GYNECOLOGIC CANCER IN FOCUS

Current Developments in the Management of Gynecologic Cancer

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Management of Low-Grade Serous Carcinoma of the Ovary

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H&O How common is low-grade serous ovarian cancer?

RG Low-grade serous ovarian cancer accounts for fewer than 10% of new cases of epithelial ovarian cancer, so it is a rare cancer. However, patients with this disease tend to live longer than those with high-grade serous ovarian cancer, which increases its prevalence.

H&O What are the mutations that occur in patients with this type of cancer?

RG Unlike patients who have high-grade serous ovarian cancer, those who have low-grade serous ovarian cancer generally do not have a *P53* or *BRCA* mutation. Instead, low-grade serous ovarian cancer is most often associated with mutations affecting the RAS/RAF/mitogen-activated protein kinase (MAPK) pathway. The most common of these is a *KRAS* mutation, which is found in approximately one-third of patients who have low-grade serous ovarian cancer. About 6% to 8% of patients who have low-grade serous ovarian cancer have a *BRAF* V600E mutation. Alterations in *NF1* and *NRAS* can also occur.

H&O How often does the condition recur after treatment?

RG Unfortunately, much like cases of high-grade serous ovarian cancer, most cases of low-grade serous ovarian cancer are diagnosed at an advanced stage. As a result, the rate of recurrence is approximately 50% to 80%.

H&O What treatment options were available for recurrent low-grade serous ovarian cancer before the approval of avutometinib plus defactinib in May of 2025?

RG Until recently, we treated low-grade serous ovarian cancer the same way we treat high-grade serous ovarian cancer, using chemotherapy drugs and endocrine agents such as the aromatase inhibitor letrozole. Even though these were considered the standard of care, the response rate to these medications is approximately 13% or lower in the setting of recurrent disease. The phase 2/3 Gynecologic Oncology Group (GOG) 281/LOGS study, in which the MEK inhibitor trametinib (Mekinist, Novartis) was used as a single agent, showed a more promising response rate of 26% in patients with recurrent low-grade serous ovarian cancer, vs 6% in the standard-of-care group.[1] This finding did not lead to a US Food and Drug Administration (FDA) indication for trametinib in patients with low-grade serous ovarian cancer, but the National Comprehensive Cancer Network Compendium has added trametinib as an option for patients with recurrent disease.

H&O What are the mechanisms of action of avutometinib and defactinib?

RG Avutometinib (Avmapki, Verastem) and defactinib (Fakzynja, Verastem), which are available in combination (Avmapki Fakzynja Co-pack, Verastem), are both oral agents. Avutometinib is a RAF/MEK clamp, and defactinib is a FAK inhibitor. Avutometinib targets the MAPK

pathway at 2 different locations to provide effective blockade. This dual blockade is believed to make avutometinib more effective than a drug that blocks a single location, such as a MEK inhibitor. Defactinib works by helping to prevent compensatory reactivation of the MAPK pathway, reducing the development of resistance.

H&O Could you describe the study that led to the approval of this drug combination?

RG RAMP 201 was a phase 2 study that was designed to answer multiple questions, which is very important in these rare patient populations—we want to make sure we can use the data to answer as many questions as possible.[2] When the study first opened, patients who had recurrent low-grade serous ovarian cancer and had received at least one prior line of platinum-based chemotherapy were randomly assigned to either a higher dose of avutometinib alone (4 mg by mouth twice weekly, 3 weeks on, 1 week off) or the standard dose of avutometinib (3.2 mg by mouth twice weekly, 3 weeks on, 1 week off) in combination with defactinib. Patients were stratified by *KRAS* mutation status. The goal of the first component of the study was to determine which regimen produced a better response rate and was better tolerated: avutometinib monotherapy at a higher dose or standard-dose avutometinib plus defactinib.

> Patients with *KRAS* wild-type low-grade serous ovarian cancer have the worst prognosis, which makes the response rate of 17% encouraging.

A preplanned interim analysis determined that the response rate to the combination of avutometinib and defactinib was higher than the response rate to avutometinib alone, and the toxicity profiles of the 2 regimens were similar. Therefore, the combination of avutometinib plus defactinib was chosen as the go-forward regimen.

As subsequent patients were added to expansion cohorts, we gained additional information about the response rate and progression-free survival rate. We also added a dose optimization cohort, in which we looked at a lower dose of avutometinib (1.6 mg by mouth twice weekly, 3 weeks on, 1 week off) in combination with defactinib at its standard dose. The lower-dose regimen was found to be suboptimal when compared with the standard dose, establishing the optimal dose of avutometinib in combination with defactinib and showing that the combination was more efficacious than avutometinib as a single agent. Not only did we see a response rate of 31% in the overall population of patients—with a median duration of response of 31.1 months—we saw a response rate of 44% for patients who had a *KRAS* mutation. The response rate was 17% in the *KRAS* wild-type population

We know that *KRAS* mutation status is a prognostic indicator in ovarian cancer, with patients who have a *KRAS* mutation tending to do better whether they are treated with MEK inhibitors, chemotherapy, or endocrine agents. Patients with *KRAS* wild-type low-grade serous ovarian cancer have the worst prognosis, which makes the response rate of 17% encouraging. The median progression-free survival was 22.0 months in the *KRAS*-mutant cohort and 12.8 months in the *KRAS* wild-type cohort.

On the basis of these unprecedented results in the *KRAS*-mutant population, the FDA granted accelerated approval of this combination for use in women with *KRAS*-mutant disease. Because this study did not have a control arm, it was unable to establish the relative benefit of the combination vs the standard of care in patients with *KRAS* wild-type disease.

The ongoing phase 3 RAMP 301 study[3] has inclusion criteria that are very similar to those of the RAMP 201 study. This study is also enrolling patients who have recurrent low-grade serous ovarian cancer and have received at least one prior platinum-based chemotherapy, but patients are being randomized to either the standard dose of avutometinib plus defactinib or the investigator's choice of standard chemotherapy or endocrine therapy. Like the earlier study, RAMP 301 is enrolling both patients with and patients without a *KRAS* mutation. This study has been accruing patients rapidly, which is great to see when we are dealing with a rare disease, and we hope to complete accrual in the first quarter of 2026.

H&O What adverse events were seen in RAMP 201 with this combination?

RG The most common adverse events with these drugs are similar to the ones we typically see with MEK inhibitors. An acneiform rash can develop that is especially likely to occur on the face and upper chest. Peripheral edema in the hands and feet and periorbital edema can also develop. Elevations in creatine phosphokinase levels are very common and require monitoring, although patients are usually completely asymptomatic. Another possible

adverse effect is ocular toxicity. When visual changes occur, they most often start within the first week of therapy and frequently go away on their own without any need for dose interruption, reduction, or discontinuation, but patients must be followed by an eye care professional when on treatment with these drugs. Unlike what we see in patients receiving antibody-drug conjugates, patients who exhibit ocular toxicity with MEK inhibitors typically do not have keratitis and do not require prophylactic eye drops.

Over the past years of treating patients with MEK inhibitors, we have learned that the best way to prevent skin toxicity with avutometinib plus defactinib is by using prophylactic oral antibiotics and avoiding excessive sun exposure. An agent such as minocycline or doxycycline should be started at the time of drug initiation to reduce the risk of an acneiform rash, and patients should use ultraviolet protection (ie, hat, long sleeves, sun protection factor) while on therapy.

Disclosures

Dr Grisham reports personal fees from AstraZeneca, SpringWorks Therapeutics, Incyte, Incyclix Bio, Genmab, Verastem, and Merck. She was the Gynecologic Oncology Group Primary Investigator (GOG PI) of the RAMP 201 study and is the Global PI of the RAMP 301 study.

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