PRACTICE AID

FDA-Approved PARP Inhibitors for the Treatment of Ovarian Cancer

PeerView Oncology

MLI Medical Learning Institute, Inc.

Agent	Indications[1-3]	FDA-Approved Companion Diagnostic[4]
Niraparib	Indicated in patients with advanced ovarian cancer who have been treated with ≥3 prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD)–positive status	HRD status testing using myChoice CDx
	Indicated as maintenance treatment in patients with recurrent ovarian cancer who are in a CR or PR to platinum-based chemotherapy	No requirement for biomarker testing
	Indicated as maintenance treatment in adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in CR or PR to first-line platinum-based chemotherapy	No requirement for biomarker testing
Olaparib	Indicated in patients with g*BRCA*m advanced ovarian cancer previously treated with ≥3 chemotherapies	*BRCA1/2* testing using BRACAnalysis CDx or next-gen sequencing using FoundationOne CDx
	Indicated as maintenance treatment in patients with recurrent ovarian cancer who are in CR or PR to platinum-based chemotherapy	No requirement for biomarker testing
	Indicated as first-line maintenance treatment in patients with g*BRCA*m or s*BRCA*m advanced ovarian cancer who are in CR or PR to first-line platinum-based chemotherapy	*BRCA1/2* testing using BRACAnalysis CDx or next-gen sequencing using FoundationOne CDx
	Indicated in combination with bevacizumab for the first-line maintenance treatment in patients with advanced ovarian cancer who are in CR or PR to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status	HRD status testing using myChoice CDx
Rucaparib	Indicated in patients with g*BRCA*m and/or s*BRCA*m advanced ovarian cancer previously treated with ≥2 chemotherapies	*BRCA1/2* testing using BRACAnalysis CDx or next-gen sequencing using FoundationFocus CDx *BRCA* or FoundationOne CDx
	Indicated as maintenance treatment in patients with recurrent ovarian cancer, achieving CR or PR to platinum-based chemotherapy	No requirement for biomarker testing

BRCA: breast cancer gene; CR: complete response; g*BRCA*m: germline *BRCA* mutation; PARP: poly(ADP)-ribose polymerase; PR: partial response; s*BRCA*m: somatic *BRCA* mutation.

1. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208447s015s017lbledt.pdf. 2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208558s014lbl.pdf. 3. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/209115s004lbl.pdf.
4. https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools.

Access the activity, "Optimizing Precision Medicine in Ovarian Cancer: Expert Insights on Clinical Implications of PARP Inhibitor Therapy and Companion Diagnostics," at **PeerView.com/OvarianCancer-Live**

PRACTICE AID

Adapted Guidelines for Genetic Testing and Counseling of Patients With Ovarian Cancer

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Recommendations on Genetic Testing[1,2]

What is the difference between germline testing and somatic testing?[3]

Germline testing	Somatic testing
• Identifies inherited mutations that may be passed on to offspring • Performed on blood and/or saliva • Patient may not be affected • Used to identify patients with inherited cancer predisposition syndromes • Patient often receives genetic counseling	• Identifies mutations in the tumor (ie, acquired changes) • Performed on tumor tissue • Patient has cancer • Used to identify treatment options and determine prognosis • Patient not often counseled

Who should undergo molecular testing in ovarian cancer?

Germline and somatic tests in ovarian cancer	Which patients should be tested?
Germline testing for *BRCA1*, *BRCA2*, and other ovarian cancer susceptibility genes	All women diagnosed with epithelial ovarian cancer
Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants	Patients with epithelial ovarian cancer who tested negative for germline *BRCA1/2* variants
Homologous recombination deficiency (HRD) assay	Patients with epithelial ovarian cancer who tested negative for germline and somatic *BRCA1* and *BRCA2*
Somatic tumor testing for mismatch repair deficiency (dMMR)	Patients with clear-cell, endometrioid, or mucinous ovarian cancer plus other histologic types of epithelial ovarian cancer
Individualized genetic risk evaluation, counseling, and genetic testing	Any blood relatives of a patient with ovarian cancer with a known germline pathogenic mutation or variant

When should patients be tested?

- Germline testing should occur at the time of diagnosis
- Patients not tested at the time of diagnosis should be offered germline genetic testing as soon as feasible
- Somatic tumor testing for *BRCA1* and *BRCA2* pathogenic variants should be offered when the patient's germline test results come back negative
- Somatic testing may be reserved for when disease returns for women who have completed upfront therapy and are in observation



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Recommendations on Genetic Testing[1,2] (Cont'd)



Which mutations should be tested?

Gene mutations and variants that are definitely or possibly relevant to ovarian cancer include *ATM, BRCA1, BRCA2, BRIP1, EPCAM, MSH2, MLH1, MSH6, NBM, PALB2, PMS2, RAD51C, RAD51D,* and *STK11*

Which testing technologies are recommended?[4]

- Next-generation multigene panel testing is standard of care
  - Genetic testing companies offer different multigene panels that vary widely in the number of mutations in their panels
  - Testing can be performed using blood, saliva, or buccal mucosa
- Limitations of multigene panel testing
  - Due to the large number of genes that are tested with next-generation sequencing (NGS), the number of variants of uncertain significance (VUS) that may be identified is a concern
  - Further, in large panels, many of the genes assessed are newly identified, so cancer risks are not well characterized, there are no guidelines for medical management, and the role of predictive testing for family members is uncertain

Which testing recommendations are not recommended?

- Germline whole-genome/exome sequencing
  - Data suggest that WES and WGS are unlikely to yield more actionable results than an expanded NGS panel
  - Also expensive, yields many VUS and potential false-positive results, and likely to generate secondary findings
- Direct-to-consumer (DTC) *BRCA1/2* testing
  - DTC company 23andMe to include *BRCA1* and *BRCA2* testing in its Personal Genome Service Genetic Health Risk report
  - Testing includes only the three *BRCA1/2* Ashkenazi Jewish founder mutations; no analysis of other potential variants
  - Positive results from DTC testing need to be confirmed and interpreted in a clinical laboratory; high rates of false-positive results, including discrepancies about result interpretation, as well as false-negative results
  - Important concern: Women at average risk for breast cancer with negative DTC *BRCA1/2* test results may have a false sense of safety and skip necessary screening appointments and healthcare visits as a result

How should identified genomic alterations guide therapeutic decision-making?

- Patients with epithelial ovarian cancer and germline or somatic pathogenic or variants in *BRCA1* and *BRCA2* genes should be offered FDA-approved treatments, including PARP inhibitor therapy, in the first-line maintenance or recurrent settings
- Clinical decisions should not be based on VUS
- Patients with recurrent ovarian cancers with identified dMMR mutations should be offered FDA-approved treatments, including immune checkpoint inhibitors
- HRD assays can provide information that can be used for ovarian cancer treatment stratification

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Recommendations on Genetic Counseling[1,2]

Which HCPs should be involved in the evaluation and counseling of patients?

Genetic counselors, medical geneticists, oncologists, surgeons, oncology nurses, and other HCPs familiar with the diagnosis and management of hereditary cancer syndromes

What are the components of pre-test genetic counseling?

- Evaluation of patient's knowledge of the benefits, risks, and limitations of genetic testing for cancer risk, and goals for family risk assessment
- Detailed medical/surgical and family history, including three generations of maternal and paternal relatives
- Focused physical examination
- Mathematic risk assessment modeling
- Generation of differential diagnosis and patient education on inheritance patterns, penetrance, variable expressivity, and the possibility of genetic heterogeneity
- Preparation for the possible outcomes of testing, including positive, negative, uncertain variants, and mosaic results; medical management recommendations; and implications for relatives
- Written informed consent
- Discussion of financial considerations and legal protection against genetic discrimination

What are the components of post-test genetic counseling?

- Discussion of genetic test results and associated medical risks
- Interpretation of results in the context of personal and family history of cancer
- Discussion of recommended medical management options
- Offer of assistance with informing and testing at-risk family members
- Discussion of available patient resources (eg, high-risk clinics, disease-specific support groups, research studies)
- For patients of reproductive age, discussion of reproductive assistance options, including prenatal diagnosis, assisted reproduction, and pre-implantation genetic diagnosis; should include known risks, limitations, and benefits of these technologies



HCP: healthcare professional; PARP: poly(ADP)-ribose polymerase; WES: whole exome sequencing; WGS: whole genome sequencing.

1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. V1.20. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf. 2. https://www.asco.org/gynecologic-cancer-guideline. 3. www.cancer.gov/about-cancer/causes-prevention/genetics. 4. Lim MC, Randall LM. *J Gynecol Oncol*. 2017;28:e51.

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PRACTICE AID

Novel Approaches in Ovarian Cancer[a]: Selected Recent and Ongoing Trials of PARP Inhibitors[1]

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First-Line Treatment

PRIMA (NCT02655016) Phase 3

- Advanced, high-grade, predominantly serous or endometrioid, ovarian cancer
- N = 733
- Niraparib *vs* placebo
- 1° endpoint: PFS

Recruiting

DUO-O (NCT03737643) Phase 3

- Newly diagnosed , advanced, high-grade ovarian cancer
- Planned N = 1,056
- Chemo + bevacizumab + durvalumab followed by durvalumab + bevacizumab ± olaparib
- 1° endpoint: PFS in non-t*BRCA*m patients

VELIA (NCT02470585) Phase 3

- Newly diagnosed, previously untreated, high-grade serous ovarian cancer
- N = 1,140
- Chemo ± veliparib
- 1° endpoint: PFS

First-Line Maintenance

SOLO-1 (NCT01844986) Phase 3

- *BRCA*m advanced ovarian cancer
- Completed first-line platinum-based chemo
- N = 450
- Olaparib *vs* placebo
- 1° endpoint: PFS

SOLO-2 (NCT01874353) Phase 3

- High-grade serous ovarian cancer or endometrial cancer with *BRCA*m
- CR or PR on platinum chemo
- N = 327
- Olaparib *vs* placebo
- 1° endpoint: PFS

PAOLA-1 (NCT02477644) Phase 3

- High-grade serous ovarian cancer or endometrial cancer
- Completed first-line platinum-taxane chemo and ≥3 cycles of bevacizumab in combo with the last 3 cycles of chemo
- N = 806
- Olaparib + bevacizumab *vs* placebo + bevacizumab
- 1° endpoint: PFS

Recruiting

KEYLYNK-001 (NCT03740165) Phase 3

- *BRCA*-nonmutated, advanced ovarian cancer
- Completed/eligible for primary or interval debulking surgery
- Candidate for carboplatin and paclitaxel chemo
- Planned N = 1,086
- Pembrolizumab + chemo + olaparib
- 1° endpoints: OS and PFS

Recruiting

ATHENA (NCT03522246) Phase 3

- Newly diagnosed, advanced ovarian cancer
- Planned N = 1,012
- Rucaparib + nivolumab
- 1° endpoint: PFS

OVARIO (NCT03326193) Phase 2

- High-grade, serous or endometrioid, newly diagnosed ovarian cancer
- N = 106
- Niraparib + bevacizumab
- 1° endpoint: PFS at 18 mo

Second-Line Treatment

BAROCCO (NCT03314740) Phase 2

- Relapsed/progressive high-grade ovarian cancer
- Any line of treatment (after the first)
- Any "last" chemo line, including paclitaxel (administered <6 mo before study beginning)
- N = 100
- Cediranib + olaparib *vs* chemo
- 1° endpoints: PFS and number of evacuations per day

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PRACTICE AID

Novel Approaches in Ovarian Cancer[a]: Selected Recent and Ongoing Trials of PARP Inhibitors[1]

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Late-Line Treatment

SOLO-3 (NCT02282020) Phase 3

- High-grade serous ovarian cancer or endometrial cancer
- g*BRCA1/2* m
- ≥2 lines of prior platinum chemo
- N = 266
- Olaparib *vs* physician's choice single-agent chemo
- 1° endpoint: PFS

Recruiting

ARIEL4 (NCT02855944) Phase 3

- *BRCA*m, high-grade serous or grade 2 or 3 endometrioid ovarian cancer
- Planned N = 345
- Rucaparib *vs* chemo
- 1° endpoint: PFS

ARIEL2 (NCT01891344) Phase 2

- High-grade serous or grade 2 or 3 endometrioid ovarian cancer
- N = 493
- Rucaparib
- 1° endpoints: Disease progression and ORR

QUADRA (NCT02354586) Phase 2

- High-grade, serous ovarian cancer with recurrent disease
- N = 463
- Niraparib
- 1° endpoint: ORR

TOPACIO (NCT02657889) Phase 2

- High-grade, serous or endometrioid ovarian cancer
- Niraparib + pembrolizumab
- 1° endpoint: ORR

MEDIOLA (NCT02734004) Phase 1/2

- Progressive advanced/metastatic
- g*BRCA*m ovarian cancer
- 4-wk run-in olaparib followed by olaparib + durvalumab
- 1° endpoint: ORR

Late-Line Maintenance

NOVA (NCT01847274) Phase 3

- Platinum-sensitive, high-grade, serous or g*BRCA*m ovarian cancer
- N = 553
- Niraparib *vs* placebo
- 1° endpoint: PFS

ARIEL3 (NCT01968213) Phase 3

- High-grade serous or endometrioid ovarian cancer
- N = 564
- Rucaparib *vs* placebo
- 1° endpoint: PFS

[a] Ovarian cancer = epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancers.

*BRCA*m: *BRCA* mutation; CR: complete response; g*BRCA*: germline *BRCA*; HRD: homologous recombination deficiency; ORR: objective response rate; PD-L1: programmed cell death ligand 1; PR: partial response; t*BRCA*: tumor *BRCA*.

1. https://clinicaltrials.gov/.

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