

Diagnosis and Management of Low-Grade Serous Ovarian Cancer

Low-grade serous ovarian cancer (LGSOC) is a rare ovarian cancer that is insidious, persistent, and ultimately fatal.¹⁻⁵ It is molecularly and histopathologically distinct and clinically different from high-grade serous ovarian cancer (HGSOC) and deserves different treatment.^{1,6,7} While once thought to be on a continuum with HGSOC, LGSOC is now recognized as a distinct ovarian cancer, with different characteristics from HGSOC.⁸ This resource outlines key considerations for diagnosis and management of LGSOC.

	LGSOC ⁹	HGSOC ⁹
Median age at diagnosis (years)	43-48 ^{6,10}	63
Frequency (% of all serous ovarian neoplasms)	3%-9%	90%
Presumed precursor	Serous borderline	STIC of the fallopian tube
CA-125	Not clinically useful	Clinically useful
Positive family history	Rare	10%-22%
Chemo-sensitivity	Rare	90%
Clinical course	Slow	Rapid
Median progression-free survival (months)	92	35
Median overall survival (months)	97	72
Gene mutations reported (%)		
• BRAF	2%-20%	<1%
• KRAS	19%-55%	<1%
• TP53	8%	>95%
• BRCA	1%-5%	15%

LGSOC=low-grade serous ovarian cancer; HGSOC=high-grade serous ovarian cancer; STIC=serous tubal intraepithelial carcinoma.

Differentiating LGSOC from HGSOC

Histopathological and molecular characteristics between LGSOC and HGSOC.

Managing LGSOC depends on distinguishing it from HGSOC.

LGSOC	HGSOC
<p>HISTOPATHOLOGICAL CHARACTERISTICS</p> <p>Mild to moderate nuclear atypia¹¹</p> <p>Low mitotic index (12 mitoses per 10 high-power fields)¹¹</p> <p>MOLECULAR CHARACTERISTICS</p> <p>TP53 wild type¹²</p> <p>KRAS, BRAF, NRAS, and PIK3CA mutations^{10,13}</p>	<p>HISTOPATHOLOGICAL CHARACTERISTICS</p> <p>Tumors are pleomorphic with marked nuclear pleomorphism ($\geq 3:1$ size variation)¹¹</p> <p>High mitotic index (≥ 12 mitoses per 10 high-power fields)¹¹</p> <p>MOLECULAR CHARACTERISTICS</p> <p>TP53 mutation and BRCA1/2 mutations¹⁰</p>

Key characteristics of LGSOC

Germline testing

BRCA mutations rare (approximately 5%)¹⁴

Somatic testing

Can be helpful to determine prognosis and response to certain therapies¹⁵

Activating mutations in RAS/MAPK pathway promote tumorigenesis¹⁵

- *KRAS* mutations common (~1/3 patients)¹⁰
- *NRAS*¹⁰
- *BRAF*¹⁰
- *NF1*¹⁰
- *RAF1*¹⁶

Less common mutations found in LGSOC tumors: *ERBB2* and *PIK3CA*^{10,17}

Somatic tumor testing may identify patients for novel and emerging treatment options or clinical trials¹⁵

National Comprehensive Cancer Network® (NCCN®) recommended treatment for LGSOC stages IA-IC

Cytoreductive surgery is the primary treatment for all epithelial ovarian cancers¹⁸

Fertility-sparing surgery is an option in stage IA-C1 LGSOC. Oocyte retrieval from an unaffected ovary is an option in the surgical management of LGSOC.^{15,18}

Adjuvant treatment options

Stage IA-IB ¹⁸	Stage IC ¹⁸
<p>Observe¹⁸</p> <p>(Consider surgical setting and resection of residual disease if not done previously)</p>	<p>Observe (category 2B)^a</p> <p>Systemic chemotherapy^b Followed by observation, or maintenance letrozole (2B), or other hormonal therapy (2B)^c</p> <p>Hormonal therapy (category 2B)^b</p>
<p>PREFERRED REGIMENS FOR STAGE 1C</p> <ul style="list-style-type: none"> • Paclitaxel/carboplatin q3weeks^{d,e} ± maintenance letrozole,^f or other hormonal therapy (2B)^{18,c} • Hormone therapy (aromatase inhibitors: letrozole,^f exemestane)(2B)¹⁸ 	
<p>OTHER RECOMMENDED REGIMENS</p> <ul style="list-style-type: none"> • Carboplatin/liposomal doxorubicin ± maintenance letrozole^f or other hormonal therapy (2B)^{18,c} • Docetaxel/carboplatin ± maintenance letrozole^f or other hormonal therapy (2B)^{18,c} • Hormone therapy (leuprolide acetate, goserelin acetate, fulvestrant) (2B)¹⁸ 	
<p>USEFUL IN CERTAIN CIRCUMSTANCES</p> <ul style="list-style-type: none"> • Paclitaxel/cisplatin¹⁸ 	

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

^aIf not previously done, consider surgical staging and resection of residual disease.

^bSee Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

^cOther hormonal therapy options include: aromatase inhibitors (ie, anastrozole, exemestane), leuprolide acetate, goserelin acetate.

^dAlbumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.

^eIndividuals >70 years of age and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]). Based on clinical judgment and expected tolerance to therapies, alternate dosing (OV-C, 7 of 12) may be appropriate for these individuals with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity.

^fFor low-grade serous, maintenance letrozole is an NCCN Category 2A recommendation.

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NCCN-recommended treatment for LGSOC stages II-IV¹⁸

Cytoreductive surgery is the primary treatment for all epithelial ovarian cancers¹⁸

Adjuvant treatment options

Stage II-IV¹⁸

Chemotherapy^h

Followed by maintenance letrozole, or other hormonal therapy (2B)ⁱ

Hormonal therapy (category 2B)^h

PREFERRED REGIMENS

- Paclitaxel/carboplatin q3weeks^{kl} ± maintenance letrozoleⁱ (2A) or other hormonal therapy (2B)¹⁸ⁱ
- Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab^{18,j,m}
- Hormone therapy (aromatase inhibitors: anastrozole, letrozole, exemestane) (2B)¹⁸

OTHER RECOMMENDED REGIMENS

- Paclitaxel weekly/carboplatin weekly^{18,j,k,n}
- Docetaxel/carboplatin ± maintenance letrozoleⁱ (2A) or other hormone therapy (2B)^{18,i}
- Carboplatin/liposomal doxorubicin ± maintenance letrozoleⁱ (2A) or other hormonal therapy (2B)^{18,i}
- Paclitaxel weekly/carboplatin q3weeks^{18,j}
- Docetaxel/carboplatin/bevacizumab + maintenance bevacizumab^{18,f}
- Hormone therapy (leuprolide acetate, goserelin acetate, fulvestrant) (2B)¹⁸

USEFUL IN CERTAIN CIRCUMSTANCES

- Paclitaxel/cisplatin¹⁸
- Docetaxel/oxaliplatin/bevacizumab + maintenance bevacizumab (2B)^{18,m}

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

^hSee Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

ⁱOther hormonal therapy options include: aromatase inhibitors (ie, anastrozole, exemestane), leuprolide acetate, goserelin acetate.

^jAlbumin-bound paclitaxel may be substituted for those experiencing a hypersensitivity reaction to paclitaxel. However, albumin-bound paclitaxel will not overcome infusion reactions in all patients.

^kIndividuals >70 years of age and those with comorbidities may be intolerant to the combination chemotherapy regimens recommended in these NCCN Guidelines[®]. Based on clinical judgment and expected tolerance to therapies, alternate dosing (OV-C, 7 of 12) may be appropriate for these individuals with epithelial ovarian cancer (including carcinosarcoma, clear cell, mucinous, and low-grade serous). Algorithms have been developed for predicting chemotherapy toxicity. See the NCCN Guidelines for Older Adult Oncology.

^lFor low-grade serous, maintenance letrozole is a category 2A recommendation.

^mAn FDA-approved biosimilar is an appropriate substitute for bevacizumab.

ⁿRegimen may be considered for those with poor performance status.

Monitoring and follow-up for recurrence¹⁸

- Visits every 2 to 4 months for 2 years, 3 to 6 months for 3 years, annually after 5 years
- Physical exam, including pelvic exam as clinically indicated
- Tumor molecular testing, if not previously done^p
- Refer for genetic risk evaluation, if not previously done^q
- Chest/abdominal/pelvic CT, MRI, PET/CT, or PET (skull base to mid-thigh) as clinically indicated^r
- CBC and chemistry profile as indicated
- CA-125^s or other tumor markers if initially elevated
- Long-term wellness care

^pValidated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), *BRCA1/2*, HRD status, MSI, MMR, TMB, *BRAF*, FRα (*FOLR1*), *RET*, and *NTRK* if prior testing did not include these markers. More comprehensive testing may be particularly important in LCOC with limited approved therapeutic options (OV-B).

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

^rCT is preferred with oral and IV contrast (unless contraindicated) and rectal contrast as needed.

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

Managing recurrent disease

Treatment options for recurrent disease in LGSOC are limited and include secondary cytoreduction, clinical trials, chemotherapy, endocrine therapy, or RAF- and MEK-targeted therapies.^{10,18,19} Recent expert consensus is that there is no defined standard-of-care treatment for recurrent LGSOC.¹⁵ Though there are no FDA-approved treatments specifically for LGSOC,²⁰ NCCN does recommend the following:

NCCN recurrence therapy recommendations

Recurrence therapy options^{15,18}

- Secondary cytoreductive surgery
- Trametinib¹
- Binimetinib (category 2B)¹
- Dabrafenib + trametinib (for *BRAF* V600E positive tumors)¹
- Hormonal therapy
 - Use of an aromatase inhibitor (ie, letrozole, anastrozole, exemestane) is preferred if not used previously
 - Use fulvestrant, leuprolide acetate or goserelin acetate if an aromatase inhibitor was given previously
- Chemotherapy if not previously used (see OV-C 6 of 12)
- Other systemic therapy^u
- Observation

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

No standard sequencing of drugs for recurrent disease; individual patient factors will play a role in decision making¹⁸

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

¹See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

^uData are limited on maintenance therapy for recurrent/resistant LCOC. See OV-8 for maintenance options after platinum-based therapy, and a patient selection criteria.

Snapshot of emerging treatment options in LGSOC

Updated as of 8/6/2024

Drug	MoA	Phase	Trial	Treatment Setting
Trametinib + navitoclax ²¹	MEK inhibitor + BCL2 inhibitor	Ib/II	NCT02079740	Advanced solid tumors that carry KRAS or NRAS mutations, including ovarian tumors
Abemaciclib + fulvestrant ²¹	CDK4/6 inhibitor	II	NCT03531645	Neoadjuvant therapy in women with unresectable, untreated stage III-IV LGSOC
Avutometinib vs avutometinib + defactinib ^{20,22}	Dual RAF/MEK inhibitor + FAK inhibitor	II	RAMP 201 NCT04625270	Recurrent LGSOC with and without KRAS mutation
Biomarker-driven therapies ²⁰	Multiple MOAs based on biomarker	II	BOUQUET NCT04931342	Persistent or recurrent rare epithelial ovarian, fallopian tube, or primary peritoneal tumors
Onapristone ± anastrozole ²³	PR inhibitor	II	NCT03909152	PR-positive gynecologic cancers including recurrent LGSOC
Pembrolizumab + chemotherapy ²¹	ICI	II	PERCEPTION NCT04575961	Platinum-sensitive recurrent LGSOC
Regorafenib + fulvestrant ²¹	Antiangiogenic agent	II	NCT05113368	Recurrent LGSOC
Ribociclib + letrozole ²¹	CDK4/6 aromatase inhibitor	II	GOG 3026 NCT03673124	Recurrent LGSOC
Palbociclib + binimetinib ²⁴	Kinase inhibitors	II	ComboMATCH Treatment Trial NCT05554367	RAS-mutated cancers; previously treated with a MEK inhibitor
Abemaciclib + letrozole ²⁵	Aromatase inhibitor + CDK4/6 inhibitor	II	ALEPRO NCT05872204	Recurrent estrogen receptor-positive rare ovarian cancer
Avutometinib + defactinib ²⁶	Kinase inhibitors	III	RAMP 301 NCT06072781	Recurrent LGSOC
Letrozole ²¹	Aromatase inhibitor	III	MATAO NCT04111978	ER-positive HGSOC, LGSOC, or endometrial ovarian tumors, stages II-IV whose cancer has not progressed on platinum-based chemotherapy
Letrozole + paclitaxel and carboplatin ²¹	Aromatase inhibitor	III	NRG-GY-019 NCT04095364	Stage II-IV LGSOC, fallopian tube, or primary peritoneal cancer

For a complete list, visit clinicaltrials.gov.

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