Epithelial Ovarian Cancer: Evolution of Management in the Era of Precision Medicine

Stephanie Lheureux, MD, PhD[1,2]; Marsela Braunstein, MSc, PhD [3]; Amit M. Oza, MD (Lon)[4,5]

[1]Clinician Investigator, Bras Drug Development Program; and Staff Medical Oncologist and Gynecology Site Leader, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [2]Assistant Professor, University of Toronto, Toronto, ON, Canada; [3]Scientific Associate, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [4]Chief, Division of Medical Oncology and Hematology; Director, Cancer Clinical Research Unit; and Director, Bras Drug Development Program, Princess Margaret Cancer Centre, University Health Network and Mt. Sinai Health System, Toronto, ON, Canada; [5]Professor of Medicine, University of Toronto, Toronto, ON, Canada.

Corresponding author: Amit M. Oza, MD (Lon), FRCP, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, 610 University Ave, Toronto, ON M5G 2M9, Canada; amit.oza@uhn.ca

DISCLOSURES: Marsela Braunstein has two patents pending for diagnostic gene signatures predictive of anthracycline benefit in breast cancer patients. Stephanie Lheureux reports that she is a principal investigator or coinvestigator on clinical trials in ovarian cancer involving drugs from Roche, AstraZeneca, Merck, Tesaro, and Clovis. Amit M. Oza serves on the steering committee for the following (all of which are noncompensated): AstraZeneca, Clovis Oncology, Merck & Company, and Tesaro Inc.

doi: 10.3322/caac.21559. Available online at cacancerjournal.com

Abstract: Ovarian cancer is the second most common cause of gynecologic cancer death in women around the world. The outcomes are complicated, because the disease is often diagnosed late and composed of several subtypes with distinct biological and molecular properties (even within the same histological subtype), and there is inconsistency in availability of and access to treatment. Upfront treatment largely relies on debulking surgery to no residual disease and platinum-based chemotherapy, with the addition of antiangiogenic agents in patients who have suboptimally debulked and stage IV disease. Major improvement in maintenance therapy has been seen by incorporating inhibitors against poly (ADP-ribose) polymerase (PARP) molecules involved in the DNA damage-repair process, which have been approved in a recurrent setting and recently in a first-line setting among women with *BRCA1/BRCA2* mutations. In recognizing the challenges facing the treatment of ovarian cancer, current investigations are enlaced with deep molecular and cellular profiling. To improve survival in this aggressive disease, access to appropriate evidence-based care is requisite. In concert, realizing individualized precision medicine will require prioritizing clinical trials of innovative treatments and refining predictive biomarkers that will enable selection of patients who would benefit from chemotherapy, targeted agents, or immunotherapy. Together, a coordinated and structured approach will accelerate significant clinical and academic advancements in ovarian cancer and meaningfully change the paradigm of care. **CA Cancer J Clin 2019;69:280-304. © 2019 The Authors. CA A Cancer Journal for Clinicians published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.**

Keywords: clinical trials, gynecologic oncology, medical oncology, molecularly targeted therapies, ovarian neoplasms

Introduction

Outcomes in ovarian cancer depend on timely diagnosis and access to appropriate surgery and systemic therapy, which can be considered indicators of the effectiveness of a country's health care system. Over the past 30 years, all cancers collectively have shown an increase in the 5-year relative survival rate of 20%.[1] For many cancers, the increase in survival has largely been attributed to cutting-edge research and advances in screening, surgery, and treatment methods. Despite these advances, survival rates for ovarian cancer have changed modestly for decades, even in high-resource countries such as the United States and Canada, and remain at only 47% 5 years after diagnosis; by comparison, breast cancer has a 5-year survival rate of 85%.[2,3] Globally, there are 239,000 new cases (3.6% of all cancer cases) and 152,000 deaths annually (4.3% of all cancer deaths), making ovarian cancer the seventh most common cancer, the eighth most common cause of cancer death in women, and the second most common cause of gynecologic cancer death (after cancer of the cervix uteri) (Fig. 1).[4]

The mortality-to-incidence ratio in ovarian cancer is >0.6, and studies from US and UK registries estimate that 1 in 6 women die within the first 90 days of

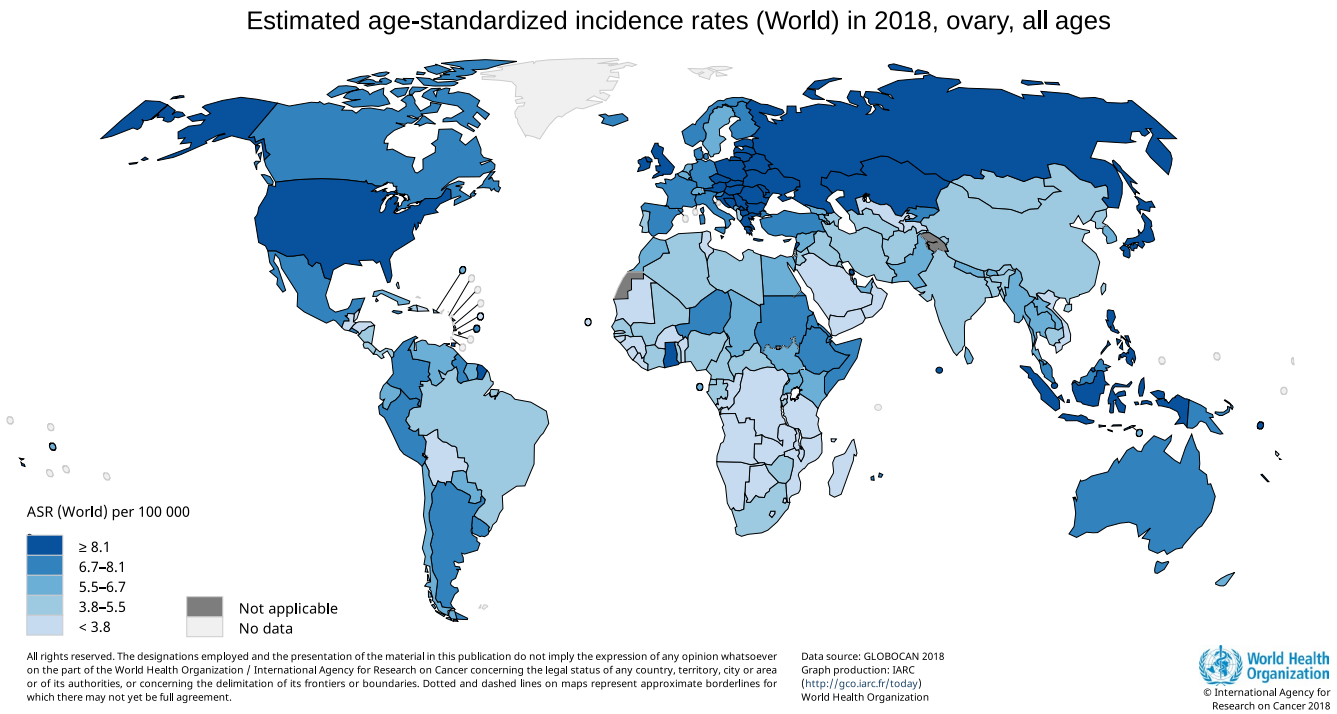


FIGURE 1. Global Incidence of Ovarian Cancer in 2018. ASR indicates age-standardized rate.

diagnosis, reflecting the potential high morbidity and mortality caused by presentation with advanced-stage disease and challenges to effective therapy, which, with appropriate therapy, should be largely avoidable.[5] These somber numbers are due in part to the lack of effective screening options to detect ovarian cancer at an early stage and a lack of early, specific warning signs or symptoms that lead to a diagnostic delay. Although early-stage disease is highly curable (Fig. 2),[6,7] the majority of women present with stage III/IV disease, and over 75% of patients with late-stage ovarian cancer die of their disease.[8] Cytoreductive surgery and combination platinum-taxane chemotherapy have remained the mainstay of therapy for decades.[9] During this time, well-conducted clinical trials have established important principles that guide therapy internationally, shape the direction of clinical research, and benchmark international consensus recommendations, which have been published by the Gynecologic Cancer Inter Group (GCIG).[10-12] These fundamental principles emphasize the importance of surgery by a gynecologic oncologist with reduction of tumor bulk to no residual disease (R0) whenever possible, a pathologic diagnosis defining the subtype of ovarian cancer, and the appropriate systemic treatment based on tumor and patient characteristics with potential access to maintenance therapy. Each of these topics is discussed below, but it is important to ensure that these fundamental principles of good treatment are followed for all women with ovarian cancer.

Improving the survival of patients with ovarian cancer also relies on prevention. Risk factors for ovarian cancer are inherited risk (germline mutations in breast cancer susceptibility genes [*BRCA1*/*BRCA2*] and Lynch syndrome), nulliparity, infertility, endometriosis, obesity, age, and recent evidence implicates an association with perineal talc application.[13] Gravidity and oral contraceptive use are associated with reducing risk, as well as epidemiologic evidence of protection conferred by the regular use of aspirin or nonsteroidal anti-inflammatory agents.[14,15] *BRCA* mutations confer a lifetime risk of 40% to 60% with *BRCA1* and 11% to 27% with *BRCA2* of developing ovarian cancer, and conversely germline *BRCA* mutations can be detected in approximately 14% to 18% of women with ovarian cancer, particularly the high-grade serous ovarian cancer (HGSOC) subtypes, compared with approximately 1% in the general population.[16,17] Therefore, it is important to offer genetic testing to first-degree relatives of women with known *BRCA1*/*BRCA2* mutations. To date, population screening in ovarian cancer has not been effective or validated. However, women at increased risk because of family history and/or *BRCA1*/*BRCA2* mutations are offered risk-reducing surgery, which is usually performed after childbearing years. Efforts are ongoing to evaluate chemoprevention that leverages epidemiologic and biologic evidence supporting the use of aspirin in women at high risk by virtue of a *BRCA1*/*BRCA2* mutation (the STICs and STONEs trial investigating aspirin in the prevention of HGSOC; clinicaltrials.gov identifier NCT03480776).

Biology

Molecular Features of Ovarian Cancer

Epithelial ovarian cancer (EOC) accounts for over 95% of ovarian malignancies.[16,18] Nonepithelial cancers represent

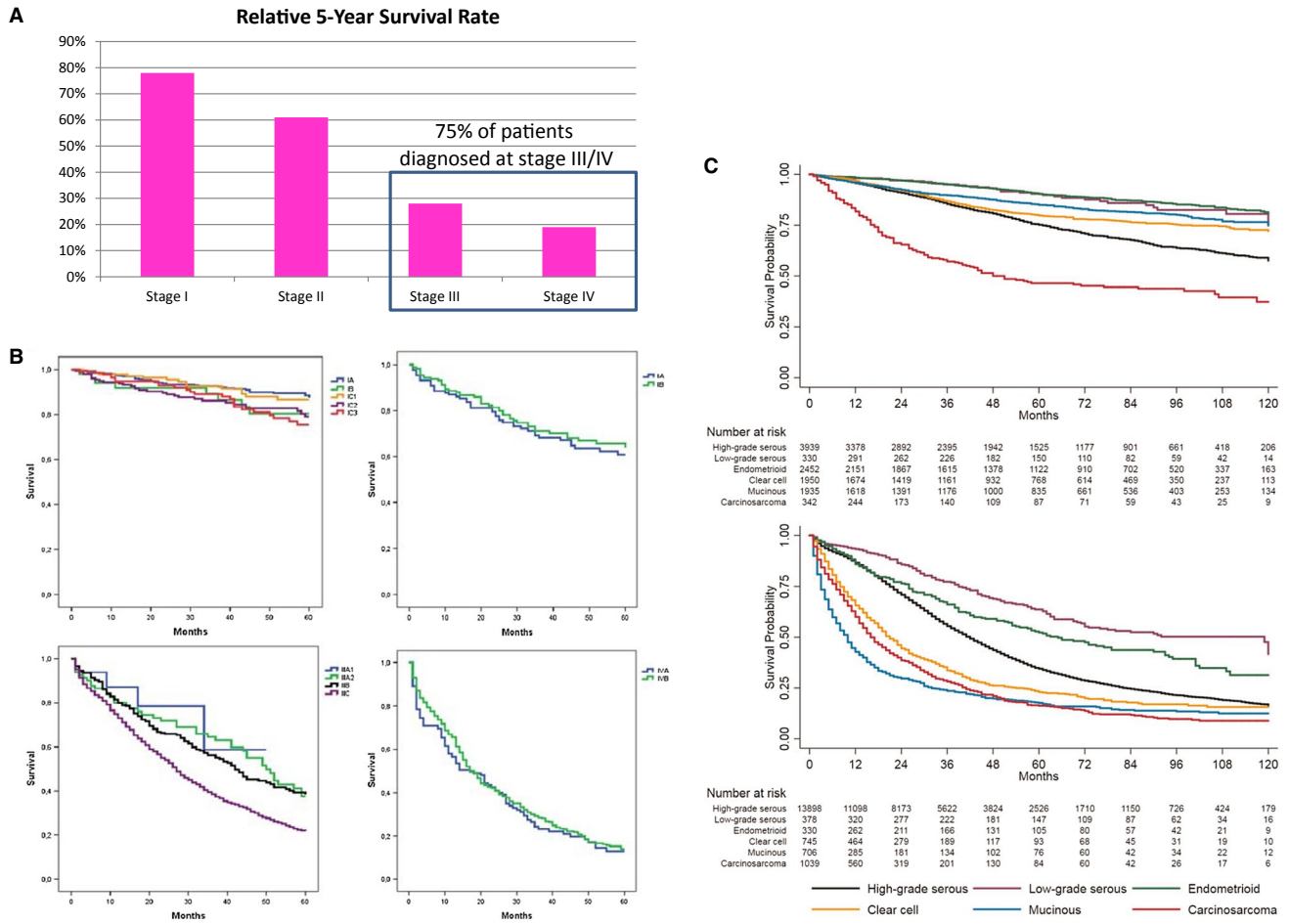


FIGURE 2. Invasive Epithelial Ovarian Cancer 5-Year Survival Rate. (A) The 5-year survival rate in women with invasive epithelial ovarian cancer is illustrated. Data were obtained from American Cancer Society. (B) Kaplan-Meier curves for 2013 Federation of Gynecology and Obstetrics stages are illustrated. Adapted from Rosendhal M, Hogdall CK, Mosgaard BJ. Restaging and survival analysis of 4036 ovarian cancer patients according to the 2013 FIGO classification for ovarian, fallopian tube and primary peritoneal cancer. *Int J Gynecol Cancer.* 2016;26:680-687 with permission from BMJ Publishing Group Ltd.[6] (C) Kaplan-Meier survival curves of invasive epithelial ovarian cancer are illustrated by stage and histotype (2004-2014, Surveillance, Epidemiology, and End Results data), including (*Top*) localized and regional stage disease and (*Bottom*) distant-stage disease. Adapted from Peres LC, Cushing-Haugen KL, Kobel M, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. *J Natl Cancer Inst.* 2019;111:60-68 with permission from Oxford University Press.[7]

up to 5% of ovarian cancers and include predominantly germ cell and sex-cord stromal cancers, as well as rare, small cell carcinoma and ovarian sarcoma.[16] Given the high incidence and mortality of EOC relative to other ovarian cancer histologies, this review will focus on the current management of EOC.

EOC is a heterogeneous disease consisting of tumors with different types of histologies, grades, and molecular and microenvironmental features, all of which contribute to treatment response and outcome. Histologically, EOC is classified into 5 major subtypes: high-grade serous, low-grade serous, clear cell, endometrioid, and mucinous ovarian cancer. All of these subtypes have distinct patterns of presentation and clinical outcomes, as well as responses to therapies. The distinct behaviors are based on intrinsic tumor biology, which affects prognosis and outcome. We are at the cusp of stratified trials with predictive biomarkers—starting with histology as a biomarker and gradually embedding molecular genomics.

High-Grade Serous Ovarian Cancer

HGSOC is the most common histologic subtype, accounting for over 70% of EOCs.[18] Microscopically, HGSOCs show papillary and solid growth, with large mononuclear cells that exhibit pleomorphic nuclei with prominent nucleoli and mitotic activity.[19] The majority of HGSOCs are sporadic, but approximately 15% to 20% of women diagnosed with EOC have a hereditary predisposition to the disease, with mutations in *BRCA1* and *BRCA2*[17] or less common alterations in other homologous recombination genes[20] included in the BROCA-Cancer Risk Panel.[21] BRCA1/BRCA2 proteins are tumor suppressors involved

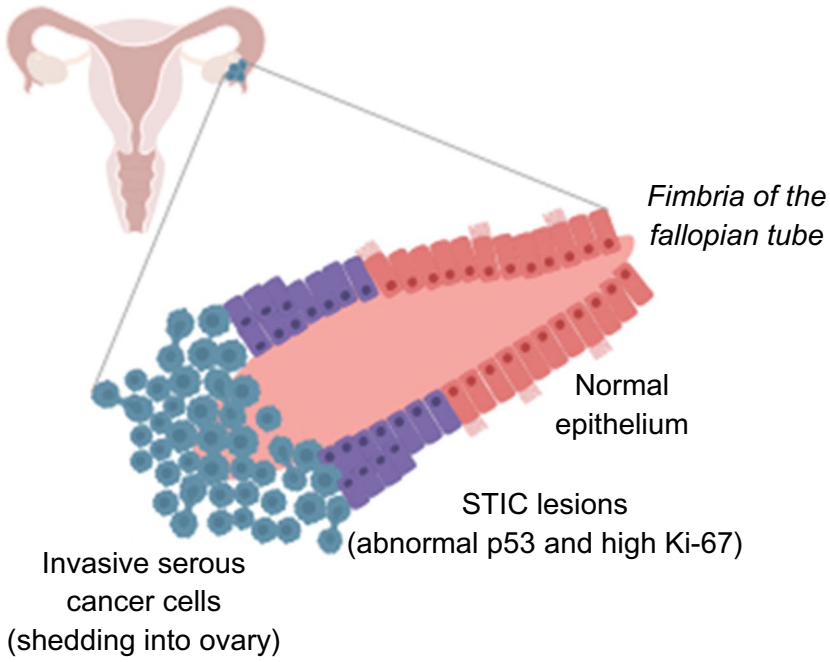


FIGURE 3. High-Grade Serous Ovarian Cancer (HGSOC) Development: From Serous Tubal Intraepithelial Carcinoma (STIC) to High-Grade Serous Cancer.

in maintenance of genomic stability and the DNA damage repair process through homologous recombination. Hallmarks of ovarian cancer in women with genetic susceptibility are: 1) younger age of presentation, often ≥10 years younger than the median age; 2) patient's history of other cancers, such as a breast malignancy; and 3) family history of malignancy, particularly breast and ovarian cancers in female relatives and prostate cancer in male relatives. Importantly, triaging for genetic testing based on family cancer history alone can no longer be recommended,[22] because a significant percentage of women screened positive for *BRCA1*/*BRCA2* mutation, although they did not report any family history of cancer.[17]

Although its name suggests an ovarian tissue of origin, for the most common type of ovarian cancer that is high-grade serous cancer, examination of tissues removed during prophylactic, risk-reducing salpingo-oophorectomy in *BRCA1*/*BRCA2* mutation gene carriers identified the presence of cancer precursor lesions called serous tubal intraepithelial carcinoma (STIC) in the distal end of the fallopian tube, and not in the ovary.[23] Because lesions were commonly observed in fimbria of the fallopian tube, it has been postulated that fallopian tube epithelium is the probable site of tumor initiation (Fig. 3). Precursor STIC lesions have the exact type of tumor protein p53 (*TP53*) mutations as those observed in HGSOC in the fimbrial ends of the fallopian tubes, demonstrating a clonal relationship and a direct evolutionary descent from these cells for most, if not all, HGSOCs (Fig. 3).[24]

HGSOC is characterized by the presence of acquired or inherited mutations in different DNA repair pathways. Mutations in *TP53* are a nearly universal characteristic of HGSOC (97%); this gene encodes a transcription factor that activates genes involved in DNA repair, the cell cycle, and apoptosis upon irreparable DNA damage. DNA double-strand breaks are repaired by the homologous recombination repair pathway, which is an error-free process requiring a homologous DNA template to function. BRCA1, BRCA2, and various other homologous recombination proteins are responsible for the repair of DNA damage that maintains genomic stability and promotes cell survival and replication. Ovarian cancers with *BRCA1* alterations (germline and somatic mutations in 12% of cases, DNA hypermethylation in 11% of cases) and *BRCA2* alterations (germline and somatic mutations in 11% of cases),[20] or other defects in homologous recombination repair genes, such as *EMSY*, *RAD51*, *ATM*, *ATR*, Fanconi anemia, *BARD1*, *BRIP1*, *PALB2*, *RB1*, *NF1*, *CDKN2A*, and the suppression of *BRCA1* transcriptional activation through gene methylation (11%),[25,26] are associated with homologous recombination deficiency (HRD). The finding that HRD contributes to approximately 50% of HGSOCs[20] provided a rationale for using cytotoxic platinum-based chemotherapy and exploring the activity of poly (ADP-ribose) polymerase (PARP) inhibitors in HGSOC, as discussed below (see Targeted Therapies). Indeed, it has been demonstrated that PARP inhibitors are active in HGSOC beyond those with *BRCA* mutations.[27]

TP53 mutations, when combined with *BRCA1/BRCA2* inactivation, also has an enormous impact on chromosomal instability that results in the widespread accumulation of copy number alterations (CNAs), a typical molecular feature of HGSOC. A known CNA involving the amplification and overexpression of the 19q12 genomic region containing *CCNE1*, a gene encoding cell-cycle protein cyclin E1,[28] leads to unscheduled DNA replication, centrosome amplification, and overall chromosomal instability.[26] Other pathways involved in HGSOC include FXM1, which is altered in nearly 84% of HGSOCs, followed by the Rb1 (67%), phosphatidylinositol-4,5-biphosphate 3-kinase (PI3K) (45%), and Notch 1 (22%) pathways, all of which could lead to novel therapeutic opportunities for patients with HGSOC.[20]

Gene expression studies have stratified HGSOC into 4 prognostic subtypes: differentiated, immunoreactive, mesenchymal, and proliferative. The immunoreactive subtype is associated with superior overall survival (OS), and the mesenchymal subtype is associated with the worst OS.[20,29] Although these signatures were refined and validated independently,[30,31] their clinical implementation is challenging, and their potential predictive role is untested. Recently, a genome-sequencing study has revealed 7 CNA signatures in HGSOC that predict OS and the probability of relapse after platinum-based chemotherapy.[32] This clarifies some of the mutational mechanisms that preclude the structural alterations that dominate in HGSOC, and should contribute toward improved clinical-translational study designs.

In addition, ovarian cancer cells overexpress specific proteins at the surface, such as folate receptor and mesothelin (Fig. 4), which have been used as targets for antibody-drug conjugates (ADCs)[33] for cancer cell-specific–directed therapy. This new class of biopharmaceutical drugs has been used for treatment with a high therapeutic index. ADCs are complex molecules composed of a dedicated antibody (targeting the folate receptor[34] or mesothelin[35]) linked to a biologically active cytotoxic drug used for treatment.

Low-Grade Serous Ovarian Cancer

Low-grade serous ovarian cancer (LGSOC) represents about 10% of EOCs.[36] Microscopically, LGSOCs display small papillae with cells of uniform nuclei and various amounts of hyalinized stroma; psammoma bodies may be present.[19] On the basis of the molecular features that are quite distinct from HGSOC, a dualistic model of pathogenesis has been proposed for HGSOCs and LGSOCs. It is hypothesized that LGSOC develops from an atypical, proliferative (borderline) tumor by following a pathway that is independent and molecularly quite distinct from that of HGSOC.[36] Mutations in B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) (38%) or Kirsten rat sarcoma viral oncogene homolog (*KRAS*) (19%), which are mutually exclusive, are the most common aberrations detected in LGSOC.[37] Although they are associated with a constitutively active mitogen-activated protein kinase (MAPK) pathway, mutations in *BRAF* or *KRAS* represent a favorable prognostic factor.[36] An activated MAPK pathway is detected in up to 80% of LGSOCs and in 78% of their putative precursors—serous borderline tumors—suggesting a causative effect[38]; it also provides a rationale for exploring MAPK kinase (MEK) inhibitors in the treatment LGSOC. There is also a relatively high proportion of estrogen receptor-positive/progesterone receptor-positive cancers (Fig. 4),[39] leading to the use of hormonal therapy in this specific ovarian cancer subgroup. In contrast to HGSOC, high CNAs and mutations in *TP53* are rare; LGSOC does not seem to be related to *BRCA1/BRCA2* gene mutations.

Ovarian Clear Cell Carcinoma

Ovarian clear cell carcinoma (OCCC) represents approximately 5% of ovarian cancers in North America and Europe; it is more prevalent in Japan, where it tends to occur in almost 25% of all patients with EOC.[40] Microscopically, OCCCs show combinations of tubules, solid areas, and complex papillae, and cells with prominent nucleoli and clear cytoplasm filled with glycogen. The pathogenesis of OCCC is not well understood; it is thought to be associated with endometriosis, a benign disorder characterized by the ectopic presence of endometrial tissue. Japanese investigators have proposed a mechanism that initiates in endometriotic cysts with the increased iron content that, through iron-induced oxidative stress, causes DNA damage, mutations, and carcinogenesis.[41] Mutations in the SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin-remodeling complex genes, the PI3K/Akt signaling pathway, and the receptor tyrosine kinase (RTK)/Ras signaling pathway are the major molecular aberrations observed in nearly 50%, 40%, and 29% of OCCCs, respectively. Among the SWI/SNF subunits, AT-rich interaction domain 1A (*ARID1A*) is the most frequently mutated gene, detected in 40% to 67% of OCCCs.[42,43] In the PI3K signaling pathway, activating mutations in PIK3 catalytic subunit α (*PIK3CA*) (33%) and loss of phosphatase and tensin homolog (*PTEN*) (37%) are the most common aberrations.[42,44] Activating *PIK3CA* mutations result in abnormal cellular growth, proliferation, survival, and angiogenesis. Interestingly, activation of either the PI3K pathway or the RTK pathway was associated with better OS,[42] although this finding needs to be validated independently. Emerging evidence from an evaluation of 25 OCCC samples for gene expression changes and chromosomal instability suggests that OCCCs may cluster into

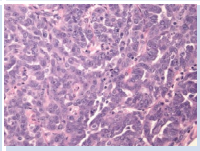
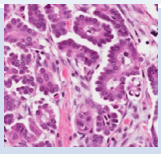
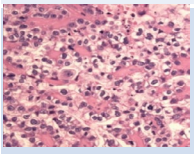
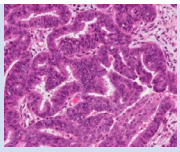
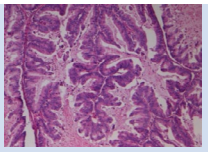
	HGSOC	LGSOC	Clear Cell	Endometrioid	Mucinous
Clinical information	Age, heredity, clinical examination, imaging, staging				
Subtype-specific clinical information	Inherited predisposition in 15-25%	Evolution from borderline tumor	Associated with endometriosis	Synchronous primary ~10% in endometriosis	Exclude GI primary
Pathology					
Molecular features	CNA high *TP53* *BRCA1/2* HRD	CNA low MAPK act. *KRAS* *BRAF*	*ARID1A* PI3K/AKT act. RTK/Ras act. MMR	*PI3KCA* *ARID1A* *KRAS* Wnt/β-catenin act. *PTEN*	*KRAS* *HER2* amplif.
Platinum Chemotherapy	Sensitive	Relatively Resistant	Relatively Resistant	Sensitive	Relatively Resistant
PARP inhibitor	Yes	-	-	Yes for high grade	-
Folate receptor	Yes	-	-	Yes	-
Hormone receptor	30% PR 80% ER	57% PR 87% ER	8% PR 19% ER	67% PR 76% ER	16% PR 20% ER
Hormonal therapy use	-	Yes	-	Yes	-
Mesothelin	50-80%		38%	?	10-30%
MMR deficiency	-	-	Yes	Yes	-
Anti-PD1	?	?	Yes	Yes	?

FIGURE 4. Multidisciplinary Diagnostics of Ovarian Cancer: Broad Molecular Classifiers, Gene Mutations/Pathways, and Histopathological Classification. AKT indicates AKT serine/threonine kinase 1; anti–PD-1, programmed death 1 antibody; ARID1A, AT-rich interaction domain 1A; *BRAF*, B-Raf proto-oncogene, serine/threonine kinase; CNA, copy number alterations; ER, estrogen receptor; GI, gastrointestinal; *HER2* amplif., human epidermal growth factor 2 amplification; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; MMR, mismatch repair; PARP, poly (ADP-ribose) polymerase; PI3K, phosphatidylinositol-4,5-biphosphate 3-kinase; *PI3KCA*, phosphatidylinositol-4,5-biphosphate 3-kinase catalytic subunit α; *TP53*, tumor protein p53; *BRCA*1/2, breast cancer type 1 susceptibility protein 1/2; *PTEN*, phosphatase and tensin homolog. We thank Marjan Rouzbahman, MD, and Patricia Shaw, MD, for providing the H & E images of ovarian cancer.

3 prognostic groups.[45] Compared with HGSOCs, most OCCCs are characterized by considerably fewer CNAs, and mutations in *TP53* and *BRCA1/BRCA2* genes are uncommon.[40] Recently, a pilot study highlighted a unique subset of OCCCs that have microsatellite instability associated with enhanced immunogenicity, which may be susceptible to immunotherapy. This subgroup of OCCCs exhibited a significantly higher number of tumor-infiltrating lymphocytes (TILs), particularly programmed cell death protein 1 (PD-1)-positive TILs, compared with microsatellite-stable OCCCs as well as HGSOCs, and uniformly expressed programmed death-ligand 1 (PD-L1) in tumor cells and/or intraepithelial or peritumoral immune cells.[46]

Endometrioid Ovarian Cancer

Endometrioid cancer of the ovary represents approximately 10% of EOCs. Microscopically, endometrioid ovarian cancers may be cystic or predominantly solid.[19] It is thought that endometrioid and clear cell ovarian cancers arise from similar precursor cells of transformed endometrial origin. In addition, women with Lynch syndrome (hereditary nonpolyposis colorectal cancer) are also at an increased risk of developing endometrioid and clear cell ovarian cancer. Loss of expression of mismatch-repair genes (mutS homolog 6 [*MSH6*], *MSH2*, *MLH1*, and *PMS1* homolog 2, mismatch repair system component [*PMS2*]) is a characteristic of Lynch syndrome and is found in nearly 8% of Lynch syndrome-associated endometrioid and clear cell ovarian cancers.[47] An animal model has shown that deregulated WNT/β-catenin and PI3K/PTEN signaling pathways are pivotal in the development of murine cancers that resemble human endometrioid ovarian cancer[48] and has implicated the distal oviduct as the site of origin because of notable precursor lesions that lead to endometrioid ovarian cancer.[49] Molecular profiling of human endometrioid ovarian cancers revealed that the most prevalent mutations are similar to those observed in OCCC and include *PIK3CA* (40%), *ARID1A* (30%), *KRAS* (30%), *PTEN* (16%), and *PPP2R1A* (16%).[50] Interestingly, mutations in *CTNNB1*, a gene encoding β-catenin, are particularly common, occurring in approximately 50% of low-grade endometrioid ovarian cancers.[50] High-grade endometrioid is a different entity than low-grade endometrioid and shares similarities with HGSOC.

Mucinous Ovarian Cancer

Mucinous ovarian cancer is a rare subtype representing 2.4% of EOCs.[51] Some may arise from borderline tumors.[52] Microscopically, mucinous ovarian cancer is heterogeneous and often is composed of benign, borderline, noninvasive, and invasive components that coexist within the tumor microenvironment.[19] Mucinous ovarian cancer is characterized by the presence of multiocular cysts filled with an opaque, mucoid substance and larger solid regions and papillae that project into the cysts. Evidence suggests that, based on the degree of stromal invasion, mucinous ovarian cancer may be classified into expansile (no invasion) and infiltrative types.[19] In terms of the molecular features, *KRAS* mutations are the most common and are found in 50% of mucinous ovarian cancers. Mutations in the *KRAS* gene usually stimulate cellular growth. Interestingly, amplifications of *HER2* are detected in approximately 18% of mucinous cancers.[53]*TP53* and *BRCA* do not seem to play a prominent role in the carcinogenesis of mucinous ovarian cancers.

Treatment of Ovarian Cancer—Surgery, Systemic Therapy, and Radiation

Treatment of ovarian cancer in the early days was largely based on observations and opportunities and was less structured in an objective, evidence-based manner. To date, there has not been a randomized assessment of the role of debulking surgery versus no surgery in advanced ovarian cancer. Likewise, platinum-based chemotherapy was introduced widely through a phase 2 trial with no randomized control.[54] Similarly, whole-abdominal radiation was explored extensively in many cancers, but without key randomization against a control.[55] However, the treatment of ovarian cancer has matured over the last 50 years to an evidence-based approach that integrates optimal surgery and systemic therapy with ovarian cancer subtype specificity; it has also matured to offer a well-developed algorithm of integrated, multidisciplinary care, albeit with some important unanswered questions. Treatment decisions are based on disease stage and biology, prior therapy, and comorbidities. At present, the only opportunity for cure is at primary treatment, and the efficacy depends on stage and histology. Early-stage disease is curable in 90% of women, even in those with more aggressive histologic subtypes (Fig. 2),[6,7] emphasizing the importance of early detection and timely specialist treatment. Unfortunately, the majority of women are still diagnosed late, challenging the efficacy of surgery, chemotherapy, and targeted agents.

Surgery

Surgery allows for accurate surgical staging, which is documented using the International Federation of Gynecology and Obstetrics (FIGO) (Table 1) and TNM staging classifications,[56-58] and is also therapeutic by debulking disease.

Primary debulking surgery

Surgery has been an important bedrock of therapy for ovarian cancer, although it is important to point out that what have not been definitively demonstrated for advanced ovarian cancer are the exact role and level of benefit of

TABLE 1. 2014 International Federation of Obstetrics and Gynecology Ovarian, Fallopian Tube, and Peritoneal Cancer Staging System and Corresponding TNM

Stage I. Tumor confined to ovaries or fallopian tube(s)
T1-N0-M0
IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1a-N0-M0
IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
T1b-N0-M0
IC: Tumor limited to one or both ovaries or fallopian tubes, with any of the following:
IC1: Surgical spill
T1c1-N0-M0
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
T1c2-N0-M0
IC3: Malignant cells in the ascites or peritoneal washings
T1c3-N0-M0
Stage II. Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
T2-N0-M0
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries
T2a-N0-M0
IIB: Extension to other pelvic intraperitoneal tissues
T2b-N0-M0
Stage III. Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
T1/T2-N1-M0
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):
IIIA1(i): Metastasis up to 10 mm in greatest dimension
IIIA1(ii): Metastasis more than 10 mm in greatest dimension
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
T3a2-N0/N1-M0
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes
T3b-N0/N1-M0
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)
T3c-N0/N1-M0
Stage IV. Distant metastasis excluding peritoneal metastases
Stage IVA: Pleural effusion with positive cytology
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)
Any T, any N, M1

Adapted from Prat J; FIGO Committee on Gynecologic Oncology. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. J Gynecol Oncol. 2015;26:87-89. doi:10.3802/jgo.2015.26.2.87[58]

debulking per se. Sequential clinical trials have established the significant impact of surgery undertaken by a qualified gynecologic oncologist with the goal of achieving optimal debulking with no residual disease (R0).[59] Surgical staging by a qualified gynecologic oncologist is essential and involves laparotomy through a midline incision, with full exploration of the abdomen and pelvis, followed by at least total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy. The recent LION study (Lymphadenectomy In Ovarian Neoplasms) showed that systematic pelvic and paraaortic lymphadenectomy of clinical negative lymph nodes in

patients with advanced EOC and complete resection may be omitted to reduce postoperative morbidity and mortality.[60] All areas of disease should be resected, ideally with no macroscopic residual disease. Du Bois et al clearly demonstrated the impact of residual disease on outcome and showed that macroscopic residual disease after debulking is associated with inferior OS.[59] Riester et al have investigated biologic and genomic characteristics and developed predictive signatures to establish whether such features could be predictive of making disease more or less debulkable as of inferior outcome.[61] Pathways significantly associated with suboptimal debulking included migration/invasion, angiogenesis, metastasis, and activation of tumor-associated fibroblasts. A recent study investigated the molecular subtypes of HGSOC and identified 5 subtypes associated with surgical outcome; in particular, a mesenchymal tumor molecular subtype was correlated with suboptimal debulking surgery.[62]

It is imperative to consider disease biology when evaluating choice of therapy as well as the sequence of surgery/systemic therapy. Surgery clearly has a major impact on reducing tumor burden, and this is important when systemic therapy is less effective, as in low-grade serous, clear cell, and mucinous carcinoma subtypes.[63] Evaluating and incorporating biologic predictive biomarkers for R0 debulking remains an active area of development.

Interval debulking surgery

Surgery that is deferred until after chemotherapy is commenced because upfront surgery is not possible due to extensive disease, the clinical condition of the patient, or potential logistic reasons is termed *interval debulking surgery* (IDS). The therapeutic intent is the complete resection of residual disease and is generally considered after 3 cycles of chemotherapy. Two prospective, randomized clinical trials have evaluated primary debulking surgery (PDS) versus IDS[64,65] and demonstrated no survival disadvantage in the patients who were randomized to IDS. Although the criticisms of these studies include potential recruitment bias, with a preponderance of patients at an advanced stage, the low frequency of R0 resections and surgical effort (time of procedure), the use of neoadjuvant chemotherapy (NACT) has increased in practice. However, the debate between PDS or IDS continues, with centers leaning one way or another; an additional randomized trial of neoadjuvant chemotherapy versus PDS in patients with advanced EOC is ongoing in select centers with R0 rates ≥50% (Trial on Radical Upfront Surgery in Advanced Ovarian Cancer [TRUST]; NCT02828618). Optimizing assessment of the feasibility of R0 resection at presentation using imaging and, more recently, laparoscopy is becoming increasingly routine and may refine a clinical algorithm for primary management.[66,67] The additional benefit of accurate surgical staging and the availability of sufficient tissue for accurate pathologic assessment are important considerations.

Second-look surgery

Second-look surgery to restage EOC, including the excision of residual disease, was a common practice until a randomized clinical trial demonstrated no benefit to patients, and it has now largely been abandoned.[68]

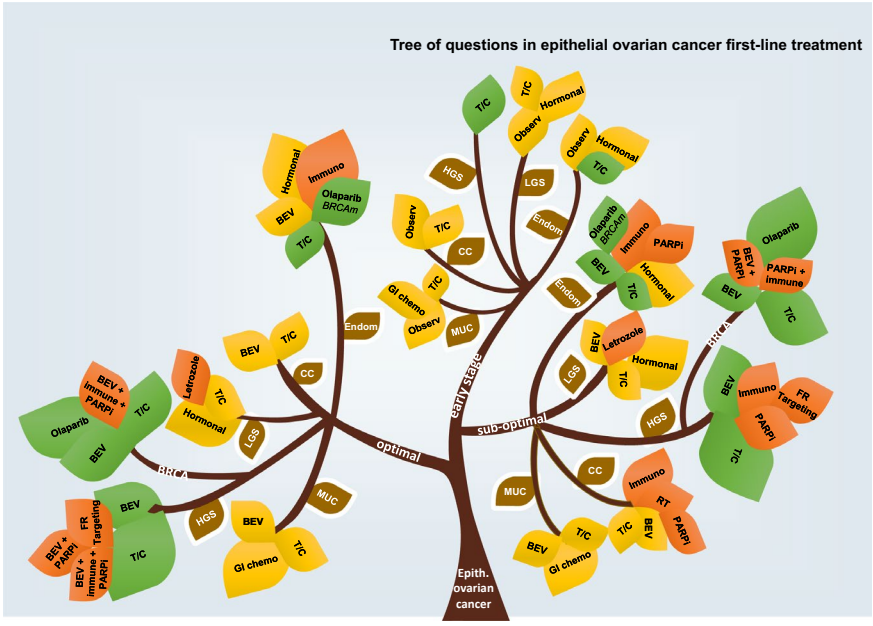
Secondary (and beyond) debulking surgery for recurrent EOC

The randomized Desktop III/ENGOT OV20 trial conducted in patients with relapsed, platinum-sensitive EOC has shown a 5-month improvement in progression-free survival (PFS) from 14 to 19.6 months for women who underwent secondary debulking compared with controls who did not undergo surgery (hazard ratio, 0.66; 95% CI, 0.52-0.83), with continuation of benefit to the time to first subsequent treatment. The magnitude of benefit was greater with R0 resection. Findings reported in the Gynecologic Oncology Group (GOG) 0213 study—a double-randomized clinical trial evaluating surgery and the addition of bevacizumab in patients with platinum-sensitive recurrence—showed that secondary cytoreduction was not associated with improved OS compared with no surgery in this population.[69] Differences in the magnitude of findings may be because of differences in patient selection between Study Comparing Tumor Debulking Surgery Versus Chemotherapy Alone in Recurrent Platinum-Sensitive Ovarian Cancer (DESKTOP III) and GOG-0213 (given use of the German Gynecological Oncology Group [AGO] score as inclusion criteria in the Desktop trial), differences in upfront debulking or abrogation of the benefit of surgery by adding bevacizumab, and the difference in the primary objective. Secondary debulking surgery should be considered for selected patients with platinum-sensitive recurrence where R0 is achievable.

Systemic Therapy

Systemic therapy has evolved from single to combination chemotherapy approaches that now incorporate the addition of targeted therapy when appropriate. As newer agents arise, they will reshape first-line therapy (see below). Standard practice now takes into account histology, stage, genomic profile, and residual disease. Contemporary stratified trials are evaluating combinations of chemotherapy, targeted agents, and immunotherapy to further refine treatment precision tailored to individual, patient-based, predictive factors. The sections below summarize key evidence for first-line therapies and touch upon recurrent-disease therapy related to these modalities, with a nuanced tree of

A



B

	Epithelial ovarian cancer subtype	Approved treatment with Level I evidence	NCCN guidelines	Treatments in academic development
Incomplete surgery	HGSOC	Carboplatin/Paclitaxel Bevacizumab	Platinum-based chemo Bevacizumab concurrent and maintenance	PARP inhibitor Immunotherapy Folate receptor targeting
	HGSOC with BRCA1/2m	Carboplatin/Paclitaxel Bevacizumab Olaparib	Platinum-based chemo Bevacizumab concurrent and maintenance or Olaparib maintenance	Bevacizumab + PARP inhibitor Immunotherapy + PARP inhibitor
	LGSOC		Chemotherapy Hormonal therapy Bevacizumab	Letrozole *vs.* letrozole/chemo
	Clear cell		Platinum-based chemo Bevacizumab	Immunotherapy Radiation PARP inhibitor
	Endometrioid OC	Carboplatin/Paclitaxel Bevacizumab High grade endometrioid BRCAm: olaparib	Grade 1: Chemotherapy or Hormonal therapy Grade 2/3: Platinum-based chemo Bevacizumab or Olaparib maitenance for BRCA1/2m	Immunotherapy PARP inhibitor
	Mucinous		Platinum based Chemo + Bevacizumab or 5-FU+leucovorin+oxaliplatin+/-bevacizumab or capecitabine+oxaliplatin +/- bevacizumab	
Complete surgery No residual disease	HGSOC	Carboplatin/Paclitaxel Bevacizumab	Platinum-based chemo Bevacizumab concurrent and maintenance	Bevacizumab + PARP inhibitor Bevacizumab + PARP inhibitor + Immunotherapy Folate receptor targeting
	HGSOC with BRCA1/2m	Carboplatin/Paclitaxel Bevacizumab Olaparib	Platinum-based chemo Bevacizumab concurrent and maintenance or Olaparib maintenance	Bevacizumab + PARP inhibitor + Immunotherapy
	LGSOC		Chemotherapy Hormonal therapy	Letrozole *vs.* letrozole/chemo
	Clear cell		Platinum-based chemo Bevacizumab	
	Endometrioid OC	Carboplatin/Paclitaxel High grade endometrioid BRCAm: olaparib	Grade 1: Chemotherapy or Hormonal therapy Grade 2/3: Platinum-based chemo Bevacizumab or Olaparib maitenance for BRCA1/2 m	Immunotherapy
	Mucinous		Platinum based Chemo +/- Bevacizumab or 5-FU+leucovorin+oxaliplatin+/-bevacizumab or capecitabine+oxaliplatin +/- bevacizumab	
Early stage	HGSOC	Carboplatin/Paclitaxel	Platinum-based chemo	
	LGSOC		Stage IA/IB: Observe Stage IC: Observe or Platinum-based chemo or Hormone therapy	
	Clear cell		Stage IA: platinum-based chemo or Observe Stage IB/IC: Platinum-based chemo	
	Endometrioid OC	Carboplatin/Paclitaxel	Grade 1, Stage IA/IB: Observe Grade 1, Stage IC: Observe or Platinum-based chemo or Hormone therapy	
	Mucinous		Stage IA/IB: Observe Stage IC: Observe or Platinum-based chemo or 5- FU+leucovorin+oxalplatin or Capecitabine+oxalplatin	

FIGURE 5. (A) Tree of Questions in Epithelial Ovarian Cancer First-Line Treatment. If NCCN guidelines match approved treatment with Level I evidence, then the treatments are shown in green color only; if the guidelines are not based on Level I evidence, the treatments are shown in yellow color. Orange indicates treatments in academic development. (B) Epithelial Ovarian Subtypes. +/- indicates with or without; BEV, bevacizumab; BRCA1/2m, mutation of the *BRCA1/BRCA2* genes; CC, clear cell; chemo, chemotherapy; Endom, endometrioid; EOC, epithelial ovarian cancer; FR, folate receptor; GI, gastrointestinal; HGS, high-grade serous; HGSOC, high-grade serous ovarian cancer; Immuno, immunotherapy; IP, intraperitoneal; IV, intravenous; LGS, low-grade serous; LGSOC, low-grade serous ovarian cancer; MUC, mucinous; NCCN, National Comprehensive Cancer Network; Observ, observation; OC, ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum-free interval; R0, reduction of tumor bulk with no residual disease; RT, radiotherapy; T/C, paclitaxel/carboplatin.

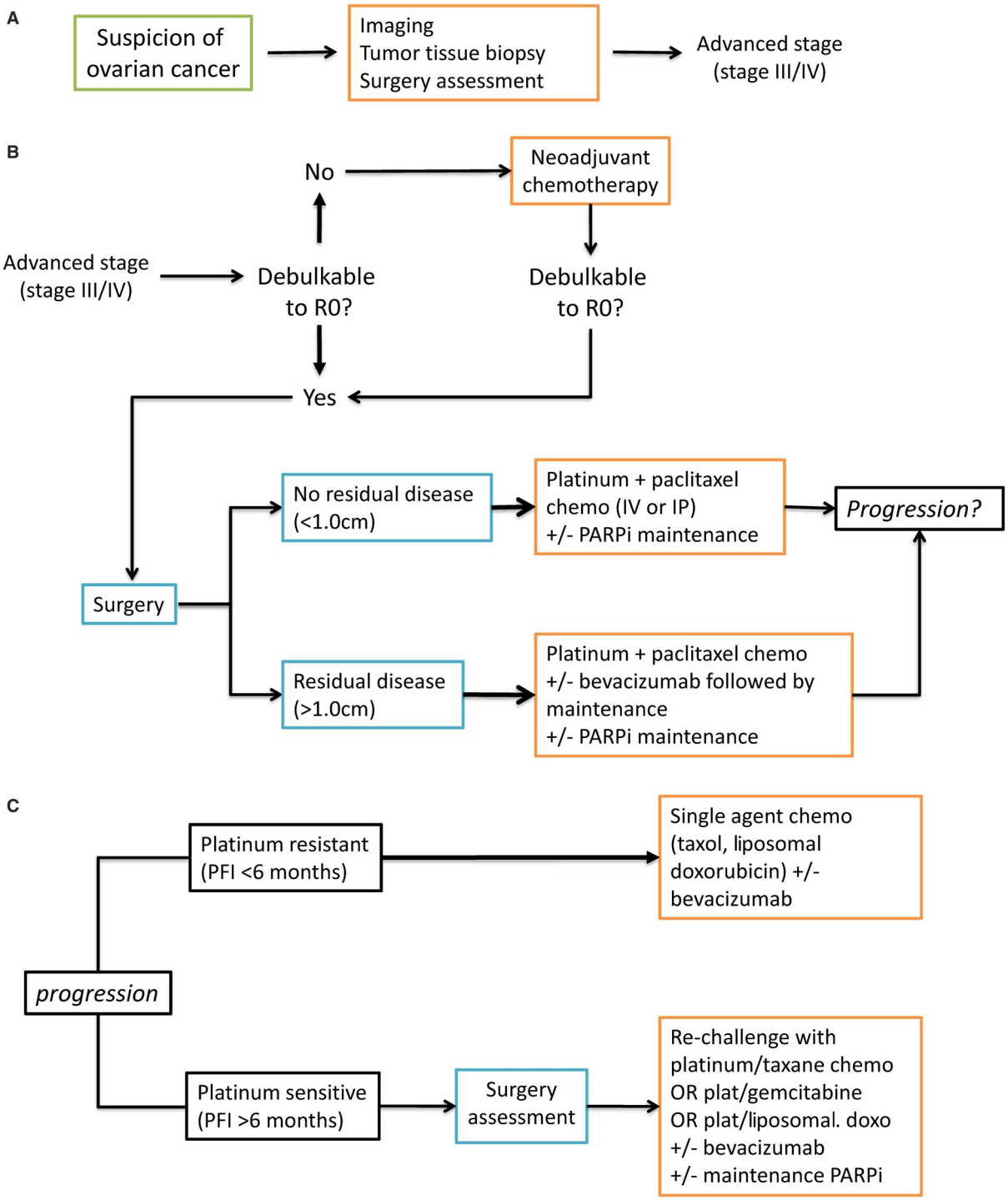


FIGURE 6. Advanced Ovarian Cancer Treatment Guidelines. (A) Diagnosis, (B) frontline management, and (C) treatment upon recurrence are illustrated. +/- indicates with or without; chemo, chemotherapy; doxo, doxorubicin; IP, intraperitoneal; IV, intravenous; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum-free interval; plat, platinum; R0, reduction of tumor bulk with no residual disease.

thought-provoking questions in the management of ovarian cancer (Fig. 5) and practical guidelines (Fig. 6) for the reader.[70]

Chemotherapy

The early days of chemotherapy in ovarian cancer explored alkylating agent chemotherapy with evidence of benefit, but important milestones were the introduction of platinum in 1976,[54] cisplatin-based combination therapy during 1984 through 1986,[71-73] and paclitaxel in 1993.[74-76] These milestones dramatically improved outcome in women with advanced disease, and their combined use has been refined over the past 20 to 30 years through clinical trial participation as an international community effort. Patients with

EOC (particularly high-grade serous disease) respond very well to initial chemotherapy, with responses noted in approximately 80% of patients, but, over time, many of these patients will recur. There have been several randomized clinical trials that have addressed questions of dose, dose density, choice of platinum and/or taxane, schedule, mode of administration (intravenous [IV], intraperitoneal [IP]), role of hyperthermia, and additional chemotherapeutic agents. In brief, these studies demonstrate the following:

- Carboplatin is as effective as cisplatin and is better tolerated.[77]
- Dose is important, and the target dose is an area under the concentration-time curve (AUC) of 5 (AUC 5) to AUC 6 for carboplatin or 75 mg/m^2 cisplatin.[78]
- Higher doses of cisplatin or carboplatin above the target do not improve long-term outcome.[79]
- Giving carboplatin weekly instead of every 3 weeks is well tolerated.[80,81]
- More than 2 chemotherapy drugs in combination do not improve outcome. Several randomized trials of adding a third drug to doublet chemotherapy, either as sequential doublets or triplets, have shown there is no additional benefit to adding a third drug (International Collaborative Ovarian Neoplasm 5 [ICON5] trial)[82]; doublet chemotherapy is optimal.
- Weekly dose-dense chemotherapy in addition to carboplatin in a Japanese study with a carboplatin dose of AUC 6 with paclitaxel 80 mg/m^2 on days 1, 8, and 15 improved PFS and OS.[80,81] Other studies (the Multicenter Italian Trials in Ovarian Cancer [MITO]-7 trial; NCT00660842; weekly carboplatin at AUC 2 with weekly paclitaxel 60 mg/m^2, lower dose intensity)[83] or ICON8 (NCT01654146)[84] did not show this benefit, leading to the possibility that pharmacogenomic differences between Japanese and white patients may affect response to treatment.
- IP chemotherapy has been introduced because ovarian cancer spread is initially typically limited to the intra-abdominal cavity; thus, cellular exposure directly to IP chemotherapy has likely advantages in direct diffusion and lethality of chemotherapy in cancer cells. The biologic, molecular, physical, and mathematical basis of this would suggest that, for an IP therapy to be effective, it should be given when the residual postsurgical disease volume is small (<1 cm) and ideally microscopic at individual sites. Several randomized trials have demonstrated significant improvements in PFS and OS with the administration of IP therapy.[85,86] These IP trial designs varied, as many allowed additional dose/intensity in the IP arm, which has impeded conclusions on IP or IV administration, dose for dose. The randomized trials that have shown benefit from IP chemotherapy used cisplatin at a dose of 100 mg/m^2, which improved OS but was associated with significant toxicity.[87] Substitution of carboplatin with cisplatin improves tolerability, and, in an effort to improve tolerability, the dose of IP cisplatin has been lowered to 75 mg/m^2; it is unclear whether the efficacy advantage is retained with the reduced dosage.[86] However, as an aggregate, and through meta-analysis, evidence would still suggest it is reasonable to consider IP therapy in optimally debulked patients.[88] PFS outcome from the GOG 252 trial (NCT00951496), in which all patients were treated with bevacizumab 15 mg/kg IV on cycles 2 through 22 and were randomized to receive 6 cycles of 1) IV carboplatin AUC 6 and IV weekly paclitaxel 80 mg/m^2 (IV arm), or 2) IP carboplatin AUC 6 and IV weekly paclitaxel 80 mg/m^2 (IP-carboplatin arm), or 3) IV paclitaxel 135 mg/m^2, IP cisplatin 75 mg/m^2, IP paclitaxel 60 mg/m^2 (IP-cis arm), suggests no difference between the 3 arms and no advantage to IP therapy trial when bevacizumab is incorporated.[89] Survival outcome from the Intraperitoneal Therapy for Ovarian Cancer With Carboplatin (iPocc) study (NCT01506856), comparing IV carboplatin and IV paclitaxel administered weekly with IP carboplatin and IV paclitaxel administered weekly, may provide additional data related to IP therapies.
- The hyperthermic IP chemotherapy (HIPEC) technique introduces instillation of heated chemotherapy into the abdominal cavity at the time of surgery. Two randomized clinical trials have recently investigated the feasibility and benefit from adding a cycle of IP therapy during surgery.[90,91] A 245-patient, multicenter, randomized, phase 3 trial demonstrated that HIPEC was feasible and tolerable.[90] Specifically, there was a significant improvement in outcome among women who underwent cytoreductive surgery with HIPEC (the surgery-plus-HIPEC group) (hazard ratio for disease recurrence or death, 0.66; 95% CI, 0.50-0.87; $P = .003$). The median recurrence-free survival was 10.7 months in the surgery group and 14.2 months in the surgery-plus-HIPEC group. The median OS was 33.9 months in the surgery group and 45.7 months in the surgery-plus-HIPEC group.[90] Although debate remains regarding the use of HIPEC,[92] more research on this technology seems warranted and might be considered in the frontline setting for ovarian cancer.
- Treatment after recurrence follows a complex algorithm based on initial benefit, judged by the platinum-free interval from the last dose of platinum-based chemotherapy, which has used a period of 6 months as a guide. Recurrence after an interval of over 6 months

suggests platinum sensitivity and, as such, rechallenge with doublet platinum-based chemotherapy is proposed. Shorter intervals create the opportunity to incorporate other nonplatinum agents, such as liposomal doxorubicin, weekly paclitaxel, and gemcitabine; however, as single agents, these have only modest activity that diminishes with repeated lines of therapy. This has fueled the search for novel targeted and experimental agents, with several promising agents in early-phase and late-phase trials.

Our understanding continues to evolve to this day. The GCIG has hosted consensus meetings, most recently in Tokyo 2016, to set benchmark standards that can be adopted for clinical trial design.[10] The current consensus standard for chemotherapy is a combination of carboplatin and paclitaxel, both administered every 3 weeks, or carboplatin every 3 weeks and paclitaxel weekly, in a dose-dense manner. Women who are optimally debulked can also be treated with IP chemotherapy. Major advances in efficacy are now being seen with the addition of targeted therapy to chemotherapy. There remains an active debate about IP and dose-dense chemotherapy, with European recommendations leaning away from these.[93,94] However, in appropriate settings, both can be considered with a balanced evaluation of the risks and benefits. The community standard is to offer a total of 6 cycles of IV paclitaxel and carboplatin, on a 3-week cycle. The regimen is generally well tolerated but is associated with side effects, including nausea, vomiting, muscle pains, myelosuppression, peripheral neuropathy, and alopecia. Some of these can be effectively mitigated by appropriate supportive measures, including antiemetics, but careful attention has to be taken in managing patients on therapy.

Recurrent disease is common in ovarian cancer, and the timing from prior therapy or platinum therapy is a key concept that has shaped decision making on the choice of subsequent therapy. The GCIG definition of platinum-free interval is simple and practical but not without limitations, because it does not take into account how progression is defined (cancer antigen 125 [CA 125], radiological and/or symptomatic recurrence) or the impact of maintenance therapy on the subsequent platinum-free interval and disease biology.[95] Nonetheless, the categorization is a useful guideline, which is likely to evolve over time as our thinking evolves to view ovarian cancer as a chronic disease in which each relapse might be defined and managed differently with available options.

Targeted Therapy

Targeted agents have been gradually introduced into clinical trials for the treatment of recurrent disease to gauge activity as single agents, followed by combination treatments, before being introduced into front-line therapy. Over the past decade, there has been significant progress with improved activity and nonoverlapping toxicity from the introduction of concurrent bevacizumab and sequential bevacizumab and PARP inhibitors. Both of these agents have demonstrated significant improvements in some women undergoing first-line therapy and can be selected on the basis of either risk or genomics.

Bevacizumab

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Early studies demonstrated improved PFS and OS in many cancers, particularly colorectal, lung, and renal cancers. Ovarian cancer is a disease that has many of the hallmark features of excessive VEGF—inferior outcome associated with angiogenesis/microvessel density, ascites (capillary leakiness because of VEGF overproduction), and immediate benefit from the reduction of ascites with bevacizumab, both as a single agent as well as in combinations. Pivotal studies that assessed the role of concurrent and maintenance bevacizumab were GOG-0218 (primary endpoint, PFS) and ICON7 (primary endpoints, PFS and OS).[96,97] Both trials demonstrated significant improvements in PFS overall in the intent-to-treat populations with concurrent and maintenance bevacizumab. In the ICON 7 trial, the prespecified high-risk group (inoperable stage III, unable to be debulked to <1 cm maximum disease, and stage IV disease) showed the greatest benefit from bevacizumab. This patient group had a significant improvement in median OS of 9 months with the addition of bevacizumab.[98] Similarly, the GOG-0218 study suggested that patients with FIGO stage IV disease may derive a survival advantage from bevacizumab when administered with and after front-line chemotherapy.[99] The 2 studies examined different doses and durations of bevacizumab; the results suggest that the effect is somewhat independent of dose, with 7.5 mg/kg demonstrating similar benefit to 15 mg/kg. However, continued therapy with bevacizumab may have additional benefit, because findings from the ROSiA trial suggest that longer therapy is better.[100] We are awaiting data from the confirmatory AGO trial (BOOST study; NCT01462890). Recently, the randomized, phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17 also suggested that receiving bevacizumab at recurrence after receiving it as first-line therapy still offers an additional improvement in PFS.[101]

Other antiangiogenics have been assessed in ovarian cancer, all with modest-to-moderate demonstrations of activity in PFS in recurrent and first-line settings. These include pazopanib, sorafenib, sunitinib, cediranib, VEGF trap (aflibercept), and AMG386. However, none have been

adopted in routine clinical practice because of issues of toxicity and/or the cost of licensing. Currently, bevacizumab is the only antiangiogenic in routine clinical practice.

Bevacizumab has also become a key agent in the management of patients with recurrent disease. Studies have demonstrated a significant improvement in PFS among women with platinum-sensitive, recurrent disease when added to combination chemotherapy with either carboplatin and gemcitabine (a study of Carboplatin and Gemcitabine Plus Bevacizumab in Patients With Ovary, Peritoneal, or Fallopian Tube Carcinoma [OCEANS])[102] or carboplatin and paclitaxel (GOG-0213 trial).[103] In addition, Pujade-Lauraine et al demonstrated a significant PFS improvement for women with platinum-resistant recurrence when bevacizumab was added to physician's-choice chemotherapy of weekly paclitaxel, liposomal doxorubicin, or topotecan.[104] These trials and others have made bevacizumab an important therapeutic agent in conjunction with chemotherapy and as a single agent for maintenance therapy in women with primary or recurrent disease. The additional toxicities related to bevacizumab need to be factored into the decision making, particularly those relating to delayed wound healing, hypertension, and propensity for bowel perforation or fistulization in the setting of bulky disease in close proximity to bowel. However, the close attention to patient selection and treatment has allowed this agent to become a major part of the standard of care in women with ovarian cancer.

The recurrent ovarian cancer treatment paradigm continues to push boundaries, as antiangiogenic agents currently are being investigated in combination with PARP inhibitors. Several ongoing trials are assessing this combination 1) as first-line maintenance therapy in the Platine, Avastin, and Olaparib in First-Line (PAOLA-1) trial (NCT02477644); 2) at the time of platinum-sensitive recurrence as treatment in the NRG-GY004 trial (NCT02446600; completed to accrual) or as maintenance in the ICON-9 trial (NCT03278717); and 3) at the time of platinum-resistant recurrence in the NRG-GY005 trial (NCT02502266). Efforts are ongoing to identify biomarkers of response or toxicities.[105]

Poly (ADP-ribose) polymerase inhibitors

PARP enzymes, particularly PARP-1 and PARP-2, play a critical role in the repair of DNA single-strand breaks. Inhibition of PARP leads to an accumulation of single-strand breaks, causing the collapse of replication forks and the accumulation of double-strand breaks, which are commonly repaired by homologous recombination enzymes.[106] Ovarian cancers with *BRCA1*/*BRCA2* mutations or other HRDs are particularly sensitive to PARP inhibitors because of the accumulation of unrepaired DNA breaks that lead to cellular death.[107] This has been referred to as "synthetic lethality" to describe the phenomenon of cell death caused by mutation or lack of function of 2 or more genes. PARP inhibitors also interfere with the NHEJ (nonhomologous end-joining) DNA-repair pathway, which is upregulated when homologous recombination pathways are deficient,[106] or cause trapping of PARP-1 and PARP-2 at the level of DNA breaks, resulting in the obstruction of DNA replication forks.[108]

Germline or somatic mutations in homologous recombination genes are usually associated with an increased response to platinum-based chemotherapy, a longer disease-free interval, and a better prognosis.[109] However, some HGSOCs show similar clinical behavior without identifiable mutations in *BRCA1*/*BRCA2* or other homologous recombination genes.[110-112] Several PARP inhibitors (olaparib, niraparib, and rucaparib) have been investigated and are now available as treatment or maintenance therapy for patients with HGSOC.[113-119] PARP inhibitors have also shown promising results in other solid tumors harboring *BRCA1*/*BRCA2* mutations, such as HER-2–negative breast cancer, metastatic pancreatic cancer, and castration-resistant prostate cancer.[113,120,121] Three PARP inhibitors currently have regulatory approval in the United States from the US Food and Drug Administration for use in ovarian cancer as maintenance therapy after response to platinum-based therapy at the time of recurrence; olaparib and rucaparib are also being approved for the treatment of *BRCA1*/*BRCA2* mutation-related disease. The trials,[115,116,119,122] which are summarized in Table 2, demonstrate a quite striking and consistent improvement in PFS using maintenance therapy with the addition of PARP inhibitors as switch maintenance after a response to platinum-based chemotherapy for platinum-sensitive recurrence, with a range of efficacy on a continuum from patients with mutated *BRCA1*/*BRCA2*, to those with HRD (defined by a Myriad or Foundation Medicine loss-of-heterozygosity assay), to those with no HRD. Importantly, because all patients benefited, the current functional biomarker of choice for the introduction of switch maintenance is the demonstration of a response to platinum-based chemotherapy. The concurrent use of chemotherapy and olaparib is limited by overlapping hematologic toxicities, which necessitate a dose reduction for both platinum and olaparib. The randomized trial for platinum-sensitive ovarian cancer revealed that the key benefit in PFS was driven by maintenance therapy.[123] Efforts are underway to investigate whether patients who do not achieve a response also benefit, because subgroup analyses do demonstrate a benefit in patients who have stable disease[124] and also show

TABLE 2. Landmark Trials Supporting the Use of PARP Inhibitors in the Treatment of Ovarian Cancer

THERAPY	CLINICAL PHASE	PATIENT POPULATION	BENEFIT	CONCLUSION
Olaparib maintenance	Phase 3	In first line for newly diagnosed, advanced ovarian cancer with *BRCA1*, *BRCA2* (or both) mutation after complete or partial clinical response to platinum-based chemotherapy	The risk of disease progression or death was 70% lower with olaparib than with placebo at median follow up of 41 months 60% vs. 27% (hazard ratio for disease progression or death, 0.30; 95 % confidence interval, 0.23 to 0.41; $P < .001$)	The use of maintenance therapy with olaparib provided a substantial benefit with regard to progression-free survival among women with newly diagnosed advanced ovarian cancer and a *BRCA1/2* mutation, with a 70% lower risk of disease progression or death with olaparib than with placebo Moore et al. 2018[128]
Olaparib maintenance	Phase 2	Platinum-sensitive, relapsed ovarian cancer	PFS was significantly longer with olaparib than with placebo: 8.4 vs 4.8 mo from randomization to completion of chemotherapy	Olaparib as maintenance significantly improved PFS among patients with platinum-sensitive, relapsed, high-grade serous ovarian cancer Interim analysis showed no overall survival benefit Ledermann 2012[116]
Olaparib (tablets) maintenance	Phase 3	Platinum-sensitive, relapsed, high-grade serous ovarian cancer with a *BRCA1* or *BRCA2* mutation	Median PFS was significantly longer with olaparib than with placebo: 19.1 vs 5.5 mo	Olaparib tablet maintenance significantly improved PFS with no detrimental effect on quality of life in patients with platinum-sensitive, relapsed ovarian cancer and a *BRCA1/BRCA2* mutation Pujade-Lauraine 2017[115]
Niraparib maintenance	Phase 3	Platinum-sensitive, recurrent ovarian cancer (categorized by the presence or absence of germline *BRCA* [g*BRCA*] mutation)	Median duration of PFS was significantly longer with niraparib than placebo: 21.0 vs 5.5 mo in patients with g*BRCA* 12.9 vs 3.8 mo in patients with non-g*BRCA*	Among patients with platinum-sensitive, recurrent ovarian cancer, the median duration of PFS was significantly longer among those receiving niraparib than among those receiving placebo, regardless of the presence or absence of g*BRCA* mutations Mirza 2016[119]
Rucaparib maintenance	Phase 3	Platinum-sensitive, recurrent, high-grade ovarian cancer	Median PFS was significantly longer with rucaparib than with placebo in: Patients with *BRCA*-mutant carcinoma: 16.6 vs 5.4 mo Patients with HRD carcinoma: 13.6 vs 5.4 mo The intention-to-treat population: 10.8 vs 5.4 mo	Across all primary analysis groups, rucaparib significantly improved PFS survival in patients with platinum-sensitive ovarian cancer who had achieved a response to platinum-based chemotherapy Coleman 2017[122]

Abbreviations: HRD, homologous recombination deficiency; PARP, poly (ADP-ribose) polymerase; PFS, progression-free survival.

evidence of additional antitumor activity in patients who have a partial response after platinum-based chemotherapy.[125] Careful evaluation of toxicity and quality of life has demonstrated good maintenance of quality of life with all 3 PARP inhibitors and delay or avoidance of symptoms related to recurrence or therapy for recurrence.[126,127]

These investigational activities have led to 2 first-line switch-maintenance trials in women who were selected on the basis of mutated *BRCA1*/*BRCA2* genes (Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy [SOLO1]; NCT01844986) or were unselected (a Study of Niraparib Maintenance Treatment in Patients With Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy [PRIMA]; NCT02655016). SOLO1 demonstrated a

significant improvement in PFS over placebo when olaparib was used as switch maintenance after first-line chemotherapy in *BRCA1/BRCA2* carriers who were in complete or partial response. The median PFS for the olaparib group has not been reached, but, at 3 years, 60% of women were progression-free in the olaparib group compared with 27% in the placebo group, with a hazard ratio of 0.30 (95% CI, 0.23-0.41; $P < .0001$).[128] That trial led to US Food and Drug Administration approval in December 2018 for olaparib first-line maintenance in women with *BRCA*-mutated cancer after a response to platinum-based chemotherapy.

This trial now sets the scene for a stratified approach to systemic therapy, with the incorporation of bevacizumab based on residual disease after surgery and switch maintenance on the basis of mutations in *BRCA1/BRCA2*. This requires upfront testing for all HGSOCs. Knowledge of *BRCA1/BRCA2* mutational status (at least germline but preferably somatic as well) should be a part of the standard of care. National Comprehensive Cancer Network and Society of Gynecologic Oncology guidelines suggest universal genetic counseling and testing of all women with ovarian cancer, including fallopian tube and peritoneal cancer.[129,130] Additional testing of somatic *BRCA1/BRCA2* status, as well as mutations in other homologous recombinantion (HR) genes, upon diagnosis would further expand our knowledge about who would benefit from PARP-inhibitor maintenance therapy.

The key questions regarding overlap or combinations of antiangiogenics and PARP inhibitors are being addressed in upfront clinical trials. Studies in long-term responders and patients who develop resistance are beginning to leverage next-generation sequencing technologies to identify key factors, which may allow for exceptional sensitivity or extreme resistance.[131,132]

Evolving Therapies

Folate receptor targeting

Although normal ovarian tissue does not express folate receptor (FR), approximately 70% of primary EOCs and 80% of recurrent EOCs do express FR,[133] providing an opportunity to exploit FR as a selective biomarker for the delivery of ADCs. Recent trials used mirvetuximab soravtansine (IMGN853), which is an ADC consisting of an anti-FRα antibody linked to the tubulin-disrupting maytansinoid DM4 drug, a potent antimitotic agent. As such, this ADC delivers a toxic drug in a highly selective manner to ovarian cancer cells expressing FRα. In addition, active DM4 metabolites diffuse into surrounding tumor cells, inducing a "bystander" killing effect.[134] Phase 1 and 2 trials have demonstrated proof-of-principle activity in women with recurrent, platinum-resistant ovarian cancer who received from 1 to 3 prior lines of therapy; of 37 women treated as part of the 3 phase 1 expansion cohorts who met the enrollment criteria of moderate-to-high tumor FRα levels (≥50% of cells with ≥2+ FRα expression), objective tumor responses were observed in 17 individuals (1 complete response and 16 partial responses) for an overall response rate of 46% (95% CI, 29.5%-63.1%) and a median PFS of 6.7 months (95% CI, 4.1-9.0 months).[135] These preliminary results are encouraging and have led to the design of PH3 Study of Mirvetuximab Soravtansine vs Investigator's Choice of Chemotherapy in Women With FRa+ Adv. EOC, Primary Peritoneal or Fallopian Tube Cancer (FORWARD I), a randomized phase 3 clinical trial in platinum-resistant ovarian cancer as single agent (NCT02631876)[136] and further phase 1/2 trials evaluating the combination.

Immunotherapy

The presence of TILs, particularly CD3-positive T cells, in the pathology at the time of diagnosis of ovarian cancer confers an 8-fold improvement in the 5-year survival rate.[137] However, various histological and molecular subtypes of ovarian cancer differ in their immunogenicity[29,31,138] and are likely related to a slow development of neoantigens, allowing for immune ignorance. In addition, tumors often downregulate major histocompatibility complex 1 (human leukocyte antigen A [HLA-A], HLA-B, and HLA-C) to evade recognition by natural killer cells and express PD-L1 or secrete molecules, such as VEGF and transforming growth factor β (TGF-β), that inactivate effector T cells and promote immunosuppressive T-regulatory cells and tumor-associated macrophages, thus fueling cancer's escape and impeding the ability of the immune system to respond because of functional exhaustion. At this stage, the tumor is not eliciting an immune response and is considered "cold." The complex interplay between cancer's genomic changes and intricate microenvironment, not only involving immune cells but also developing hypoxic conditions and angiogenesis, are challenges in the development of effective immunotherapy. Therefore, the current goals of immunotherapy are to balance the recognition and elimination of ovarian cancer without excessive toxicity elicited by activation of the immune system. There has been tremendous progress recently in the development of innovative immunotherapies.

Despite the high expression of PD-L1 in ovarian cancer, immune checkpoint inhibitors as single agents targeting PD-1/PD-L1 or cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) have shown modest response rates of approximately 10% to 15%.[139] Assessments of the antitumor activity as well as the safety of pembrolizumab in patients with recurrent, advanced ovarian cancer have been performed as part of the KEYNOTE-100

study (NCT02674061), which demonstrated modest response and suggested that pembrolizumab monotherapy might have a higher overall response rate in patients with PD-L1 expression.[140] There are presently no approved immune therapies for ovarian cancer.[141] Current approaches are ongoing to enhance the activity of checkpoint inhibitors, such as combination with anti–CTLA-4 and anti–PD-1,[142] or a combination of checkpoint inhibitors with chemotherapy, such as pegylated liposomal doxorubicin (JAVELIN Ovarian 200; NCT02580058) or weekly paclitaxel,[143] epigenetic modifiers such as the DNA demethylating agent azacytidine (Hypomethylating Agent Oral Azacitidine and Durvalumab in Advanced Solid Tumors [METADUR]; NCT02811497), antiangiogenic agents such as bevacizumab (Platinum-Based Chemotherapy With Atezolizumab and Niraparib in Patients With Recurrent Ovarian Cancer [ANITA]; NCT03598270), and PARP inhibitors (the TOPACIO [NCT02657889[144]] and MEDIOLA [NCT02734004] trials). After these early-phase trials, 5 large phase 3 trials have been leveraged in the front-line setting combining a PD-L1 inhibitor with chemotherapy and bevacizumab, potentially with the addition of a PARP inhibitor.

Another approach involves the use of autologous cell therapy in which a patient's cancer antigen-specific T cells are selected and expanded ex vivo before reinfusion. Preliminary results in ovarian cancer showed feasibility and an initial modest response.[145] A variation of adoptive T-cell therapy involves a gene-transfer technology to introduce a chimeric antigen receptor (CAR) that provides antigen specificity and the ability to trigger T-cell activation. Currently, clinical trials are investigating CARs that target mesothelin, a membrane glycoprotein overexpressed on ovarian cancer cells.

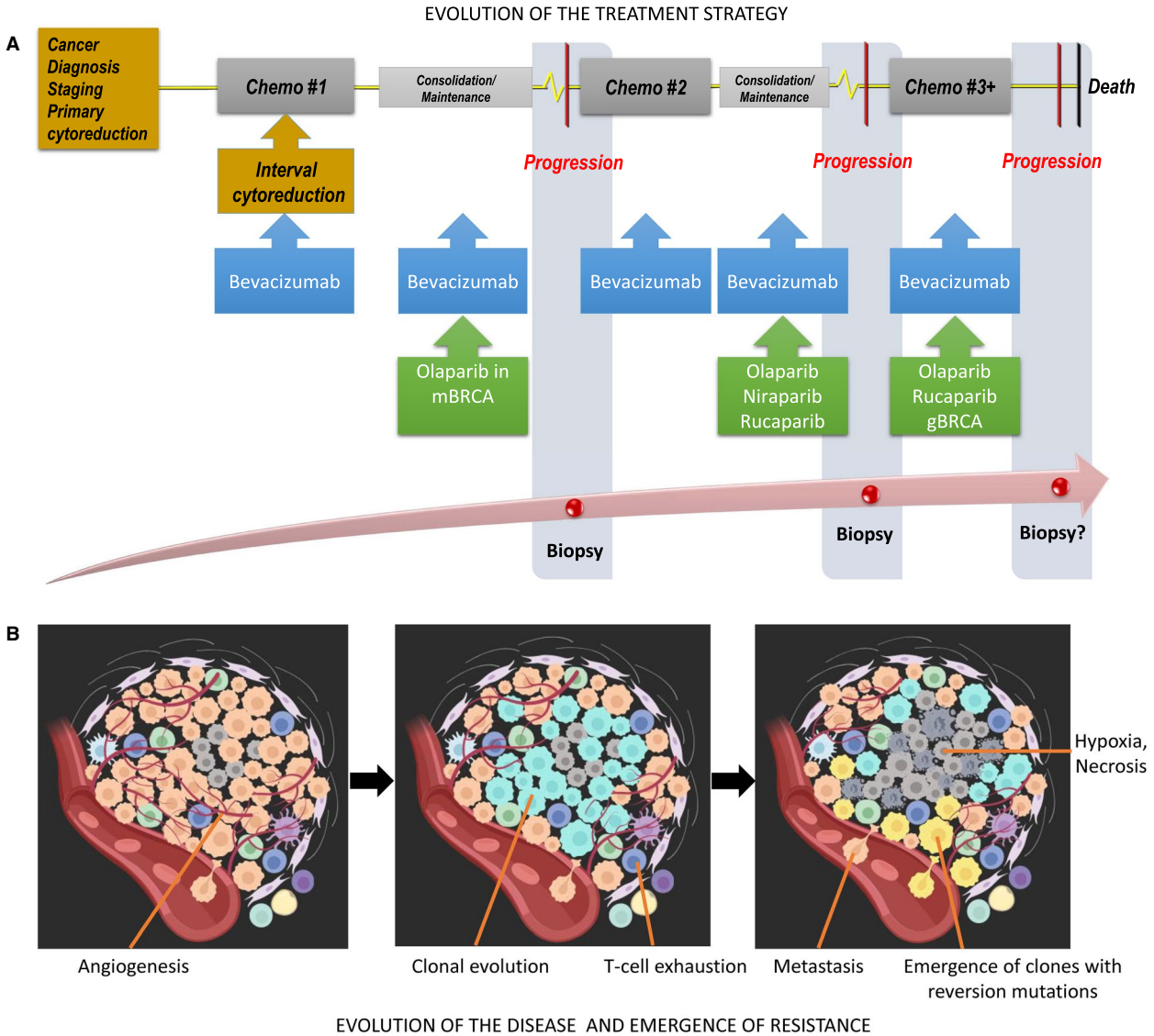


FIGURE 7. Evolution of the Disease and Its Treatment Strategy. Chemo indicates chemotherapy; gBRCA, *BRCA* germline mutation; mBRCA, *BRCA* germline or somatic mutation germline mutation.

Vaccines have not worked well against cancer cells as single agents because of a highly immunosuppressive cancer microenvironment. Current efforts are focusing on combination treatments. For instance, the DeCidE trial is investigating a vaccine-based therapy against survivin, a molecule involved in the regulation of cancer cell death, replication, and progression, in combination with chemotherapy (cyclophosphamide) and epacadostat, a potent inhibitor of IDO1, which engages immune tolerance during cancer development (NCT02785250).[146] Similarly, the vaccine against survivin is being investigated in a triple-combination immunotherapy with chemotherapy (cyclophosphamide) and anti–PD-1 (pembrolizumab) as part of the PESCO clinical trial (NCT03029403). Finally, a patient-specific cancer "mutanome" is being explored as a customized and personalized approach to cancer vaccines.[147,148]

Improving Outcomes

Ovarian Cancer Subtypes

To date, first-line treatment guidelines have largely been driven by HGSOC management. Recent advances in our understanding of EOC have resulted in an adjustment to treatment strategy based on the histological subtype. The management of ovarian cancer is evolving from a one-size-fits all approach to more of an approach in which we are becoming more precise about using surgery, chemotherapy, and several novel therapeutics in the management of the treatment of newly diagnosed and recurrent ovarian cancer. HGSOCs and high-grade endometrioid ovarian cancers are initially highly sensitive to platinum-based chemotherapy (Fig. 4), which remains the backbone of treatment. However, the use of chemotherapy in OCCC and LGSOC is questionable, because they are relatively chemoresistant. Different approaches are being assessed in these rare histologic subtypes exploring hormonal therapy in LGSOC and immunotherapy in OCCC. On the basis of their disease biology, MEK-inhibitor treatment has been evaluated in recurrent LGSOC. Selumetinib has been investigated in a phase 2 trial and produced an overall response rate of 15% and stable disease in 60% of patients with relapsed LGSOC, without a correlation between mutational status and response.[149] These preliminary results were not confirmed in a randomized study (MEK Inhibitor in Low-Grade Ovarian Cancer [MILO]; NCT01849874), which failed to demonstrate an improvement in PFS with the MEK1/MEK2 inhibitor binimetinib (MEK162, ARRY-162) compared with physician-choice chemotherapy after platinum-based chemotherapy.[150]

Further investigations are warranted in this area, and collaboration with the GCIG and the rare tumors network is key to developing innovative trials in this population.

Sensitivity and Resistance to Therapy

In addition to distinct subtypes of ovarian cancer demonstrating different sensitivity and resistance to systemic therapy, recent studies have established considerable molecular heterogeneity based on anatomic location of disease in the same individual. This has been demonstrated at both genomic and immunologic levels. The potential causes of this heterogeneity relate to the differential evolution of cancer clones, either as a consequence of the disease or as adaptive responses to therapy, as well as the local tumor microenvironment.[151] The consequences of this heterogeneity create a more complex landscape of ovarian cancer, which is dynamic and changing over time in response to clonal evolutionary and therapeutic pressures (Fig. 7). The genomic instability of all HGSOCs and the deficiency in DNA repair in almost 50% of HGSOCs are vulnerabilities that have allowed susceptibility to platinum chemotherapy and PARP inhibitors. Tumor and circulating cell-free DNA (cfDNA) analyses now demonstrate evolutionary adaptation in response to platinum chemotherapy and PARP inhibitors and, in some patients, result in the emergence of bridging reversion mutations, whereas in other patients they lead to multiple parallel mutations, which overcome the prior therapeutic vulnerability and confer resistance.[117,152]

Treatment at Recurrence

A tremendous amount of research has been conducted and is ongoing to understand sensitivity to therapy as well as intrinsic or acquired resistance and to evaluate strategies to overcome treatment failure. Clinically, HGSOCs and high-grade endometrioid ovarian cancers seem to be sensitive to chemotherapy at presentation, and approximately 80% of patients respond. The median survival for all patients with advanced ovarian cancer is approximately 5 years, but only about 20% will remain disease free after initial therapy. Unfortunately, most patients will recur and follow a chronically relapsing course, requiring repeated systemic therapies. Recurrent disease is not curable, and treatment goals are to control disease, prolong the treatment-free period, control symptoms, and maintain quality of life. A balanced approach to therapy, clinical trials, symptom control, and palliative management is needed. Intrinsic resistance is seen in 10% to 15% of patients defined as *platinum refractory* and is associated with a poor median survival of <9 months. Approximately 20% to 30% of patients will recur or progress within 6 months of completing chemotherapy (termed *platinum resistant*) and have a median OS of approximately 12-18 months. Patients who remain disease free for at least 6 months after completing primary chemotherapy are *platinum sensitive* and will respond better to re-challenge with platinum or platinum doublets

than to alternative chemotherapeutic agents. Patients with platinum-resistant or platinum-refractory disease have poor responses to alternative single-agent chemotherapy, with response rates <15%. The addition of antiangiogenic agents has improved response rates and PFS significantly in platinum-sensitive and platinum-resistant disease and should be considered in these settings. Clinical trials are of paramount importance to define mechanisms of resistance and alternative methods of controlling disease. Currently, frontline clinical trials in ovarian cancer are assessing the combination of chemotherapy, an antiangiogenic agent, a PARP inhibitor, and immune therapy, which will also affect the approach to the disease at recurrence. Strong translational studies are built into these trials to guide patient selection and further therapy development.

Because disease progression is frequently symptomatic, the management of symptoms and attention to patient quality of life have to be considered. Particularly troubling in ovarian cancer are symptoms of bowel obstruction related to peritoneal disease infiltrating into the bowel or causing extrinsic compression. This requires careful conservative management, with attention to diet, fluid intake, bowel rest, and avoidance of a high-fiber diet. Occasionally, if obstruction is caused by single-level obstruction, palliative or defunctioning surgery may provide relief.[153]

The management of recurrent, clear cell, low-grade serous and mucinous carcinomas present more of a therapeutic dilemma because of a lack of responsiveness to conventional chemotherapy. In this setting, the options considered are the potential for surgery or radiation and the availability of clinical trials. Precision medicine approaches to define predictive biomarkers, such as mismatch repair (as in a subset of clear-cell cancers) or mutations in targetable genes are increasingly options for consideration but are still within the realms of experimental therapies and clinical trials.

On the basis of evidence, changing the standard of care requires an objective evaluation of a new treatment through the conduct of different phases of clinical trials. If clinical meaningful benefit has been observed for a patient, this new treatment can be approved by the regulatory agency and be made available for practice. Clinical trials provide access to innovation and may be a new option for patient care. Clinical trials have evolved now in their design to integrate biomarker analyses and to identify potential predictive markers to understand biologically why patients may or may not respond to a given therapy.

Delivery of Care

The variability in providing treatment to all women with ovarian cancer may explain the diversity of outcomes nationally as well as internationally.[154] Making known treatments available should reduce avoidable ovarian cancer deaths that arise from inequity related to access to cancer care within countries. Although *equality* in cancer care refers to the same treatment being available to all, *equity* means that all patients should have fair and equal access to available treatment opportunities. In well-resourced countries, inequities can stem from several factors, creating great disparity in access to cancer care: demographics, socioeconomic status, and rural/remote residence.[154,155] Socioeconomic status, which is a measurement based on a person's education, occupation, income, and overall wealth, is closely associated with person's sex, belonging to a minority group, and exposures to cancer risk factors. Rural patients with cancer experience an additional burden of access to treatment that affects their decisions regarding treatment and, ultimately, their quality and longevity of life. To put this in perspective, the 2010 census indicated that 1 in 5 individuals in the total US population (or 19.3%) lives in a rural/remote area.[156] For ovarian cancer, African American women or women of lower socioeconomic status were less likely to access standard treatment and more likely to delay treatment and to receive nonstandard treatment or no treatment at all.[157,158]

Population-based studies have revealed substantial disparities in cancer survival between countries with similar wealth and health care system.[159] Recently, the International Cancer Benchmarking Partnership analyzed population-based cancer registry data from 1995 through 2007 in Canada, the United Kingdom, Australia, and 3 European countries (Sweden, Norway, and Denmark). Globally, the incidence of ovarian cancer in all 6 countries has been falling since 1985, and these declines are largely attributed to the protective effects of oral contraceptives, as well as increased diagnostic intensity that permits earlier diagnosis and treatment of borderline or premalignant lesions, all of which could have contributed to this trend in the long run.[159] However, disparities were still observed, because ovarian cancer survival was the highest in Canada, Australia, and Sweden, followed by Norway, and it was the lowest in Denmark and the United Kingdom.[159] International differences in the cancer registration process were not the likely factors contributing to this trend, because most countries collected high-quality data.[159] Geographical differences were also observed within Canada and Australia, where the ovarian cancer survival rate varied substantially between the regions examined; however, within well-resourced countries, a decrease in disparity is achievable when the resources become properly allocated to increase access to cancer care. Studies have demonstrated that combining outreach efforts with treatment programs for uninsured patients and using patient navigators for access to screening and treatment can nearly eliminate the disparity gap in underserved populations.[160-163] It is important to ensure

that underserved populations have access to established, evidence-based care to improve ovarian cancer outcomes.

Prevention and Screening

Currently, there is no validated, population-based screening for standard practice. In an unselected population, CA 125 and ultrasound were associated with false-negative and false-positive results and hence were not recommended.[164] Screening high-risk populations by virtue of known inherited predisposition (*BRCA* mutations) is effective, and there are efforts to genomically identify high-risk patients in populations as genomic testing becomes easier and less expensive. In some cases, for example Ashkenazi populations, susceptibility can readily be identified using screening for 3 founder mutations. In addition, efforts are ongoing to improve genomic screening strategy.[165] Potential biomarkers, such as human epididymis protein 4 (HE4) (a glycoprotein secreted by Mullerian epithelia of the female reproductive tract), have been tested in combination with CA 125; a risk of ovarian cancer algorithm has been developed, and transvaginal sonography has been assessed as a biomarker test,[166,167] but larger confirmatory studies are required. One potential approach involves analyzing DNA methylation patterns in cfDNA as a way to detect EOC early.[168] DNA methylation is a common epigenetic event that causes conformational changes of chromatin or interference with transcription factor binding sites, ultimately resulting in gene transcription silencing.[169] In contrast to the effect observed in normal cells, DNA methylation of tumor-suppressive genes is commonly observed during cancer cell development and progression.[169,170] Toward this end, genome-wide DNA methylation mapping is tissue-specific[171] and may be used to distinguish between tumor-specific (circulating tumor DNA [ctDNA]) and normal cfDNA. Different studies are ongoing to assess DNA methylation as a potential screening tool.[168] The screening strategy is also evolving based on understanding of ovarian cancer carcinogenesis and potential risk factors.

Conclusions

The management of ovarian cancer has evolved from a "one-size-fits-all" approach to one in which we are becoming more precise about using surgery, chemotherapy, and targeted therapy. This approach will continue to evolve as we discover predictive biomarkers that will help select patients who are most likely to benefit from the therapeutic approach. The use of next-generation sequencing assays upfront will also play a key role for patients with newly diagnosed ovarian cancer, particularly as we continue to challenge treatment paradigms in the first-line management of ovarian cancer. Treatment at the time of recurrence will be guided by further understanding the disease evolution and the resistance mechanism developed by the tumor under treatment pressure. ■

Acknowledgements: We would like to thank Katherine Karakasis for editorial assistance, and Patricia Shaw, MD and Marjan Rouzbahman, MD for providing H&E pictures of ovarian cancers.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018; 68:7-30.
2. Canadian Cancer Statistics Advisory Committee. Canadian Cancer Statistics 2017. Toronto, ON: Canadian Cancer Society; 2018. cancer.ca/en/cancer-information/cancer-101/canadian-cancer-statistics-publication/?region=on#ixzz51GNbcorh Rm. Accessed October 23, 2018.
3. Noone AM, Howlader N, Krapcho M, et al, eds. SEER Cancer Statistics Review, 1975-2015 (seer.cancer.gov/csr/1975_2015). Bethesda, MD: National Cancer Institute; 2018.
4. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68: 394-424.
5. The World Ovarian Cancer Coalition. The Every Woman Study Summary Report. 2018. worldovariancancercoalition.org/wp-content/uploads/2018/11/WOCC-Every-Woman-Study-Summary-Report-Nov-08.pdf. Accessed February 18, 2019.
6. Rosendhal M, Hogdall CK, Mosgaard BJ. Restaging and survival analysis of 4036 ovarian cancer patients according to the 2013 FIGO classification for ovarian, fallopian tube and primary peritoneal cancer. *Int J Gynecol Cancer*. 2016;26: 680-687.
7. Peres LC, Cushing-Haugen KL, Kobel M, et al. Invasive epithelial ovarian cancer survival by histotype and disease stage. *J Natl Cancer Inst*. 2019;111:60-68.
8. Banerjee S, Kaye SB. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res*. 2013;19: 961-968.
9. Piver MS. Treatment of ovarian cancer at the crossroads: 50 years after single-agent melphalan chemotherapy. *Oncology (Williston Park)*. 2006;20:1156, 1158.
10. Karam A, Ledermann JA, Kim JW, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: first-line interventions. *Ann Oncol*. 2017;28:711-717.
11. Wilson MK, Pujade-Lauraine E, Aoki D, et al. Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup: recurrent disease. *Ann Oncol*. 2017;28:727-732.
12. McGee J, Bookman M, Harter P, et al. Fifth Ovarian Cancer Consensus Conference: individualized therapy and patient factors. *Ann Oncol*. 2017;28: 702-710.
13. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. *Epidemiology*. 2018;29:41-49.

14. Trabert B, Poole EM, White E, et al. Analgesic use and ovarian cancer risk: an analysis in the Ovarian Cancer Cohort Consortium. *J Natl Cancer Inst.* 2019;111:137-145.
15. Merritt MA, Rice MS, Barnard ME, et al. Prediagnosis and post-diagnosis use of common analgesics and ovarian cancer prognosis (NHS/NHSII): a cohort study. *Lancet Oncol.* 2018;19:1107-1116.
16. Torre LA, Trabert B, DeSantis CE, et al. Ovarian cancer statistics, 2018. *CA Cancer J Clin.* 2018;68:284-296.
17. Alsop K, Fereday S, Meldrum C, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol.* 2012;30:2654-2663.
18. Prat J. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. *Virchows Arch.* 2012;460: 237-249.
19. Prat J. New insights into ovarian cancer pathology. *Ann Oncol.* 2012;23(suppl 10): x111-x117.
20. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. *Nature.*2011;474: 609-615.
21. Walsh T, Lee MK, Casadei S, et al. Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc Natl Acad Sci U S A.* 2010;107: 12629-12633.
22. Risch HA, McLaughlin JR, Cole DE, et al. Population BRCA1 and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. *J Natl Cancer Inst.* 2006;98:1694-1706.
23. Kurman RJ. Origin and molecular pathogenesis of ovarian high-grade serous carcinoma. *Ann Oncol.* 2013;24(suppl 10): x16-x21.
24. Labidi-Galy SI, Papp E, Hallberg D, et al. High grade serous ovarian carcinomas originate in the fallopian tube. *Nat Commun.* 2017;8:1093.
25. Bowtell DD, Bohm S, Ahmed AA, et al. Rethinking ovarian cancer II: reducing mortality from high-grade serous ovarian cancer. *Nat Rev Cancer.* 2015;15: 668-679.
26. Kroeger PTJr, Drapkin R. Pathogenesis and heterogeneity of ovarian cancer. *Curr Opin Obstet Gynecol.* 2017;29: 26-34.
27. Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol.* 2011;12:852-861.
28. Etemadmoghadam D, George J, Cowin PA, et al. Amplicon-dependent CCNE1 expression is critical for clonogenic survival after cisplatin treatment and is correlated with 20q11 gain in ovarian cancer. *PLoS One.* 2010;5:e15498.
29. Tothill RW, Tinker AV, George J, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. *Clin Cancer Res.* 2008;14:5198-5208.
30. Verhaak RG, Tamayo P, Yang JY, et al. Prognostically relevant gene signatures of high-grade serous ovarian carcinoma. *J Clin Invest.* 2013;123:517-525.
31. Konecny GE, Wang C, Hamidi H, et al. Prognostic and therapeutic relevance of molecular subtypes in high-grade serous ovarian cancer. *J Natl Cancer Inst.* 2014;106:dju249.
32. Macintyre G, Goranova TE, De Silva D, et al. Copy number signatures and mutational processes in ovarian carcinoma. *Nat Genet.* 2018;50:1262-1270.
33. Lambert JM, Berkenblit A. Antibody-drug conjugates for cancer treatment. *Annu Rev Med.* 2018;69:191-207.
34. Moore KN, Martin LP, O'Malley DM, et al. A review of mirvetuximab soravtansine in the treatment of platinum-resistant ovarian cancer. *Future Oncol.* 2018;14:123-136.
35. Hilliard TS. The impact of mesothelin in the ovarian cancer tumor microenvironment. *Cancers (Basel).* 2018;10:E277.
36. Kaldawy A, Segev Y, Lavie O, Auslender R, Sopik V, Narod SA. Low-grade serous ovarian cancer: a review. *Gynecol Oncol.* 2016;143:433-438.
37. 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.
38. Hsu CY, Bristow R, Cha MS, et al. Characterization of active mitogen-activated protein kinase in ovarian serous carcinomas. *Clin Cancer Res.* 2004;10: 6432-6436.
39. Feng Z, Wen H, Ju X, et al. Expression of hypothalamic-pituitary-gonadal axis-related hormone receptors in low-grade serous ovarian cancer (LGSC). *J Ovarian Res.* 2017;10:7.
40. Fujiwara K, McAlpine JN, Lheureux S, Matsumura N, Oza AM. Paradigm shift in the management strategy for epithelial ovarian cancer. *Am Soc Clin Oncol Educ Book.* 2016;35:e247-e257.
41. Yamaguchi K, Mandai M, Toyokuni S, et al. Contents of endometriotic cysts, especially the high concentration of free iron, are a possible cause of carcinogenesis in the cysts through the iron-induced persistent oxidative stress. *Clin Cancer Res.* 2008;14:32-40.
42. Itamochi H, Oishi T, Oumi N, et al. Whole-genome sequencing revealed novel prognostic biomarkers and promising targets for therapy of ovarian clear cell carcinoma. *Br J Cancer.* 2017;117:717-724.
43. Shibuya Y, Tokunaga H, Saito S, Shimokawa K, Katsuoka F, Bin L, et al. Identification of somatic genetic alterations in ovarian clear cell carcinoma with next generation sequencing. *Genes Chromosomes Cancer.* 2018;57:51-60.
44. Hashiguchi Y, Tsuda H, Inoue T, Berkowitz RS, Mok SC. PTEN expression in clear cell adenocarcinoma of the ovary. *Gynecol Oncol.* 2006;101:71-75.
45. Uehara Y, Oda K, Ikeda Y, et al. Integrated copy number and expression analysis identifies profiles of whole-arm chromosomal alterations and subgroups with favorable outcome in ovarian clear cell carcinomas. *PLoS One.* 2015;10: e0128066.
46. Howitt BE, Strickland KC, Sholl LM, et al. Clear cell ovarian cancers with microsatellite instability: a unique subset of ovarian cancers with increased tumor-infiltrating lymphocytes and PD-1/PD-L1 expression. *Oncoimmunology.* 2017;6:e1277308.
47. Vierkoetter KR, Ayabe AR, VanDrunen M, Ahn HJ, Shimizu DM, Terada KY. Lynch syndrome in patients with clear cell and endometrioid cancers of the ovary. *Gynecol Oncol.* 2014;135:81-84.
48. Wu R, Hendrix-Lucas N, Kuick R, et al. Mouse model of human ovarian endometrioid adenocarcinoma based on somatic defects in the Wnt/beta-catenin and PI3K/Pten signaling pathways. *Cancer Cell.* 2007;11:321-333.
49. van der Horst PH, van der Zee M, Heijmans-Antonissen C, et al. A mouse model for endometrioid ovarian cancer arising from the distal oviduct. *Int J Cancer.* 2014;135:1028-1037.
50. McConechy MK, Ding J, Senz J, et al. Ovarian and endometrial endometrioid carcinomas have distinct CTNNB1 and PTEN mutation profiles. *Mod Pathol.* 2014;27:128-134.

51. Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. *Am J Surg Pathol.* 2003;27:985-993.
52. Jang JYA, Yanaihara N, Pujade-Lauraine E, et al. Update on rare epithelial ovarian cancers: based on the Rare Ovarian Tumors Young Investigator Conference. *J Gynecol Oncol.* 2017;28:e54.
53. Ledermann JA, Luvero D, Shafer A, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for mucinous ovarian carcinoma. *Int J Gynecol Cancer.* 2014;24(9 suppl 3):S14-S19.
54. Wiltshaw E, Kroner T. Phase II study of cis-dichlorodiammineplatinum(II) (NSC-119875) in advanced adenocarcinoma of the ovary. *Cancer Treat Rep.* 1976;60:55-60.
55. Thomas GM, Dembo AJ. Integrating radiation therapy into the management of ovarian cancer. *Cancer.* 1993;71(4 suppl): 1710-1718.
56. Amin MB, Edge S, Greene F, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
57. Prat J; FIGO Committee on Gynecologic Oncology. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *Int J Gynaecol Obstet.* 2014;124:1-5.
58. Prat J; FIGO Committee on Gynecologic Oncology. FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. *J Gynecol Oncol.* 2015;26:87-89.
59. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). *Cancer.* 2009;115:1234-1244.
60. Harter P, Sehouli J, Lorusso D, et al. LION: lymphadenectomy in ovarian neoplasms—a prospective randomized AGO study group led Gynecologic Cancer InterGroup trial [abstract]. *J Clin Oncol.* 2017;35(15 suppl):5500.
61. Riester M, Wei W, Waldron L, et al. Risk prediction for late-stage ovarian cancer by meta-analysis of 1525 patient samples. *J Natl Cancer Inst.* 2014;106; dju048.
62. Wang C, Armasu SM, Kalli KR, et al. Pooled clustering of high-grade serous ovarian cancer gene expression leads to novel consensus subtypes associated with survival and surgical outcomes. *Clin Cancer Res.* 2017;23:4077-4085.
63. Lheureux S, Karakasis K, Kohn EC, Oza AM. Ovarian cancer treatment: the end of empiricism? *Cancer.* 2015;121: 3203-3211.
64. Kehoe S, Hook J, Nankivell M, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. *Lancet.* 2015;386: 249-257.
65. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med.* 2010;363:943-953.
66. Gomez-Hidalgo NR, Martinez-Cannon BA, Nick AM, et al. Predictors of optimal cytoreduction in patients with newly diagnosed advanced-stage epithelial ovarian cancer: time to incorporate laparoscopic assessment into the standard of care. *Gynecol Oncol.* 2015;137: 553-558.
67. Fleming ND, Nick AM, Coleman RL, et al. Laparoscopic surgical algorithm to triage the timing of tumor reductive surgery in advanced ovarian cancer. *Obstet Gynecol.* 2018;132:545-554.
68. Nicoletto MO, Tumolo S, Talamini R, et al. Surgical second look in ovarian cancer: a randomized study in patients with laparoscopic complete remission—a Northeastern Oncology Cooperative Group-Ovarian Cancer Cooperative Group study. *J Clin Oncol.* 1997;15: 994-999.
69. Coleman RL, Enserro D, Spirtos N, et al. A phase III randomized controlled trial of secondary surgical cytoreduction (SSC) followed by platinum-based combination chemotherapy (PBC), with or without bevacizumab (B) in platinum-sensitive, recurrent ovarian cancer (PSOC): an NRG Oncology/Gynecologic Oncology Group (GOG) study [abstract]. *J Clin Oncol.* 2018;36(15 suppl):5501.
70. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Fort Washington, PA: National Comprehensive Cancer Network; 2018.
71. Williams CJ, Mead GM, Macbeth FR, et al. Cisplatin combination chemotherapy versus chlorambucil in advanced ovarian carcinoma: mature results of a randomized trial. *J Clin Oncol.* 1985;3: 1455-1462.
72. Neijt JP, ten Bokkel Huinink WW, van der Burg ME, et al. Randomised trial comparing two combination chemotherapy regimens (Hexa-CAF vs CHAP-5) in advanced ovarian carcinoma. *Lancet.* 1984;2:594-600.
73. Omura G, Blessing JA, Ehrlich CE, et al. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group study. *Cancer.* 1986;57:1725-1730.
74. McGuire WP, Hoskins WJ, Brady MF, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med.* 1996;334:1-6.
75. McGuire WP, Hoskins WJ, Brady MF, et al. A phase III trial comparing cisplatin/cytoxan and cisplatin/paclitaxel in advanced ovarian cancer [abstract 808]. *Proc Am Soc Clin Oncol.* 1993;12:255a.
76. Einzig AI, Wiernik PH, Sasloff J, Runowicz CD, Goldberg GL. Phase II study and long-term follow-up of patients treated with taxol for advanced ovarian adenocarcinoma. *J Clin Oncol.* 1992;10:1748-1753.
77. Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol.* 2003;21:3194-3200.
78. Calvert AH, Newell DR, Gumbrell LA, et al. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol.* 1989;7:1748-1756.
79. Jodrell DI, Egorin MJ, Canetta RM, et al. Relationships between carboplatin exposure and tumor response and toxicity in patients with ovarian cancer. *J Clin Oncol.* 1992;10:520-528.
80. Katsumata N, Yasuda M, Takahashi F, et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. *Lancet.* 2009;374: 1331-1338.
81. Katsumata N, Yasuda M, Isonishi S, et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary

peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. *Lancet Oncol.* 2013;14:1020-1026.

82. Bookman MA. GOG0182-ICON5: 5-arm phase III randomized trial of paclitaxel (P) and carboplatin (C) vs combinations with gemcitabine (G), PEG-lipososomal doxorubicin (D), or topotecan (T) in patients (pts) with advanced-stage epithelial ovarian (EOC) or primary peritoneal (PPC) carcinoma [abstract]. *J Clin Oncol.* 2006;24(18 suppl):5002.
83. 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.
84. Clamp AR, McNeish I, Dean A, et al. ICON8: a GCIG phase III randomised trial evaluating weekly dose-dense chemotherapy integration in first-line epithelial ovarian/fallopian tube/primary peritoneal carcinoma (EOC) treatment: results of primary progression-free survival (PFS) analysis. *Ann Oncol.* 2017;28(suppl 5):v605-v649.
85. 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.
86. Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med.* 2006;354:34-43.
87. Markman M, Bundy BN, Alberts DS, et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol.* 2001;19:1001-1007.
88. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database Syst Rev.* 2016;1:CD005340.
89. Walker JL, Brady MF, Wenzel L, et al. Randomized trial of intravenous versus intraperitoneal chemotherapy plus bevacizumab in advanced ovarian carcinoma: an NRG Oncology/Gynecologic Oncology Group study [published online April 19, 2019]. *J Clin Oncol.* doi:10.1200/jco.18.01568.
90. van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med.* 2018;378:230-240.
91. Lim MC, Chang SJ, Yoo HJ, Nam BH, Bristow R, Park SY. Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer [abstract]. *J Clin Oncol.* 2017;35(15 suppl):5520.
92. Fotopoulou C, Sehouli J, Mahner S, et al. HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer?*Ann Oncol.* 2018;29:1610-1613.
93. Monk BJ, Chan JK. Is intraperitoneal chemotherapy still an acceptable option in primary adjuvant chemotherapy for advanced ovarian cancer?*Ann Oncol.* 2017;28(suppl 8):viii40-viii45.
94. Broekman KE, Jalving M, van Tinteren H, Sessa C, Reyners AKL. Clinical benefit of controversial first line systemic therapies for advanced stage ovarian cancer—ESMO-MCBS scores. *Cancer Treat Rev.* 2018;69:233-242.
95. Pujade-Lauraine E. How to approach patients in relapse. *Ann Oncol.* 2012;23 (suppl 10):x128-x131.
96. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med.* 2011;365:2473-2483.
97. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med.* 2011;365: 2484-2496.
98. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol.* 2015;16:928-936.
99. Burger RA, Enserro D, Tewari KS, et al. Final overall survival (OS) analysis of an international randomized trial evaluating bevacizumab (BEV) in the primary treatment of advanced ovarian cancer: an NRG Oncology/Gynecologic Oncology Group (GOG) study [abstract]. *J Clin Oncol.* 2018;36(15 suppl):5517.
100. Oza AM, Selle F, Davidenko I, et al. Efficacy and safety of bevacizumab-containing therapy in newly diagnosed ovarian cancer: ROSiA single-arm phase 3B study. *Int J Gynecol Cancer.* 2017; 27:50-58.
101. Pignata S, Lorusso D, Joly F, et al. Chemotherapy plus or minus bevacizumab for platinum-sensitive ovarian cancer patients recurring after a bevacizumab containing first line treatment: the randomized phase 3 trial MITO16B-MaNGO OV2B-ENGOT OV17 [abstract]. *J Clin Oncol.* 2018;36(15 suppl):5506.
102. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol.* 2012;30:2039-2045.
103. Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 2017;18:779-791.
104. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol.* 2014;32:1302-1308.
105. Monk BJ, Minion LE, Coleman RL. Anti-angiogenic agents in ovarian cancer: past, present, and future. *Ann Oncol.* 2016; 27(suppl 1):i33-i39.
106. Helleday T, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy. *Nature Rev Cancer.* 2008;8:193-204.
107. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature.* 2005;434:917-921.
108. Murai J, Huang SY, Das BB, et al. Trapping of PARP1 and PARP2 by clinical PARP inhibitors. *Cancer Res.* 2012;72:5588-5599.
109. Pennington KP, Walsh T, Harrell MI, et al. Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res.* 2014;20:764-775.
110. Tan DS, Rothermundt C, Thomas K, et al. "BRCAness" syndrome in ovarian cancer: a case-control study describing the clinical features and outcome of patients with epithelial ovarian cancer associated with BRCA1 and BRCA2 mutations. *J Clin Oncol.* 2008;26: 5530-5536.

111. Turner N, Tutt A, Ashworth A. Hallmarks of BRCAness in sporadic cancers. *Nat Rev Cancer*. 2004;4:814-819.

112. Konstantinopoulos PA, Spentzos D, Karlan BY, et al. Gene expression profile of BRCAness that correlates with responsiveness to chemotherapy and with outcome in patients with epithelial ovarian cancer. *J Clin Oncol*. 2010;28: 3555-3561.

113. Kaufman B, Shapira-Frommer R, Schmutzler RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015;33:244-250.

114. Kim G, Ison G, McKee AE, et al. FDA approval summary: olaparib monotherapy in patients with deleterious germline BRCA-mutated advanced ovarian cancer treated with three or more lines of chemotherapy. *Clin Cancer Res*. 2015;21:4257-4261.

115. 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.

116. Ledermann J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366:1382-1392.

117. Swisher EM, Lin KK, Oza AM, et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:75-87.

118. Balasubramaniam S, Beaver JA, Horton S, et al. FDA approval summary: rucaparib for the treatment of patients with deleterious BRCA mutation-associated advanced ovarian cancer. *Clin Cancer Res*. 2017;23:7165-7170.

119. 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.

120. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017;377:523-533.

121. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med*. 2015;373:1697-1708.

122. 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.

123. Oza AM, Cibula D, Benzaquen AO, et al. Olaparib combined with chemotherapy for recurrent platinum-sensitive ovarian cancer: a randomised phase 2 trial. *Oncol*. 2015;16:87-97.

124. Oza AM, Cibula D, Oaknin A, et al. 950P. Olaparib maintenance therapy in patients (pts) with platinum-sensitive relapsed (PSR) ovarian cancer (OC) and stable disease (SD) following platinum-based chemotherapy. Abstract book of the 43rd ESMO Congress (ESMO 2018) 19-23 October 2018, Munich, Germany. *Ann Oncol*. 2018;29(suppl 8): 158.

125. Oza AM, Combe P, Ledermann J, et al. 965P. Evaluation of tumor responses and olaparib efficacy in platinum-sensitive relapsed ovarian cancer (PSROC) patients (pts) with or without measurable disease in the SOLO2 trial (ENGOT Ov-21). Abstract book of the 42nd ESMO Congress (ESMO 2017) 8-12 September 2017, Madrid, Spain. *Ann Oncol*. 2017;28(suppl 5):36.

126. Oza AM, Matulonis UA, et al. Quality of life in patients with recurrent ovarian cancer treated with niraparib versus placebo (ENGOT-OV16/NOVA): results from a double-blind, phase 3, randomised controlled trial. *Lancet Oncol*. 2018;19:1117-1125.

127. Friedlander M, Gebski V, Gibbs E, et al. Health-related quality of life and patient-centered outcomes with olaparib maintenance after chemotherapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT Ov-21): a placebo-controlled, phase 3 randomised trial. *Lancet Oncol*. 2018;19:1126-1134.

128. 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.

129. Lancaster JM, Powell CB, Chen LM, Richardson DL. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. 2015;136:3-7.

130. Daly MB, Pilarski R, Berry M, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2. 2017. *J Natl Compr Cance Netw*. 2017;15:9-20.

131. Lheureux S, Bruce JP, Burnier JV, et al. Somatic BRCA1/2 recovery as a resistance mechanism after exceptional response to poly (ADP-ribose) polymerase inhibition. *J Clin Oncol*. 2017;35: 1240-1249.

132. Scott CL, Swisher EM, Kaufmann SH. Poly (ADP-ribose) polymerase inhibitors: recent advances and future development. *J Clin Oncol*. 2015;33:1397-1406.

133. Kalli KR, Oberg AL, Keeney GL, et al. Folate receptor alpha as a tumor target in epithelial ovarian cancer. *Gynecol Oncol*. 2008;108:619-626.

134. Kovtun YV, Audette CA, Ye Y, et al. Antibody-drug conjugates designed to eradicate tumors with homogeneous and heterogeneous expression of the target antigen. *Cancer Res*. 2006;66: 3214-3221.

135. Moore KN, Matulonis UA, O'Malley DM, et al. Mirvetuximab soravtansine (IMGN853), a folate receptor alpha (FR)-targeting antibody-drug conjugate (ADC), in platinum-resistant epithelial ovarian cancer (EOC) patients (pts): activity and safety analyses in phase I pooled expansion cohorts [abstract]. *J Clin Oncol*. 2017;35(15 suppl):5547.

136. Moore KN, Vergote I, Oaknin A, et al. FORWARD I: a phase III study of mirvetuximab soravtansine versus chemotherapy in platinum-resistant ovarian cancer. *Future Oncol*. 2018;14:1669-1678.

137. Zhang L, Conejo-Garcia JR, Katsaros D, et al. Intratumoral T cells, recurrence, and survival in epithelial ovarian cancer. *N Engl J Med*. 2003;348:203-213.

138. Thorsson V, Gibbs DL, Brown SD, et al. The immune landscape of cancer. *Immunity*. 2018;48:812-830.e14.

139. Pujade-Lauraine E. New treatments in ovarian cancer. *Ann Oncol*. 2017;28 (suppl 8):viii57-viii60.

140. Matulonis UA, Shapira-Frommer R, Santin A, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: interim results from the phase 2 KEYNOTE-100 study [abstract]. *J Clin Oncol*. 2018;36(15 suppl):5511.

141. Odunsi K. Immunotherapy in ovarian cancer. *Ann Oncol*. 2017;28(suppl 8): viii1-viii7.

142. Burger R, Sill M, Zamarin D, et al. NRG Oncology phase II randomized trial of nivolumab with or without ipilimumab in patients with persistent or recurrent ovarian cancer. Paper presented at: 17th Biennial Meeting of the International Gynecologic Cancer Society; September 14-16, 2018; Kyoto, Japan.

143. Wenham RM, Fridley B, Boulware D, et al. Phase 2 trial of weekly paclitaxel

with pembrolizumab in platinum resistant recurrent ovarian cancer. Paper presented at: 17th Biennial Meeting of the International Gynecologic Cancer Society; September 14-16, 2018; Kyoto, Japan.

144. Konstantinopoulos PA, Waggoner SE, Vidal GA, et al. TOPACIO/Keynote-162 (NCT02657889): a phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—results from ROC cohort [abstract]. *J Clin Oncol*. 2018;36(15 suppl):106.

145. Pedersen M, Westergaard M, Nielsen M, et al. 1145PD. Adoptive cell therapy with tumor-infiltrating lymphocytes for patients with metastatic ovarian cancer: a pilot study. *Ann Oncol*. 2017; 28(suppl 5):v403-v427.

146. Dorigo O, Tanyi JL, Strauss J, et al. Clinical data from the DeCidE1 trial: assessing the first combination of DPX-Survivac, low dose cyclophosphamide (CPA), and epacadostat (INCB024360) in subjects with stage IIc-IV recurrent epithelial ovarian cancer [abstract]. *J Clin Oncol*. 2018;36(15 suppl):5510.

147. Sahin U, Derhovanessian E, Miller M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature*. 2017;547:222-226.

148. Sahin U, Tureci O. Personalized vaccines for cancer immunotherapy. *Science*. 2018;359:1355-1360.

149. Farley J, Brady WE, Vathipadiekal V, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. *Lancet Oncol*. 2013;14:134-140.

150. Array BioPharma Inc. Array BioPharma announces decision to discontinue MILO study in ovarian cancer [press release]. Boulder, CO: Array BioPharma; April 1, 2016.

151. Zhang AW, McPherson A, Milne K, et al. Interfaces of malignant and immunologic clonal dynamics in ovarian cancer. *Cell*. 2018;173:1755-1769.e22.

152. Kondrashova O, Nguyen M, Shield-Artin K, et al. Secondary somatic mutations restoring RAD51C and RAD51D associated with acquired resistance to the PARP inhibitor rucaparib in high-grade ovarian carcinoma. *Cancer Discov*. 2017;7:984-998.

153. Lee YC, Jivraj N, O'Brien C, et al. Malignant bowel obstruction in advanced gynecologic cancers: an updated review from a multidisciplinary perspective. *Obstet Gynecol Int*. 2018;2018:1867238.

154. Ahmed S, Shahid RK. Disparity in cancer care: a Canadian perspective. *Curr Oncol*. 2012;19:e376-382.

155. de Souza JA, Hunt B, Asirwa FC, Adebamowo C, Lopes G. Global health equity: Cancer care outcome disparities in high-, middle-, and low-income countries. *Gynecol Oncol*. 2016;34:6-13.

156. 2011-2015 American Community Survey, 5-year estimates and 2015 American Community Survey, 1-year estimates. In: Bureau USC, editor. 2016.

157. Long B, Chang J, Ziogas A, Tewari KS, Anton-Culver H, Bristow H. Impact of race, socioeconomic status, and the health care system on the treatment of advanced-stage ovarian cancer in California. *Am J Obstet Gynecol*. 2015; 212:468. e1-468.e9.

158. Chornokur G, Amankwah EK, Schildkraut JM, Phelan CM. Global ovarian cancer health disparities. *Gynecol Oncol*. 2013;129:258-264.

159. Coleman MP, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* (London, England)2011;377: 127-138.

160. Raich PC, Whitley EM, Thorland W, Valverde P, Fairclough D. Denver Patient Navigation Research P. Patient navigation improves cancer diagnostic resolution: an individually randomized clinical trial in an underserved population. *Cancer Epidemiol Biomarkers Prev*. 2012;21:1629-1638.

161. Paskett ED, Katz ML, Post DM, et al. The Ohio Patient Navigation Research Program: does the American Cancer Society patient navigation model improve time to resolution in patients with abnormal screening tests?. *Cancer Epidemiol Biomarkers Prev*. 2012;21:1620-1628.

162. Percac-Lima S, Grant RW, Green AR, et al. A culturally tailored navigator program for colorectal cancer screening in a community health center: a randomized, controlled trial. *J Gen Intern Med*. 2009;24:211-217.

163. Grubbs SS, Polite BN, Carney J, Jr., et al. Eliminating racial disparities in colorectal cancer in the real world: it took a village. *J Clinical Oncol*. 2013;31: 1928-1930.

164. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet (London, England)* 2016;387:945-956.

165. Skates SJ, Greene MH, Buys SS, et al. Early detection of ovarian cancer using the risk of ovarian cancer algorithm with frequent CA125 testing in women at increased familial risk - combined results from two screening trials. *Clin Cancer Res*. 2017;23:3628-3637.

166. Moore RG, McMeekin DS, Brown AK, et al. A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. *Gynecol Oncol*. 2009;112:40-46.

167. Rosenthal AN, Fraser LSM, Philpott S, et al. Evidence of stage shift in women diagnosed with ovarian cancer during phase II of the United Kingdom Familial Ovarian Cancer Screening Study. *J Clinical Oncol*. 2017;35:1411-1420.

168. Widschwendter M, Zikan M, Wahl B, et al. The potential of circulating tumor DNA methylation analysis for the early detection and management of ovarian cancer. *Genome Med*. 2017;9:116.

169. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. *Nat Rev Genet*. 2002;3:415-428.

170. Momparler RL, Bovenzi V. DNA methylation and cancer. *J Cell Physiol*. 2000; 183:145-154.

171. Lehmann-Werman R, Neiman D, Zemmour H, et al. Identification of tissue-specific cell death using methylation patterns of circulating DNA. *Proc Natl Acad Sci USA*. 2016;113:E1826-E1834.