic analysis of low-grade serous ovarian carcinoma to identify key drivers and therapeutic vulnerabilities. J Pathol 2021;253:41–54.
33. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609–615.
34. Patch AM, Christie EL, Etemadmoghadam D, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature 2015;521:489–494.
35. Gershenson DM, Sun CC, Westin SN, et al. The genomic landscape of low-grade serous ovarian/peritoneal carcinoma and its impact on clinical outcomes. Gynecol Oncol 2022;165:560–567.
36. Gourley C, Farley J, Provencher DM, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for ovarian and primary peritoneal low-grade serous carcinomas. Int J Gynecol Cancer 2014;24:S9–13.
37. Gershenson DM, Sun CC, Lu KH, et al. Clinical behavior of stage II-IV low--grade serous carcinoma of the ovary. Obstet Gynecol 2006;108:361–368.
38. Amin M, Edge S, Greene F, et al, eds. AJCC Cancer Staging Manual, 8th ed. Cham, Switzerland: Springer Nature Switzerland AG; 2017.
39. Cobb LP, Sun CC, Iyer R, et al. The role of neoadjuvant chemotherapy in the management of low-grade serous carcinoma of the ovary and peritoneum: further evidence of relative chemoresistance. Gynecol Oncol 2020;158:653–658.
40. Gershenson DM, Bodurka DC, Coleman RL, et al. Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. J Clin Oncol 2017;35:1103–1111.
41. Fader AN, Bergstrom J, Jernigan A, et al. Primary cytoreductive surgery and adjuvant hormonal monotherapy in women with advanced low-grade serous ovarian carcinoma: reducing overtreatment without compromising survival? Gynecol Oncol 2017;147:85–91.
42. Gershenson DM, Sun CC, Iyer RB, et al. Hormonal therapy for recurrent low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol 2012;125:661–666.
43. Gershenson DM, Sun CC, Bodurka D, et al. Recurrent low-grade serous ovarian carcinoma is relatively chemoresistant. Gynecol Oncol 2009;114:48–52.
44. Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. Lancet 2022;399:541–553.
45. Monk BJ, Grisham RN, Banerjee S, et al. MILO/ENGOT-ov11: binimetinib versus physician's choice chemotherapy in recurrent or persistent low-grade serous carcinomas of the ovary, fallopian tube, or primary peritoneum. J Clin Oncol 2020;38:3753–3762.
46. U.S. Food & Drug Administration. FDA grants accelerated approval to dabrafenib in combination with trametinib for unresectable or metastatic solid tumors with BRAF V600E mutation. Accessed July 1, 2022. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-dabrafenib-combination-trametinib-unresectable-or-metastatic-solid
47. Tafinlar (capsules) [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2022.
48. Mekinist (tablets) [prescribing information]. East Hanover, New Jersey: Novartis Pharmaceuticals Corporation; 2022.
49. Salama AKS, Li S, Macrae ER, et al. dabrafenib and trametinib in patients with tumors with BRAFV600E mutations: results of the NCI-MATCH trial subprotocol H. J Clin Oncol 2020;38:3895–3904.