

## AVMAPKI™ plus FAKZYNJA™: The First-Ever Treatment FDA-Approved for Adults with *KRAS*-mutated Recurrent Low-Grade Serous Ovarian Cancer

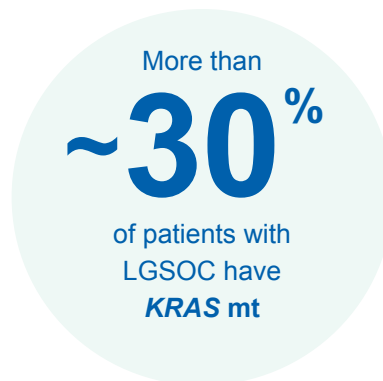
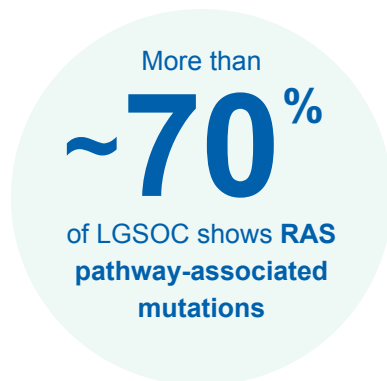
AVMAPKI (avutometinib) plus FAKZYNJA (defactinib) is only commercially available in the U.S. by prescription as a convenient oral combination co-packaged as AVMAPKI™ FAKZYNJA™ CO-PACK. It is indicated for the treatment of adult patients with *KRAS*-mutated recurrent low-grade serous ovarian cancer (LGSOC) who have received prior systemic therapy.

AVMAPKI FAKZYNJA CO-PACK is the first and only FDA-approved medicine for this disease. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

### Addressing an Unmet Treatment Need

LGSOC is a rare ovarian cancer that is insidious and persistent, with more than 80% of patients experiencing recurrence. There are approximately 6,000 to 8,000 women with LGSOC living in the U.S., and 1,000 to 2,000 cases are diagnosed each year. LGSOC is most commonly diagnosed in women between the ages of 20 to 30 and 50 to 60.

The RAS/MAPK pathway is a primary driver of tumor growth: mutations that activate the pathway, including mutations in the *KRAS* gene, are found in many cancers and often correlate with poor prognosis.



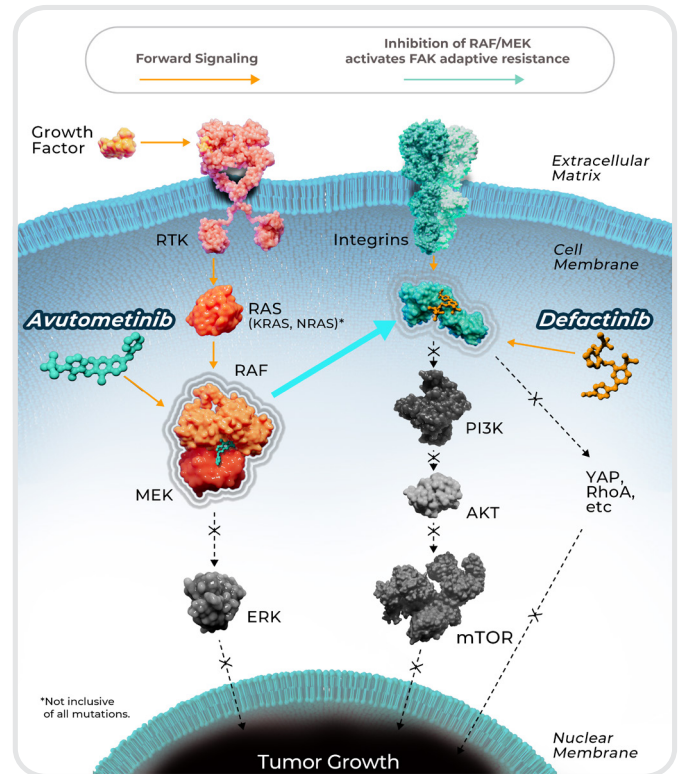
Until now, there have been no approved treatments for adult patients with *KRAS*-mutated recurrent LGSOC. Patients have been typically treated with surgery and off-label use of hormonal therapy, targeted therapy, and chemotherapy, which offer poor to moderate response rates and are often discontinued due to toxicity and poor tolerability. As a result, many patients cycle through therapy. Current treatment guidelines provide guidance on managing the disease, but no standard sequencing of treatment for recurrent disease exists.

## Blocking RAS/MAPK Signaling and Inhibiting Resistance Pathways

Cancer is highly dependent on the RAS/MAPK signaling pathway for its growth, and blocking any single node in this pathway is generally insufficient for deep and durable anti-cancer activity as the cancer will compensate by activating other signaling proteins within the RAS pathway or in parallel pathways.

AVMAPKI (avutometinib) inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream RAF. RAF and MEK proteins are regulators of the RAS/RAF/MEK/ERK (MAPK) pathway. Blocking RAF and/or MEK activates FAK, a key mediator of drug resistance. FAKZYINJA (defactinib) is a FAK inhibitor.

The avutometinib and defactinib combination was designed to provide a more complete blockade of the signaling that drives the growth and drug resistance of RAS/MAPK pathway-dependent tumors.



## Clinical Trial Results

The efficacy of AVMAPKI plus FAKZYINJA was evaluated in the RAMP 201 study (ENGOT-ov60/GOG3052) (NCT04625270), an open-label, multicenter Phase 2 study that included 57 adult patients with measurable *KRAS*-mutated recurrent LGSOC. Patients were required to have received at least one prior systemic therapy, including a platinum-based regimen.

Efficacy was primarily determined by overall response rate (ORR) assessed by a blinded independent review committee (BIRC) according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Efficacy was additionally determined by duration of response (DoR).

**44%** confirmed overall response rate in *KRAS* mt  
N=57 (95% CI: 31, 58)

**3.3–31.1** MONTHS Range of duration of response  
N=57

To see the full results of the Phase 2 RAMP 201 clinical trial, please [click here](#).

## AVMAPKI FAKZYNJA CO-PACK Dosing and Administration



The recommended dosage of AVMAPKI capsules is 3.2 mg (four 0.8 mg capsules) taken orally twice weekly (Day 1 and Day 4) for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity. Take AVMAPKI at the same time with each dose. AVMAPKI should be taken with food.



The recommended dosage of FAKZYNJA tablets is 200 mg (one tablet) taken orally twice daily for the first 3 weeks of each 4-week cycle until disease progression or unacceptable toxicity. Take each dose of FAKZYNJA with food.

Not actual size.

## Important Safety Information

### Warnings and Precautions

- **Ocular Toxicities:** Ocular toxicities, including visual impairment and vitreoretinal disorders, occurred. Perform comprehensive ophthalmic evaluation at baseline, prior to cycle 2, every three cycles thereafter, and as clinically indicated. Withhold AVMAPKI FAKZYNJA CO-PACK for ocular toxicities until improvement at the same or reduced dose. Permanently discontinue AVMAPKI FAKZYNJA CO-PACK for any grade 4 toxicity.
- **Serious Skin Toxicities:** Skin toxicities, including photosensitivity and severe cutaneous adverse reactions (SCARs), occurred. Adhere to concomitant medications. Monitor for skin toxicities and interrupt, reduce or permanently discontinue AVMAPKI FAKZYNJA CO-PACK based on severity, tolerability and duration.
- **Hepatotoxicity:** Monitor liver function tests prior to each cycle, on day 15 of the first 4 cycles, and as clinically indicated. Withhold, reduce or discontinue AVMAPKI FAKZYNJA CO-PACK based on severity and persistence of abnormality.
- **Rhabdomyolysis:** Monitor creatine phosphokinase prior to the start of each cycle, on day 15 of the first four cycles, and as clinically indicated. If increased CPK occurs, evaluate patients for rhabdomyolysis or other causes. Withhold, reduce or permanently discontinue AVMAPKI FAKZYNJA CO-PACK based on severity and duration of the adverse reaction.
- **Embryo-Fetal Toxicity:** AVMAPKI FAKZYNJA CO-PACK can cause fetal harm. Advise patients of the potential risk to a fetus and to use effective contraception.

### Adverse Reactions

The most common ( $\geq 25\%$ ) adverse reactions, including laboratory abnormalities, were increased creatine phosphokinase, nausea, fatigue, increased aspartate aminotransferase, rash, diarrhea, musculoskeletal pain, edema, decreased hemoglobin, increased alanine aminotransferase, vomiting, increased blood bilirubin, increased triglycerides, decreased lymphocyte count, abdominal pain, dyspepsia, dermatitis acneiform, vitreoretinal disorders, increased alkaline phosphatase, stomatitis, pruritus, visual impairment, decreased platelet count, constipation, dry skin, dyspnea, cough, urinary tract infection, and decreased neutrophil count.

## Important Safety Information (Cont'd)

### Drug Interactions

- **Strong and moderate CYP3A4 inhibitors:** Avoid concomitant use with AVMAPKI FAKZYNJA CO-PACK.
- **Strong and moderate CYP3A4 inducers:** Avoid concomitant use with AVMAPKI FAKZYNJA CO-PACK.
- **Warfarin:** Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with warfarin and use an alternative to warfarin.
- **Gastric acid reducing agents:** Avoid concomitant use of AVMAPKI FAKZYNJA CO-PACK with proton pump inhibitors (PPIs) or H2 receptor antagonists. If use of an acid-reducing agent cannot be avoided, administer FAKZYNJA 2 hours before or 2 hours after the administration of a locally acting antacid.

### Use in Specific Populations

- **Lactation:** Advise not to breastfeed.
- **Fertility:** May impair fertility in males and females.

Click here for full [Prescribing Information](#).