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The combination of avutometinib and defactinib in treating recurrent low-grade serous ovarian cancer: a plain language summary of the Phase II clinical trial ENGOT-OV60/GOG-3052/RAMP 201

Susana N. Banerjee, Els Van Nieuwenhuysen, Carol Aghajanian, Véronique D'Hondt, Bradley J. Monk, Andrew Clamp, Emily Prendergast, Ana Oaknin, Kari Ring, Nicoletta Colombo, Robert W. Holloway, Manuel Rodrigues, Hye Sook Chon, Charlie Gourley, Alessandro D. Santin, Premal H. Thaker, Christine Gennigens, Gregg Newman, Erin Salinas, Hagop Youssoufian, Kathleen N. Moore, Stephanie Lustgarten, David M. O'Malley, Toon Van Gorp & Rachel N. Grisham

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Plain Language Summary of Publication

Future ONCOLOGY

The combination of avutometinib and defactinib in treating recurrent low-grade serous ovarian cancer: a plain language summary of the Phase II clinical trial ENGOT-OV60/GOG-3052/RAMP 201

Susana N. Banerjee[a], Els Van Nieuwenhuysen[b], Carol Aghajanian[c,d], Véronique D'Hondt[e], Bradley J. Monk[f], Andrew Clamp[g], Emily Prendergast[h], Ana Oaknin[i], Kari Ring[j], Nicoletta Colombo[k,l], Robert W. Holloway[m], Manuel Rodrigues[n,o], Hye Sook Chon[p], Charlie Gourley[q], Alessandro D. Santin[r], Premal H. Thaker[s], Christine Gennigens[t], Gregg Newman[u], Erin Salinas[v], Hagop Youssoufian[w], Kathleen N. Moore[x], Stephanie Lustgarten[w], David M. O'Malley[y], Toon Van Gorp[b] & Rachel N. Grisham[c,d]
Author affiliations can be found at the end of this article

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Where can I find the original article on which this summary is based?

The original article is titled 'Efficacy and safety of avutometinib ± defactinib in recurrent low-grade serous ovarian cancer: Primary analysis of ENGOT-OV60/GOG-3052/RAMP 201,' and it can be read for free at: https://doi.org/10.1200/JCO-25-00112.

Summary

How to say (download PDF and double click sound icon to play sound)...

- **Avutometinib:** Uh-VU-toe-MEH-ti-nib
- **Defactinib:** De-FAK-ti-nib

What is this summary about?
This plain language summary describes the results of the ENGOT-OV60/GOG-3052/RAMP 201 clinical study, which were published in 2025. The Phase II study evaluated treatments for patients with a rare type of ovarian cancer, low-grade serous ovarian cancer (LGSOC). The study specifically involved those whose cancer came back or persisted, despite already having surgery and previous chemotherapy. Researchers investigated the effect of avutometinib on its own and in combination with defactinib to see which treatment would be more effective and to determine if both treatments were safe. They also investigated the combination of a lower dose of avutometinib with defactinib. All trial participants were tested for a specific *KRAS* **genetic mutation** (non-hereditary, also called somatic). The main goal of the study was to determine the confirmed objective response rate of each treatment. This is the percentage of patients whose cancer shrinks by at least 30% after treatment and maintains this shrinkage for at least 2 months. The study also closely monitored for any adverse events associated with each treatment and looked at other measures of treatment effectiveness.

What were the results?
The percentage of patients with an objective response was 31% in the combination treatment group and 17% in the avutometinib-only group. Amongst patients receiving the combination, the **objective response rate** was 44% in the group of participants with a ***KRAS*** mutation and 17% in the group without a *KRAS* mutation. The lower dose of avutometinib used in combination with defactinib was not as effective as the standard dose.

In the standard dose combination treatment group, most **adverse events** were not severe (categorized as grade 1 or 2 on a scale of 0 to 5) and were managed with **dose holds** or **dose reductions**. The most frequent adverse events reported were nausea, increased **creatine phosphokinase (CPK)**, diarrhea, **peripheral edema**, and rash. A total of 10% of participants discontinued treatment due to adverse events.

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What do the results mean?
The results of the study support using the combination of avutometinib and defactinib as a treatment option for women with recurrent LGSOC.

Genetic mutation (non-hereditary, also called somatic): A change in the DNA of your tumor cells that happens during your lifetime. It is not something you were born with and cannot be passed on to your children. It can sometimes lead to cancer by causing cells to grow abnormally.
Objective response rate: The measurement of how well a cancer treatment is working. It looks at the percentage of patients whose tumors shrink, called a partial response, or disappear, called a complete response, after receiving treatment.
***KRAS*:** The KRAS gene helps control how cells grow and divide. In some people with LGSOC, this gene has a mutation that tells cells to keep growing when they should stop.
Adverse event: Any health problem that happens while you're taking a medication or participating in a medical study, even if it's not clear whether the medicine or treatment caused it.
Dose hold: Temporarily stopping a medication, usually because of an adverse event or health concern, to give your body time to recover before restarting treatment.
Dose reduction: Changing the amount of medicine you take, either lowering the dosage or reducing the number of times you take it, to help reduce adverse events.
Creatine phosphokinase: A muscle-related protein in the blood.
Peripheral edema: Swelling in the legs, feet, or hands caused by fluid buildup.

What is the purpose of this plain language summary?

- The purpose of this plain language summary is to help you understand the findings from the ENGOT-OV60/GOG-3052/RAMP 201 trial.
- Avutometinib and defactinib as a co-pack (combination of these 2 treatments) received accelerated approval from the US Food and Drug Administration (FDA) for patients who have LGSOC with a *KRAS* gene mutation, and whose disease has come back (is recurrent) after receiving prior treatment for their cancer.
  - » Accelerated approval is when the FDA approves promising new treatments faster based on early signs that the treatment might help.
- The combination of avutometinib and defactinib is approved by the FDA to treat the condition in patients with a *KRAS* mutation who are discussed in this summary.
- Avutometinib and defactinib are currently not approved outside of the United States.
- The results of this study may differ from those of other studies. Health professionals should make treatment decisions based on all available evidence, not on the results of a single study.

Who should read this article?

This summary may be helpful for both patients with LGSOC and the healthcare professionals who care for them, especially those exploring treatment options. It may also be helpful for patients' families, patient advocates, and caregivers.

Who sponsored this study?

This study was **sponsored** by Verastem Oncology.

Sponsor: A company or organisation that oversees and pays for a clinical research study. The sponsor also collects and analyses the information from the study.

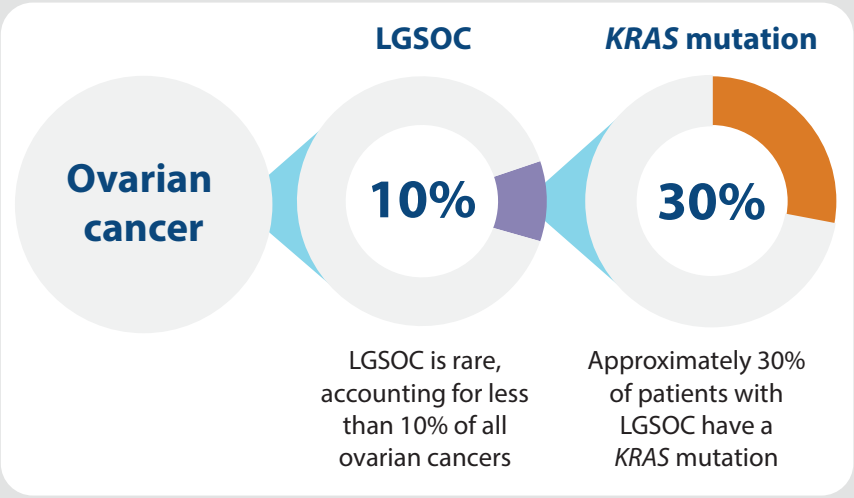
What is LGSOC?

Ovarian cancer is a type of cancer that starts in the ovaries. Researchers have discovered that low-grade serous ovarian cancer (LGSOC), a rare type of ovarian cancer, often involves changes in genes, like *KRAS* genetic mutations, which affect how the cancer grows and responds to treatment. These changes activate **signaling pathways, like MAPK**, which represent opportunities for new **targeted therapies** that offer more personalized treatment options for patients. This study adds to growing evidence that these treatments may improve outcomes for patients with LGSOC.

MAPK (mitogen-activated protein kinase) signaling pathway: A chain of proteins inside a cell, like a set of instructions, that communicates signals from the surface of the cell to the DNA in the nucleus. It helps control important cell functions, such as growth, division, and survival. When this pathway is overactive or mutated, it can lead to diseases like cancer.

Targeted therapies: Treatments designed to block specific genes or proteins that help cancer cells grow and survive.

LGSOC accounts for less than 10% of all ovarian cancers. It usually presents at a younger age and is less responsive to chemotherapy than some other forms of ovarian cancer. LGSOC can be driven by abnormalities in molecular pathways, such as changes in the MAPK (mitogen-activated protein kinase) signaling pathway, which may or may not involve mutations in DNA. Mutations in this signaling pathway can promote tumor growth. Approximately 30% of patients with LGSOC have a *KRAS* mutation within the MAPK pathway. Studies have found that patients with LGSOC who have this specific mutation have overall better outcomes than patients who do not have a *KRAS* mutation.



Why was the study done?

Treatment for advanced LGSOC often starts with surgery, which attempts to remove all cancerous tissue, followed by chemotherapy alone, endocrine therapy (treatment that targets the hormone estrogen) alone, or chemotherapy followed by endocrine therapy.

Despite surgery, most patients will have their cancer return in the advanced stages, at which point chemotherapy or endocrine therapy is again generally the recommended treatment.

Currently available chemotherapies and endocrine therapies generally have a response rate of less than 13% in patients with recurrent LGSOC. Some treatments targeting MEK, one component of the MAPK (mitogen-activated protein kinase) pathway, have shown response rates of up to 26%. However, for some patients, the adverse events that accompany the treatment can be limiting.

Prior studies with MEK-only inhibitors (trametinib and binimetinib) have reported that approximately one-third of participants discontinued treatment due to unmanageable adverse events.

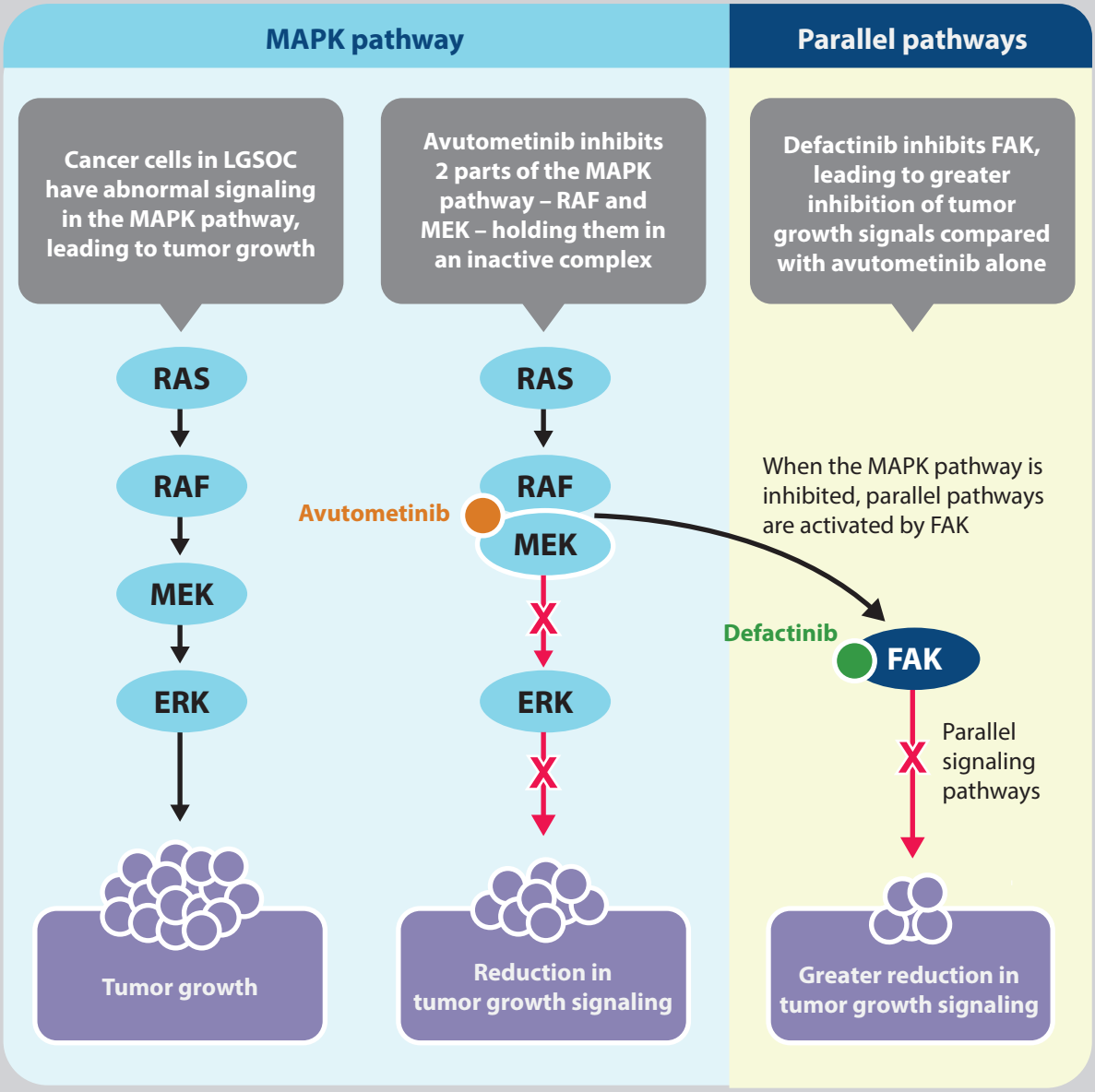
This study looked at a new combination treatment in patients with LGSOC that targets 2 pathways involved in tumor growth in the hopes that the treatment could be more effective and present fewer unmanageable adverse events in a greater number of patients.

10.1080/14796694.2025.2595130

What are avutometinib and defactinib?

Avutometinib is a new type of targeted therapy medication taken by mouth. It blocks MEK, a key component of the MAPK (mitogen-activated protein kinase) pathway, as well as RAF, another component of the pathway. Blocking both MEK and RAF is hypothesized to result in better inhibition of the MAPK pathway than inhibiting MEK alone. However, when the MAPK pathway is inhibited, another pathway involved in tumor growth can be activated via FAK.

Defactinib, another new targeted therapy medication also taken by mouth, inhibits FAK. Together, avutometinib and defactinib inhibit 2 pathways to slow the growth of cancer cells. In the Phase I/II FRAME trial, the combination of avutometinib and defactinib was found to be effective and safe enough for patients to support further studies.

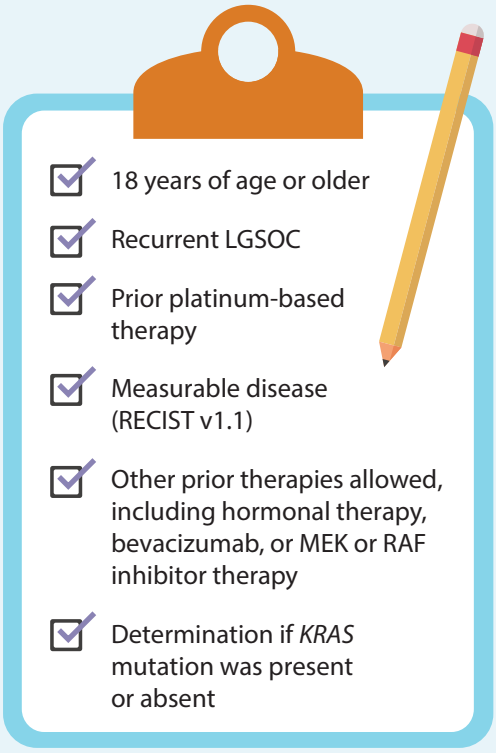


What did the researchers study?

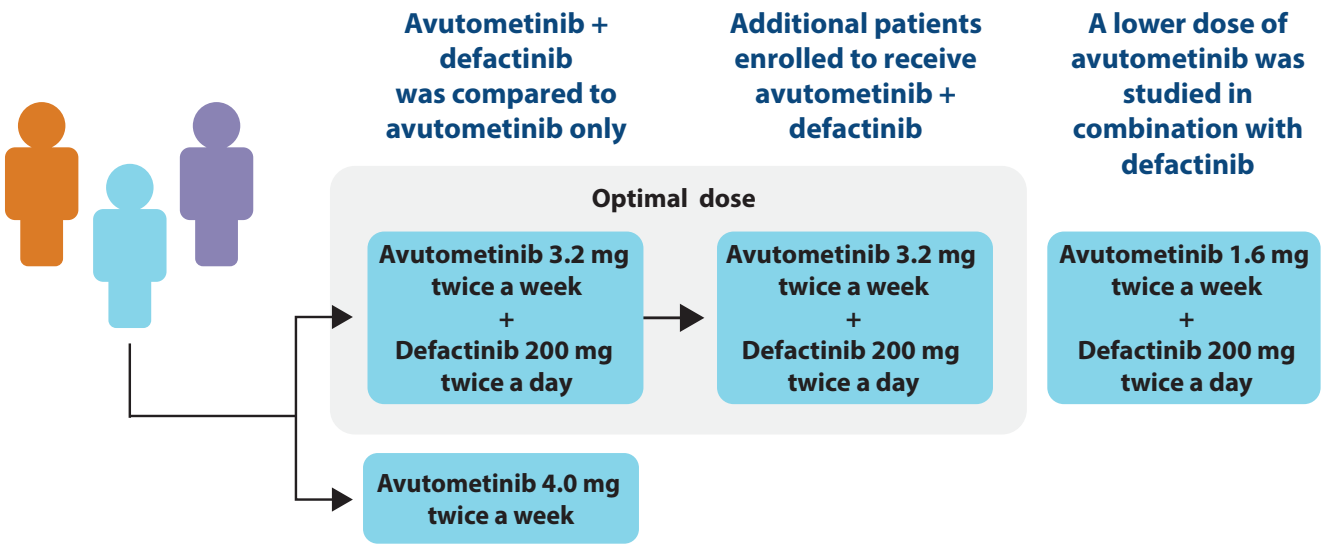
Who took part in the study?

To qualify for the study, participants were required to be over 18 years of age and also have a diagnosis of LGSOC, which was confirmed through tissue sampling. Furthermore, they must have had their disease return despite having received platinum-containing chemotherapy. Patients were allowed to enroll if they had received other therapies in the past, including hormonal therapy, bevacizumab, or prior MEK inhibitor therapy (e.g., trametinib or binimetinib).

The study included participants from the United States, United Kingdom, France, Spain, Italy, Belgium, and Canada.



What did the researchers do?



- **Avutometinib, in capsule form, and defactinib, in tablet form, were both administered orally by mouth.**
- **Avutometinib and defactinib were given on a schedule of 3 weeks on medication followed by 1 week of no medication.**

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ENGOT-OV60/GOG-3052/RAMP 201 is a Phase II trial. Phase II trials are conducted in a small group of patients to determine if a drug or drug combination is safe and effective. The study included patients with confirmed LGSOC who had their cancer return despite surgery and at least 1 course of platinum-based chemotherapy (e.g., carboplatin). All participants had testing done to see if there was a *KRAS* mutation in the DNA of their tumor. Patients could enroll with or without the mutation in their cancer, and the study was designed to allow for equal numbers of patients with and without a *KRAS* mutation present.

Researchers tested the effectiveness and safety of avutometinib alone versus combination therapy of both agents. These findings determined that combination treatment was more effective, and this combination was expanded for further study. In a separate part of the study, a lower dose of avutometinib was tested in combination with defactinib.

At the time of the analysis, 115 patients had received avutometinib + defactinib treatment: 58 patients with a *KRAS* mutation (*KRAS* mt) and 57 patients without a *KRAS* mutation (*KRAS* wild-type or *KRAS* wt). A total of 70 patients received avutometinib alone (31 patients with *KRAS* mt and 39 patients with *KRAS* wt). A total of 27 patients received the lower dose of avutometinib in combination with defactinib (11 patients with *KRAS* mt and 16 with *KRAS* wt).

What were the goals of the study?

The main goals of ENGOT-OV60/GOG-3052/RAMP 201 were to determine the objective response rate, which is the percentage of participants who had their tumors shrink by at least 30% and maintained this shrinkage for at least 2 months after receiving the treatment.

The other goals of the study included:

- Determining the duration of response, which is how long the response lasted.
- Determining the disease control rate, which is the proportion of patients who achieved an objective response rate or stable disease for a specified period of time.
  - » The disease control rate is useful for understanding how many patients benefit from a treatment.
  - » Stable disease is when the tumor shrinks less than 30% or does not grow more than 20%.
- Determining progression-free survival, which is how long each participant lived without their cancer getting substantially worse after the start of treatment.
  - » Progression-free survival tells us how long that benefit lasts.
- Determining the adverse events that participants experienced with treatment.

What were the results of the study?

Finding the right dose

Participants who received both avutometinib 3.2 mg twice a week and defactinib 200 mg twice a day, 3 weeks on and 1 week off, had an objective response rate of 31%. This combination and dosing were determined to have better **efficacy** than the other doses studied. Participants who received only avutometinib at the 4.0 mg twice a week dose, 3 weeks on and 1 week off, had an objective response rate of 17%.

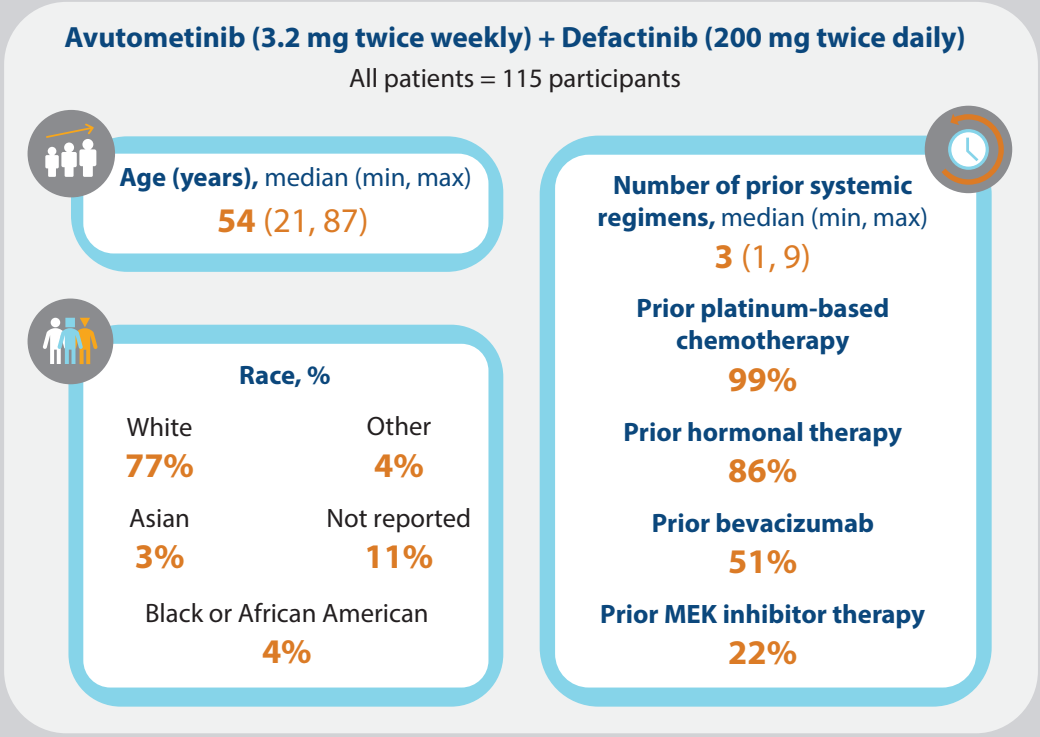
Efficacy: How well a treatment works.

The lower dose of avutometinib in combination with the standard dose of defactinib was not as successful at keeping the disease from growing back compared to the standard dose of avutometinib. More patients on the low dose had their cancer worsen within 4 months compared to the standard dose (22% with progression on the low dose compared to 12% of patients whose disease progressed while receiving standard dose).

Results with optimal dose

The results summarized below are for the avutometinib 3.2 mg twice a week and defactinib 200 mg twice a day dose group. This is the dose that received accelerated approval from the FDA for patients with *KRAS*-mutated recurrent LGSOC.

The below figure summarizes the demographics of the study participants in the combination treatment group.

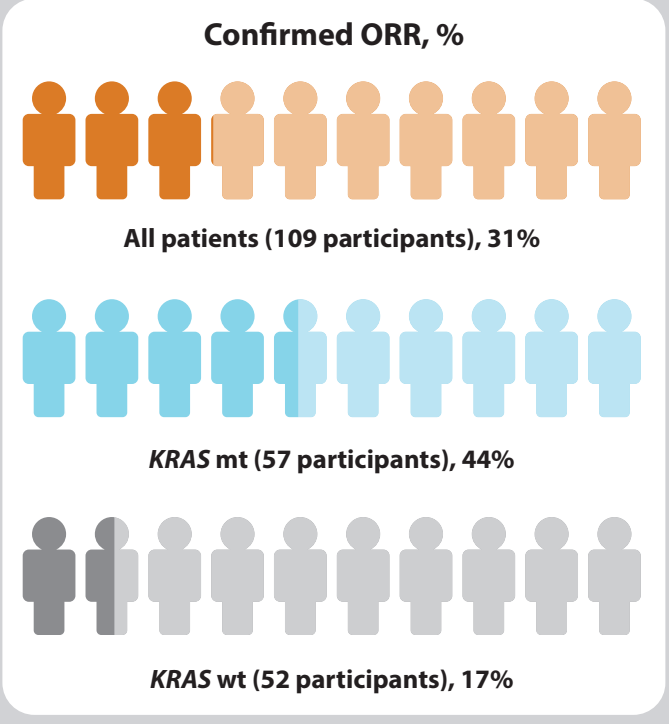


Note: Some of the subgroups included in this summary were small, which means there may not have been enough participants to fully analyze how treatments worked in each group.

As noted above, the objective response rate, ORR, in participants who received both avutometinib 3.2 mg twice a week and defactinib 200 mg twice a day was 31%.

The percentage of patients who had a response was greater in those with a *KRAS* mutation.

The objective response rate was 44% in the group of participants with a *KRAS* mutation and 17% in the group without a *KRAS* mutation.



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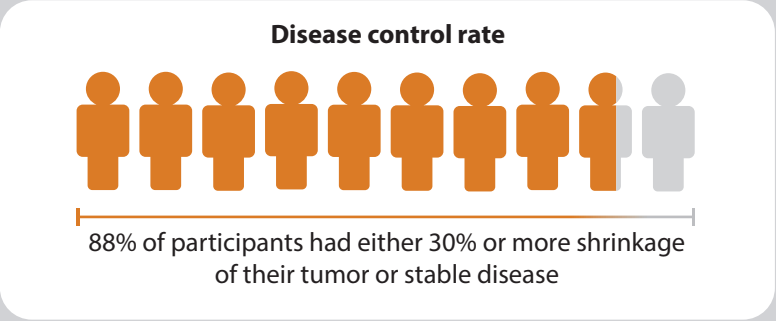
An additional 57% of participants had stable disease as their best response (the tumor shrank less than 30% – the cutoff for objective response rate – but did not grow more than 20%).

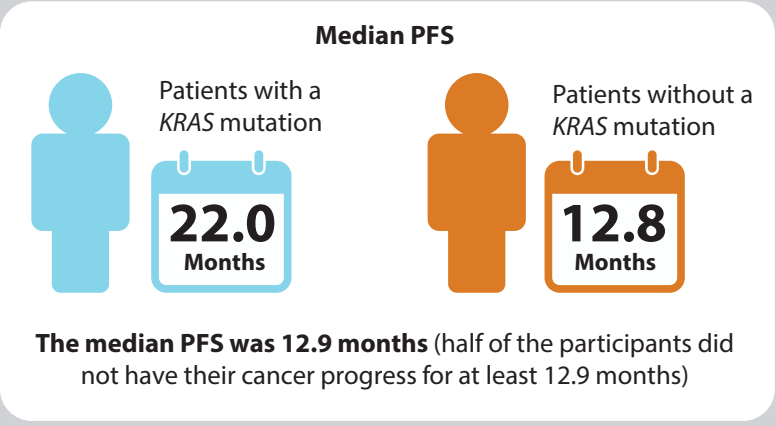
Together, 88% of participants had either 30% or more shrinkage of their tumor or stable disease. This is referred to as the disease control rate. The disease control rate was maintained for over 6 months in 61% of patients, 70% in those with *KRAS* mutations and 50% in those without.



The majority of patients (82%) had some reduction in their tumor, regardless of *KRAS* mutation status.

Half of the patients taking the combination treatment had no worsening of their disease for over one year (median **progression-free survival, PFS**, of 12.9 months). For those with a *KRAS* mutation, the median time was longer – about 22 months. For patients without the mutation, it was about 12.8 months.

Progression-free survival (PFS): How long a person lives without their cancer progressing after starting treatment. It shows how long the benefit of the treatment lasts before the cancer begins to grow or spread again.



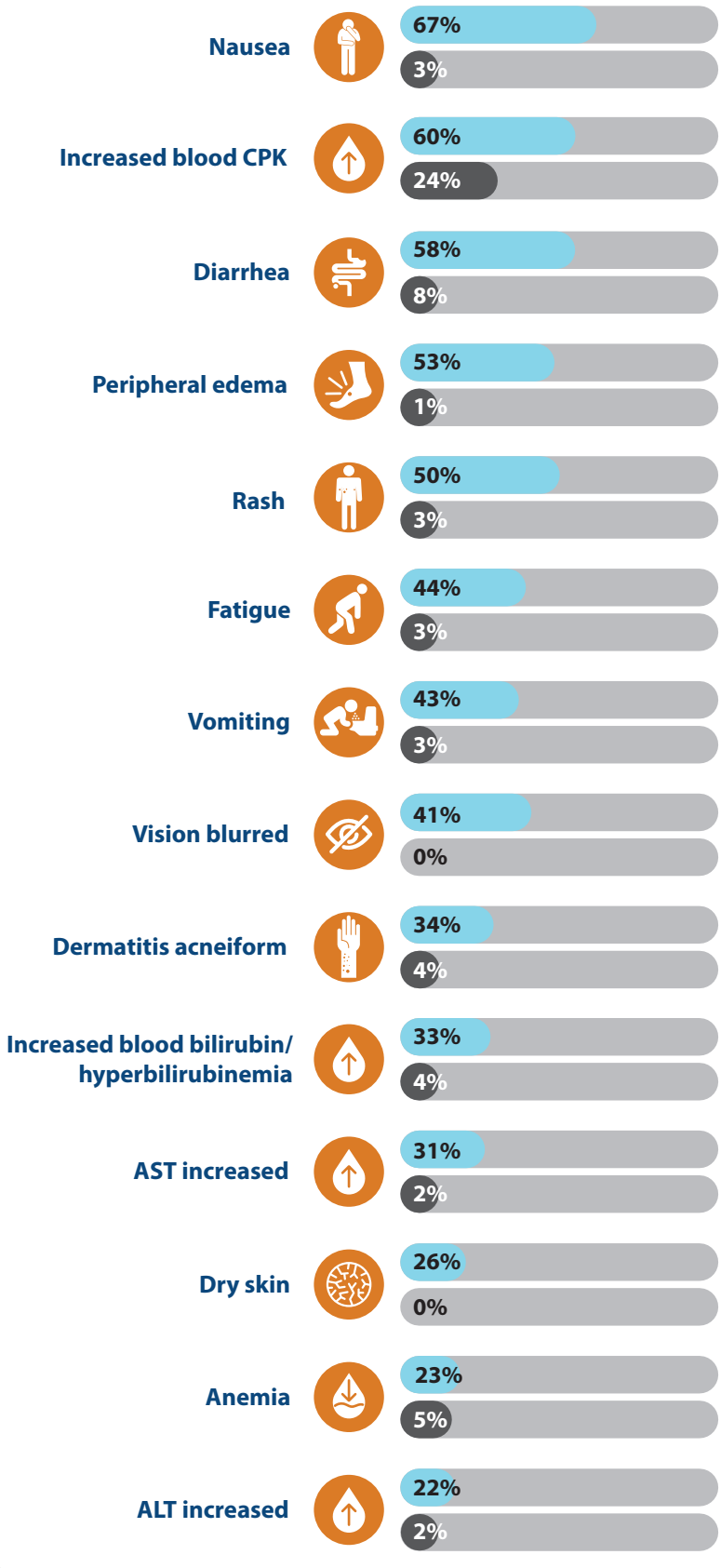
How safe were the treatments?

The figure on the next page shows the most common adverse events considered to be related to the treatment by the treating physician, including the percentage of patients with grade 3 or higher, or more severe, adverse events.

The most common adverse events that were considered severe were diarrhea (severe in 8% of patients), anemia (low number of healthy red blood cells, severe in 5% of patients), and dermatitis acneiform (an acne-like skin rash, severe in 4% of patients). Increased CPK (an enzyme created in muscle breakdown) occurred in 60% of patients; 24% of cases were severe.

If a patient experienced an adverse event during the study, the researchers could temporarily pause treatment (dose hold) or lower the dose (dose reduction) so that the adverse event could resolve. This helped manage adverse events and allowed many patients to continue their treatment. Treatment-related adverse events led to dose holds of avutometinib and defactinib in 56% of patients and to dose reductions in 10% of patients. For example, increases in CPK were generally managed (to decrease levels) by pausing the dose. Some adverse events like blurred vision (which happened early in treatment) often resolved without dose reductions or holds. Dermatologic, or skin-related, adverse reactions were common, but few were severe. Patients applied sunscreen and were given hydrocortisone cream and certain antibiotics to help avoid skin reactions prior to treatment.

A total of 10% of patients discontinued treatment due to adverse events. There were no treatment-related deaths reported among study participants.



Creatine phosphokinase (CPK) is a protein that helps your cells produce energy and is usually found in skeletal muscle, and to a lesser extent your heart and brain. This means there is more CPK in your blood than usual.

Peripheral edema is swelling that occurs in the arms and legs due to the accumulation of excess fluid.

Adverse events

All grades:

Grade 3 or more:

Dermatitis acneiform is a skin condition characterized by small, raised, acne-like bumps that typically appear on the face, scalp, chest, and upper back.

When bilirubin, a yellow substance made when the body breaks down old red blood cells, builds up in the blood, it can cause a condition called hyperbilirubinemia.

When liver cells are damaged, AST (aspartate aminotransferase), an enzyme found in the liver, heart, and muscles, can leak into the blood.

Anemia is a condition in which the body lacks enough healthy red blood cells or hemoglobin to effectively carry oxygen to its tissues. Hemoglobin is the iron-rich protein in red blood cells responsible for transporting oxygen from the lungs to the rest of the body.

When liver cells are damaged, ALT (Alanine Aminotransferase), an enzyme found mostly in the liver, can leak into the blood.

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What do the results mean?

Participants who received the combination treatment had significantly more shrinkage of their tumors compared with those who received only avutometinib. Most patients treated with the combination had some reduction in the size of their tumor, including patients with and without a *KRAS* mutation. Overall, half of participants receiving combination treatment did not have their cancer progress or get worse for at least 12.9 months (22.0 months in the group with a *KRAS* mutation). For all measurements, those who had *KRAS* mutations had better outcomes.

Why is this important?

The combination of avutometinib 3.2 mg twice weekly with defactinib 200 mg twice daily, 3 weeks on and 1 week off, resulted in significant reduction and stabilization of many patients' LGSOC tumors.

Patients with and without *KRAS* mutations had reductions in their tumor, and those with *KRAS* mutations showed greater benefit from the treatment. Most adverse events were mild and could be managed by holding or reducing the dose.

The findings of this study support the combination of avutometinib and defactinib as a promising new treatment option for women with recurrent LGSOC.

What were the limitations of the study?

Study limitations may affect how complete or reliable the results of a research study are. One limitation of this study is that it didn't include a comparison group receiving the current standard treatment. This means we can't directly compare how well the new treatment works versus what's typically used today.

However, more research is underway to better understand how this combination treatment compares to current standard therapies. A randomized Phase III study, RAMP 301, of avutometinib and defactinib versus investigator's choice of therapy for women with recurrent LGSOC is currently ongoing. You can find details about the study at: https://clinicaltrials.gov/study/NCT06072781 using the ClinicalTrials.gov identifier NCT06072781.

Where can patients find more information on LGSOC?

Educational resources:
You can find out more about LGSOC on the following websites:

- STAAR Low-Grade Serous Ovarian Cancer: https://www.staaroc.org/
- Low-Grade Serous Ovarian Cancer Initiative: https://lgsoc.org/
- Not These Ovaries: https://www.nottheseovaries.org/
- National Ovarian Cancer Coalition: https://ovarian.org/

Original article:
The article is titled 'Efficacy and safety of avutometinib ± defactinib in recurrent low-grade serous ovarian cancer: Primary analysis of ENGOT-OV60/GOG-3052/RAMP 201,' and it can be read for free at: https://doi.org/10.1200/JCO-25-00112.

The clinical trial began on December 21, 2020. The main part of the study was finished on November 15, 2024. The entire study is expected to be completed by December 2026.

Reference:
Banerjee SN, Nieuwenhuysen EV, 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. *JCO*. 2025;43(25):2782–2792. doi:10.1200/JCO-25-00112

Additional reference:
Gonzalez, A, Nagel, CI, and Haight, PJ. Targeted Therapies in Low-Grade Serous Ovarian Cancers. *Current Treatment Options in Oncology*. 2024;25:854–868. doi:10.1007/s11864-024-01205-4

Acknowledgments

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Disclosure statement

Susana N. Banerjee: Stock and Other Ownership Interests: Perci Health, Innovative Diagnostics. Honoraria: AstraZeneca, GlaxoSmithKline, Immunogen, MSD Oncology, AbbVie, Eisai, Pharma&, Verastem. Consulting or Advisory Role: GlaxoSmithKline, MSD Oncology, AstraZeneca, Seagen, Immunogen, Myriad Genetics, Verastem, Zymeworks, AbbVie, BioNTech SE, Eisai, Gilead Sciences, Gray Wolf Therapeutics, Incyte, ITM Oncologics, TORL Biotherapeutics, Genmab, BioGene, Lilly. Research Funding: GlaxoSmithKline (Inst), AstraZeneca (Inst). Travel, Accommodations, Expenses: GlaxoSmithKline, AstraZeneca, Verastem, Zymeworks. Uncompensated Relationships: Royal Society of Medicine President Oncology Section, International Cancer Foundation Board.

Els Van Nieuwenhuysen: Consulting or Advisory Role: Regeneron (Inst), Oncoinvent, AstraZeneca (Inst), Merck Serono (Inst). Speakers' Bureau: GlaxoSmithKline (Inst), AstraZeneca (Inst), MSD. Research Funding: AstraZeneca (Inst), Lilly (Inst), Merck (Inst), Seagen (Inst), Roche (Inst), Novartis (Inst), Regeneron (Inst), Oncoinvent (Inst) Travel, Accommodations, Expenses: Regeneron (Inst), GlaxoSmithKline (Inst).

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Véronique D'Hondt: Travel, Accommodations, Expenses: Lilly, Pfizer, MSD, Novartis.

Bradley J. Monk: Honoraria: AstraZeneca, BioNTech SE, Corcept Therapeutics, DSI, Eisai, Lilly, Genmab/Seagen, GOG Foundation, GlaxoSmithKline, Immunogen, AbbVie, Incyte, Karyopharm Therapeutics, Merck, Mersana, Mural, Myriad Genetics, Natera, Novartis, Novocure, Onco4, Panavance Therapeutics, Pharma&, ProfoundBio, Genmab, Regeneron, Roche/Genentech, Sutro Biopharma, Tubulis GmbH, Verastem, Zentalis, Zymeworks. Consulting or Advisory Role: AstraZeneca, Eisai, Genmab/Seattle Genetics, GOG Foundation, ImmunoGen, Merck, Mersana, Myriad Pharmaceuticals, Regeneron, Roche/Genentech, Karyopharm Therapeutics, Novocure, Gradalis, Novartis, OncoC4, Panavance Therapeutics, Verastem, Zentalis, Alkermes, BioNTech SE, Tubulis GmbH, Corcept Therapeutics, DSI, Lilly, AbbVie, Incyte, Natera, Pharma&, ProfoundBio, Sutro Biopharma, Zymeworks. Speakers' Bureau: AstraZeneca, Eisai, TESARO/GSK, Merck, Lilly, Immunogen/AbbVie. Research Funding: Novartis (Inst), Amgen (Inst), Genentech (Inst), Lilly (Inst), Janssen (Inst), Array BioPharma (Inst), Tesaro (Inst), MORPHOTEK (Inst), Pfizer (Inst), Advaxis (Inst), AstraZeneca (Inst), Immunogen (Inst), Regeneron (Inst), NuCana (Inst).

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