

Avutometinib and Defactinib (Avmapi Fakzynja Co-Pack®) for the Management of KRAS-mutated recurrent low-grade serous ovarian cancer

Description: The purpose of this PQI is to discuss clinical considerations and general management of patients receiving treatment with avutometinib and defactinib for KRAS-mutated recurrent low-grade serous ovarian cancer (LGSOC).

Background: LGSOC is a rare subtype of epithelial ovarian cancer characterized by frequent MAPK pathway alterations, including KRAS mutations. Avutometinib is a dual RAF/MEK clamp, and defactinib is a selective FAK inhibitor. Together, they target complementary pathways involved in tumor growth and treatment resistance.

FDA-approved Indication:

- Treatment of adult patients with KRAS-mutated recurrent LGSOC who have received prior systemic therapy.

Common adverse reactions include:

- Increased CPK, nausea, fatigue, increased AST, rash, diarrhea, musculoskeletal pain, and edema.

PQI Process:

1. Verify Patient Eligibility
 - Confirm diagnosis of recurrent LGSOC
 - Confirm presence of a KRAS mutation through tumor molecular testing
 - Confirm prior systemic therapy
2. Dosage and Administration
 - Avutometinib and defactinib are administered on a 28-day cycle consisting of 3 weeks on treatment followed by 1 week off treatment.
 - Store the Co-Pack refrigerated at 2°C to 8°C (36°F to 46°F) in the original bottles.

Recommended (Standard) Dose

- Avutometinib: 3.2 mg (four 0.8-mg capsules) orally *twice weekly* on Days 1 and 4 during Weeks 1-3.
- Defactinib: 200 mg (one tablet) orally *twice daily* during Weeks 1-3.

Table 1. Recommended dosing schema for avutometinib and defactinib

	Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Weeks 1-3	AM	Avut 3.2 mg + Defac 200 mg	Defac 200 mg	Defac 200 mg	Avut 3.2 mg + Defac 200 mg	Defac 200 mg	Defac 200 mg	Defac 200 mg
	PM	Defac 200 mg	Defac 200 mg	Defac 200 mg	Defac 200 mg	Defac 200 mg	Defac 200 mg	Defac 200 mg
Week 4	One week break: Do NOT administer avutometinib or defactinib during week 4							

3. Monitoring and Toxicity Management

- **Ocular:** Refer to a qualified eye care professional for a comprehensive ophthalmic examination at baseline, prior to Cycle 2, every 3 cycles thereafter, and as clinically indicated.
- **Dermatologic:** Initiate prophylaxis for skin reactions with 1% hydrocortisone cream once daily to the face, scalp, neck, upper chest, and upper back and an oral antibiotic. Continue prophylactic skin care for at least the first 2 cycles. During clinical trials, patients received doxycycline 100 mg PO twice daily or minocycline 100 mg PO daily.
- **CPK:** Monitor CPK prior to the start of each cycle, on Day 15 of the first 4 cycles, and as clinically indicated. If increased CPK occurs, evaluate for rhabdomyolysis or other causes.
- **Hepatic:** Monitor AST, ALT, and bilirubin prior to the start of each cycle, on Day 15 of the first 4 cycles, and as clinically indicated.
- **Pregnancy:** Verify pregnancy status in females of reproductive potential prior to initiating treatment.

4. Dosage and Administration Modifications

- Treatment Continuity: With a median time to confirmed response of 3.7 months², proactive adverse event management is important to support treatment continuity.
- The most common dose modification is to withhold treatment. Following resolution or improvement of an adverse reaction, treatment may be resumed at the same or reduced dose, as appropriate.
- There is one recommended dose reduction, which requires reduction of both avutometinib and defactinib (see table 2 below).
 - Avutometinib: 2.4 mg (three 0.8 mg capsules) orally *twice weekly* on Days 1 and 4 during Weeks 1-3.
 - Defactinib: 200 mg (one tablet) orally *once daily* during Weeks 1-3.
- Permanently discontinue both avutometinib and defactinib in patients unable to tolerate treatment after one dose reduction.
- Refer to the full prescribing information (Section 2.4) for adverse reaction-specific dosage modification and discontinuation recommendations.

Table 2: Reduced dosing schema for avutometinib and defactinib

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Weeks 1-3	Avut 2.4 mg + Defac 200 mg	Defac 200 mg	Defac 200 mg	Avut 2.4 mg + Defac 200 mg	Defac 200 mg	Defac 200 mg	Defac 200 mg
Week 4	One week break: Do NOT administer avutometinib or defactinib during week 4						

Patient-Centered Activities:

- Provide patients with [NCODA Patient Education Sheet](#) and [Patient Treatment Calendar](#)
- Review concomitant medications for acid-reducing agents and CYP3A4 inhibitors/inducers.
- Review administration instructions, including taking both medications with food, swallowing medications whole, and appropriate management of missed doses or vomiting.
- Educate patients on required eye care and to report blurred vision, visual disturbances, eye pain, or redness.
- Educate patients on required skin care, including avoiding sun exposure and using SPF >30, and to report rash.
- Counsel patients to report signs or symptoms of hepatotoxicity, including jaundice, dark urine, severe fatigue, or right upper quadrant pain.
- Counsel patients to report signs or symptoms of CPK elevation/rhabdomyolysis, including muscle pain, weakness, cramping, tenderness, or dark urine.
- Counsel patients on contraception and breastfeeding recommendations during and following treatment.
- Ensure access to antiemetics and antidiarrheals, per institutional guidelines.

References:

1. AVMAPKI™ FAKZYNJA™ CO-PACK (avutometinib; defactinib) [package insert]. Needham, MA: Verastem, Inc.; 2025
2. Banerjee SN, Van Nieuwenhuysen E, Aghajanian C, et al. Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201. *J Clin Oncol*. 2025;43(25):2782-2792. doi:10.1200/JCO-25-00112