OVERVIEW

In this CME activity, Susana Campos, MD, MS, MPH, reviews some of the recent clinical developments in treatment of advanced ovarian cancer with PARP inhibitors. We welcome you to learn more about the updated data from key clinical studies of PARP inhibitor maintenance therapy in advanced ovarian cancer, and the implications of the results on the current and emerging concepts in ovarian cancer clinical practice.

CONTENT AREAS

- Platinum-sensitive recurrent ovarian cancer
- Advanced ovarian cancer with *BRCA* mutation
- PARP inhibitor maintenance therapy
- Patient-reported outcomes
- Individualized PARP inhibitor dosing based on patient characteristics
- Long-term safety and tolerability of PARP inhibitor therapy

TARGET AUDIENCE

This activity was developed for a national audience of medical oncologists, gynecologic oncologists, and other healthcare professionals involved in the treatment of advanced ovarian cancer.

FACULTY

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LEARNING OBJECTIVE

At the conclusion of this activity, participants should be better able to:

- Summarize the latest evidence on poly ADP ribose polymerase (PARP) inhibitors in ovarian cancer
- Incorporate evidence-based research into clinical practice to improve patient outcomes

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The estimated time to complete the activity is .50 hour.

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Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial

Dr. Wu and colleagues, published in the *Annals of Oncology,* April 2021.

Annals of Oncology

Susana Campos, MD: This article describes the NORA trial showing that niraparib maintenance therapy reduced the risk of disease progression or death by 68% and prolonged progression-free survival in patients with platinum-sensitive recurrent ovarian cancer. The study showed that individualized niraparib dosing was effective and, most importantly, safe.

The study confirmed that an individualized niraparib starting dose based on baseline body weight and platelet count improves tolerability without affecting treatment outcomes. This is the first trial of a PARP inhibitor maintenance therapy for patients with ovarian cancer conducted exclusively in the Asian patient population.

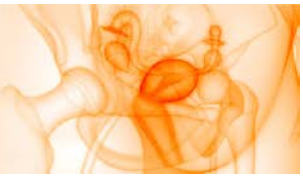
This was a phase 3, double-blinded, placebo-controlled trial conducted at 30 centers in China with 265 patients accrued to the study. Patients had platinum-sensitive recurrent ovarian cancer and had responded to their most recent platinum-containing chemotherapy. Patients were randomized 2:1 to receive either oral niraparib or a matched placebo until disease progression or unacceptable toxicity.

Of the 265 patients, 16 were randomized to receive niraparib or matched placebo at a fixed dose of 300 mg/day. After a protocol amendment, 249 patients were randomized using an individualized starting dose. Patients with a body weight less than 77 kg, or a platelet count less than 150,000, received an individual dose of 200 mg of niraparib or matched placebo per day, while all other patients received 300 mg/day. With the ISD-based randomization, 14 patients received niraparib at 300 mg or matched placebo. They had a median body weight 82.5 kg or 235, and 235 received niraparib 200 mg or a matched placebo. They had a median body weight 59 kg.

The primary endpoint was progression-free survival assessed by blinded independent central review. Secondary endpoints included chemotherapy-free interval, time to first subsequent treatment and overall survival.

The key findings in the NORA study showed that niraparib maintenance treatment reduced the risk of disease progression or death by 68% compared to placebo. At an overall median follow-up of 15.8 months, the median progression-free survival was 18.3 months for patients receiving niraparib compared to 5.4 months for those receiving placebo. The hazard ratio for niraparib vs placebo was 0.32, statistically significant.

The progression-free survival benefit, interestingly, was similar in patients receiving individualized dosing regardless of BRCA mutational status. The median progression-free survival was longer for niraparib vs placebo among patients with germline BRCA mutations and those without BRCA mutations, 11.1 vs 3.9 months with a hazard ratio of .4. In patients receiving an individualized dosing, the median



progression-free survival was 18.3 months with niraparib vs 5.4 months with placebo. The hazard ratio was 0.3.

In addition, niraparib maintenance therapy yielded a significantly longer median CFI, 18.5 vs 9.7 months with a hazard ratio of 0.34, and a median TFST compared to patients with placebo. At the time of the data cut-off, median follow-up for overall survival had not been reached in either treatment group.

Treatment-emergent adverse events, grade 3 or higher, occurred in 50.8% of niraparib-treated and 19.3% of placebo-treated patients. The most common grade 3 or 4 adverse events were hematological in nature. In the niraparib and placebo groups respectively, these AEs were decreased neutrophil count, 20.3% vs 8%; anemia, 14.7% vs 2.3%; and a decreased platelet count, 11.3% vs 1.1%. In surveillance for the adverse events of interest, one case of treatment-related fatal acute leukemia was reported in the niraparib group after the primary cut-off date.

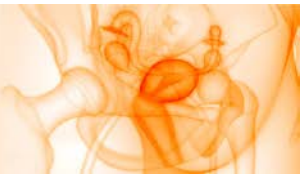
Dose reductions related to treatment-associated adverse effects occurred in 59.9% and 13.6% of patients in the niraparib and placebo groups respectively. In the niraparib group, the most common AEs leading to dose reductions were hematological. Most AEs were adequately controlled as indicated by a low proportion of treatment discontinuation due to treatment-emergent AEs, about 4% in the niraparib group compared to about 5% of in the placebo group.

Here is my analysis of the study. Clearly, this study paralleled previous studies. The NOVA study, published several years ago, showed that niraparib improved progression-free survival in all comers, whether they were BRCA mutation carriers or not. This study also adds to results from the RADAR study published several years ago in the *Annals of Oncology*. It confirmed that if you were to individualize the dose in a patient whose body weight was less than 77 kg or their platelet count was less than 150,000, and the 300 mg dose was amended to 200 mg, the efficacy would not change. However, what would change is tolerability and that is extremely important. So, this study added to an existing body of literature, namely the RADAR study. And if we look at the PRIMA data which is niraparib in first-line therapy, after first-line therapy, that trial was also amended to use this individualized standard dose.

The study also highlights a very important point. It was conducted specifically in the Asian population and oftentimes when patients enroll in a clinical study we have little information about how ethnicity may affect pharmacokinetics. I wish we had a little more of that type of data in this particular study, and I think that is something we must be mindful of and perhaps incorporate into prospective studies.

Whenever a study is published, we ask how the information impacts our current practice. In many ways, this study validates our current common practice. We are very familiar with the RADAR study, once again utilizing individual dosing. This adds to the RADAR study. It adds NOVA data and it gives us information, more importantly now, as to how to treat patients in the up-front setting, again utilizing this individual standardized dose and confirming that we're not minimizing efficacy for that.

How does this information impact future practice? I think most of us are using this



individualized standardized dosing as we treat patients today. I think we must be cognizant that even though we're using standardized dosing, we must always be mindful of the toxicities of these drugs, and continue checking our patients' CBC every week for the first month, and monthly thereafter. Even though the individualized standardize dosing is important in these patients, we must be aware that there could still be toxicity.

What questions remain unanswered in the NORA study? The NORA study was well done. Unfortunately, they not have a group of patients that we often like to have information on and that is individuals who are homologous, HRD-positive. In China, they don't have a validated test for HRD and therefore we don't have this information to glean from the NORA study.

Additionally, what we don't have is quality of life data from the NORA study, which I think would be very important, especially because this study was specifically in the Asian population. But overall, this is an excellent study. It allowed us to study niraparib utilizing individualized dosing.

Patient-centred outcomes and effect of disease progression on health status in patients with newly diagnosed advanced ovarian cancer and a *BRCA* mutation receiving maintenance olaparib or placebo (SOLO1): a randomised, phase 3 trial

Dr. Michael Friedlander and colleagues, published in *The Lancet Oncology*, May 2021.

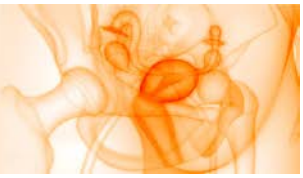
The Lancet Oncology

Susana Campos, MD: This article states that maintenance olaparib continued to provide progression-free survival benefit without a detriment to health-related quality of life measures, with clinically-meaningful quality-adjusted benefits in progression-free survival and time without significant symptoms of toxicity compared to placebo.

This updated report on SOLO1 highlights the importance of patient-centered outcome benefits in addition to the clinical benefit of substantial progression-free survival extension with maintenance olaparib in women with newly diagnosed ovarian cancer and a BRCA mutation.

Before my analysis of the study, let's review some key findings and methods of the SOLO1 trial. It was a randomized, placebo-controlled, double-blind, international phase 3 trial conducted in 118 centers in 15 countries. The SOLO1 group included about 391 women aged 18 years or older with an ECOG performance score of 0 to 1. These patients were newly diagnosed with advanced, high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer or fallopian tube cancer. These patients had to have had a BRCA mutation. They also had to have experienced complete clinical or partial response to platinum-based chemotherapy.

Patients were randomized 2:1 to receive either 300 mg of olaparib tablets or placebo twice a day and treated for up to 2 years. In the primary analysis, the primary endpoint was progression-free survival and previously



published data from this trial showed that the maintenance olaparib reduced the risk of disease progression or death significantly compared to placebo. The hazard ratio was 0.30. Long-term follow-up showed that 48% of olaparib-treated patients were progression-free at 5 years vs 20.5% with placebo.

However, health-related qualify of life was a secondary endpoint and this 2021 article, reports data for the prespecified primary health-related qualify of life endpoint of change from baseline in the Functional Assessment of Cancer Therapy pertaining to the ovarian cancer, the FACT-O Trial Outcome Index score for the first 24 months. Additionally, prespecified exploratory endpoints, quality-adjusted progression-free survival and time without significant symptoms of toxicity, TWiST, were also included in the analysis in this report. Both the characteristics and the mean TOI scores after first-line therapy at baseline were balanced between the 2 groups.

It is important to note that when the investigators looked at the data, there was no clinically meaningful change in TOI score noted at 24 months, within or between the olaparib and placebo groups. Between-group differences in TOI score was -3 and within the olaparib group the adjusted mean change in score from baseline over 24 months was 0.3 points vs 3.3 in the placebo group. The median progression-free survival was not reached in the olaparib group. It was, however, 13.8 months in the placebo group.

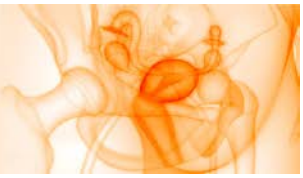
The mean quality-adjusted progression-free survival was significantly longer with olaparib at 29.75 months vs 17.58 months with placebo, for a difference of 12.17 months. This was statistically significant.

The time without significant toxicity symptoms was also prolonged with olaparib. The mean duration of TWiST with olaparib was 33.15 months vs 20.24 months with placebo, for a difference of 12.92 months. Once again, statistically significant.

Interestingly and importantly is that after commencing olaparib or placebo, a between-group difference at week 5 was observed, indicating early impact of AEs in some patients. Thirty percent of olaparib patients reported still being bothered by treatment side effects compared to about 11% of placebo-treated patients. However, over time, the proportion of patients not bothered or only a little bothered by treatment side effects increased, with relatively small differences between these treatment groups.

Of importance, the radiographical progression was associated with decreasing health status overall, a clinically meaningful 7-point worsening was noted on the EQ-5D-5L VAS score compared with the last progression-free visit. The proportion of patients reporting any problems with the EQ-5D-5L domains of anxiety or depression, pain or discomfort, or self-care, did increase after progression.

The take-home message from this study was the fact that we continue to see a progression-free survival benefit with olaparib in patients that are BRCA mutation carriers. This is first-line therapy. Progression-free survival was monumental, but most importantly what the study showed was that in addition to having the progression-free survival benefit, there was no clinically meaningful change in the TOI score noted at 24 months. And this is between and within the olaparib and placebo groups. The mean quality adjusted progression-free survival



was significantly longer with olaparib. It was almost 30 months compared to placebo at 18 months. That's a difference of about 12 months, statistically significant.

Likewise, the time without significant toxicity symptoms was also prolonged with olaparib compared to placebo. A very interesting point in this particular study—and I'm glad the study did highlight this—was that shortly after commencing olaparib, when you look at the difference between olaparib and the placebo, at 5 weeks, there was an impact on the patients and patients that took olaparib actually did have more side effects. And this is important. As a clinician, it's important to understand how to finesse the drug and in order to mitigate some of these side effects because clearly there's a median progression-free survival with olaparib vs placebo. Keeping these patients on olaparib for as long as you possibly can, as outlined in study, is exceptionally important. And you can do this in many ways. You could be quite diligent in micromanaging every side effect, nausea, monitoring hematological toxicity, but we can also do it in a different way. In my clinical practice, what I tend to do is 200 twice a day for about a week and then I increase it to 300 twice a day. I think people tend to acclimate to this particular drug. A very important point is that a patient can only get the benefit from the SOLO1 data as long as they stay on the drug and so micromanaging and finessing the delivery of the drug is exceptionally important. But it's also very reassuring data. If they can get through a couple of weeks of olaparib, the quality of life is no different at 24 months, and I think that's actually quite important. It's an important message to send to patients if they are struggling a little bit, at least early on.

How does this information impact current practice? I think it is important data to share with my colleagues. It's important to share with my patients, especially as they start this drug, especially if they may have some side effects early on. You can talk to them about mitigating some of these side effects, knowing that this does improve over time. I think this is important for the future because, once again, if you mitigate the early impact of AEs, you're more likely to keep the patient on this particular drug and they're more likely to benefit in terms of progression-free survival.

One often asks, when you look at any study, what questions remain unanswered. Well, this is a brilliantly done trial and it's important data to share with clinicians, and it's important data to share with our patients, specifically. But keep in mind that the health-related quality of outcome, quality of life, was only assessed at 24 months. I think it might be interesting if they had extended that beyond the 24 months because, as we all know, quality of life during a study is often measured in these studies, but there are times when quality of life after a study is finished is also impacted by certain anxiety and certain anticipation. So, I think it would be interesting if they had done the health-related quality of life assessment after 24 months.

Olaparib tablets as maintenance therapy in patients with platinum-sensitive relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a final analysis of a double-blind, randomised, placebo-controlled, phase 3 trial

Dr. Andres Poveda and colleagues, published in *The Lancet Oncology*, May 2021.

The Lancet Oncology

Susana Campos, MD: To summarize the article, olaparib provided a mean overall survival benefit of 12.9 months compared with placebo in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation. The importance of this article is that this is the first report of final overall survival data from a phase 3 trial of maintenance olaparib in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation. Although the overall survival difference between olaparib and placebo did not meet the prespecified threshold for statistical significance, the overall survival extension is nevertheless clinically meaningful.

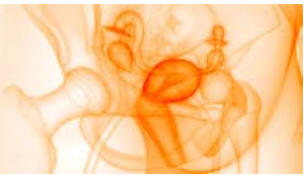
Before we review the importance of this article and my take on it, we're going to spend a couple of minutes just going through the, the actual content of the study. So, just to review a couple of points. This was a double-blind, randomized, placebo-controlled, phase 3 trial conducted across 123 medical centers in 16 countries. The trial involved 295 patients 18 or older, performance status of 0 or 1, with histologically confirmed, relapsed, high-grade serous or high-grade endometrioid ovarian cancer, including primary peritoneal or fallopian tube cancers.

Patients had to have received 2 or more previous platinum regimens, and they had to have harbored a BRCA1/2 mutation. Patients were randomized 2:1 to receive olaparib tablets, 300 mg twice daily, or matching placebo. All patients randomized had a germline BRCA1/2 mutation.

Patients were stratified by response to previous chemotherapy and the length of platinum-free interval. Baseline characteristics were well balanced between the 2 groups. The primary endpoint was progression-free survival. In the primary analysis, the median progression-free survival was significantly longer with olaparib than with placebo. To be specific, 19.1 months vs 5.5 months. The hazard ratio of 0.3, is statistically significant. This was in patients with platinum-sensitive, relapsed ovarian cancer, that harbored a BRCA1 or 2 mutation. Safety was assessed in all patients who received at least 1 treatment dose. Overall survival was the key secondary endpoint.

Some of the key findings: the mean total treatment duration was 29.1 months and 13.1 months for the olaparib and the placebo groups, respectively. At the final analysis, median follow-up for overall survival was 65.7 months with the olaparib and 64.5 months with placebo. The data reached 61% maturity at final analysis after 59% of the olaparib-treated patients and 66% of the placebo-treated patients had passed.

The median overall survival was 51.7 months with olaparib and 38.8 months with placebo. The hazard ratio was 0.74, with a *P* value of 0.054. This outcome did not meet the



predefined statistical threshold. However, the median time to first subsequent therapy or death was 27.4 months with olaparib vs 7.2 months with placebo. It had a hazard ratio of 0.37.

The median time to second subsequent therapy or death was 35.8 months with olaparib and 18.9 months with placebo, a hazard ratio of 0.51. In a prespecified sensitivity analysis in 286 patients with a germline BRCA1 or 2 mutation confirmed, using the Myriad Genetics BRCA test, that median overall survival was longer with olaparib compared to placebo, namely 52.4 months vs 37.4 months with a hazard ratio of 0.71. The *P* value was 0.031.

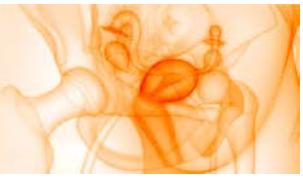
The most common grade 3 or worse treatment-emergent AE was anemia, occurring in about 21% and 2% of patients with the olaparib and placebo groups, respectively. A serious treatment-emergent AE was reported in 26% and 8% of patients with olaparib and placebo groups, respectively. Treatment-emergent AEs leading to a fatal outcome occurred in 8 patients or 4%, all receiving olaparib, 6 of which were judged to be treatment-related, With 3 each attributed to myelodysplastic syndrome and acute myeloid leukemia.

Anemia was seen in 7 patients or 4% of patients, AML 2%, MDS 1%, neutropenia 1%, and thrombocytopenia 1%. These were the most common treatment-emergent AEs leading to treatment discontinuation in the olaparib group.

I think this study actually shows us some very, very important points that when we look at this data, it is extremely important to note that we are seeing survival data for the first time with a PARP inhibitor in platinum-sensitive, relapsed ovarian cancer. This is exceptionally important! Even though it did not meet its statistically significant landmark, there's no question that patients who did receive olaparib lived longer than those that did not. Equally important, and I think this is something we're starting to see in our own clinic and we're starting to educate our patients with is that when patients get treated with olaparib, one has to be mindful of the fact that there could be more side effects. So, these treatment-emergent AEs that led to a fatal outcome occurred in 8% of patients. Keep in mind that when this study was designed in a platinum-sensitive recurrent ovarian cancer, patients were asked to be on a PARP inhibitor until progression or unacceptable toxicity. And so, I do think it raises some questions that we should start asking ourselves. For example, is it important to treat these patients until progression or is there a finite amount of time that patients should be treated, even in a platinum-sensitive recurrent ovarian cancer, especially knowing that there could be more toxicity in terms of neurological toxicities?

Nonetheless, one cannot argue that olaparib improves not only median progression-free survival but numerically also showed us survival benefit in patients that did receive the PARP inhibitor.

How does this play into our current practice? I think this adds to a body of literature that is currently in practice. It reinforces the benefit of olaparib not only in the SOLO2 trial, but this actually extends to other patients, patients perhaps that do not carry the BRCA mutation. This was played out a little bit more in the study 19 data. But once again, it reinforces how powerful this drug is as maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer. It also almost becomes an issue



of the toxicities and we must be mindful in terms of following patients very, very closely for this.

How does this information impact further practice? In my patients with platinum-sensitive recurrent ovarian cancer, especially if they're BRCA mutation carriers, we introduce them to PARP inhibitors. However, some of the information that was gleaned from this article actually reinforces our practice, but at the same time makes me more cognizant that I have to be mindful of potential late-time toxicity. So we are very keen about sharing this information with patients and on keeping an eye on their hematological profile.

I think a question that remains unanswered, is a question that's come up in our clinical practice. We have patients that are BRCA mutation carriers, they are on PARP inhibitors, olaparib for one, and they're out 3–4 years and they haven't relapsed, which is wonderful. The question really is how long do we keep patients on the PARP inhibitors? If we think back in terms of the up-front therapy and we take a look at the SOLO1 data, the SOLO1 kept patients on for 24 months. The PRIMA data kept patients on for 3 years. In the recurrent platinum-sensitive ovarian cancer, the studies were designed to keep the patients, as mentioned, until patients progress or until there was unacceptable toxicity.

Is there a time—a strict time—that these patients should be on PARP inhibitors? What is the maximum gain and when? I think this is a question that we should start sharing with patients. We don't have the answer to this. The studies don't provide an answer to that. But again, it's a thought process, it's a dialog that we continue to have with patients.