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A plain language summary of publication of the efficacy and safety of individualized niraparib dosing based on baseline body weight and platelet count in the PRIMA/ENGOT-OV26/GOG-3012 trial

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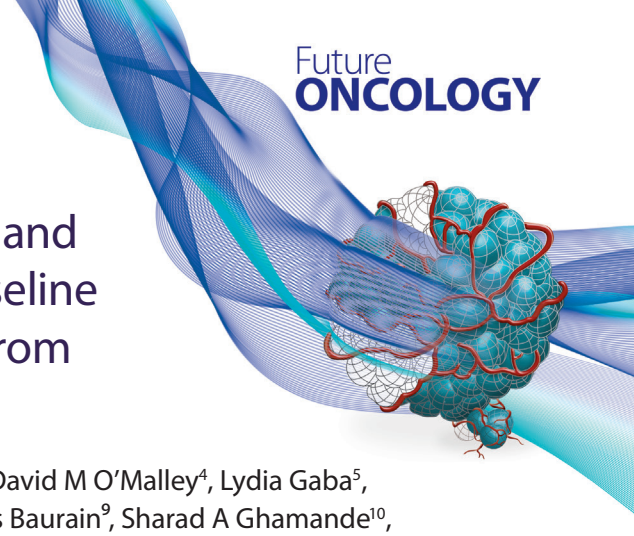

Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: results from the PRIMA/ENGOT-OV26/GOG-3012 trial

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Full affiliation information can be found at the end of this plain language summary.

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Summary

What is this summary about?

This document provides a summary of results from the article that evaluated the safety and efficacy of the **fixed and individualized starting doses** of niraparib in the PRIMA study. The original article was published in the journal *Cancer* in March 2023.

The PRIMA study included adult patients with newly diagnosed advanced ovarian cancer who had finished treatment with chemotherapy and surgery. Once patients entered the study, they were treated with an oral medication called niraparib or placebo (substance with no effects that a doctor gives to a patient instead of a drug). The amount of drug (dose) prescribed for patients to take at the start of treatment was determined by the study plan (a document that describes in detail how the study will be performed). Some patients were treated with a fixed starting dose (300 milligrams [mg] once daily), while others were treated with an individualized dose (200 or 300 mg once daily) based on how much they weighed and the results of their blood test. The individualized dose was tested to see if it improved patient safety without changing how well the drug worked (efficacy).

How to say (double click sound icon to play sound)...

- **Niraparib:** nih-RAP-uh-rib
- **Homologous:** huh-MAA-luh-guhs
- **Recombination:** ree-kaam-buh-NAY-shn
- **BRCA:** brah-KUH
- **Platelets:** PLAYT-luhts

Fixed starting dose: The same prescribed starting dose for all patients.

Individualized starting dose: A prescribed starting dose that is individualized or tailored to each patient based on their characteristics (for example, weight).

What were the results?

The individualized starting dose of niraparib improved patient safety, with a lower proportion of patients experiencing **side effects** than the fixed starting dose. The individualized starting dose of niraparib also delayed the cancer from coming back (recurring) or getting worse (progressing) compared with placebo. The delay in the cancer coming back or getting worse with niraparib treatment was generally similar in patients who received the individualized starting dose and those who received the fixed starting dose of niraparib.

What do the results mean?

The results support the use of the individualized starting dose of niraparib, which uses a patient's body weight and blood test results to determine how much drug they should receive at the start of treatment. The study found that the individualized starting dose improved safety compared with the fixed starting dose while still delaying the cancer from coming back or getting worse.

The individualized starting dose of niraparib is approved in multiple countries worldwide for the first-line maintenance treatment of patients with advanced ovarian cancer whose cancer responded to initial treatment. Niraparib approval varies by country; please check with your local provider for more details.

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

The original article is titled 'Prospective evaluation of the tolerability and efficacy of niraparib **dosing** based on baseline body weight and platelet count: results from the PRIMA/ENGOT-OV26/GOG-3012 trial' and is free to access by clicking here: https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34706.

Dosing: The prescribed amount of drug that a patient should take and how often they should take it.

What is the purpose of this PLSP?

The purpose of this PLSP is to help you to understand the findings from recent research.

Zejula (niraparib) is approved to treat the condition under study, which is discussed in this summary. Approval varies by country; please check with your local provider for more details. 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. The study described is still ongoing; therefore, the final outcomes of this study may differ from the outcomes described in this summary.

Who sponsored the study?

This study was **sponsored** by GSK (MA, USA).

Sponsor: A sponsor is a company or organization that oversees and pays for a clinical research study. The sponsor also collects and analyzes the information that was generated during the study.

What question does this PLSP answer?

Can an individualized approach to the amount of niraparib that a patient takes (niraparib dosing) help to decrease the proportion of patients who experience **side effects** while still delaying the cancer from coming back or getting worse?

Yes

The proportion of patients who experienced side effects was lower in patients who received an individualized starting dose of niraparib, with the greatest reductions seen in blood cell–related side effects, such as thrombocytopenia (low levels of thrombocytes, also known as platelets, which can cause problems with blood clotting) and anemia (low levels of red blood cells, which can cause tiredness).

Patients taking an individualized dose generally had a similar length of time before the cancer came back or got worse as participants who received the fixed starting dose.

Side effect: Any unintended, unpleasant, or harmful symptom a patient develops when taking a drug. Side effects may or may not be caused by the drug and can vary in severity from mild to life-threatening..

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Who should read this PLSP?

This PLSP may be helpful for patients with newly diagnosed advanced ovarian cancer and their family members or caregivers. It may also be helpful for patient advocates and other health care professionals who interact with patients with ovarian cancer.

Background

Most patients with ovarian cancer have advanced (severe) disease at the time of diagnosis.

Patients with advanced ovarian cancer are usually treated with surgery and chemotherapy to remove as much of the cancer as possible.

The disease may go away (often referred to as remission or no evidence of disease) after first treatment, but it often comes back or gets worse.

Maintenance treatments are medicines given after surgery and chemotherapy to try to extend the amount of time before the cancer comes back or gets worse.

What medicine was tested?

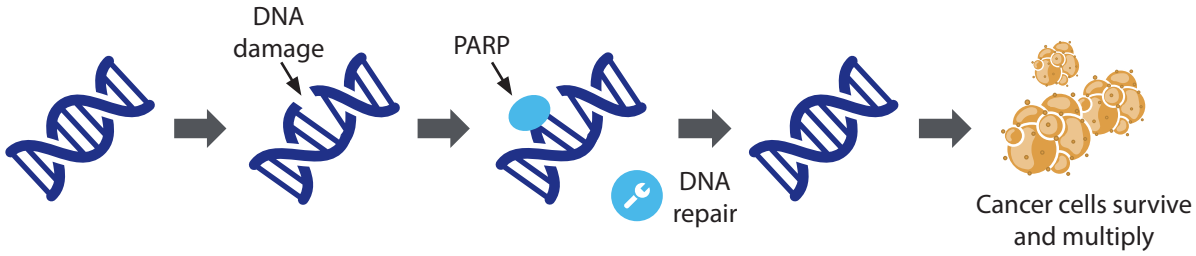
Niraparib was the medicine tested in the PRIMA study.Some of these proteins replace proteins that exist naturally in the body, like insulin (these are called recombinant proteins).

- Niraparib belongs to a category of drugs called **'PARP inhibitors'**
- Niraparib is used as maintenance treatment in patients who responded to chemotherapy (their tumors disappeared or shrank in size after treatment)
- Niraparib is an oral medication, taken by mouth once daily in the PRIMA study as 100-mg capsules

PARP inhibitors: Anticancer drugs that work by blocking DNA repair and helping to kill cancer cells.

How does niraparib work?

Chemotherapy kills cancer cells by damaging their **DNA**. Cancer cells resist chemotherapy by using **PARP** enzymes to fix the DNA damage and stay alive.



Niraparib attaches to the PARP enzyme and stops it from fixing the DNA. With niraparib blocking DNA repair, the damage gets worse over time, and the cancer cells die.

PARP inhibitors block DNA repair in all cells but have the potential to have a greater effect in cells with specific **mutations** in their DNA. Homologous recombination (HR) is a repair method used to fix DNA. DNA mutations that make cells HRd, or **homologous recombination-deficient**, may help PARP inhibitors work better. These mutations are found by genetic testing that an oncologist will do on a patient's tumor sample. Patients with **BRCA gene** mutations have tumors that are HRd.

Accordingly, niraparib may be a particularly good treatment option for some patients based on their tumor DNA testing results.

DNA: The molecule that carries genetic information for an organism.
PARP: Enzymes that help to repair damaged DNA.
Mutation: a change in the DNA sequence of an organism. Mutations in genes can stop them from working properly.
Homologous recombination-deficient (HRd): cells that cannot repair DNA using homologous recombination repair.
Homologous recombination-proficient (HRp): cells that can repair DNA using homologous recombination repair.
BRCA: the *BRCA1* and *BRCA2* genes are involved in DNA repair and play an important role in preventing cancer and slowing cancer growth. Cells with BRCA mutations cannot fix DNA using homologous recombination repair and are classified as HRd.
Gene: a short section of DNA. Many genes contain instructions to make different molecules that cells need to function.

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What study are these results from?

These results are from the PRIMA study, which is the name of the clinical trial. Researchers wanted to see if niraparib could help to delay the time it took for the cancer to come back or get worse. To do this, the PRIMA study tested maintenance treatment with niraparib compared with placebo (substance with no effects that a doctor gives to a patient instead of a drug).

The PRIMA study is ongoing at the time of the publication of this PSLP, and multiple articles have been published that report results from different parts of the study. This PLSP discusses an article that was published in 2023. The first results from the PRIMA study were published in 2019 in the *New England Journal of Medicine*.

Results from the 2019 article found that maintenance treatment with niraparib after surgery and chemotherapy significantly delayed how long it took for the cancer to come back or get worse compared with placebo.

Why was this analysis done?

In earlier studies that evaluated niraparib, many patients experienced side effects from taking niraparib. Side effects are any effects of a drug or treatment that occur in addition to the drug's intended effect.

Review of the previous studies found that patients with either low body weight or low platelet counts before taking niraparib were more likely to experience side effects while taking niraparib. Platelets are small cell fragments found in blood. They play an important role in forming blood clots to slow or stop bleeding. Patients with low platelet counts can bruise easily and have difficulty stopping bleeding from cuts or other injuries.

In the PRIMA study, the amount of drug (dose) given when patients first started treatment was changed to try to reduce the number of side effects. The article on which this PLSP is based presents findings from the PRIMA study focused on the amount of drug received at the start of treatment.

Which patients participated in the PRIMA study?

Patients with advanced ovarian cancer who had:

- Stage III or IV ovarian cancer at diagnosis. For patients with stage III and stage IV ovarian cancer, the cancer is present in one or both ovaries. In stage III disease, the cancer has also spread to lymph nodes and/or other parts of the abdomen. In stage IV disease, the cancer has spread outside of the abdomen to distant sites such as the lungs.
- A complete or partial response to initial **platinum-based chemotherapy**. A complete response means the disappearance of all tumors. A partial response means no new tumors and decrease in the size of existing tumors.
- A tumor tissue sample taken for genetic testing.

Patients participated whether or not they had a BRCA mutation.

The PRIMA study included patients with stage III ovarian cancer who either still had some visible disease after surgery or whose tumors were too big or too many in number to be removed by a surgeon. Patients with stage III ovarian cancer who did not receive chemotherapy before surgery and had no visible disease after surgery (tumors were completely removed) were not able to participate in the PRIMA study.

Platinum-based chemotherapy:
Platinum-based chemotherapy is a type of chemotherapy that uses drugs containing platinum. The drugs kill cancer cells and are thought to work because the platinum molecules bind to and damage the DNA in cancer cells.

What were the characteristics of patients in the PRIMA study?

487 Patients were assigned to receive niraparib

246 Patients were assigned to receive placebo

Average age was 62 years

Of all patients, 51% had tumors that were HRd
- Of the patients with HRd tumors, 60% had BRCA mutations

How did dosing change in the PRIMA study?

The start of the study: fixed starting dose

65% of patients received the fixed dose

300 mg once daily

When the PRIMA study started, all patients received the same amount of drug.

Study update: individualized starting dose

35% of patients received an individualized dose

Body weight and blood test

The PRIMA study was updated to individualize the amount of drug given at the start of the study based on a patient's weight and blood test results.

300 mg once daily

Weight
At least 170 lbs (77 kg)

AND

Platelet count
At least 150,000/microliters (μL)

200 mg once daily

Weight
Less than 170 lbs (77 kg)

OR

Platelet count
Less than 150,000/μL

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How many patients received each starting dose?

475 Patients received a fixed starting dose
315 Niraparib
158 Placebo
2 Were not treated

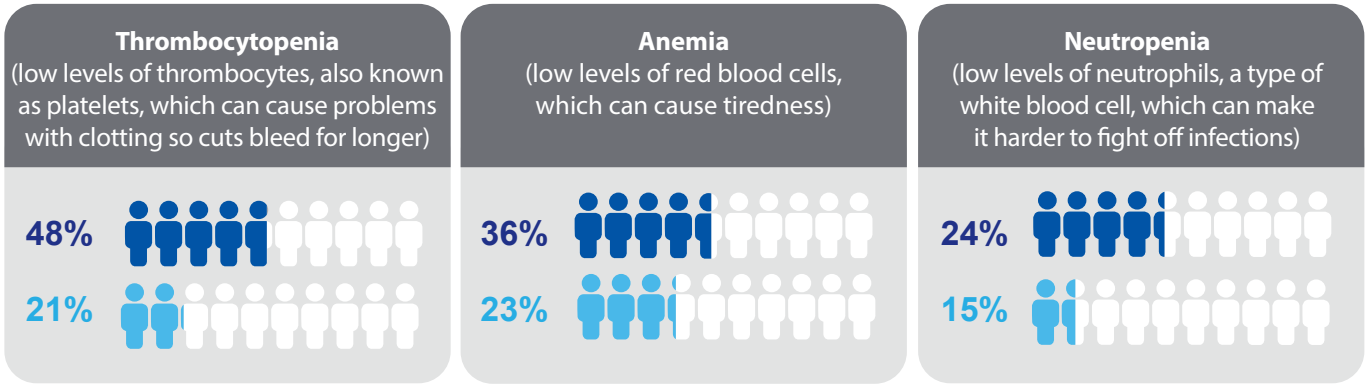
258 Patients received an individualized starting dose
169 Niraparib
86 Placebo
3 Were not treated

What were the safety findings?

Researchers tracked side effects that developed after a patient started treatment. In some cases, side effects can be severe and cause symptoms that require treatment. Side effect severity is graded on a scale from 1 (least severe) to 5 (most severe). Side effects that are grade 3 or higher are considered severe.

Niraparib is known to cause blood cell-related side effects. Some of the most common severe blood cell-related side effects are summarized below.

The proportion of patients who experienced blood–cell related side effects was lower in patients who received an individualized starting dose of niraparib than in patients who received a fixed starting dose of niraparib.



In rare cases, patients with advanced ovarian cancer can develop a type of blood cancer called myelodysplastic syndrome (MDS) after treatment for ovarian cancer. In some instances, MDS can lead to a type of cancer called acute myeloid leukemia (AML). AML is a type of blood cancer (leukemia) in which new cells that become white blood cells (types of cells in the immune system) change and begin to grow unusually quickly. The bone marrow becomes filled with these abnormal new white blood cells and can no longer make mature blood cells. Both chemotherapy and PARP inhibitor treatment may contribute to the development of MDS/AML.

In the first article from the PRIMA study that was published in 2019, 1 niraparib-treated patient developed MDS, and no niraparib-treated patients developed AML. No placebo-treated patients developed MDS or AML. For some side effects, the oncologist may direct a patient to take a lower dose of the drug (dose reduction) or temporarily pause taking the drug (dose interruption).

Patients taking an individualized starting dose tolerated niraparib better. This resulted in a lower proportion of patients undergoing dose reductions and dose interruptions because of side effects.

Niraparib starting dose	Lower dose of drug (dose modification)	Temporary pause in treatment (dose interruption)
Fixed	76%	84%
Individualized	62%	72%

In some cases, side effects may result in a patient being told to stop taking the drug all together (treatment discontinuation). Of niraparib-treated patients, 12% experienced a side effect resulting in treatment being stopped completely.

Safety and the patient experience in the PRIMA study

Most side effects in patients taking niraparib were mild (no treatment or management needed) or moderate (minimal or noninvasive treatment needed) in severity. Most dose reductions because of side effects occurred early during treatment; the dose generally remained stable after month 4.

Throughout the PRIMA study, patients were given surveys asking them about how they were feeling, how they were functioning, and what impact treatment had on their daily lives to assess overall health-related quality of life. Surveys completed by patients did not show any differences in health-related quality of life scores between patients taking niraparib and patients taking placebo.

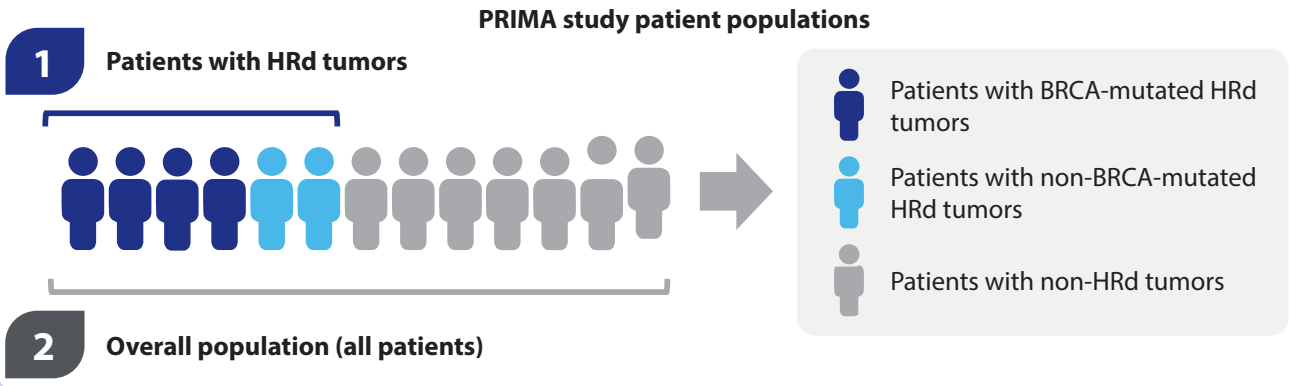
What were the findings on delaying the cancer from coming back or getting worse?

The PRIMA study was designed to evaluate results in 2 main groups of patients. Per the study plan, the patient groups were examined in a specific order, with all calculations for the first group to be completed before the second group was assessed.

Patient groups were determined based on tumor genetic testing results.

1 Patients with HRd tumors: this population included only patients with HRd tumors and was evaluated first

2 Overall population: this population included all patients no matter what their HR status was and was evaluated second



Patients with HRd tumors, including patients with BRCA gene mutations, typically have better responses to PARP inhibitors such as niraparib because they cannot repair DNA using a method known as homologous recombination (HR) repair. Patients with non-HRd tumors included patients with HR-proficient tumors and patients with tumors whose homologous recombination, or HR, status could not be determined. HR-proficient means that the tumor cells could repair DNA using **homologous recombination repair**. HR status not determined means that the tumor sample was tested for genetic markers, but the results were inconclusive or that the sample was not tested.

Homologous recombination repair:
a method of DNA repair used to fix damaged or broken DNA.

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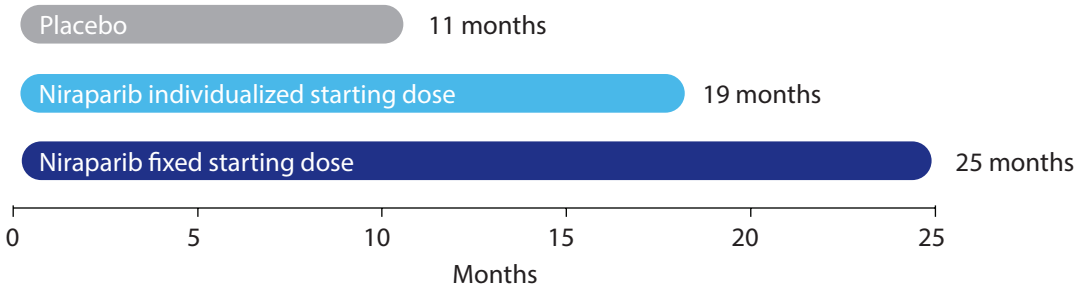
1 Patients with HRd tumors

In patients with HRd tumors, which included patients with BRCA mutations, the delay in the cancer coming back or getting worse was significantly longer with niraparib than with placebo.

Median delay in the cancer coming back or getting worse in patients with HRd tumors



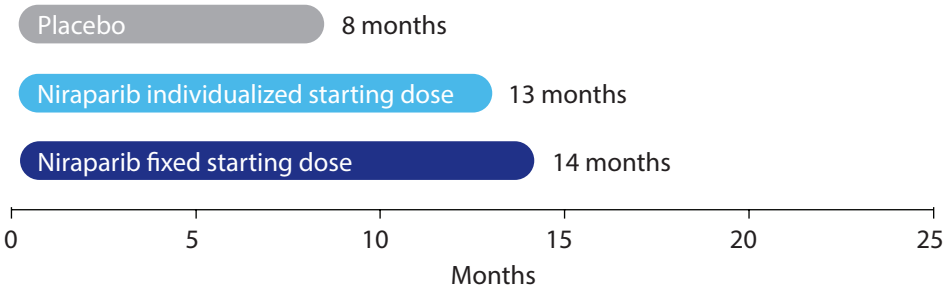
In patients with HRd tumors, the median delay in the cancer coming back or getting worse was generally similar with fixed and individualized niraparib dosing.

Median is the middle value when all values are sorted from lowest to highest. Therefore, half of the patients had a shorter delay in the cancer coming back or getting worse, and half of the patients had a longer delay in the cancer coming back or getting worse, than the numbers presented on the graph above.

2 Overall population (all patients)

In the overall population, the delay in the cancer coming back or getting worse was significantly longer with niraparib than with placebo.

Median delay in the cancer coming back or getting worse for all patients



In the overall population, the median delay in the cancer coming back or getting worse was similar with fixed and individualized niraparib dosing. Although patients are grouped by starting dose, results for the cancer coming back or getting worse reflect the overall treatment experience, including patients who experienced dose reductions and dose interruptions.

The individualized starting dose of niraparib delayed the cancer from coming back or getting worse compared with placebo.
Results with the individualized starting dose of niraparib were similar to results with the fixed starting dose of niraparib.

How do these results help patients and physicians?

These results support determining the niraparib starting dose based on an individual's body weight and platelet count. The individualized starting dose of niraparib improved patient safety and delayed the cancer from coming back or getting worse similar to the fixed starting dose. Based on these results, the niraparib individualized starting dose was approved for use in the USA, UK and EU.

Where can readers find more information?

The PRIMA study

The first results from the PRIMA study were published in 2019 in the *New England Journal of Medicine*.

- The full title of the article is "Niraparib in patients with newly diagnosed advanced ovarian cancer"
- You can read the free-to-access article by clicking https://www.nejm.org/doi/full/10.1056/NEJMoa1910962
- A PLSP of the article can be accessed by clicking https://www.trialsummaries.com/Study/StudyDetails?id=14456&tenant=MT_GSK_9011

The article this PLSP is based on was published in the journal *Cancer* in 2023.

- The full title of the article is 'Prospective evaluation of the tolerability and efficacy of niraparib dosing based on baseline body weight and platelet count: results from the PRIMA/ENGOT-OV26/GOG-3012 trial'
- You can read the free-to-access article by clicking https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.34706

At the time of the publication of this PLSP, the PRIMA study is ongoing but no longer accepting new patients.

Study number: NCT02655016 Study sponsor: GSK

Partnership with ENGOT and GOG

The PRIMA study was conducted in partnership with ENGOT and GOG and is also known as the ENGOT-OV26 study and the GOG-3012 study. ENGOT stands for the European Network for Gynaecological Oncological Trial groups, and GOG stands for the Gynecologic Oncology Group. Both groups are dedicated to promoting research to improve care for patients with gynecologic cancers.

Additional resources about ovarian cancer

Read more about ovarian cancer at these websites:
The American Cancer Society: https://www.cancer.org/cancer/ovarian-cancer.html
The European Society for Medical Oncology: https://www.esmo.org/for-patients/patient-guides/ovarian-cancer

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Competing interests disclosure

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