Molecular changes driving low-grade serous ovarian cancer and implications for treatment

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ABSTRACT

Low-grade serous ovarian cancer was previously thought to be a subtype of high-grade serous ovarian cancer, but it is now recognized as a distinct disease with unique clinical and molecular behaviors. The disease may arise de novo or develop from a serous borderline ovarian tumor. Although it is more indolent than high-grade serous ovarian cancer, most patients have advanced metastatic disease at diagnosis and recurrence is common. Recurrent low-grade serous ovarian cancer is often resistant to standard platinum–taxane chemotherapy, making it difficult to treat with the options currently available. New targeted therapies are needed, but their development is contingent on a deeper understanding of the specific biology of the disease. The known molecular drivers of low-grade tumors are strong hormone receptor expression, mutations in the mitogen-activated protein kinase (MAPK) pathway (*KRAS*, *BRAF*, and *NRAS*), and in genes related to the MAPK pathway (*NF1/2*, *EIF1AX,* and *ERBB2*). However, MAPK inhibitors have shown only modest clinical responses. Based on the discovery of *CDKN2A* mutations in low-grade serous ovarian cancer, cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors are now being tested in clinical trials in combination with hormone therapy. Additional mutations seen in a smaller population of low-grade tumors include *USP9X*, *ARID1A,* and *PIK3CA,* but no specific therapies targeting them have been tested clinically. This review summarizes the clinical, pathologic, and molecular features of low-grade serous ovarian cancer as they are now understood and introduces potential therapeutic targets and new avenues for research.

INTRODUCTION

Low-grade serous ovarian carcinomas are a rare subtype of epithelial ovarian cancer. Because they represent only 2–5% of all ovarian carcinomas, research investigating the biology and treatment of low-grade tumors has been sparse compared with research in high-grade serous ovarian carcinomas.[1 2] While low- and high-grade serous ovarian tumors were once thought to be on a continuum of the same disease, increasing evidence of differences in origin, clinical course, molecular pathways, pathology, and response to treatment has resulted in more distinct classifications.[3] Low-grade tumors may arise de novo or from a precursor lesion known as a serous borderline ovarian tumor (Figure 1). There are multiple theories on the origin of borderline ovarian tumors, with some focusing on fallopian tube hyperplasia; however, the most recent theory is that borderline tumors develop from ovarian serous cystadenomas.[4]

Serous borderline tumors are non-invasive, proliferative, serous epithelial tumors that share cytological features with low-grade serous tumors. Because the micropapillary subtype of borderline tumors is associated with an increased risk of developing low-grade ovarian cancer, it has been posited that micropapillary tumors represent the intermediate stage of the development of borderline into low-grade.[5] Furthermore, while only 4–7% of patients with borderline tumors eventually develop carcinomas, approximately 60% of low-grade tumors contain areas of borderline pathology.[1 3] Therefore, studying the molecular changes between these tumors may provide key insights into the driving factors of malignancy in low-grade ovarian cancer.[3]

Low- and high-grade serous ovarian cancers share some risk factors, such as higher body mass index and smoking; however, their affected populations and course of disease are notably different.[6–8] Low-grade ovarian cancer affects a younger population of women than high-grade, with a median age at diagnosis of 43–47 years.[9] Whereas younger age is associated with longer survival in high-grade, the opposite trend is observed in low-grade. Women diagnosed with low-grade ovarian cancer before 35 years of age have shorter progression-free and overall survival rates, as well as a higher rate of recurrence than those aged over 35 years.[9] Low-grade serous cancer has generally been characterized by a more gradual disease progression and higher 5-year survival rates than high-grade (89.3% vs 80.8% for early stage and 57.7% vs 35.3% for late stage).[10] However, in both low- and high-grade ovarian cancer, most patients are diagnosed at a late stage, classified as stage III–IV by the International Federation of Gynecology and Obstetrics (FIGO), and relapse, ultimately succumbing to the disease.[11] As in high-grade ovarian cancer, tumor stage at diagnosis is strongly associated with survival in low-grade, with stage I and II patients having significantly higher 5- year relative survival rates (89% and 87%) than stage III and IV patients (49% and 25%).[12]

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Received 17 January 2024
Accepted 21 May 2024

Check for updates

To cite: Kelliher L, Yoeli-Bik R, Schweizer L, *et al. Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2024-005305

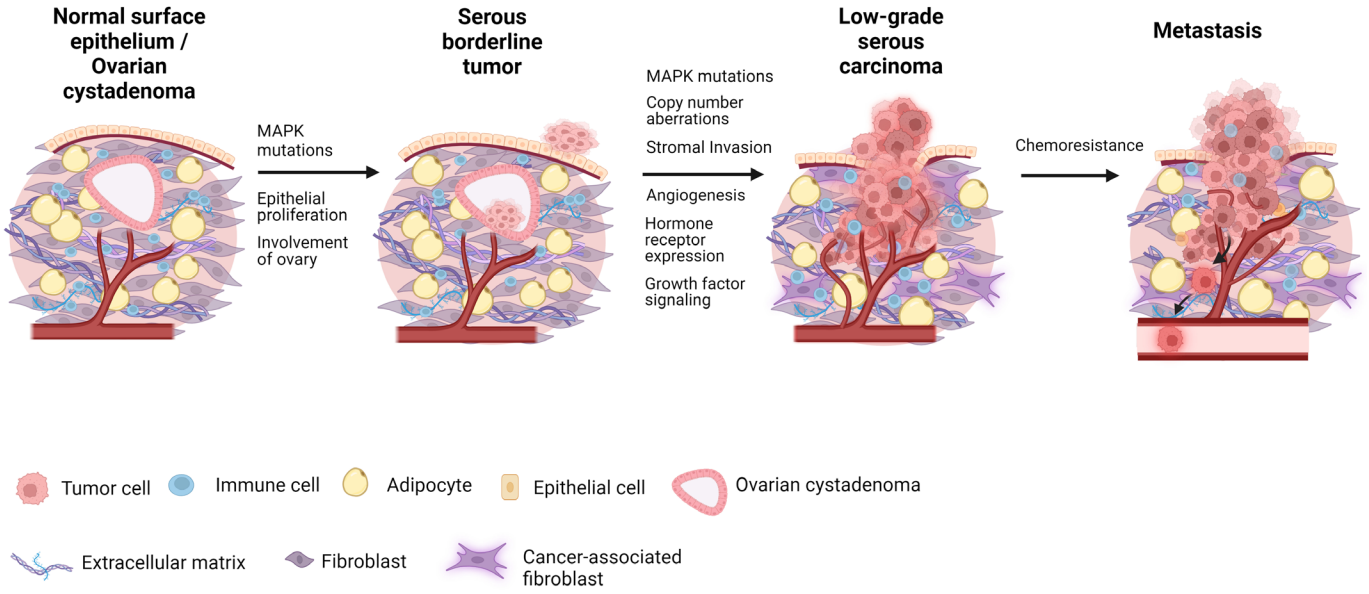

Figure 1 Low-grade serous ovarian cancer stepwise progression pathway. MAPK, mitogen activated protein kinase. (Created with BioRender.com)

PATHOLOGY

Consistent with their markedly different clinical trajectories, the immunohistochemical and histopathological profiles of low- and high-grade serous ovarian cancer are very distinct. Low-grade tumor cells are described as a uniform population of cuboidal or columnar cells showing clear stromal invasion with mild to moderate nuclear atypia. Invasive branches may exhibit various architectural patterns. Psammoma bodies are prevalent, and nuclei are small and consistent[1] (Figure 2). High-grade tumors are present in various histopathologic architectures, which is often a feature of homologous recombination-deficient tumors.[13] High-grade nuclei are large and atypical, and necrosis is common within the tumors[13] (Figure 2). In contrast to high-grade serous cancer, which is characterized by *TP53* mutations and the diffusely positive expression of p16, low-grade and borderline serous tumors are typically p53 wild-type and display patchy p16 staining. Both low- and high-grade tumors are positive for PAX8 and WT-1, which confirms that serous differentiation is present. Most low-grade ovarian cancer is strongly positive for both estrogen and progesterone receptors, which are less common in high-grade.[1] The Ki-67 proliferation index is typically high in high-grade tumors, but low in low-grade tumors. This is consistent with the characterization of low-grade serous ovarian cancer as a more indolent, slower-growing disease, which enables its resistance to chemotherapy drugs that inhibit proliferation.[3]

It is challenging to distinguish serous borderline tumors from low-grade serous carcinomas by cytological features alone, thus an accurate diagnosis may rely on histopathological examination. Borderline tumors are defined by their hierarchical branching papillae with stromal cores and stratified epithelium (Figure 2). The micropapillary subtype, which has been associated with the development of low-grade ovarian cancer, can be identified by elongated micropapillae without stromal cores, arising directly from large papillae and surrounded by clear space.[1] This is referred to as the 'medusa head' appearance.[1]

Psammoma bodies are abundant in borderline tumors, as they are in low-grade. Perhaps the most important pathologic feature that differentiates borderline tumors and low-grade carcinomas is the presence of invasion to the basement membrane in low-grade, and its absence in borderline (Figure 1). Approximately 14% of women with serous borderline tumors have extraovarian implants, which were previously classified as invasive or non-invasive.[5] However, in 2020, WHO classifications changed, and the term 'invasive implant' is no longer recommended.[1] This is because a borderline tumor is, by definition, a non-invasive tumor, therefore, 'invasive implant' is synonymous with a low-grade serous metastasis. If invasion is present in either the ovarian tumor or the extraovarian implants, the diagnosis of low-grade serous cancer must be made.[1] Extraovarian implants of low-grade serous carcinoma are more commonly seen concurrent with borderline ovarian tumors of the micropapillary subtype.[1] This further supports the theory that the micropapillary subtype is the intermediate stage between borderline tumors and low-grade serous cancer.[1]

MOLECULAR CHANGES IN LOW-GRADE SEROUS OVARIAN CANCER

Borderline and low-grade tumors share similar mutational profiles, which differ significantly from high-grade tumors. Therefore, understanding the distinct genomic alterations of low-grade ovarian cancer (Table 1) may lead to novel and more effective therapeutic targets. High-grade serous carcinomas are characterized by high microsatellite instability driven by mutations in homologous recombination repair genes, including *BRCA1/2*, whereas low-grade tumors are microsatellite stable with a low mutational burden.[14] The most common genomic changes in borderline and low-grade tumors are mutually exclusive mutations of *BRAF*, *KRAS*, and *NRAS*—all upstream regulator genes of the mitogen-activated protein kinase (MAPK) pathway.

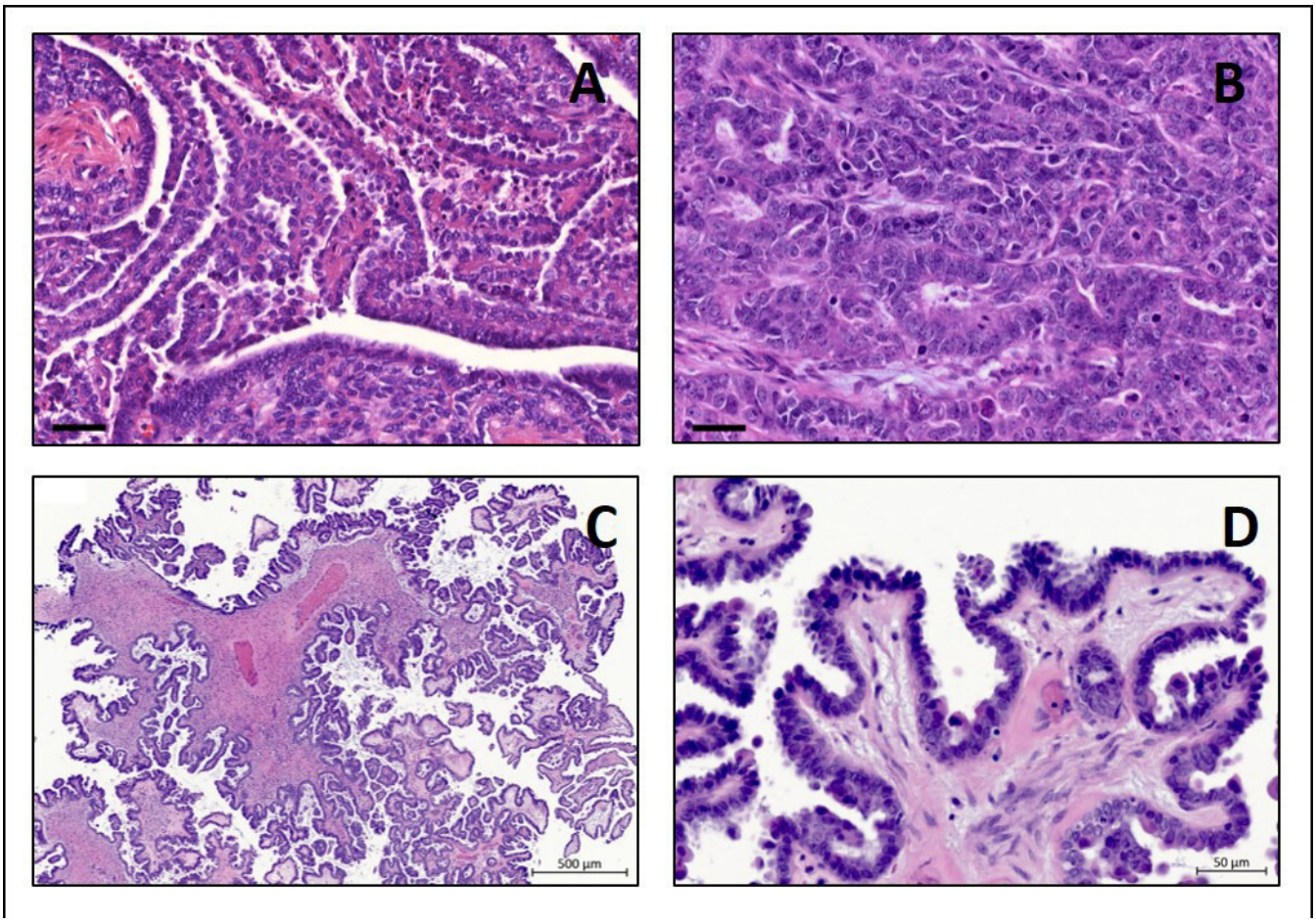

Figure 2 Hematoxylin and eosin: (A) low-grade serous ovarian cancer; (B) high-grade serous ovarian cancer; (C–D) serous borderline ovarian tumor.

In a genomic study of low-grade serous tumors, MAPK mutations were represented in 60% of all tumor samples: *KRAS* (33%), *BRAF* (11%), and *NRAS* (11%) (n=119).[14] In borderline tumors, somatic mutations in *KRAS* (37%) and *BRAF* (39%) were common (n=57).[15] However, *NRAS* mutations were absent in the borderline samples, suggesting that these mutations may play a significant oncogenic role in low-grade serous carcinomas.[15 16] The MAPK pathway is activated by ligands, such as epidermal growth factor or c-Met, which bind to receptor tyrosine kinases and trigger a signaling cascade of protein kinases (mostly MAPK) that ends in the mobilization of transcription factors which regulate various biological processes. Dysregulation of the MAPK pathway has been associated with tumorigenicity, since it promotes cell proliferation and invasion, decreases apoptosis, and increases angiogenesis.[17] However, a recent multivariable analysis of tumors from a cohort of patients with low-grade serous ovarian carcinoma found that a MAPK tumor alteration was associated with improved overall survival.[18] MAPK-mutated tumors were found in 32.6% of patients aged <35 years at diagnosis and 58% of patients aged ≥35 years.[18] These findings could explain the surprising correlation between older age and longer survival in patients with low-grade serous ovarian cancer.[9]

Other genes related to the MAPK pathway which are upregulated in low-grade tumors include *NF1, NF2, EIF1AX,* and *ERBB2* (Table 1). *NF1*, *NF2*, and *ERBB2* are external regulators of the MAPK pathway and mutations in these genes may further contribute to the dysregulation of the pathway in many low-grade and borderline tumors.[18] A co-occurrence of *NRAS* and *EIF1AX* mutations has also been observed in recent sequencing studies on low-grade tumors.[19] *EIF1AX* is a translation initiation factor part of the 43S pre-initiation complex at the AUG start codon of mRNA.[19] Functional experiments revealed increased cell proliferation and clonogenic abilities in cells with high mutant *NRAS* and *EIF1AX* expression.[19] These results suggest that there may be a novel tumorigenic mechanism characterized by their synergism.[20] A 2015 study identified *EIF1AX* mutations in 1.7% of serous borderline tumors compared with 15% of low-grade serous carcinoma samples, supporting the theory that this gene may play a role in tumorigenesis.[15]

CDKN2A mutations have also been identified in low-grade tumors (Table 1). Large-scale panel sequencing of low-grade tumors, performed in 2022, identified loss of chromosome 9p, specifically the region that contains *CDKN2A*, in 8% of patients.[14] Other slightly smaller studies have reported even higher prevalence.[14 15 19 21] *CDKN2A* is similar to the *p53* gene in that they both regulate the cell cycle and are commonly mutated in many different cancers.[22] *CDKN2A* encodes for the p16 protein, which can bind to and inhibit the cyclin-dependent kinases (CDK) 4 and 6.[22] The inhibition of CDK 4 and 6 arrests the cell cycle in the G1 phase, thereby preventing abnormal cell growth.[22] Upstream signaling of CDK 4/6 includes MAPK, PI3K, and estrogen receptor. Mutations in *CDKN2A* and loss of 9p are significantly increased in low-grade carcinomas

Table 1 Main genomic alterations of low-grade serous ovarian cancer as potentials for prognostic markers and novel therapeutic targets

Pathway	Nasioudis et al, 2023[55]	Gershenson et al, 202218	Manning-Geist et al, 2022[14]	Musacchio et al, 2022[21]	Cheasley et al, 2021[19]	Etemadmoghadam et al, 2017[20]
Cohort	n=324	n=215	n=119	n=56	n=71	n=23*
Method	NGS database analysis (panel sequencing, MAPK/ERK pathway gene)	NGS (multiple academic and commercial panels)	NGS using the MSK-IMPACT (panel sequencing)	NGS platform FoundationOne CDX, targeted panels (HRR, MAPK, and endocrine-resistance pathways)	NGS (panel sequencing)	WES (n=22), WGS (n=1)
RAS/RAF/MAPK main pathway	*KRAS* 29.3% *BRAF* 8% *NRAS* 8.3% *HRAS* 0.3%	*KRAS* 33% *BRAF* 8.4% *NRAS* 11.2% *MAP2K1* 1.4% *RAF1* 0.5%	*KRAS* 32.8% *BRAF* 10.9% *NRAS* 10.9% *HRAS* 0.8% *MAP3K1* 1.7%	*KRAS* 21.4% *BRAF* 10.7% *NRAS* 14.3%	*KRAS* 26.7% *BRAF* 12.6% *NRAS* 8.5%	*KRAS* 21.7% *BRAF* 13% *NRAS* 21.7%
MAPK pathway-related genes	*NF1* 3.4% (n=10/288)	*NF1* 4.2% *NF2* 3.7% *ERBB2* 2.3% *EGFR* 0.5%	*EIF1AX* 10% *NF1* 1.7% *NF2* 1.7% *ERBB2* 4.2%	*NF1* 12.5% (3/7 VUS) *NF2* 3.6% (1/2 VUS) *ERBB2* 5.5% (2/3 VUS)	*EIF1AX* 5.6% *NF1* 4.2% *NF2* 4.2% *ERBB2* 2.8%	*EIF1AX* 13% *NF1* 8.7%
Cell cycle regulation	NA	*CDKN2A* 3.3% *CDKN2A/B* 2.8%	*CDKN2A* 8%	*CDKN2A/B* 19.6%	*CDKN2A* 15.5% (loss 9.9%, OE 5.6%; IHC)	NA
Ubiquitinylation	NA	NA	NA	NA	*USP9X* 26.7%	*USP9X* 13%
Rare genes with interesting biology	NA	*PIK3CA* 1.9% *CREBBP* 1.9% *ARID1A* 0.5%	*ARID1B* 2.5% *ARID1A* 1.7% *DOTIL* 1.7%	*PIK3CA* 5.4% (1/3 VUS) *AKT1* 1.8%	*PIK3CA* 5.6% *ARID1A* 8.5% *MACF1* 11.2% *DOT1L* 5.6% *ASH1L* 4.2%	*FFAR1* 8.7%

*The paper by Etemadmoghadam et al had an additional validation cohort that is not reported here.
ERK, extracellular signal-regulated kinase; IHC, immunohistochemistry; LOH, loss of heterozygosity; NA, not assessed; NGS, next-generation sequencing; OE, overexpression; VUS, variant of uncertain significance; WES, whole exome sequencing; WGS, whole genome sequencing.

compared with borderline tumors, which could indicate that these events and subsequent loss of p16 activity are key in the progression of benign tumors to carcinomas.[15]

Additional recently discovered mutations in low-grade ovarian cancer, which do not regulate the MAPK pathway, include *USP9X*, *ARID1A,* and *PIK3CA*. Ubiquitin-specific protease 9X (USP9X) is an X chromosome-linked deubiquitinase that functions in tissue homeostasis and promotes apoptosis. *USP9X* mutations, common in neurocognitive disorders and some cancers, were identified in 26.7% of 71 low-grade tumors submitted for targeted sequencing.[19] Despite their prevalence in low-grade serous cancer, *USP9X* mutations were found in only 2.6% of serous borderline tumors, and have not been identified in other ovarian cancer subtypes, indicating that *USP9X* is a driver unique to low-grade carcinomas.[15 19] However, it has been difficult to determine exactly how *USP9X* drives low-grade cancer because it regulates many cellular pathways.[19] The other genes listed above and in Table 1 are less commonly mutated but have potential as low-grade targets. *ARID1A* mutations were identified in multiple genomic analyses, with the highest expression in 8.5% of 71 low-grade tumors.[19] Loss of *ARID1A* is found in approximately 50% of ovarian clear cell carcinomas, another subtype of epithelial ovarian cancer, strongly suggesting that *ARID1A* functions as a tumor suppressor gene. *ARID1A* is a subunit of the SWI/SNF complex that repositions nucleosomes during transcription, so mutations in this gene can be expected to broadly affect gene expression.[23]

Mutations in *PIK3CA,* which are considered characteristic of endometrioid and clear cell ovarian carcinomas, have been reported in only 1.9% of patients with low-grade cancer[18] (Table 1). While this is a relatively low expression, *PIK3CA* codes for class IA phosphoinositide 3-kinase (PI3K), a major effector of the canonical PI3K/AKT/mTOR pathway, which regulates physiologic cellular processes. The PI3K/AKT/mTOR pathway is also downstream of the insulin-like growth factor pathway, which is consistently upregulated in low-grade tumors.[24] Dysregulation of PI3K has also been linked to chemoresistance in ovarian cancer.[25] One study found that patients who did not respond to standard platinum/taxane chemotherapy had significantly higher levels of p-p70S6K, a direct effector of the PI3K pathway.[25] While PI3K mutations are not sufficiently frequent in the low-grade serous subtype to be considered the cause of chemoresistance in these tumors, they may be a contributing factor.

TREATMENT OF LOW-GRADE SEROUS OVARIAN CANCER

Standard Treatment

The current standard of care for early FIGO (2013) stage I low-grade serous ovarian cancer involves, at the least, the removal of an ovary and surveillance. Younger patients diagnosed with stage IA and IC1 might choose fertility-sparing surgery such as unilateral salpingo-oophorectomy, preserving the uterus and the contralateral ovary.[26] Typically, complete surgical staging and an omental biopsy is included as well to confirm there is no metastasis.[26] The surgical treatment for advanced disease or for patients who do not want to preserve fertility is upfront debulking.[26] This entails a hysterectomy, bilateral salpingo-oophorectomy, staging, and a major effort to remove all tumors completely.[26] Residual disease after primary surgery is an important prognostic factor in low-grade cancer that substantially affects the risk of recurrence.[27 28]

Patients with complete resection (no macroscopic residual disease) have a 5-year relative survival rate of 73%, while patients with optimal cytoreduction (≤1 cm macroscopic residual disease) and suboptimal cytoreduction (>1 cm macroscopic residual disease) have relative survival rates of 47% and 22%, respectively.[12] Advanced-stage disease (FIGO II–IV) will always require adjuvant therapy in addition to primary cytoreductive surgery.[26]

The use of adjuvant therapy in low-grade serous cancer mainly derives from the knowledge gained from high-grade serous treatment and often includes platinum/taxane chemotherapy regimens.[29] However, response to these agents is low in patients with low-grade cancer.[29] While some patients do receive neoadjuvant chemotherapy followed by interval debulking surgery, this is an unfavorable option for most patients with low-grade disease and yields lower response rates owing to the chemoresistant nature of low-grade serous cancer and its deeply invasive growth pattern.[12] Therefore, primary cytoreductive surgery is the preferred initial management, even if optimal gross resection is unachievable.[30]

Hormonal Therapy

Low-grade serous ovarian cancer has strong estrogen and progesterone receptor expression: approximately 85% and 50%, respectively.[31] Therefore, hormonal therapy is commonly used as adjuvant treatment or as maintenance following chemotherapy.[32] A retrospective study using the MD Anderson patient database found that patients who received hormonal maintenance therapy had a lower risk of disease progression than those who underwent routine observation after primary cytoreductive surgery and platinum/taxane chemotherapy.[33]

Aromatase inhibitors, a class of drugs, which lower the levels of circulating estrogen, have been garnering attention. In a 2019 phase II basket trial, 36 patients with estrogen or progesterone receptor-positive recurrent or metastatic low-grade or borderline tumors received the aromatase inhibitor, anastrozole[34] (Table 2). Of these patients, 64% experienced a clinical benefit at 3 months, with a median duration of clinical benefit of 9.5 months.[34] A partial response was reported in 14% of patients and stable disease in 50%.[34] Patients who responded to anastrozole also reported less pain and fatigue.[34]

Furthermore, hormone receptor-positive breast cancer has been successfully treated with various Federal Drug Administration (FDA)-approved CDK4/6 inhibitors in combination with hormone therapy, such as aromatase inhibitors. The robust estrogen receptor expression of low-grade serous ovarian cancer is similar to that of hormone receptor-positive breast cancer, which suggests that CDK4/6 inhibitors might also be effective in low-grade ovarian cancer.[35] In 2020, a phase II clinical trial of letrozole (an aromatase inhibitor) and ribociclib (a CDK4/6 inhibitor) showed promising results in estrogen receptor-positive, relapsed low-grade serous ovarian cancer.[36] Although the results are limited by a very small number of cases (only three patients with low-grade cancer were included), one woman had a complete response and two had partial responses lasting over 2 years.[36] These findings have led to additional ongoing promising clinical trials as mentioned below.

Targeted Therapy

Because of the prevalence of MAPK-related mutations in low-grade and borderline tumors, drug therapies targeting MAPK-activating enzymes MEK1 and/or MEK2 have been developed and tested in multiple clinical trials, but the results have been mixed (Table 2). In 2020, a phase III clinical study evaluating binimetinib found no significant difference in progression-free or overall survival compared with standard-of-care therapy.[37] A phase II study from the same year, reported an objective response rate of 12.1% (all partial responses) using pimasertib in patients with recurrent low-grade and borderline tumors.[38] This objective response rate is noteworthy, considering that the objective response rate for the treatment of low-grade serous carcinomas with platinum-based chemotherapy is between 4% and 23.1%.[30 39] However, 84.4% of patients treated with pimasertib experienced grade 3–4 adverse effects, and these high toxicity rates resulted in early trial termination.[38]

In an early phase II study, the MEK inhibitor, selumetinib, achieved a complete or partial response in 15% of patients with recurrent low-grade serous ovarian cancer, and was well-tolerated.[40] Most recently, in 2022, in a phase II/III study, trametinib led to significant improvement in both median progression-free and overall survival in comparison with standard-of-care therapies[41] (Table 2). Based on careful evaluation of the evidence from these trials, the National Comprehensive Cancer Network (NCCN) decided to include MEK inhibitors as a treatment option for recurrent low-grade serous ovarian cancer.[42] Overall, most MEK inhibitors were well-tolerated without severe side effects.[37 40 41] There have also been interesting genomics findings regarding MAPK mutations and MEK inhibitor response: surprisingly, in patients who did not receive a MEK inhibitor, MAPK-mutated tumors were associated with better progression-free and overall survival. There was no difference in survival based on MAPK mutations in patients who received an MEK inhibitor.[18]

Because they also target the MAPK pathway, BRAF inhibitors have been receiving attention as a potential treatment option for low-grade cancer. As *BRAF* is an upstream regulator of the MAPK pathway, mutations in *BRAF* may lead to continuous activation and therefore uncontrolled cell proliferation. Remarkable clinical response to BRAF inhibitors in *BRAF*-mutant cancers, especially melanoma, has been reported; however, other *BRAF*-mutant cancers have not shown as robust of a response.[43] A 2018 study assessed the pervasiveness of *BRAF* mutations in a cohort of women with low-grade serous ovarian carcinomas (14%) and the efficacy of a BRAF inhibitor, dabrafenib. Two patients with recurrent, chemoresistant low-grade cancer, and a somatic *BRAF*-V600E mutation were identified as good candidates for targeted therapy. One patient experienced a complete and sustained response, while the other achieved a partial response.[43] Although these are only case reports, their results support the efficacy of BRAF inhibitors in a small subgroup of patients with recurrent, *BRAF*-mutated low-grade serous ovarian cancer as well as the role of the genomic profiling of low-grade tumors in guiding effective management and treatment.

A case study from 2023 also showed exciting results with a combination of epidermal growth factor receptor inhibitors (afatinib and erlotinib) and Bruton's tyrosine kinase inhibitor (ibrutinib) in a patient with recurrent, chemoresistant low-grade serous ovarian cancer.[44] The researchers used patient-derived tumor organoids to perform a high-throughput drug sensitivity screening and identify the most efficient drugs.[44] After treatment, the patient had a significant improvement in pain and quality of life, as well as a decrease

Table 2 Completed clinical trials in recurrent low-grade serous ovarian cancer

Class	MEK inhibitors or MEK inhibitor therapy combinations				Aromatase inhibitor
Reference	**Gershenson et al, 2022**[41]	**Monk et al, 2020**[37]	**Farley et al, 2013**[40]	**Arend et al, 2020**[38]	**Tang et al, 2019**[34]
Trial	**GOG 281/LOGS (NCT02101788)**	**MILO/ ARRAY-162–311/ ENGOT-ov11 (NCT01849874)**	**GOG-0239 (NCT00551070)**	**EMR 20006–012 (NCT01936363)**	**PARAGON (ACTRN1261000796088)** part of basket trial
Design	Phase II/III	Phase III	Phase II	Phase II	Phase II
Randomization	Randomized, open-label (1:1)	Randomized, open-label (2:1)	Single arm, open-label	Randomized, double-blind placebo-controlled (1:1)	Single arm, open-label
Cohort	Recurrent LGSOC	Recurrent or persistent LGSOC	Recurrent LGSOC	Recurrent SBOT and LGSOC	ER and/or PR-positive recurrent or metastatic LGSOC or SBOT
Intervention	Trametinib 2 mg once daily vs physician's choice (paclitaxel, pegylated liposomal doxorubicin, topotecan, letrozole, tamoxifen)	Binimetinib 45 mg twice daily vs physician's choice (paclitaxel, pegylated liposomal doxorubicin, topotecan)	Selumetinib 50 mg twice daily	Pimasertib 60 mg daily with SAR245409 (PI3K/mTOR dual kinase inhibitor) 70 mg daily vs pimasertib 60 mg twice daily	Anastrozole 1 mg daily
Dates	2014–2018	2013–2016	2007–2009	2012–2014	2012–2016
Number of patients	**Trametinib** n=130 **Standard-of-care** n=130	**Binimetinib** n=201 **Standard-of-care** n=102	**Selumetinib** n=52	**Pimasertib with SAR** n=32 (6 SBOT) **Pimasertib** n=33 (6 SBOT)	**Anastrozole** n=36 (2 SBOT)
Median progression-free survival	**Trametinib:** 13.0 months (95% CI 9.9 to 15.0) **Standard-of-care:** 7.2 months (95% CI 5.6 to 9.9) **HR=0.48 (95% CI 0.36 to 0.64)**	**Binimetinib:** 9.1 months (95% CI 7.3 to 11.3) **Standard-of-care:** 10.6 months (95% CI 9.2 to 14.5) **HR=1.21 (95% CI 0.79 to 1.86)**	**Selumetinib:** 11.0 months (95% CI 3.6 to 15.9)	**Pimasertib with SAR:** 10 months (95% CI 3.4 to 12.8) **Pimasertib:** 7.23 months (95% CI 4.2 to NR)	**Anastrozole:** 11.1 months (95% CI 3.2 to 11.9)
Median overall survival	**Trametinib:** 37.6 months (95% CI 32.0 to NR) **Standard-of-care:** 29.2 months (95% CI 23.5 to 51.6) **HR=0.76 (95% CI 0.51 to 1.12)**	**Binimetinib:** 25.33 months (95% CI 18.46 to NR) **Standard-of-care:** 20.83 months (95% CI 17.45 to NR) **HR=0.85 (95% CI 0.49 to 1.48)**	**Selumetinib:** Median OS has not been reached; 2 year OS was 55% (95% CI 40% to 71%)	Not reported	Not reported
Response rate	**Trametinib:** ORR 26% (34/130), SD 59% (77/130) **Standard-of-care:** ORR 6% (8/130), SD 71% (92/130)	**Binimetinib:** ORR 16% (32/198), SD 60% (119/198) **Standard-of-care:** ORR 13% (13/101), SD 60% (61/101)	**Selumetinib:** ORR 15% (8/52), SD 65% (34/52)	**Pimasertib with SAR:** ORR 9.4% (3/32, all PR), SD 50% (16/32) **Pimasertib:** ORR 12.1% (4/33, all PR), SD 36.4% (12/33)	**Anastrozole:** ORR 14% (5/36, all PR), SD 50% (18/36). Clinical benefit at 3 months (primary endpoint) 63.9% (22/36 SD, 1/36 PR, 0 CR). Clinical benefit at 6 months 60.8% (22/36).
Median duration of response	**Trametinib:** 13.6 months (95% CI 8.1 to 18.8) **Standard-of-care:** 5.9 months (95% CI 2.8 to 12.2)	**Binimetinib:** 8.05 months (95% CI 5.55-NR) **Standard-of-care:** 6.67 months (95% CI 3.71-NR)	**Selumetinib:** 10.5 months (95% CI 8.2-not estimable)	Not reported	**Anastrozole:** 9.5 months (95% CI 8.3 to 25.8) median duration of clinical benefit at 3 months (n=23)

ER, estrogen receptor; HR, hazard ratio; LGSOC, low-grade serous ovarian carcinoma; NR, not reached; ORR, objective response rate; PR, partial response; PrR, progesterone receptor; SBOT, serous borderline ovarian tumor; SD, stable disease.

in her CA-125 level.[44] This study highlights the potential of targeting epidermal growth factor receptor, a growth factor upstream of the MAPK pathway.

In addition, a recent drug-repurposing study performing high-throughput screening in established low-grade cell lines, evaluated synergy between the most promising agents and a MEK inhibitor (trametinib).[45] The agents with the best response and toxicity profiles were a tyrosine kinase inhibitor (dasatinib), and an aldehyde dehydrogenase inhibitor (disulfiram).[45] Dasatinib and another more selective Src family kinase (SRK) inhibitor both showed synergy with trametinib, confirming that the likely mechanism of action of the dasatinib–trametinib combination is SRK inhibition.[45]

Ongoing Trials

There have also been exciting preliminary results from ongoing clinical trials with both targeted and hormonal therapies. The GOG-3026 phase II clinical trial administered dual treatment of an aromatase inhibitor (letrozole) and a CDK4/6 inhibitor (ribociclib)

to patients with recurrent low-grade serous ovarian cancer. They reported promising initial clinical data at the Society of Gynecologic Oncology (SGO) 2023 conference, with a clinical benefit of 79% and an objective response rate (all partial responses) of 23%.[46] Another phase II pilot study examined the neoadjuvant treatment of a CDK4/6 inhibitor (abemaciclib) combined with an estrogen-receptor antagonist (fulvestrant) in patients with advanced low-grade serous ovarian cancer and found partial response in 47% (7/15) patients and stable disease in 33% (5/15) patients.[47]

At the 2024 SGO meeting, the most recent data were presented from the phase II ENGOT-ov60/GOG-3052/RAMP 201 trial, showing the high efficacy of a dual RAF/MEK inhibitor (avutometinib) with a focal adhesion kinase (FAK) inhibitor (defactinib) in patients with recurrent low-grade serous ovarian cancer.[48] The combination of avutometinib and another FAK inhibitor (VS-4718) was previously tested in xenografts (PDX) derived from a patient with low-grade cancer, and displayed significant tumor growth inhibition compared with the vehicle and treatment with avutometinib alone, laying the groundwork for clinical trials.[49] In the proof of concept, FRAME study, a durable objective response rate of 46% was reported using a combined regimen of a RAF/MEK inhibitor (VS-6766) with defactinib in patients with recurrent low-grade serous ovarian cancer.[50] These results led to the initiation of a phase II trial, presented at the 2024 SGO meeting, which evaluated the optimal regimen and efficacy of avutometinib (VS-6766) and defactinib in different combinations.[50] Patients who received the avutometinib–defactinib treatment had an objective response rate of 45%, and 86% displayed tumor regression.[48] The objective response rate was higher, at 60%, in patients with *KRAS* mutations than *KRAS*-wild-type patients, who had an objective response rate of 29%.[48] These exciting results have spurred the initiation of an ongoing phase III clinical trial examining avutometinib and defactinib vs clinician's choice in patients with recurrent low-grade serous ovarian cancer.[48]

Gaps in Knowledge

As described above, recent robust genomics studies have revealed novel mutations recurring in low-grade serous ovarian tumors, beyond MAPK mutations. These findings have led to promising case studies and clinical trials involving agents such as EFGR and CDK4/6 inhibitors, and anastrozole. However, these mutations are relatively scarce and, therefore, not largely representative of low-grade ovarian cancer. The current translational and clinical research focuses on activators of the MAPK pathway and proliferation, which has not brought the hoped-for breakthroughs in treatment.

Studies of the role of other hallmarks of cancer might discover novel mechanisms of tumorigenesis and low-grade cancer progression that can be targeted. Research into the biology of low-grade tumors should expand beyond a narrow examination of MAPK signaling and investigate the role of the immune system, epigenetics, metabolism, non-coding RNAs (miRNA, lncRNA, circular RNA), and other drivers of malignancy in low-grade ovarian cancer. There has been a growing understanding of the role that the tumor microenvironment plays in tumorigenesis and in facilitating the deep invasion of these tumors. Given the importance of tumor architecture within the tumor microenvironment in low-grade serous invasion, spatial omics technologies could elucidate novel targets in the reprogrammed stroma, and yield a better, more holistic, understanding of the immune landscape of low-grade serous ovarian cancer.

Although there have been breakthroughs with the use of immunotherapy in other cancers, low-grade ovarian tumors are microsatellite stable, so immunotherapy using checkpoint inhibition has not been an effective treatment thus far.[29] The function of other branches of the immune system, including the innate immune system, have been less studied, and might play an important role in the biology of low-grade ovarian cancer. Behavior of myeloid and/or natural killer (NK) cells in the low-grade tumor microenvironment (TME) should be explored and harnessed for targeting.

A limitation hampering major progress in research into low-grade ovarian cancer is the lack of representative in vivo and in vitro models. A few low-grade cell lines have been established,[45 51 52] which exhibit the mutational profile of low-grade serous ovarian cancer, but currently, there are no established in vivo animal models for validating in vitro findings. One serous borderline ovarian tumor cell line exists, SBOT3.1, and consistent with the behavior of borderline cells, it is non-invasive and has a very low proliferation index.[53] This makes it extremely difficult, if not impossible, to use this cell line for in vitro experiments investigating the transition from borderline to low-grade cancer. Organoids and 3D models of low-grade serous ovarian cancer could also prove useful in investigating therapeutic targets and assessing drug efficiency. These organotypic models could allow us to functionally characterize the genomic changes identified by sequencing, and also test different treatments for low-grade ovarian cancer.

In vivo models are a necessary tool for predicting therapeutic response and the mechanisms of chemoresistance because they more accurately simulate the heterogeneity of the tumor and its biological environment than in vitro models, which are more susceptible to genetic and morphologic changes. A PDX model derived from low-grade serous peritoneal metastasis has been developed[54]; however, establishing these models requires access to fresh patient tissue, which can be problematic since low-grade serous ovarian cancer is rare and only diagnosed post-operatively. The slow growth of these tumors also presents a challenge when planning experiments—it will take far longer to passage and establish low-grade tumors in murine models compared with tumors of more rapidly proliferating subtypes, such as high-grade serous carcinomas.

Finally, the early diagnosis of serous borderline tumors, as well as the progression to low-grade ovarian cancer, is not yet possible. Clinical and molecular studies aiming to identify biomarkers found in body fluids, such as plasma, which may indicate disease occurrence, could lead to a breakthrough in early detection and intervention.

CONCLUSION

To successfully treat low-grade serous ovarian cancer, we must understand it as a disease distinct from high-grade serous ovarian cancer. Surgical cytoreduction remains the first-line treatment for both low- and high-grade ovarian cancer, but due to the limited efficacy of platinum/taxane chemotherapy as adjuvant treatment for low-grade cancer, novel targets and treatments are urgently needed to improve clinical outcomes for the recurrent and metastatic

disease. Thus far, the MAPK pathway has been the main driver pathway identified in low-grade tumors, but the MAPK inhibitors developed in the past decade have been only moderately effective, suggesting that other mechanisms drive the biology of low-grade serous ovarian cancer. The recent novel hormonal and molecular targets and ongoing clinical trials evaluating combinations of treatments have shown therapeutic efficacy, hopefully paving the way for new approaches in the treatment of low-grade serous ovarian carcinomas.

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Acknowledgements The authors thank Gail Isenberg for editing spelling and grammar.

Contributors The initial draft was written by LK with help from RY-B. LS and EL provided substantial edits to several revisions of the manuscript. All authors approve, and agree to be accountable for, all aspects of the work.

Funding This review was supported by the Janet Burros Memorial Foundation and NIH/NCI grant R35CA264619 (EL).

Competing interests LS is a current employee of OmicVision Biosciences ApS. EL receives research funding to study the biology of ovarian cancer from Arsenal Bioscience and AbbVie through the University of Chicago unrelated to this work. The remaining authors declare no conflicts of interest.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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