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Letter to the Editor
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Avmapki-Fakzynja Combination: A Breakthrough in Treating Low-Grade Serous Ovarian Cancer

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Dear Editor:

Low-grade serous carcinoma (LGSC) is a rare subtype of epithelial ovarian cancer with distinct clinical, histological, and molecular characteristics. Improved understanding of this entity has led to advances in tailored treatments (Manning-Geist et al., 2024). Ovarian cancer remains the most lethal gynecologic malignancy, causing over 100,000 deaths annually worldwide (Elsherif et al., 2019). Unlike high-grade serous carcinoma (HGSC), LGSC demonstrates relative chemoresistance, limiting the effectiveness of conventional platinum-based regimens. This therapeutic gap has historically forced patients to undergo cycles of treatment with minimal benefit, imposing both physical and psychosocial burdens.

Research is shifting away from extrapolating HGSC strategies and toward disease-specific approaches. While surgery remains central to management, especially at initial diagnosis and recurrence (University of Chicago Medicine, n.d.), adjuvant chemotherapy offers only modest benefit in LGSC (Gonzalez et al., 2024). Hormonal therapies, such as aromatase inhibitors and tamoxifen, have shown promise in recurrent disease with favorable toxicity profiles. Recent progress in targeted therapy includes MEK inhibitors (targeting MAPK pathway activation in KRAS- and BRAF-mutated tumors), CDK4/6 inhibitors (blocking cell cycle progression), and PI3K inhibitors (disrupting tumor survival signaling) (Wang et al., 2024).

On May 8, 2025, the U.S. Food and Drug Administration (FDA) granted accelerated approval to the Avmapki™–Fakzynja™ Co-Pack (avutometinib capsules + defactinib tablets) for the treatment of KRAS-mutated recurrent LGSC in adults who have received prior systemic therapy (Verastem, Inc., 2024). This approval represents the first FDA-approved therapy specifically for this underserved patient population.

Avutometinib is an oral inhibitor of RAF and MEK kinases, suppressing the RAS–RAF–MEK–ERK pathway to inhibit tumor proliferation (National Cancer Institute, n.d.). Defactinib, a focal adhesion kinase (FAK) inhibitor, disrupts tumor–stroma interactions mediated by integrins and growth factor receptors (Hu et al., 2024). The combined regimen exerts dual inhibition, MAPK pathway suppression and microenvironmental resistance blockade, leading to enhanced efficacy (Cancer Therapy Advisor, 2024).

In the RAMP 201 trial (NCT04625270), 57 adults with recurrent KRAS-mutated LGSC were treated with avutometinib (3.2 mg twice weekly) and defactinib (200 mg twice daily, 3 weeks on/1 week off). The confirmed overall response rate was 44%, with responses lasting up to 31 months (Verastem, Inc., 2024). A pooled meta-analysis of nine trials involving 319 ovarian cancer patients further supported MEK inhibitors as the most active agents, with particularly high benefit in BRAF^V600-mutated disease (Hendrikse et al., 2023).

While promising, the combination is associated with risks including ocular disorders, hepatotoxicity, dermatologic toxicities, and muscle injury. More common adverse events include elevated creatine phosphokinase, fatigue, rash, and gastrointestinal symptoms (WebMD, 2025). Close monitoring remains critical to ensure safe administration.

The Avmapki–Fakzynja Co-Pack marks a paradigm shift for recurrent KRAS-mutated LGSC, addressing a long-standing therapeutic void through dual MEK and FAK inhibition. Compared with emerging strategies such as CDK4/6 and PI3K inhibition, this regimen currently offers the most robust late-phase evidence. Beyond efficacy, equitable access is paramount. Policymakers, insurers, and global health stakeholders must prioritize affordability and accessibility to ensure that women worldwide, including those in resource-limited settings, benefit from this breakthrough.

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