Editorial Commentary

Current concept of low-grade serous ovarian carcinoma

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Comment on: Manning-Geist B, Gordhandas S, Liu YL, *et al*. MAPK Pathway Genetic Alterations Are Associated with Prolonged Overall Survival in Low-Grade Serous Ovarian Carcinoma. Clin Cancer Res 2022;28:4456-65.

Keywords: Genetic alterations; low-grade serous ovarian carcinoma (LGSOC); MAPK pathway; molecular targeted therapy; overall survival (OS)

Submitted Jul 07, 2023. Accepted for publication Dec 14, 2023. Published online Jan 25, 2024.
doi: 10.21037/tcr-23-1161
View this article at: https://dx.doi.org/10.21037/tcr-23-1161

Epithelial ovarian cancer (EOC) is responsible for more than 14,070 mortalities annually worldwide, making it the third most lethal malignancy affecting the female reproductive tract (1). Despite the significant advances in early diagnostic techniques, surgical techniques, and adjuvant therapy for ovarian cancer, the prognosis has remained unchanged for over 50 years. The significant postoperative prognostic factors include age, disease stage, performance status, histological subtype, tumor grade, and the extent of residual tumors (2). Among them, recognizing the histological subtypes is crucial for developing new treatment approaches due to their distinct molecular profiles. Recently, clinical, pathological, and molecular data have suggested that EOC can be broadly categorized into two subgroups as follows: types I and II (3). High-grade serous carcinomas (HGSOCs) are predominantly classified as type II tumors, representing the most common type of epithelial carcinoma, which is characterized by aggressive behaviors. Type I tumors include low-grade serous carcinoma (LGSOCs) and endometrioid, mucinous, and clear cell carcinomas.

LGSOCs are relatively rare, typically diagnosed in younger women, and account for <5% of all ovarian carcinoma cases. The average age at diagnosis for LGSOCs is 55.5 years, which is significantly lower than the average age of 62.6 years for HGSOCs (4). A median age of 45 years has also been reported in several publications. LGSOCs can affect women of all ages, with reported cases occurring between the ages of nineteen and 79 years. They are believed to originate from serous cystadenomas or adenofibromas through a sequential and indolent process. These precursor lesions subsequently progress into serous borderline tumors (SBTs), which are characterized by invasive or non-invasive implants. SBTs progress to their full pathological potential over time and manifest as LGSOCs. Although the pathological development is generally considered to be sequential, rare instances exist where certain stages of the sequence may be skipped, leading to direct progression from a classic SBT to LGSOCs. Generally, LGSOCs are characterized by a higher likelihood of survival and are considered less aggressive than HGSOCs. However, they can experience instances of multiple recurrences and may exhibit reduced sensitivity to chemotherapy (4). Despite the slow growth pattern of LGSOCs, their tendency to be diagnosed at an advanced stage and resistance to standard systemic therapies ultimately contribute to the high fatality rate associated with this subtype. LGSOCs exhibit significant resistance to chemotherapy, and no established treatment is currently tailored for LGSOCs compared with HGSOCs.

LGSOCs and HGSOCs exhibit different molecular and genetic features at the molecular level. Molecular biology investigations have identified the activation of the mitogen-activated protein kinase (MAPK) signaling pathway and the higher expression of estrogen receptors (ERs) (approximately 80.7%) and progestogen receptors (PRs) (approximately 54.4%) as factors involved in the pathogenesis of LGSOCs (5-7). HGSOCs are also characterized by widespread p53 mutations, elevated chromosomal instability, and germline alterations in the

genes involved in homologous recombination repair, including BRCA1/2 (8). Numerous studies have reported a wide range of mutation frequencies in LGSOCs. Specifically, the prevalence of *KRAS* mutations in LGSOCs reportedly ranged from 16% to 44%, *BRAF* mutations from 2% to 20%, and *NRAS* mutations up to 26% in Western countries (6,7). Furthermore, alterations within the MAPK pathway have also been implicated in 60–82% of LGSOC cases (9,10). Among patients experiencing recurrences, *KRAS* hotspot mutations were the most common alterations, accounting for 33% of cases, followed by *BRAF* and *NRAS* alterations in 11% and 11%, respectively. Notably, these mutations occurred at mutational hotspots, including *KRAS* G12R/C/D/V, *BRAF* V600E, D594N, N581I, and *NRAS* Q61R/K (9). Another report identified canonical MAPK pathway mutations in 33 cases (52.4%), which occurred mutually exclusively: 24 *KRAS* (38.1%), 6 *BRAF* (9.5%), and 3 *NRAS* (4.8%). Most of these events occurred at the known mutational hotspots (83%, 100%, and 100% of *KRAS* G12R/C/D/V, *BRAF* V600E, and *NRAS* Q61R/K, respectively) (11). Therefore, the Kirsten rat sarcoma viral oncogene homolog (KRAS)/B-raf proto-oncogene (BRAF)/extracellular signal-regulated kinase (ERK) signaling pathway is assumed to be crucial for the development of LGSOCs in Europe. Molecular therapies that target the KRAS/BRAF/ERK signaling pathway may hold promise for combating LGSOCs in Western countries.

For the first time, a single case involving a Japanese patient has shown the presence of all regions of LGSOCs (adenofibroma, atypical proliferative serous tumor, non-invasive micropapillary SBT, and LGSOC). However, the sequencing analysis of this patient did not reveal any genetic alterations in the *BRAF* or *KRAS* hotspots, contradicting the notion that the KRAS/BRAF/ERK signaling pathway is essential for the development of LGSOCs in Japanese patients (12). Subsequently, a higher prevalence of oncogenic *PIK3CA* mutations was observed in Japanese patients, with rates of 60%, 63.6%, and 8.3% in LGSOCs, SBTs, and serous cyst adenomas, respectively, which significantly exceed the frequencies observed in the Western patient populations. *BRAF* and *ERBB2* mutations were found to be 20% and 30%, respectively. Additionally, all patients harbored wild-type *KRAS* (6). The high incidence of oncogenic *PIK3CA* mutations in SBTs and LGSOCs suggests that these mutation events occur early in the development of LGSOCs. Furthermore, it indicates that PIK3CA/AKT is the primary oncogenic signaling pathway involved in the carcinogenesis of LGSOCs in Japanese patients.

Despite accumulating evidence linking somatic mutations in *KRAS* and *BRAF* to LGSOCs, Chinese patients have been noted to exhibit a low frequency of *BRAF* (2/32) or *KRAS* (9/32) mutations (13). Therefore, the genes responsible for LGSOCs may vary between Asian and Western populations. Asian populations may derive benefits from molecular treatments that target the PIK3CA/AKT signaling pathway for treating LGSOCs.

However, the optimal first-line treatment for LGSOCs remains unknown. Some newly diagnosed patients may be treated with chemotherapy followed by maintenance hormone therapy after upfront surgery, whereas others may receive hormone therapy alone. Unfortunately, 70% of the patients will relapse, with chemotherapy demonstrating a disappointingly low response rate of <5% (14). In comparison, hormonal therapy, including anastrozole, letrozole, and tamoxifen, exhibits a response rate of 9% (15). The PARAGON trial conducted the first prospective study on anastrozole, an aromatase inhibitor, in women with recurrent or metastatic LGSOCs and serous borderline ovarian tumors (SBOTs). The results showed a 61% clinical benefit rate in patients with recurrent ER-positive and/or PR-positive tumors for at least 6 months, with acceptable toxicity (16). The combination of letrozole and ribociclib showed promising activity in women with recurrent LGSOCs compared to the reported response rates associated with an aromatase inhibitor alone. Findings from the phase II GOG-3026 trial showed that the combination elicited an overall response rate of 24% among 41 patients [95% confidence interval (CI): 13.3–38.6%]. Additionally, the clinical benefit rate achieved was 86% (95% CI: 73.7–94.5%). As of July 26, 2022, 46% of patients were still on treatment, while two patients discontinued treatment because of toxicity. Therefore, combining aromatase inhibitors with other agents could yield further benefits (17).

Recent studies have focused on exploring the inhibition of MAPK signaling as a potential treatment approach for LGSOCs because of the high occurrence of *RAS/RAF* gene mutations in these tumors. Mitogen-activated protein/extracellular signal-regulated kinase (MEK), which is an important downstream protein in the MAPK pathway, has become an attractive target for inhibitor-based treatment in malignancies where this pathway is active. In the last decade, a number of extremely effective and powerful allosteric MEK inhibitors (MEKis) that are non-adenosine triphosphate-competitive have been developed and extensively evaluated in human clinical trials. MEKis inhibit

ERK activation and its downstream processes, leading to the inhibition of the proliferation, survival, and motility of some tumor cells both *in vitro* and *in vivo*. The GOG-239 was the first clinical study to demonstrate the role of MEKis in the treatment of LGSOCs. The investigations of selumetinib in this phase II trial showed encouraging results followed by a manageable toxicity profile. Moreover, this study's results dramatically improved the reported response rate to conventional chemotherapy (14), with 15% of patients exhibiting an overall response and 65% having stable disease (18). The findings indicate the necessity for further investigation to explore the potential of MAPK pathway inhibitors as a viable treatment option for LGSOCs. A large phase III study (NCT01849874), which incorporated binimetinib as a MEKi, did not demonstrate this drug's superiority over chemotherapy for LGSOC. However, a post hoc analysis in this trial indicated a potential benefit of binimetinib in patients with *KRAS* mutation. Interestingly, a recent report from a phase II/III trial (NCT02101788) investigating the use of MEKi, trametinib, in patients with recurrent LGSOC revealed a response rate of 26%. Moreover, the study demonstrated a significant improvement in both progression-free survival (PFS) and overall survival (OS) compared to conventional treatment (19). Therefore, these results imply that MEKi may provide a novel therapeutic option for a specific subset of patients with LGSOC.

Recent studies have suggested that the key oncogenic signaling pathways for Asian (with a mutation rate of 60%) and Western (with a mutation rate ranging from 16% to 54%) women are PIK3CA/AKT and KRAS/BRAF/ERK, respectively. These findings imply that race could influence the effectiveness of targeted molecular agents.

Metformin primarily exerts its anti-tumor effects by activating AMP-activated protein kinase (AMPK) and inhibiting phosphatidylinositol-3-kinase-mammalian target of rapamycin signaling. It also exerts antimitotic and antiangiogenic effects by reducing the synthesis of insulin, insulin-like growth factor-1, and vascular endothelial growth factor. *In vitro* studies showed that metformin suppressed all LGSOC cell lines. In contrast, trametinib significantly reduced the growth of LGSOC cell lines with *RAS* mutations (VOA1312 and VOA1056) without affecting the growth of VOA5646 cells lacking *RAS* mutations (20). Therefore, metformin may be beneficial in the treatment of LGSOC, either as a standalone therapy or in combination with MEKi.

Although there have been promising results, it should be noted that not all patients respond to MEKi, and resistance mechanisms typically arise in those who initially show a positive response. Reports have indicated that cancer cells may switch to other pathways to sustain their growth when the MAPK signaling pathway is suppressed, thereby developing resistance to MEKis. Additionally, the activation of alternative cellular signaling pathways, such as the PI3K/AKT/mTOR or signal transducer and activator of transcription pathways, is a commonly observed strategy employed by cancer cells to develop MEKi resistance. Therefore, combination therapies that simultaneously target multiple pathways are essential for overcoming these resistance mechanisms. Multiple MEKis are currently being evaluated in combination with other agents to enhance their effectiveness in the treatment of melanoma, ovarian, lung, and thyroid cancers. These combination therapies have been shown to prolong positive responses, delay the onset of acquired resistance, and improve PFS, OS, and tumor shrinkage. A phase II study randomly assigned 65 patients with recurrent LGSOC to receive either a combination of pimasertib (a MEKi) and voxtalisib (a PI3K inhibitor) or pimasertib alone to determine whether the combination is superior. Objective response rate (ORR) was 9.4% and 12.1% in the combination and pimasertib-alone groups, respectively. Median PFS was 7.23 and 9.99 months for pimasertib alone and the combination, respectively. Six-month PFS was 63.5% and 70.8%. Eighteen (56.3%) and 19 (57.6%) patients in the combination and pimasertib-alone groups discontinued the trial, respectively; however, this study was terminated early because of low ORR and high rate of discontinuation (21). Therefore, additional studies evaluating the role of MEKi alone or in combination with PI3K inhibitors are warranted. A dual regimen could also be better tolerated with appropriate premedication and management of side effects. In MEKi resistance screenings conducted on LGSOCs, researchers discovered that the overexpression of *MAML2* or the loss of *MAP3K1* resulted in an increased expression of the NOTCH target, *HES1*. The observed overexpression of *HES1* had a causal role in the development of resistance to MEKis, as demonstrated by the reversal of resistance following the knockdown of *HES1*. The downregulation of SHOC2 exhibited synthetic lethality with MEKis in further synthetic lethality screenings involving trametinib. However, significant effectiveness was observed in the parental LGSOC cell lines by targeting SHOC2 with pan-RAF inhibitors in combination with MEKis (22). Therefore, gaining insights into the mechanisms of MEKi resistance and subsequently

identifying rational drug combinations to overcome resistance can significantly influence treatment strategies for LGSOCs.

Recent findings indicate that the presence of *KRAS/BRAF* mutations or other MAPK pathway alterations among patients with LGSOCs is associated with improved outcomes. Wong *et al.* reported a median OS of 77.9 and 47.3 (95% CI: 22.12–72.5) months for patients with *BRAF/KRAS* mutations and those without, respectively (P=0.28) (13). In another study, patients harboring *KRAS* or *BRAF* mutations exhibited a significantly improved OS compared to those with wild-type *KRAS* or *BRAF*. The median OS for patients with *KRAS* or *BRAF* mutations and those with wild-type *KRAS* or *BRAF* was reportedly 106.7 (95% CI: 50.6–162.9) and 66.8 (95 CI: 43.6–90.05) months, respectively (P=0.018) (23). Similar results were also observed by Gershenson *et al.*; they confirmed that patients with MAPK mutated tumors (n=113) had a significantly longer OS than those with non-MAPK mutated tumors (n=102) [median OS, 147.8 (95% CI: 119.0–176.6) versus 89.5 (95% CI: 61.4–117.7) months, respectively (P=0.01)] (24). Alterations in the MAPK pathway is also independently associated with both platinum sensitivity and improved OS (10). Therefore, these findings suggest that alterations in the MAPK pathway serve as good prognostic markers in LGSOCs, indicating that MEKis are expected to be more effective and beneficial.

LGSOCs have remained incurable for many patients despite decades of intense research. Although significant progress has been made, the challenges of treatment resistance and disease recurrence continually present as the primary obstacles in the treatment and cure of LGSOCs. Many ongoing clinical trials are exploring the combination of MEKis with inhibitors targeting various other pathways. Therefore, discovering new potential biomarkers that help identify MEKi resistance is crucial. Considering the independent associations of MAPK pathways with platinum sensitivity and improved overall outcomes, incorporating MEKis in combination therapy holds the potential for enhanced benefits. However, further real-world data on this combination therapy are required to validate its efficacy. Furthermore, routine somatic tumor testing may provide prognostic information and aid in patient selection for targeted therapies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article has undergone external peer review.

Peer Review File: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1161/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1161/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Nakayama K, Razia S, Ishibashi T, Kyo S. Current concept of low-grade serous ovarian carcinoma. Transl Cancer Res 2024;13(1):6-10. doi: 10.21037/tcr-23-1161

