Redefining the Standard of Care for Low-Grade Serous Ovarian Cancer

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Abstract: Low-grade serous carcinoma is a rare epithelial ovarian cancer subtype with distinct clinical, histologic, and molecular features. Improved understanding of this disease subtype has prompted recent advances in treatment options. Although low-grade serous carcinoma historically has been treated following a high-grade serous carcinoma paradigm, new data have called into question the utility of platinum retreatment, addressed the possibility of first-line hormonal treatment, and brought forth therapeutic options targeting the MAPK pathway and cyclin D kinase in low-grade tumors. Ongoing research efforts seek to leverage the unique features of low-grade serous carcinoma to refine treatment options for patients with this rare tumor subtype.

Introduction

Low-grade serous carcinoma (LGSC) of the ovary, fallopian tube, or peritoneum accounts for approximately 5% of epithelial ovarian cancers (EOCs) and is clinically, histologically, and molecularly distinct from the more commonly encountered high-grade serous subtype. Recent advances in the understanding of LGSC have highlighted the need to treat it as a separate entity from high-grade serous carcinoma (HGSC). As a result, there has been a paradigm shift in the approach to and management of this disease. To this end, a recent clinical investigation has focused on accurately risk stratifying patients, effectively leveraging available surgical and clinical options for these patients, and developing therapeutic options that target the molecular and hormonal pathways that underpin LGSC. This review seeks to highlight these advances and contextualize them within the broader history of LGSC management.

Clinical Presentation

Although the median age at diagnosis is 43 years, LGSC presents in a bimodal age distribution. Older patients (50-60 years) more commonly display tumors with somatic mitogen-activated protein kinase (MAPK) alterations and have a better overall prognosis, whereas younger patients (20-30 years) have a poorer prognosis.[1] In a retrospective evaluation of patients diagnosed with LGSC before 2012, Gershenson and colleagues found, on multivariable analysis, that patients diagnosed at older than 35 years were 43% less likely to die of the disease compared with those who were 35 years or younger at diagnosis (hazard ratio [HR], 0.53; 95% CI, 0.37-0.74; $P<.001$).[2] As with most EOCs, LGSC is often diagnosed at an advanced stage, with approximately 60% of patients presenting with International Federation of Gynecology and Obstetrics (FIGO) stage III and higher disease.[3] Radiographic features may include calcified implants (Figure 1).

Although generally considered to have a more indolent disease course than HGSC, some clinical characteristics among patients with LGSC are associated with an aggressive disease course and poor prognosis. Established factors associated with worse progression-free survival (PFS) and overall survival (OS), such as advanced FIGO stage and gross residual disease after cytoreductive surgery, are common to all EOC subtypes. Other risk factors, such as age at diagnosis, are more specific to patients with LGSC.[2] Less established clinical risk factors for poor prognosis that have been proposed in small retrospective studies include cigarette smoking and obesity.[4,5]

Histologic Presentation

The World Health Organization defines LGSC as an invasive, serous neoplasm with low-grade malignant features. The tumor is characterized by mild to moderate nuclear atypia, uniform cellularity, and a low mitotic index (up to 12 mitoses per 10 high-powered fields). Most LGSCs have positive immunohistochemistry (IHC) staining for PAX8 and WT1, and a small minority have aberrant TP53 IHC.[6] Many LGSCs display hormone receptor positivity, with 50% to 90% having estrogen receptor positivity and 40% to 60% having progesterone receptor positivity.[7-9]

Since the early 2000s, serous ovarian cancers (SOCs) have been classified as high- and low-grade tumors, which is a departure from the historical Shimizu/Silverberg grading system of grade 1, grade 2, and grade 3 disease.[10,11] Studies have consistently demonstrated the validity of this 2-tiered grading system.[12-14] In rare cases when a tumor has LGSC with concurrent high-grade or poorly differentiated carcinoma, management should follow high-grade disease guidelines, as this confers the greatest risk.[15] Although HGSC is now thought to originate in the fallopian tube, LGSC typically arises either de novo or in a sequential fashion, progressing from a benign ovarian tumor to a serous borderline tumor (which lacks destructive stromal invasion), and ultimately to invasive LGSC. This disease process likely exists along a spectrum, and as a result, the classification of this tumor subtype has evolved. The differentiation of histology along this spectrum is important, as serous borderline tumors, including serous borderline tumors with micropapillary features (which is synonymous with the prior classification of noninvasive LGSC), should not be treated as invasive LGSC.

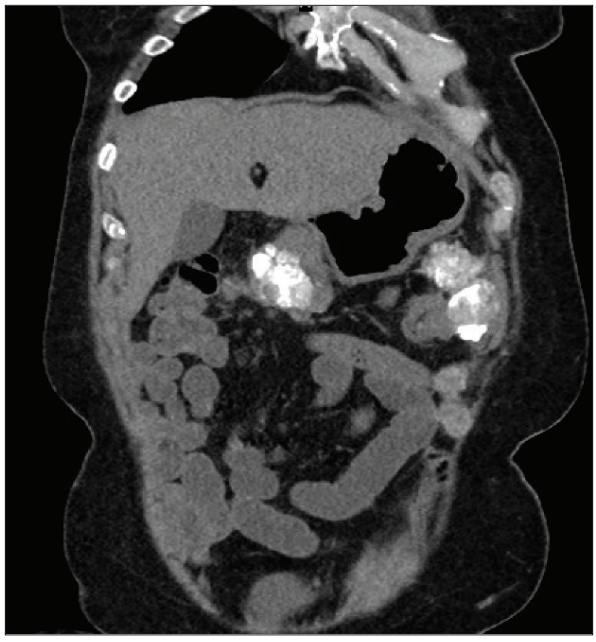

Figure 1. Coronal computed tomography scan illustrating calcified implants in a patient with newly diagnosed low-grade serous carcinoma.

It is poorly understood which patients progress from benign disease to LGSC. Population-based studies have reported a 4% to 7% absolute risk of malignant progression among all patients with serous borderline tumors.[16,17] Progression from a preinvasive tumor to LGSC can be indolent and can occur up to 20 years after the initial diagnosis of a serous borderline tumor.[18] Population-based studies have reported that women with serous borderline tumors with extraovarian disease carry up to a 16% lifetime risk of LGSC. Similarly, serous borderline tumors that exhibit micropapillary features (5%-10% of all tumors) are at increased risk for progression to LGSC.[16,17]

Data also suggest that the presence of a *BRAF* V600E mutation may help in prognostication for patients with serous borderline tumors. In fact, serous borderline tumors harboring a *BRAF* V600E mutation are less likely to progress to advanced-stage LGSC.[19] One study

found that *BRAF* V600E mutations occurred in 48% of serous borderline tumors vs 5% of LGSCs, and that *BRAF*-mutated serous borderline tumors have distinct morphologic features, including abundant eosinophilic cytoplasm, well-defined cell borders, bland nuclei, and cell budding.[20,21] As such, *BRAF* V600E IHC or sequencing can provide relevant information for prognostication, especially in patients with serous borderline tumors who are seeking more conservative management.

Molecular Underpinnings

One of the most active areas of investigation in LGSC is the characterization of its molecular landscape and correlating it with clinical outcomes. Numerous studies have demonstrated the importance of the MAPK pathway to tumorigenesis in LGSC. As a part of this pathway, oncogenic activating mutations in *RAS* and *RAF* genes, such as *KRAS* and *BRAF,* lead to overactivation of MEK1/2, subsequent RAF phosphorylation, and ultimately, extracellular signal-regulated kinase (ERK) activation, which influences cancer cell proliferation, differentiation, and survival (Figure 2).[22] Alterations in this pathway occur in approximately 50% to 60% of LGSC tumors, including 26% to 33% with *KRAS* alterations, 8% to 11% with *NRAS* alterations, 6% to 13% with *BRAF* alterations, and 2% to 4% with other alterations (eg, *HRAS, NF1, NF2*).[23-25] For patients without alterations in the MAPK pathway, an investigation is ongoing to identify candidate driver genes and illuminate pathways driving oncogenesis.[25] Notably, *TP53* alterations, which are present in most HGSCs, are largely absent from LGSCs. Studies have found that after a central pathology review, only 2% of LGSCs have *TP53* alterations. Thus, any *TP53*-altered tumors characterized as LGSC should be carefully evaluated by gynecologic pathologists to confirm the diagnosis.[23]

Alterations in the MAPK pathway have been tied to patient outcomes. For example, a study of 119 patients with LGSC reported that those with MAPK alterations had longer OS, even after controlling for platinum sensitivity.[23] Similarly, a post hoc tumor tissue analysis from the phase 3 MILO/ENGOT-ov11 study, which investigated patients randomized to the MEK1/2 inhibitor binimetinib (Mektovi, Pfizer) or physician's choice of chemotherapy, reported a nonsignificant trend toward improved PFS in patients with MAPK alterations treated with physician's choice of chemotherapy compared with those without MAPK alterations.[24] Prior studies have suggested an association between *KRAS* alterations and improved outcomes in patients with LGSC, but these studies did not control for factors such as platinum sensitivity.[26] There is, however, evidence that hormone receptor positivity, which may play a prognostic role in LGSC, may be correlated with copy number alterations and the frequency of MAPK alterations.[27]

Inherited Risk

Unlike its high-grade serous counterpart, in which up to 20% of tumors have a clear germline association, fewer than 5% of patients with LGSC carry germline *BRCA1* or *BRCA2* alterations.[23,28,29] In fact, studies on germline testing have determined that even when patients with LGSC carry germline alterations, few tumors exhibit loss of heterozygosity suggestive of a germline driver.[23] Germline testing is considered the standard of care for all patients with newly diagnosed LGSOC, with the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology, the European Society for Medical Oncology, and other consensus guidelines recommending germline testing for all patients with EOC. This testing is important owing to the possibility of histologic misdiagnoses of patients with high-grade disease who instead have a low-grade histology.[30-32]

Treatment in the Primary Setting

Primary cytoreductive surgery is the mainstay of treatment for patients with LGSC, and studies have consistently demonstrated the association of residual disease after cytoreductive surgery with poorer patient outcomes.[33] As such, guidelines recommend primary cytoreductive surgery when feasible and employing maximal surgical effort, followed by either platinum-based chemotherapy or hormonal treatment for patients with FIGO stage IC2 and higher disease.[34] Despite improved outcomes with complete gross resection compared with gross residual disease, consensus guidelines still recommend primary cytoreduction over neoadjuvant chemotherapy for LGSC histologies, even when achieving only optimal residual disease (≤1 cm). These recommendations are based on the overall lower expected response rates to chemotherapy among patients with LGSC and the dose-dependent association of residual disease volume with survival outcomes.[35,36]

Postoperatively, the optimal treatment for patients with LGSC is under active investigation. An ongoing noninferiority randomized controlled trial (NCT04095364, NRG GY019) is investigating PFS in patients with stages II to IV primary LGSC who have undergone primary cytoreductive surgery. Participants were randomized to receive either monotherapy with the aromatase inhibitor letrozole or intravenous paclitaxel and carboplatin for 6 cycles followed by maintenance letrozole. A prior retrospective study on hormonal monotherapy after cytoreductive surgery reported a 22% recurrence rate among the 27 patients after a median follow-up of 41 months (range,

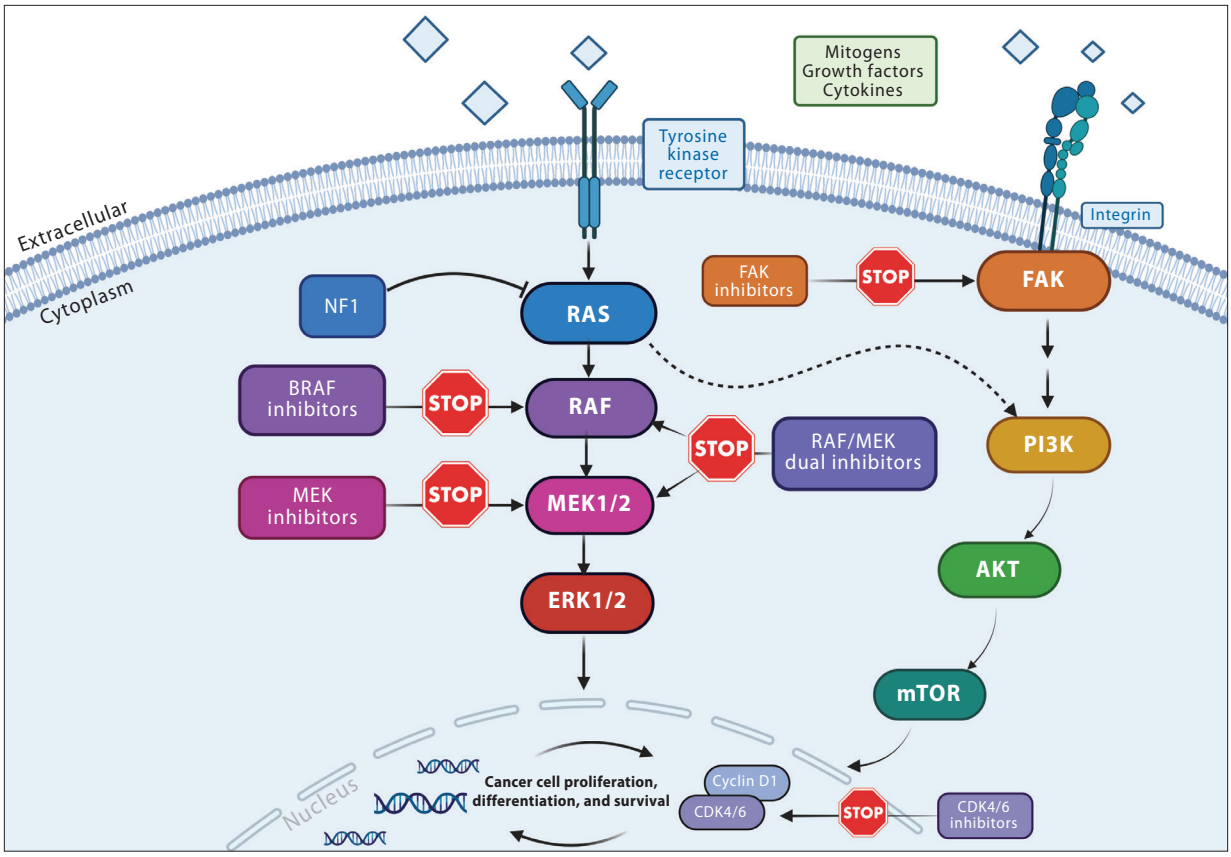

Figure 2. Targetable pathways and molecular underpinnings of low-grade serous carcinoma. mTOR, mammalian target of rapamycin; NF1, neurofibromin 1; PI3K, phosphoinositide 3-kinase. Created with BioRender.

21-114 months). In this study, the 3-year PFS rate was 79.0% and the 3-year OS rate was 92.6%, which compared favorably with historical survival data for patients receiving postoperative chemotherapy.[37]

Several prospective randomized trials have demonstrated similar PFS and OS in patients who received primary cytoreductive surgery followed by chemotherapy or neoadjuvant chemotherapy with interval cytoreductive surgery followed by postoperative chemotherapy. These trials, however, included very few patients with LGSC (1%-3% of patients enrolled).[38,39] Numerous studies have demonstrated relatively low response rates to traditional platinum-based chemotherapy in LGSC, with only 4% to 11% of these tumors responding to neoadjuvant treatment.[40,41] Nevertheless, the use of neoadjuvant chemotherapy among patients with LGSC has significantly increased in recent years, mirroring national trends observed in all patients with EOC.[42,43] According to national databases, between 2019 and 2020, 15% to 26% of patients with LGSC received neoadjuvant chemotherapy. Unfortunately, data suggest that the use of neoadjuvant chemotherapy is associated with decreased OS compared with primary cytoreductive surgery. A National Cancer Database study demonstrated a 4-year median OS rate of 56.4% in patients with LGSC who received neoadjuvant chemotherapy compared with 81.0% in patients who underwent primary cytoreduction (HR, 2.12; 95% CI, 1.55-2.90).[43] This finding reiterates the importance of accurate diagnosis of LGSC in patients with advanced-stage EOC (ideally with tissue biopsy as opposed to cytology alone), maximal cytoreductive efforts, and the need for improved treatment options for patients with LGSC who are not candidates for surgery at the time of presentation. Preliminary data from a pilot study of neoadjuvant fulvestrant, a selective estrogen receptor modulator, in combination with the oral CDK4/6 inhibitor abemaciclib (Verzenio, Lilly) for patients with advanced LGSC not amenable to primary cytoreductive surgery showed a promising response rate of 47%.[44] In this study, grade 3 and 4 toxicity rates were 13.3%, including acute kidney injury (1 of 15 patients) and neutropenia (1 of 15 patients). When available, clinical trial options should be considered for patients with advanced LGSC who are not candidates for primary cytoreductive surgery.

Maintenance Treatment

Evidence suggests there is benefit of maintenance hormonal blockade in patients with advanced-stage LGSC after upfront treatment, with letrozole at 2.5 mg orally daily being the most commonly used regimen for this purpose. A retrospective study of 203 patients with stage II to IV LGSC, who received primary surgery followed by platinum/taxane chemotherapy, compared those who received postchemotherapy hormonal maintenance (n=70) with those who underwent observation alone (n=133).[45] The median PFS was 64.9 months for patients who received postchemotherapy hormonal maintenance therapy vs 26.4 months for patients who did not (P<.001). Given the tolerability of hormonal treatments, consensus guidelines recommend considering maintenance hormonal blockade in patients with advanced disease who have completed adjuvant chemotherapy or in patients treated with first-line hormonal therapy.

Treatment in the Recurrent Setting

For patients with recurrent LGSC, secondary cytoreductive surgery should be strongly considered. Although 3 randomized trials have compared secondary cytoreduction with chemotherapy in EOC, only 0.8% to 3.0% of patients in these trials had LGSC.[46,47] A systematic review and meta-analysis addressed the limited data on the benefit of secondary cytoreduction in patients with recurrent LGSC and reported gains in survival associated with complete gross resection and, to a lesser extent, optimal cytoreduction.[48] Importantly, this systematic review reported that surgery compared with systemic therapy as the initial treatment for recurrence was also associated with improved survival. Given the relatively indolent disease course of LGSC and the poor response rates to traditional chemotherapeutics, secondary and higher-order cytoreduction should be considered when technically feasible and medically appropriate.

For patients with recurrent LGSC who are not considered candidates for surgery, available treatment options include chemotherapy, hormonal blockade, or MEK inhibition. Regarding chemotherapeutic options, numerous studies have demonstrated the chemoresistance of recurrent LGSC. Retreatment with platinum-based chemotherapy has a low yield, with objective response rates (ORRs) reported as 22% in the second-line and 10% in the third-line settings for patients with platinum-sensitive recurrence.[41] Similarly, data suggest that approximately 25% of patients with LGSC respond to second-line treatment with any cytotoxic agent.[41] Bevacizumab may improve response rates in patients with LGSC (≤48% ORR), and as such, regimens such as weekly paclitaxel with bevacizumab are often employed in the second-line setting.[49]

Despite known high rates of estrogen and progesterone receptor positivity in LGSC, low response rates to estrogen, progesterone, and androgen blockade are generally observed.[50,51] In fact, estrogen or progesterone receptor IHC as well as signal transduction pathway assays do not accurately predict response to hormonal blockade in LGSC.[52,53] In a single-institution study of 64 patients with LGSC treated with hormonal blockade, the ORR was only 9%.[51] Similarly, in a randomized trial comparing the MEK1/2 inhibitor trametinib (Mekinist, Novartis) vs physician's choice of chemotherapy or endocrine therapy (NCT02101788, GOG-281), the ORR was 0% to tamoxifen and 14% to letrozole.[54] Nevertheless, stable disease can be obtained using hormonal blockade in a high proportion of patients with LGSC (50%-61%), with some patients exhibiting durable responses. Thus, hormonal therapies are generally considered for patients with low-volume or indolent disease, or in those who are unlikely to tolerate toxicity associated with chemotherapy or targeted agents.[51,53]

Perhaps the most promising therapy in recurrent LGSC is MEK inhibition. Two large phase 3 studies have reported moderate effects of single-agent MEK inhibition in patients with LGSC: GOG-281/LOGS (trametinib; NCT02101788) and MILO/ENGOT-ov11 (binimetinib; NCT01849874).[54,55] GOG-281/LOGS reported a 26% ORR to trametinib, and MILO/ENGOT-ov11 reported a 16% ORR to binimetinib. Based on these findings, trametinib and binimetinib are now listed in the NCCN Compendium for the treatment of recurrent LGSC.[34] Notably, these targeted therapies carry significant toxicity. In MILO/ENGOT-ov11, grade 3 or higher adverse events occurred in 76% of patients who received binimetinib vs 44% of patients who received physician's choice of chemotherapy; the most common toxicities were diarrhea, nausea, vomiting, fatigue, and elevated creatine phosphokinase. Toxicities leading to discontinuation of binimetinib included decreased ejection fraction (4%, n=8), vomiting (3%, n=6), intestinal obstruction (2%, n=5), and retinal vein occlusion (2%, n=5).

Ongoing Investigation

Current efforts in therapeutic development for LGSC have focused on combination therapy that targets MAPK pathway drivers. Given the known layers of feedforward and feedback regulation in the ERK pathway beyond MEK1/2 overactivation, additional investigation has focused on dual inhibition of RAF and MEK, specifically given the feedback reactivation of RAF activity after MEK inhibition. Preclinical investigation has demonstrated that dual RAF and MEK inhibition

is more effective than RAF or MEK inhibition alone at restricting upregulation of RAF-dependent MEK phosphorylation, and results in a more robust and more prolonged pathway inhibition.

Although promising, additional investigation of resistance mechanisms has demonstrated that RAF/MEK inhibitors can induce compensatory activation of focal adhesion kinase (FAK), a nonreceptor tyrosine kinase that integrates signals from integrin and growth factor to regulate cell proliferation, survival migration, and invasion, and may act as a resistance mechanism to RAF/MEK pathway inhibition (Figure 2).[56] Further, studies have shown that FAK is activated following inhibition of the RAS/RAF/MEK pathway in several preclinical tumor models.[57,58] Thus, the combination of RAF/MEK/FAK inhibition holds particular promise in LGSC.

In the FRAME phase 1/2 proof-of-concept study (NCT04625270), there was an ORR of 46% in patients with LGSC who received both the dual RAF/MEK inhibitor avutometinib and the FAK inhibitor defactinib.[59] Based on these promising results, the combination of avutometinib with defactinib was granted breakthrough therapy designation by the US Food and Drug Administration in 2021 for the treatment of patients with LGSC who have received at least 1 prior line of platinum-based therapy. In December 2021, the RAMP 201 (ENGOTov60/GOG-3052; NCT04625270) phase 2 trial of avutometinib with or without defactinib was opened to patients with LGSC following at least 1 prior line of chemotherapy. A planned interim analysis demonstrated an ORR of 45% for patients with heavily pretreated LGSC who were treated with the combination regimen in Part A of the study.[60] In avutometinib monotherapy, the most common grade 3 and higher toxicities included dermatitis acneiform (6.3%, n=4) and increases in blood creatinine phosphokinase (14.1%, n=9). Meanwhile, in avutometinib and defactinib combination therapy, the most common grade 3 and higher toxicities mirrored those of avutometinib monotherapy, including fatigue (5.3%, n=3) and increases in blood creatinine phosphokinase (15.8%, n=9). Strategies to prevent associated dermatologic toxicities include twice-daily application of moisturizer, sunscreen with a sun protection factor of at least 50, and 1% hydrocortisone cream to affected areas; systemic antibiotics including minocycline or doxycycline can also be used prophylactically.

Another promising area of investigation is the use of endocrine treatment combined with CDK4/6 inhibition. In breast cancer, the clinical benefit from endocrine and CDK4/6 inhibition is well-established in hormone receptor–positive disease.[61-63] This combination has been proposed for the treatment of LGSC, given the similarities between LGSC and hormone receptor–positive breast cancer, as well as the known frequency of aberrant cyclin expression in LGSC (Figure 2). Although a response rate of only 4% has been reported for single-agent CDK4/6 inhibition in patients with SOC, subsequent investigation of a combination of the aromatase inhibitor letrozole and the CDK4/6 inhibitor ribociclib (Kisqali, Novartis) demonstrated partial responses in patients with recurrent LGSC.[64,65] A pilot study as part of an investigator-initiated, single-arm phase 2 trial (GOG-3026) investigating this combination reported a 26% response rate and a 19.1-month duration of response to this combination among 48 patients with advanced or recurrent LGSC.[66]

Conclusion

Given the histologic and molecularly distinct features of LGSC of the ovary, fallopian tube, or peritoneum compared with its high-grade counterpart, recent efforts have sought to define a distinct standard of care for this disease subtype. Much remains to be discovered regarding tumorigenesis in LGSC without MAPK alterations, in order to better understand how these tumors can be effectively treated. Meanwhile, continuing to refine surgical techniques to pursue complete gross resection is of the utmost importance until more effective therapeutic options are developed. Finally, it is vital that novel therapeutic trials targeting molecular and hormonal drivers of LGSC balance treatment-associated toxicity.

Disclosures

Outside of the submitted work, Dr Grisham reports honoraria from GSK, AstraZeneca, Natera, SpringWorks, Corcept, MJH Life Sciences, and Physicians' Education Resource. Dr O'Cearbhaill reports personal fees from Tesaro/GSK, Regeneron, R-PHARM US, Seagen, Fresenius Kabi, GOG Foundation, Bayer, Curio, Miltenyi Biotec, 2seventy bio, and ImmunoGen, and other from HiTech Health. She is a noncompensated steering committee member for the PRIMA, Moonstone (Tesaro/GSK), and DUO-O (AstraZeneca) studies, and is a noncompensated advisor for Carina Biotech. Her institute receives funding for clinical research from Bayer/Celgene/Juno, Tesaro/GSK, Merck, the Ludwig Center at Johns Hopkins, AbbVie/Stemcentrx, Regeneron, TCR² Therapeutics/Adaptimmune, Atara Biotherapeutics, Marker Therapeutics, Syndax, Genmab/Seagen, Sellas Life Sciences, Genentech, Kite Pharma, Acrivon, Lyell Immunopharma, and the GOG Foundation. Drs Manning-Geist and Cantor have no conflicts of interest.

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(Continues on page 226)

(Continued from page 211)

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