

Improving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer Part 1:

Cytogenetic Testing and PARP Inhibition for the Maintenance
Treatment of Patients with Advanced Ovarian Cancer



This transcript has been edited for style and clarity
and includes all slides from the presentation.

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Improving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer Part 1: Cytogenetic Testing and PARP Inhibition for the Maintenance Treatment of Patients with Advanced Ovarian Cancer

Kathleen N. Moore, MD, MS



► **Kathleen N. Moore, MD, MS:**

Hello, and welcome to this educational activity titled *Improving Interprofessional Management and Clinical Outcomes with PARP Inhibitors for Advanced Ovarian Cancer: Cytogenetic Testing and PARP Inhibition for Maintenance Treatment*.



► I'm Dr. Kathleen Moore. I'm the Virginia Kerley Cade Chair in Developmental Therapeutics and Associate Director of Cancer Research and Director of the TSET Phase I Drug Development Unit at the Stephenson Cancer Center at the University of Oklahoma.

Agenda

- What Is Cytogenetic Testing and Why Should I Use It? Identification of Patients Who Might Benefit from PARP Inhibitor Therapy
- Where Do PARP Inhibitors Fit in the Treatment Paradigm of Ovarian Cancer? Practical Strategies
- Clinical Data for PARP Inhibitors as Maintenance Therapy for Newly-Diagnosed Advanced Ovarian Cancer
- PARP Inhibitors as Maintenance Therapy and Treatment for Relapsed/Recurrent Advanced Ovarian Cancer



▶ Today, I'll be reviewing the role of genetic testing and identifying patients likely to benefit from first-line maintenance PARP inhibitor therapy, updated clinical trial data surrounding PARP inhibitors as first-line maintenance therapy, and how the earlier introduction of PARP inhibitors fits in the treatment paradigm of ovarian cancer and may benefit a greater number of patients than in the relapsed setting.

What Is Genetic Testing and Why Should I Use It?

Identification of Patients Who Might Benefit from PARP Inhibitor Therapy



▶ So, we're going to start with genetic testing, what is it and why you should use it and employ it for your patients with ovarian cancer.

Guidelines: Tumor Molecular Analyses

- Patients with ovarian cancer should have genetic risk evaluation and germline and somatic testing
- Germline and somatic BRCA1/2 status informs maintenance therapy
- In the absence of a BRCA1/2 mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy

Setting	Recommendation
Upfront	Choice of somatic testing should, at a minimum, optimize identification of molecular alterations that can inform use of interventions that have demonstrated benefit in this setting, including: BRCA1/2, LOH, or HRD status in the absence of a germline BRCA mutation
Recurrence	Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or tumor-agnostic benefit including: BRCA1/2, HRD status, MSI, MMR, TMB, BRAF, FRα, RET, and NTRK if prior testing did not include these markers



Armstrong DK, et al. NCCN Guidelines on Ovarian Cancer. Version 2.2023.
 FR α , folate receptor alpha; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; MSI, microsatellite instability;
 MMR, mismatch repair; PARP, poly(ADP-ribose) polymerase; TMB, tumor mutational burden.

► So, we're going to start off just with the guidelines. And unlike other solid tumors, where who should be tested can sometimes be a little bit complex based on family history and ethnicity, amongst other things. For epithelial ovarian cancer, it's really pretty simple. If your patient has epithelial ovarian cancer, she is eligible for genetic testing for not only BRCA1 and 2, but other high penetrance genes associated with development of ovarian cancer and also potentially associated with better response to DNA damaging therapies, which we'll talk about in a while such

as PARP inhibitors or like carboplatin, for example.

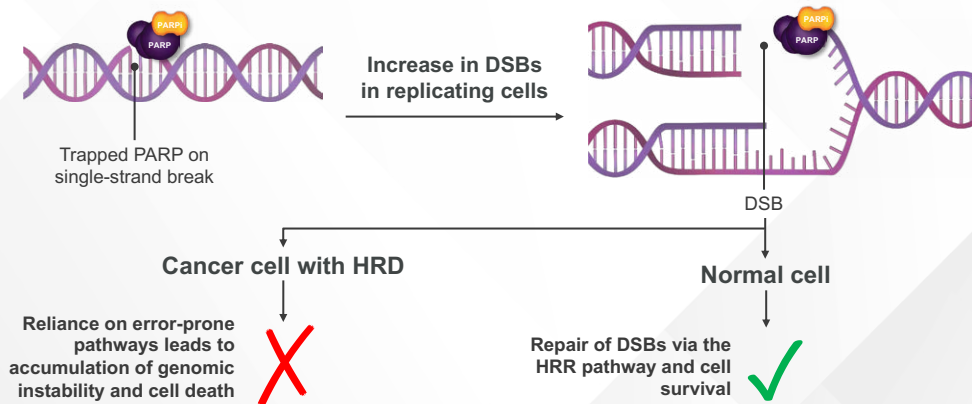
And so, all of the international guidelines agree on this. We want to offer germline testing to any patient with epithelial ovarian cancer, again, BRCA1 and 2 are our most common genes, but we're also looking for other high penetrance genes such as PALB2, BRIP1, RAD51C and D, and others. And even not so much the focus of today, but we're also looking for mismatch repair deficiency, which can happen in a small number of patients.

In the absence of finding a gene aberration associated

with homologous recombination repair or DNA repair, then we want to look for something called homologous recombination deficiency status. And that's a variety of terms for that. So, in BRCA wild-type, or BRCA-negative tumors, we want to look for other reasons that that tumor might be vulnerable to therapies that target DNA, again, PARP inhibitors and platinum, so that we can better identify those patients whose tumors would respond better to these therapies. And that's what we'll spend a lot of time talking about today.

PARP Inhibition Selectively Targets Tumors With Homologous Recombination Deficiency

PARPi trap PARP enzymes on DNA, causing cancer-specific cell death in tumors with HRD



O'Connor MJ. *Mol Cell*. 2015;60(4):547-560.

DSB, double-strand break; HRD, homologous recombination deficiency; HRR, homologous recombination repair; PARPi, poly(ADP-ribose) polymerase inhibitor.

► So, why are we looking for this? Why are we looking to identify those tumors that have some inherent vulnerability to how they're able to repair their DNA? Well, these are the tumors that are going to respond most robustly to DNA-damaging therapies. And again, we're talking about PARP inhibitors here. And the poster child for these sort of inherent vulnerabilities are BRCA mutations, BRCA1 or BRCA2. So, this schema is really simplistic, but I think it serves a point, if you start in the upper left-hand side, you see the DNA. And this is a single-strand break. And a lot of people really think that the only place that PARP protein, which is poly ADP-ribose polymerase, acts is on single-strand breaks. That's actually not true, it acts on double-strand breaks and non-homologous end joining, but its main function is to fix single-strand breaks. And so, PARP is recruited to the site of a single-strand break, it binds, and then it creates this scaffold onto which DNA repair proteins

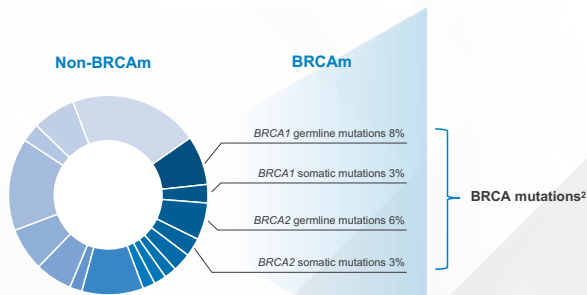
collect so that they can fix the double-strand break. Now, before that happens, a PARP protein has to dissociate from the damaged DNA for that DNA repair to happen.

So, PARP inhibitors work in a couple of ways. And you can see the PARP inhibitor signified by the kind of orange blob attached to the PARP protein. One, it inhibits the PARP inhibitor from creating the scaffold that allows the DNA proteins to come into repair. Two, some PARP inhibitors can trap the PARP protein on the surface of the DNA damage, the site of the single-strand break. So, that's called PARP trapping. And different PARP inhibitors have different degrees of PARP trapping. But the more PARP trapping it has, actually the more potent the PARP inhibitor is, because that PARP protein can't dissociate from that site of single-strand break, and that leads to the double-strand breaks, if we move from left to right on this slide, that can occur with unrepaired single-strand breaks.

So, in a setting of a tumor that has this inherent vulnerability to how it fixes its double-strand breaks – again, the poster child is BRCA, where they've lost that BRCA protein that's key for double-strand breaks, but there are other reasons a tumor is vulnerable – once you've gotten to this point, it can't fix itself. It doesn't have enough compensatory DNA repair mechanisms to fix the cell and it will die. But in a cell that's really good at fixing its DNA, and we call these homologous recombination proficient tumors, this is where PARP inhibitors, at least alone, don't really work because you can cause this damage, but the cell has so much collateral repair mechanism that it just repairs and keeps on going. And so, these HRD assays that we'll talk about, try to help us identify those tumors that have that vulnerability to how they fix their DNA, so that you can apply PARP inhibitors in the setting where the patient's going to benefit the most.

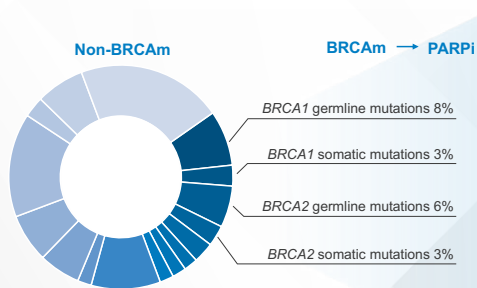
Who Should Be Treated With PARPi?

Approximately 20% of Patients With Ovarian Cancer Harbor a BRCAm^{1,2}



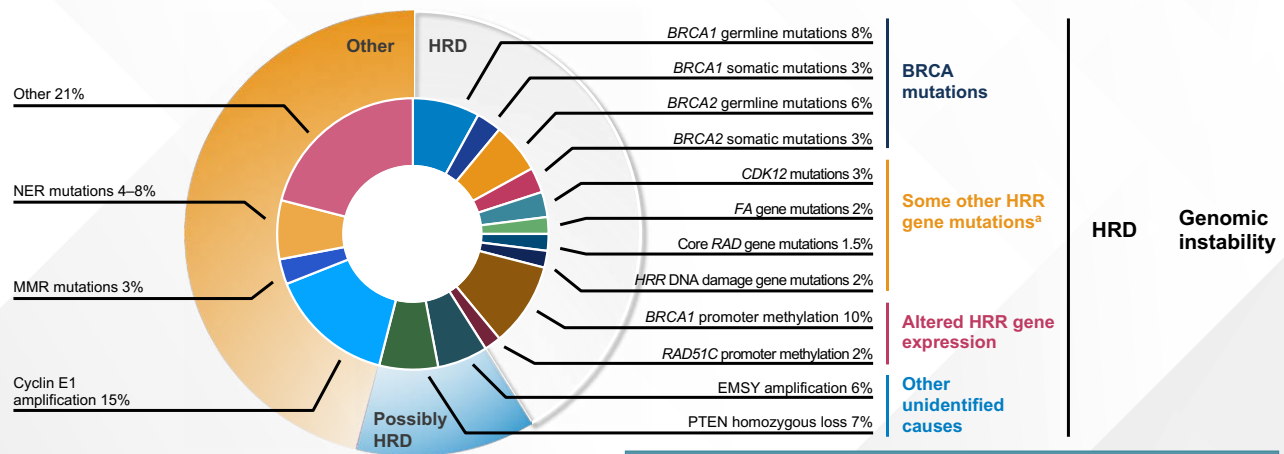
► So, who should be treated with PARP inhibitors? The easy 100% answer is any patient with a BRCA alteration either germline or somatic, meaning they weren't born with it, but it's in the tumor. This makes up about 20 to 24% of high-grade serous ovarian cancer, have some sort of BRCA 1 or 2, germline or somatic mutation. For these patients, the standard of care is treatment with combination of surgery and platinum-based chemotherapy, and at the time of response, maintenance with a PARP inhibitor for 2 years. And we'll show some of the data as to why that is the standard of care. There's really not an alternative unless a patient chooses not to have this. So, this is for BRCA, 20% and 25%. No brainer, 100% should be offered a PARP.

But What About the ~80% Without a BRCA Mutation?



► What about everyone else? It's only 20-ish%. But the other 80% that don't have a BRCA mutation? Well, this is where understanding what those other vulnerabilities are that would render a tumor sensitive to PARP really come into play.

HRR Gene Mutations, Altered Gene Expression and Other Causes Contribute to Genomic Instability¹



Actionable mutations are at a low frequency in HGSOC; therefore, genomic instability remains a key therapeutic target²

^aNot all mutations have been linked to an HRD phenotype.



Image adapted from Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5(11):1137-1154.
 1. Konstantinopoulos PA, et al. *Cancer Discov.* 2015;5(11):1137-1154. 2. Press JZ, et al. *BMC Cancer.* 2008;8:17.
 BRCA, BRCA1 and/or BRCA2; DNA, deoxyribonucleic acid; BRCA2-interacting transcriptional repressor; FA, Fanconi anemia; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; HRR, homologous recombination repair; MMR, mismatch repair; NER, nucleotide excision repair; PTEN, phosphatase and tensin homolog.

► And this figure here is an old figure, this pie graph that was made by the brilliant Dr. Panos Konstantinopoulos, and we all still use it because it really does illustrate the kind of different populations of tumors all within the rubric of high-grade serous. If you start on the upper right-hand side of this pie graph, you'll see the BRCA mutations that we already talked about, about 20%, and that's in black. In orange, you'll see some other genes that are associated with DNA repair or HRR, or homologous recombination repair, that if you have one of these gene mutations, we do think that tumor is more vulnerable and may be more responsive to PARP inhibition. In pink, you can see the altered homologous recombination repair gene expression findings. And this is really important,

because about 10% of patients with high-grade serous ovarian cancer will have BRCA1 promoter methylation – and we actually even see RAD51C promoter methylation now, it's only 2% – 10% BRCA1 promoter methylation. So, the gene's totally normal, somatic or germline, but the promoter's methylated, and so, they don't transcribe the protein. So, it's just like having a BRCA mutation. And these tumors respond incredibly well to PARP inhibitor. And while we can't really test for these promoter methylations commercially right now, they do fall into these homologous recombination or homologous recombination deficiency assays, so they are included there. So, we do pick them up indirectly there.

Now, on the other side of the pie, like from 6 to 12 o'clock in orange, you see the tumors that don't entirely not respond to PARP, but they don't respond as well. And the reasons for this, and really the reasons they have poor prognosis and poor response even to platinum-based therapy are varied and we're trying to understand that so we can develop better therapies for them. This is where you see a lot of your cyclin E1 amplifications MYC amplifications, and other abnormalities that render these tumors quite a bit more resistant to PARP inhibitors, not entirely, but quite a bit more. We need to look for better things here in this population.

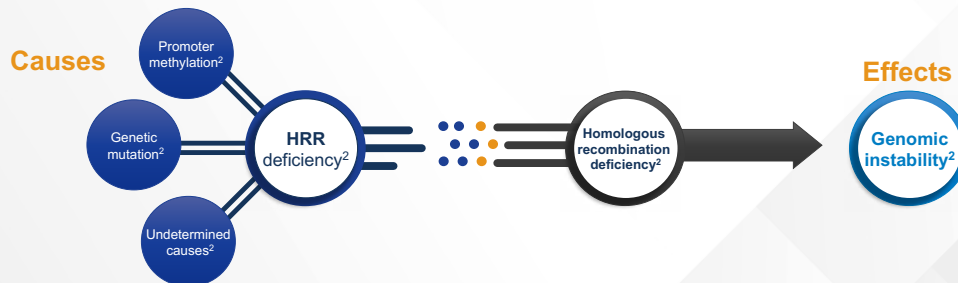
Testing for HRD: HRR Gene Panels Are ‘Cause’ Assays, Whereas HRD Genomic Instability Tests Are ‘Effect’ Assays

HRR gene panel test

Look for the **cause** of HRR loss¹
Identify pathogenic mutations in HRR genes¹

HRD genomic instability

Look for the **effect** of HRR loss¹
Quantify genomic aberrations that are characteristic of HRD,¹ sometimes referred to as a genomic scar test¹
Should be done in combination with BRCA testing³



► There are a couple of different ways outside of BRCA. So, BRCA, we test for. Okay, tumor doesn't have BRCA, then how do you identify these tumors that are vulnerable to therapeutics that target DNA? Well, there's two, kind of, routes. On the left, you can see homologous recombination repair gene panel testing. So, you're looking for BRIP1, PALB2, RAD51C, you know, all these genes that might be associated with loss of homologous recombination repair proficiency. So, that's sort of looking for the cause, like you say, okay, I found a BRIP1, that must mean I have loss of HR - homologous recombination proficiency - versus looking for the

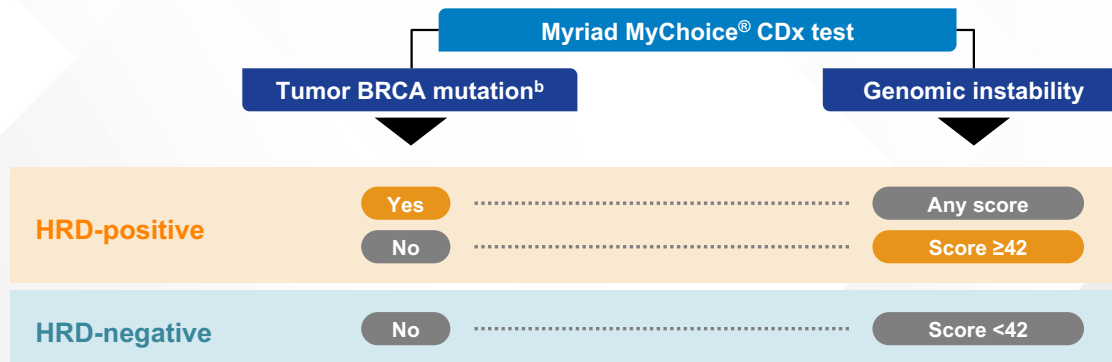
effect of loss of homologous recombination proficiency. So, there's these scars or tattoos that you can detect in the DNA that say, at some point in this tumor's natural history, it struggled to fix its DNA. It doesn't tell you what that vulnerability was, like what that mechanism was, just that at some point, and even still currently it struggles to fix its DNA.

And that's where you have these genomic instability score tests that are FDA approved and in use. Neither are perfect, neither are bad. We think the HRD genomic instability testing probably has more evidence behind it. And that's why really, it's the preference amongst

clinical trials, where we're trying to identify the tumors that are most likely to benefit from PARP inhibitors. When we think about sort of the positive and negative of these genomic instability scores, and again, in the United States, there are two FDA approved tests for this. One is the Myriad test and the other is Foundation, F1. They're different; they overlap, but they are different. And then basically, every other commercially available next gen sequencing assay has some version of their LOH or HRD test. But only two FDA approved in the U.S. at this time.

The PAOLA-1 and PRIMA Trials in Ovarian Cancer Both Incorporated the Myriad MyChoice® CDx Test to Define the HRD Status of Patients¹⁻³

The Myriad MyChoice® CDx test defines patients as HRD-positive if they have a BRCAm and/or a genomic instability score ≥ 42 ^{1,a}



^aThe European Medicines Agency has authorised olaparib in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO Stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab, and whose cancer is associated with HRD-positive status defined by either a BRCAm and/or genomic instability. HRD-positive status can be defined by a composite GIS for HRD-associated genomic alterations tested by an experienced laboratory using a validated test.⁴

^bAs well as BRCA, the Myriad myChoice® Plus CDx analyses additional genes associated with the DNA damage response and microsatellite instability.⁵ However, these do not contribute to the HRD status.



1. Ray-Coquard J, et al. ESMO Congress 2019. Abstract LBA2_PR. 2. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 3. Mirza MR, et al. *N Engl J Med*. 2016;375(22):2154-2164. 4. AstraZeneca UK Limited. Lynparza (olaparib) Summary of Product Characteristics 2021. 5. Myriad Genetics Announces Expanded Research Collaboration with AstraZeneca. <http://www.globenewswire.com/news-release/2018/01/03/1281459/0/en/Myriad-Genetics-Announces-Expanded-Research-Collaboration-with-AstraZeneca.html> BRCA(m), BRCA1 and/or BRCA2 (mutation), CDx, companion diagnostic, DNA, deoxyribonucleic acid, FIGO, International Federation of Gynecology and Obstetrics, GIS, genomic instability score, HRD, homologous recombination deficiency.

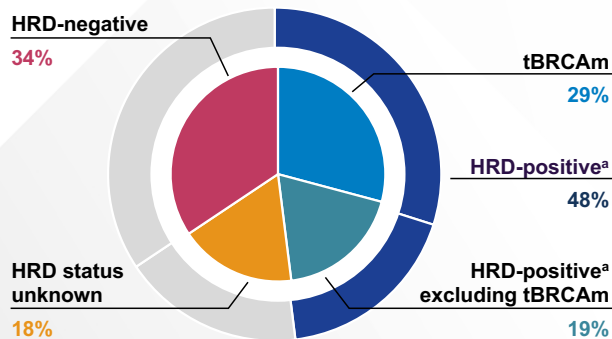
► And so how are they scored? I'm showing you just the Myriad MyChoice® test here. So, you've done your germline testing, it's germline wild-type, so you say, okay, now I'm going to send my tumor off for testing. If the tumor has a BRCA mutation, or even if you start with the tumor, and then you have to figure out if it's germline or not, but you send the tumor,

and it has a tumor BRCA mutation, that is automatically characterized as homologous recombination deficient, irrespective of the score that might be generated from the genomic instability test. By virtue of the fact that there's a BRCA, it's automatically called genomically unstable. If there's no BRCA mutation, then it has to have a score of 42 or

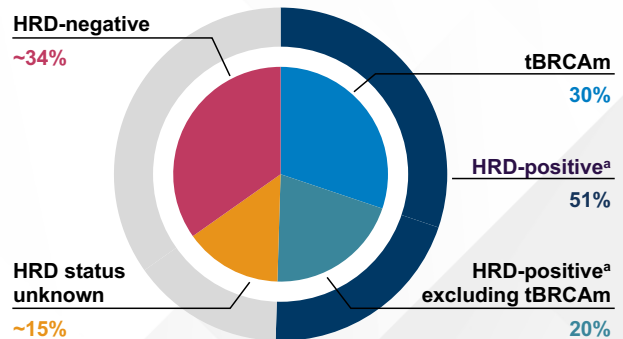
greater to be determined HRD. For BRCA wild-type with a score less than 42, this is called HRD test-negative. And this is probably the more commonly used assay in clinical trials thus far. So, there's the most sort of data that we can look at surrounding this. So, I'm going to show you most of that today.

Homologous Recombination Deficiency is Present in ~50% of Newly-Diagnosed, High-Grade, Epithelial Ovarian Cancers

PAOLA-1¹



PRIMA²



^aHRD-positive determined by tBRCAm and/or genomic instability score ≥ 42 in the Myriad myChoice[®] companion diagnostic test.
 1. Ray-Coquard I, et al. ESMO Congress 2019. Abstract LBA2_PR. 2. González-Martín A, et al. *N Engl J Med.* 2019;381(25):2391-2402.
 HRD, homologous recombination deficiency; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

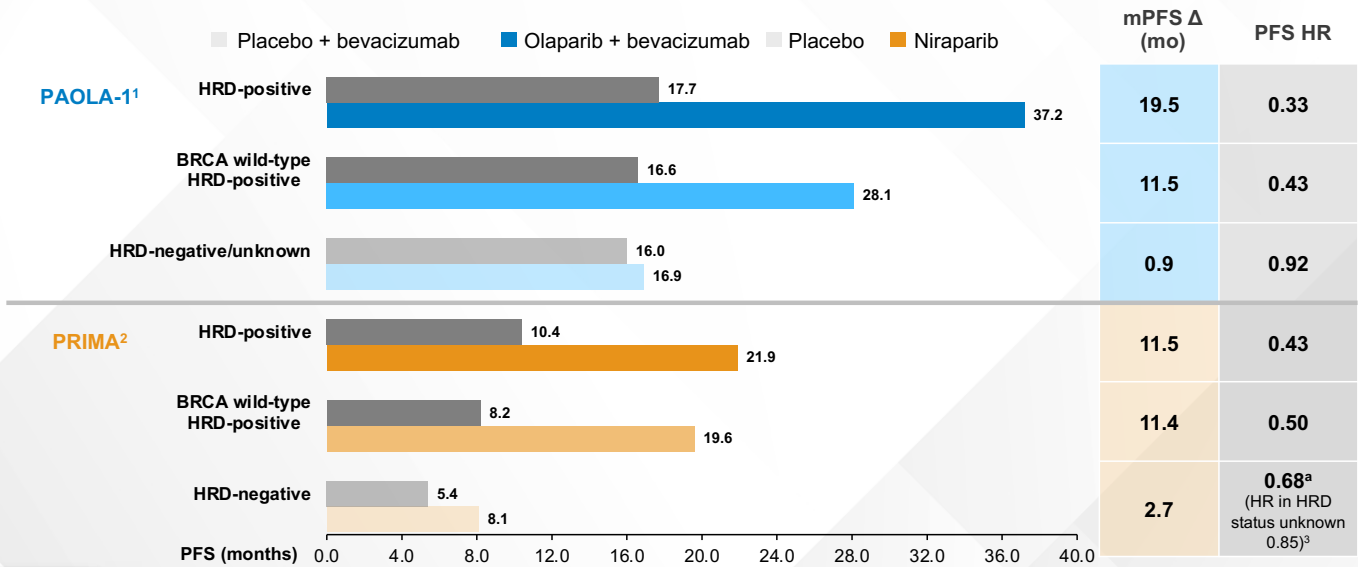
► Now, the test isn't perfect, but it's pretty good and it's pretty consistent. So, what I'm showing you here are two frontline clinical trials that we'll talk more about in a little while. On the left-hand side is PAOLA-1, which was a clinical trial of olaparib, PARP inhibitor olaparib, plus bevacizumab for maintenance, versus bevacizumab maintenance in frontline. And on the right is PRIMA, which was a trial of niraparib, which is a PARP inhibitor, versus placebo maintenance. And they have used the Myriad test to characterize the tumors of the patients who participated. And the point here is just really to give you a sense of what we find: A) it's very consistent across different populations, and B) you know, consistent between studies but also you

can kind of see the distribution of molecular subtypes for at least high-grade serous, high-grade endometrioid ovarian cancer.

These two studies were enriched for BRCA, because this was being done at a time when PARP inhibitors were not FDA approved yet for frontline use. And so, patients that knew they had a BRCA mutation came on at a higher percentage than we see in the general population. So, almost 30% of the participants on both of these studies had a tumor BRCA mutation. Total HRD-positive was right about 50% in both studies, so that leaves us about 20% of patients had tumors that are characterized as BRCA wild-type, but homologous recombination deficient. And then the remainder are either

homologous recombination deficiency test-negative, and that's about 35%, very consistent in both studies. And then you have test failures. You know, sometimes the tumor is just too necrotic or there's no tumor on the slide, or for whatever reason, technicalities, the test can't be run, this has been around about 15% across the board, but then you have to make a decision about what to do without this data. And this has been very consistent. So, this is kind of what you could expect to see, for example, probably a little less BRCA, depending on what part of the country you're in. But this 20% BRCA wild-type HRD has been pretty consistent across the board, and I think you can expect to see this your practices.

In the First-Line Maintenance Setting, HRD Genomic Instability Clearly Predicts the Magnitude of PARPi Benefit



Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended. ^aPRIMA was stratified by HRD status positive or negative/unknown. 1. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2428. 2. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 3. González-Martín A, et al. ESMO Congress 2019. Abstract #4627. HR, hazard ratio; HRD, homologous recombination deficiency; mPFS, median progression-free survival; PARPi, poly(ADP-ribose) polymerase inhibitor.

► So why do we do this testing? Well, the testing for HRD has been helpful in telling us the magnitude of benefit one could expect from use of PARP inhibitor in the maintenance setting in the frontline. So, in the top half of this slide is PAOLA-1, which again, was olaparib/bevacizumab versus bevacizumab for maintenance. So, all of these medians start after chemo, just to sort of level set. Then the bottom is PRIMA, which was niraparib versus placebo. So, you can see on the top bars for both of these are HRD-positive, inclusive of BRCA, which was a third, so pretty good fraction in both of those with hazard ratios of 0.3 and 0.4. So, like 60 to 70% reduction in the hazard of progression in these populations. When you just pull out the BRCA wild-type HRD-positive group, which is about 20% of the population, the hazard ratio and this is a subset, just to let you know,

but the hazard ratio has been pretty consistent, 0.4 to 0.5. So, be conservative, about a 50% reduction in hazard progression for use of a PARP versus placebo as maintenance in BRCA wild-type HRD.

I would say there's clinical equipoise in a lot of places, but where there's a lot of clinical equipoise is in these HRD test-negative tumors. In PAOLA, when you did olaparib/bevacizumab versus bevacizumab, and this is a subset, so non-analytic, but there wasn't really a signal that they were any different, that the PARP added anything, hazard ratio of 0.92. But in PRIMA, and actually in subsequent studies, there's a study called ATHENA, which I don't have time to tell you a lot today about, but it was rucaparib versus placebo, you see very similar hazard ratio in this HRD test-negative group of like 0.68, so like a 32 to 35% reduction in hazard of progression with use of a

PARP versus placebo in this biomarker-negative population. And so, why that is, is a little bit controversial because we don't really know, probably just has to do with the assay having a single cut point categorizing a continuous variable as positive and negative. So, you probably have some tumors in the HRD-negative who have some inherent vulnerability that we're not picking up by this test. But there may be other reasons as well. So, this is really why, at least for niraparib, there's an all-comers indication, because all three biomarkers, although there's a gradation of benefit, of course most in the BRCA and on down, no group that didn't benefit. And so, it remains an option for all of our patients. Whereas in PAOLA, the FDA approval is only in HRD, either BRCA or non-BRCA. But in the HRD test-negative group olaparib plus bevacizumab is not approved. And we'll talk about that a little bit more.

Where Do PARP Inhibitors Fit in the Treatment Paradigm of Ovarian Cancer?

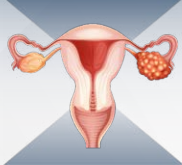
Practical Strategies

- ▶ So, kind of moving forward a little bit to where do PARP inhibitors fit in in the treatment paradigm of ovarian cancer?

AXIS
Medical Education

Most Patients With Advanced Ovarian Cancer Relapse Following First-Line Multimodality Therapy

Over **300,000** women were diagnosed with ovarian cancer in 2020¹



At least **60%** of newly diagnosed women will have **advanced disease**²



~70% of women relapse within 3 years of first-line treatment³

<50%

5-year survival for newly diagnosed advanced ovarian cancer^{2,4}

There is a significant need for better first-line treatment to improve outcomes for women with ovarian cancer^{2,3,5-8}

AXIS
Medical Education

1. Sung H, et al. *CA Cancer J Clin.* 2021;71(3):209-249. 2. du Bois A, et al. *Cancer.* 2009;115(6):1234-1244. 3. Ledermann JA, et al. *Ann Oncol.* 2013;24(Suppl 6):vi24-vi32. 4. Torre LA, et al. *CA Cancer J Clin.* 2018;68(4):284-296. 5. Tewari KS, et al. *J Clin Oncol.* 2019;37(26):2317-2328. 6. Bookman MA, et al. *J Clin Oncol.* 2009;27(9):1419-1425. 7. Burger RA, et al. *N Engl J Med.* 2011;365:2473-2483. 8. Perren TJ, et al. *N Engl J Med.* 2011;365:2484-2496.

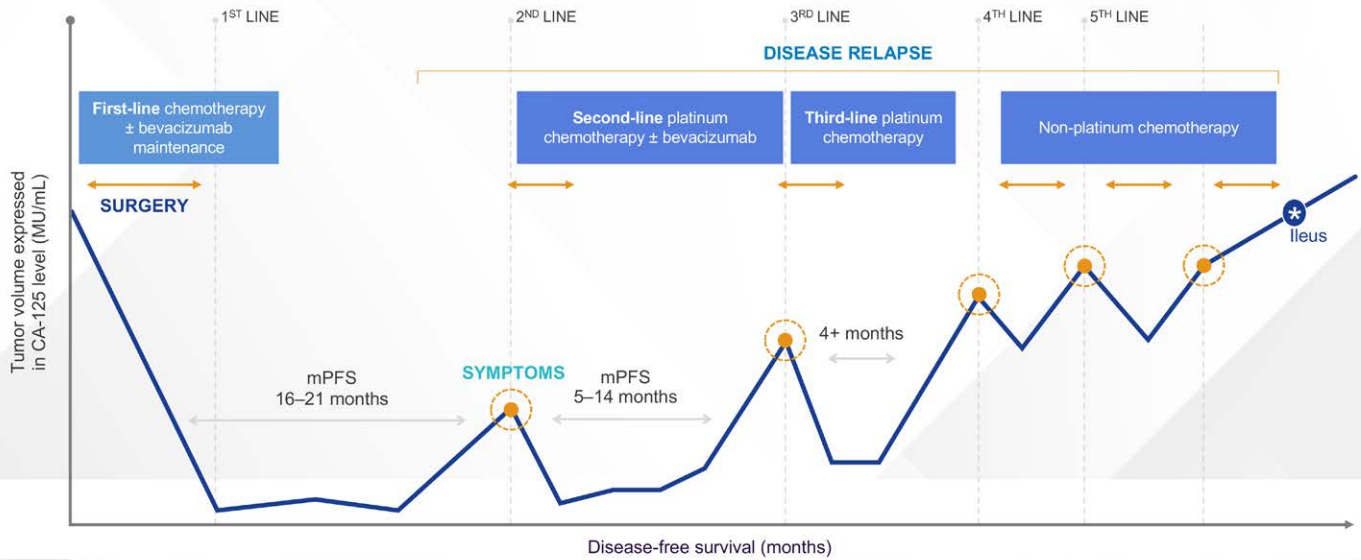
- ▶ Just to remind the audience, although I think you all know this, ovarian cancer is not super common in terms of new diagnoses. We have about 300,000 new cases globally, about 20,000 in the U.S. but 300,000 globally. And even though there's been a lot of work and continues to be a lot of work to try and screen and early diagnose ovarian cancer, we've not done it yet. And so, most patients because of that will present with advanced

disease. And I'm going to show you some exceptions to the statement in a moment.

But for non-BRCA, and even some BRCA, the expectation unfortunately is our patients will recur. And by 3 years, about 70 to 80% of our patients have already recurred. Now, we have a lot of treatments and better supportive care, and other reasons that our patients are living longer than they ever

have in the past. But they're living with disease, in large part, because once recurred, we can no longer cure. And we still are sitting right about 50% 5-year survival. That may be changing for BRCA, and I'll show you this. And we'll see if BRCA wild-type HRD changes a little bit, but we're still sitting about 50% 5-year survival. So, lots of work still needs to be done.

Multiple Lines of Chemotherapy Associated With Cumulative Toxicity While Remission Periods Decrease



Visual adapted from Giomelli GH. *Springerplus*. 2016;5(1):1197.
References in slide notes.
CA-125, cancer antigen 125; mPFS, median progression-free survival.

► Just for those of you that don't maybe take care of a lot of patients with ovarian cancer, this is really, unfortunately, what we expect. This is the natural history for a patient with ovarian cancer. If you start on the left-hand side of this graphic, because we just don't screen - not that we don't, we just can't screen - patients present usually with a lot of disease. Their CA-125s are very elevated, they have a lot of cancer. But at least in the state of high-grade serous or high-grade endometrioid, these tumors tend to be exquisitely chemo sensitive. And so, combination of surgery and platinum-based chemotherapy usually renders our patients to a state of what we call

no evidence of disease after six or eight cycles of chemo. And before maintenance, we would stop and we would just monitor patients actively. But the expectation was that they would recur.

Now, with maintenance we probably are curing more, and I'll talk to you about that in a moment. But for most, we're pushing out that time to recurrence, an appreciable amount, but we are still seeing recurrences. And then recurrences occur, usually, sometimes years later, 1, 2 years later, patients will have symptoms, CA-125 bumps, and we retreat with platinum-based therapies. And we retreat with platinum really until platinum stop working

or patients develop allergies to platinum. And then we switch to non-platinum agents once tumors become resistant to platinum. And really, without some extraordinary clinical trial interventions, every line of therapy, the duration of benefit is shorter, the amount of disease you're starting with is greater, symptoms are greater, cumulative toxicity, really until such point that most of our patients have so much intraabdominal disease that they have carcinomatous ileus, and they just die of starvation. It's a terrible end. And so really anything we can do to not have our patients enter that hamster wheel of treatments is better. And we're working on that.

Advanced Ovarian Cancer Is Characterised By Multiple Relapses

- Once the disease relapses, it is largely incurable
- First-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure

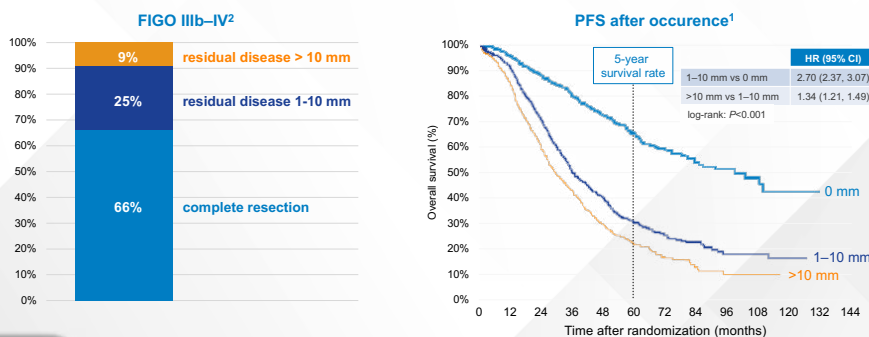
► So again, until we can screen, which is the penultimate goal, any improvements in converting patients into that cure fraction in the frontline really are our best opportunities for long-term survival and keeping our patients out of that natural history that I talked about.



Giromelli GH. *Springerplus*. 2016;5(1):1197.

Impact of Postoperative Residual Disease on Outcome in Advanced Ovarian Cancer

Data from a meta-analysis of three randomized frontline phase 3 trials (AGO-OVAR 3, 5, and 7) with 3126 patients¹



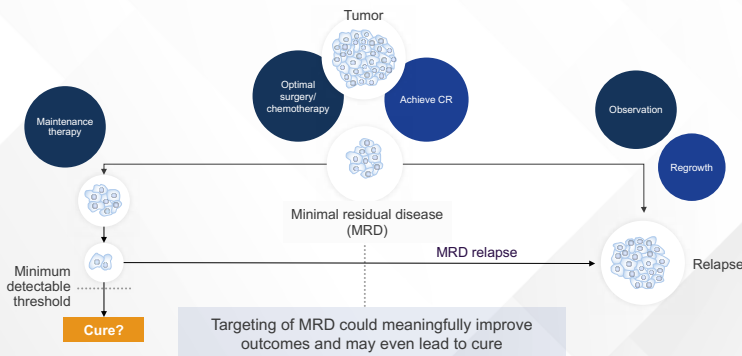
1. Du Bois, A et al. *Cancer*. 2009;115(6):1234-1244. 2. Heltz F, et al. *Gynecol Oncol*. 2016;141(2):264-270. AGO-OVAR, Arbeitsgemeinschaft Gynäkologische Onkologie Studiengruppe Ovarialkarzinom; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; PFS, progression-free survival.

► Now, I'm not going to focus too much on surgery. This is, I think, one of two slides I'm going to show you. Timing of surgery, either at the beginning or interval with a neoadjuvant, still remains very controversial, although we have done quite a few clinical trials in highly selected populations. So, there's one clinical trial still pending, called the U.S. TRUST study, that I think will be definitive one way or the other for us. So, there's still equipoise here, but I would encourage you to make sure that you, if you're a

medical oncologist, which we desperately need you, to really make sure that you are buddies with a high-volume ovarian cancer surgeon. And I do say high-volume purposefully, because I am one of those people that believes if you can operate at the beginning and have achieved no gross residual, which requires a high-volume surgeon, you do set that patient up a lot better for response to chemotherapy and potentially response to platinum. And I'll show you why I believe that in the next slide. If you cannot render that patient

no gross residual, which we can figure out before putting a big midline incision on patients now pretty well, then they should have neoadjuvant chemotherapy, it is safer. And there is no benefit to doing the surgery if you leave any residual disease. But it is still very important to consider a primary cytoreduction for the reason I'm showing you here. This is one of a billion slides I could show you. But for those patients that are rendered no gross residual the 5-year survival rate is multiple logs better than any residual disease. And so, you really want to make sure we're identifying those patients who should get primary cytoreduction and getting them to a high-volume surgeon if we can.

Treating Minimal Residual Disease: Aiming to Achieve Long-Term Disease Control



AXIS
Medical Education

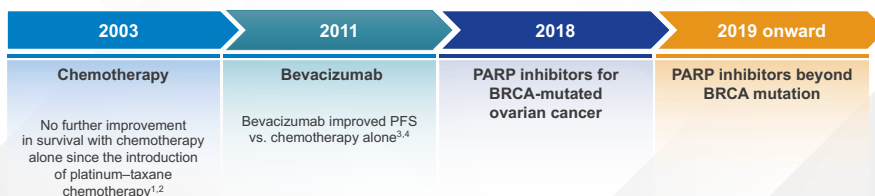
Luskin MR, et al. *Nat Rev Cancer*. 2018;18(4):255-263.
CR, complete response; MRD, minimal residual disease.

► Why do I believe that? I think everyone sort of knows this idea that if you can surgically, and with chemotherapy, cytoreduce the amount of tumor that's there so you're exposing the least number of tumor cells possible first to the chemotherapy and then to the maintenance, you actually have

a shot at hitting this like idea of minimal residual disease. And that's the group of patients we probably can convert to cure. And why is that? Because once a tumor has been exposed to chemotherapy when there's a lot of it, you start to develop these heterogeneous clones. And we are seeing data start

to emerge. It's very much like TRACERx in lung, we're seeing this out of Dr. Elizabeth Christie's lab in London and others where they're tracking these tumor heterogeneity over time with exposure to therapies. And it's humbling how quickly these tumor cells develop heterogeneity. And once they're clonally heterogeneous, again, we can treat them, but we can't cure them. So, if we can really get these patients cytoreduced, on to chemo, and then on the PARP as appropriate, and target this MRD, this is probably the group that we can cure. And I'll show you some evidence where I think this may be true. If we can't do this, then we need to do it safest, and neoadjuvant with interval surgery is the way to go. That's all I'm going to say about surgery.

Significant Progress Has Been Made in the Management of Ovarian Cancer Over the Past Decade



AXIS
Medical Education

1. McGuire WP, et al. *N Engl J Med*. 1996;334:1-8. 2. du Bois A, et al. *J Natl Cancer Inst*. 2003;95:1320-1329. 3. Burger RA, et al. *N Engl J Med*. 2011;365:2473-2483. 4. Perren TJ, et al. *N Engl J Med*. 2011;365:2484-2496.
BRCA, BRCA1 and/or BRCA2; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

► From a therapeutic standpoint, we made a lot of progress. It's taken us 20 years or more, but as a fellow in 2003 it was chemo. That's all we thought about. You just gave paclitaxel and carboplatin. And that's what we did. And sometimes we did three chemos instead

of two chemos, like that was how novel we were. And that didn't cure anyone. In 2011, we entered the bevacizumab era. And bevacizumab is a great medication for ovarian cancer in a lot of different lines of therapy. It's very important, but it's not curing more patients

and it does not impact overall survival. So, we have to say that while it still is a big part of our armamentarium it didn't really move the chains for our patients appreciably until 2018, when the first frontline studies with PARP inhibitors started to report out. And then even subsequent to that, as we've seen overall survival start to emerge, we are getting the first sense that we are curing more patients finally mainly in a biomarker population. And I'll show you that.

Phase II/III Studies of PARP Inhibitors in Ovarian Cancer Management

	PARPi in maintenance setting		PARPi in treatment setting	
	1L (maintenance)	PSR (maintenance)	PSR (treatment)	PRR (treatment)
BRCAm	SOLO-1 Olaparib vs placebo (n=391)	SOLO-2 ¹ Olaparib vs placebo (n=295)	Study 42 ² 4L+ olaparib (n=137)	
		ORZORA PMC GMA (capsule) ² gBRCAm, HRRm (n=177)	SOLO-3 ³ 3L+ olaparib vs CTX (n=286)	
		NOVA ⁴ gBRCAm, non-gBRCAm Niraparib vs placebo	QUADRA (single-arm) ⁵ HRD+ Niraparib	
			ARELA ⁶ Rucaparib vs CTX	
All patients	PAOLA-1 (ESR) Olaparib + bevacizumab vs bevacizumab (n=806)	Study 19 ¹ Olaparib vs placebo (n=265)		
	ATHENA Rucaparib vs placebo	AREL3 ⁷ Rucaparib vs placebo		
	PRIMA Niraparib vs placebo			
Non-BRCAm	DUO-O Placebo vs durvalumab vs durvalumab + olaparib (1130)	OPINION PMC GMA ⁸ Olaparib, 2L+ PMC (n=279)	QUADRA (single-arm) ⁵ HRD+ Niraparib	Phase 2 Phase 3 Phase 3b or Phase 4, PMC Niraparib Rucaparib
		ORZORA PMC GMA (capsule) ² gBRCAm, HRRm (n=177)		
		NOVA ⁴ gBRCAm, non-gBRCAm Niraparib vs placebo		

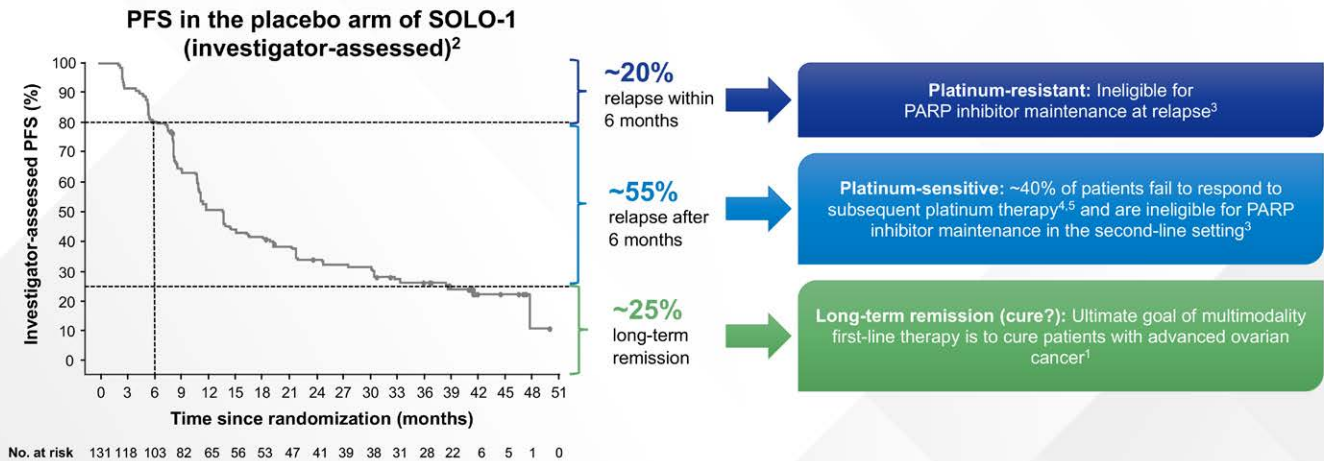
PARP inhibitors have been tested in every line of therapy. On the right-hand side of the slide, you see PARP as treatment, so instead of chemo, mainly in the recurrent setting, not as maintenance, you're just using it instead of chemo. This is really where a lot of our studies started. And then on maintenance, on the left-hand side of the slide, frontline maintenance, platinum-sensitive recurrent maintenance. So many interesting and nuanced studies. We do not have time to go through them all.

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		ORZORA PMC GMA (capsule) ² gBRCAm, HRRm (n=177)		
		NOVA ⁴ gBRCAm, non-gBRCAm Niraparib vs placebo		

I'm going to focus on the frontline today and really not even take you through all the studies but just a few to give you a flavor of where we are.

Earlier Introduction of PARP Inhibitors May Offer the Opportunity for a Greater Number of Patients to Benefit¹



1. Miller RE, et al. *Future Oncol.* 2019;15(16):1845-1853. 2. Moore K, et al. *N Engl J Med.* 2018;379:2495-2505. 3. LYNPARZA (olaparib). Prescribing Information. AstraZeneca; 2023. 4. Bruchim I, et al. *Eur J Obstet Gynecol Reprod Biol.* 2013;166(1):94-98. 5. Aghajanian C, et al. *J Clin Oncol.* 2012;30(17):2039-2045. PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

▶ Before I get into the data from SOLO-1, I want to reiterate why I'm talking just about frontline in this presentation today. And really, the reason is because A) that's really where all of the indications still are, so this is the place where almost all of our patients can still access PARP inhibitors because of the retractions and later lines of therapy. But, B) it's also the most efficacious place to use PARP inhibitors and I kind of want to show you why I think that is. There's a couple of slides to this point. This slide I really like to show. This is from SOLO-1, which I'm going to show you SOLO-1 in a moment, but just to remind you, SOLO-1 was a randomized phase 3 study only for patients with BRCA-associated cancers, they

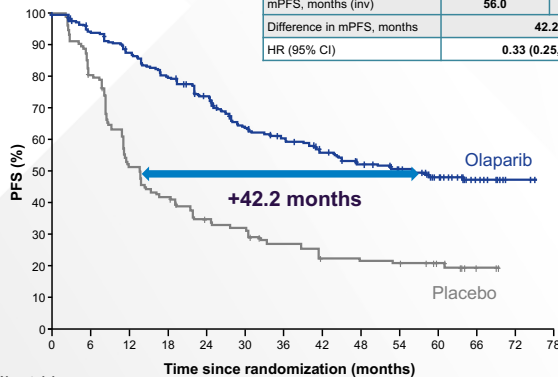
had to be in response to their chemo, and then randomized to olaparib or placebo. This is the placebo curve that I am showing you. And SOLO-1 was a very interesting population in that they were – you know, every advanced ovarian cancer is high risk, there's no such thing as low-risk advanced ovarian cancer, but they were on the lower risk of things, mostly stage 3, mostly primary cytoreduction, showed no gross residual, and BRCA. So, kind of the best prognostic group of patients you could ever hope to study on a clinical trial of ovarian cancer. And there was this mythology around them at the time that SOLO-1 embarked, which was again in 2013, that so many of these patients were cured

with chemo alone, that we were overtreating them. And so, this is what I show just to show you how high risk even this population is: by 6 months, 20% of my patients on placebo had recurred, primary platinum-resistant disease, all of these patients had BRCA. And we presented this at 41 months, by that point, 55% had recurred. So, they're going to live a long time, usually, because they're BRCA, but they're not curable anymore. And at 41 months, only 25% were still without recurrence, and that sits about 20% now at 7 years. So, that's your cure fraction for lower advanced-risk BRCA, 20%, that's the best you get. So, we have a long way to go.

The PFS Benefit Shown in SOLO-1 Compared With SOLO-2 Highlights the Importance of Introducing PARPi as Early as Possible

SOLO-1^{1,2}

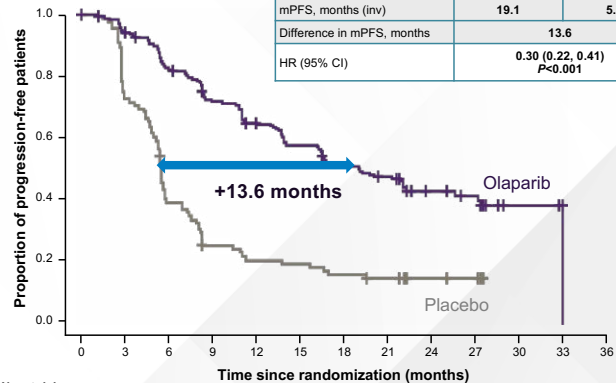
	Olaparib 1L	Placebo
Events, N (%)	118 (45)	100 (76)
mPFS, months (inv)	56.0	13.8
Difference in mPFS, months	42.2	
HR (95% CI)	0.33 (0.25, 0.43)	



No. at risk	0	6	12	18	24	30	36	42	48	54	60	66	72	78
Olaparib	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo	131	103	65	53	41	38	30	24	23	22	16	3	0	0

SOLO-2^{2,3}

	Olaparib PSR	Placebo
Events, N (%)	107 (54.6)	80 (80.8)
mPFS, months (inv)	19.1	5.5
Difference in mPFS, months	13.6	
HR (95% CI)	0.30 (0.22, 0.41) <i>P</i> <0.001	



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33
Olaparib	196	182	156	134	118	104	89	82	32	29	3	2
Placebo	99	70	37	22	18	17	14	12	7	6	0	0



Cross-trial comparisons should be done with precaution as such trials differed in design, size, time period of recruitment, location of study sites, etc.
 1. Banerjee S, et al. *Lancet Oncol*. 2021;22(12):1721-1731. 2. Lynparza. Summary of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/lynparza-epar-product-information_en.pdf. 3. Pujade-Lauraine E, et al. *Lancet Oncol*. 2017;18(9):1274-1284.
 1L, first-line; CI, confidence interval; HR, hazard ratio; inv, investigator-assessed; mPFS, median progression-free survival; PARPi, poly(ADP-ribose) polymerase inhibitor; PSR, platinum-sensitive relapsed.

► And then on this slide is really where I kind of want to convince you that frontline is the place where we get the most benefit from a PARP inhibitor. I'm showing you on the right, SOLO-2, which was platinum-sensitive recurrent disease, had to respond to their platinum, and then they were randomized to olaparib or placebo, all BRCA. And then SOLO-1 is on the left, which I just told you about. Both of these have a hazard ratio of 0.3. And so, I remember hearing people say, "Well, the hazard ratio is the same if I use it in frontline or platinum-sensitive recurrent, so I'll just wait and see if I need it, and I'll use it in the second line because I have the same

amount of benefit." And it is true that the hazard ratios are the same, but I hope what I'm convincing you with this slide is that a hazard ratio of 0.3, which is phenomenal by the way, is very different in a recurrent setting versus a frontline setting in terms of the magnitude of benefit that you're obtaining. In SOLO-2, you gained over a year, which is amazing. But why is that? Well, that's because the control arm in platinum-sensitive recurrent disease does very poorly when you stop chemo, 5.5 months is the median, versus frontline where I improve progression-free survival by 42 months, actually more than that on final analysis. And that's with the

control arm progression-free survival that was about 13 to 14 months. And the other thing is that in the frontline, you can see that plateau, those curves are not coming back together, like a banana. We see that with bevacizumab, when you withdraw the drug, the curves come back together. These patients stopped treatment at 2 years. And the curves are relatively flat because we have cured more patients with that 2 years of olaparib. And you don't have the opportunity for cure in the recurrent setting. So, frontline is where you want to use it and you don't want to miss the opportunity to treat patients in this setting.

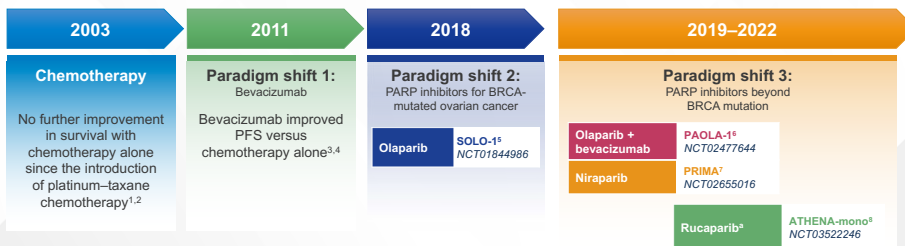
Clinical Data for PARP Inhibitors as Maintenance Therapy for Newly-Diagnosed Advanced Ovarian Cancer

- ▶ I'm going to take us through a few just to give you a flavor of the benefit of PARP inhibitor. And as promised, I'm going to come back to SOLO-1.



Significant Progress Has Been Made in the First-Line Management of Ovarian Cancer Over the Past Decade

- ▶ So, this is just a kind of more detailed view of the slide I showed with the kind of progress over the last 20 years with the PARP slides sort of populated with the studies that have been done in the frontline.



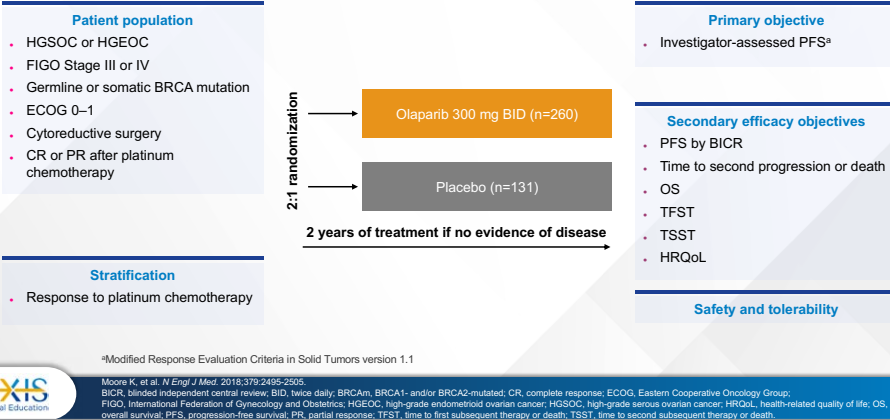
Several studies with PARP inhibitor maintenance for newly-diagnosed advanced ovarian cancer^{5–8}

*Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.



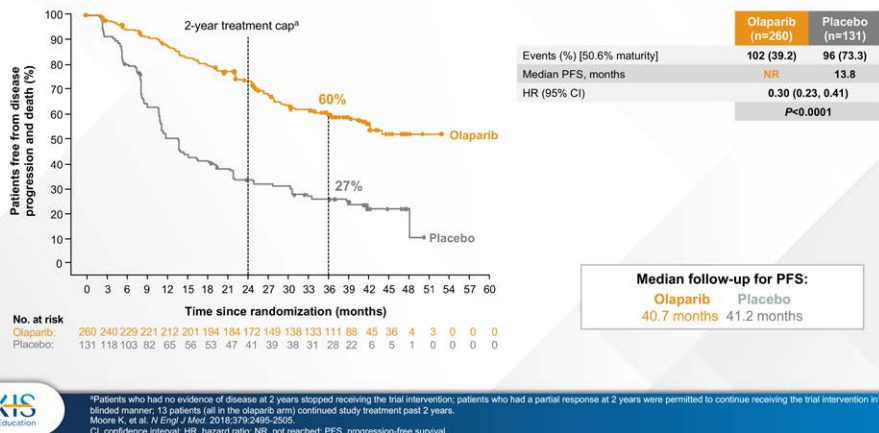
1. McGuire WP, et al. *N Engl J Med*. 1996;334:1-6. 2. du Bois A, et al. *J Natl Cancer Inst*. 2003;95(17):1320-1329. 3. Burger RA, et al. *N Engl J Med*. 2011;365:2473-2483. 4. Perren TJ, et al. *N Engl J Med*. 2011;365:2484-2496. 5. [ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01844986](https://clinicaltrials.gov/ct2/show/NCT01844986) (Accessed March 2022). 6. [ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02477644](https://clinicaltrials.gov/ct2/show/NCT02477644) (Accessed March 2022). 7. [ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02655016](https://clinicaltrials.gov/ct2/show/NCT02655016) (Accessed March 2022). 8. Monk JM, et al. *J Clin Oncol*. 2022;40(34):3952-3964. BRCA, BRCA1 and/or BRCA2; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

SOLO-1: Maintenance Olaparib for Patients With Newly-Diagnosed BRCAm Advanced Ovarian Cancer



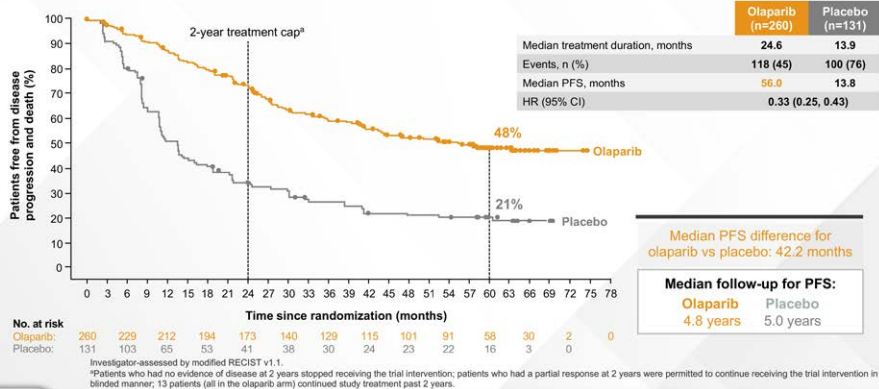
► So, SOLO-1, as I've already talked to you about, was the first study done in the frontline, started in 2013, only enrolled patients with BRCA, stage 3 or 4, they had to have surgery, and they had to have to responded to platinum-based chemotherapy, and then randomized 2:1 to olaparib or placebo. And the primary objective was investigator assessed progression-free survival, and you can see the secondary efficacy endpoints. This is the risk of reduction for progression when we first presented the data.

SOLO-1: Olaparib Reduced the Risk of Progression or Death by 70% Versus Placebo



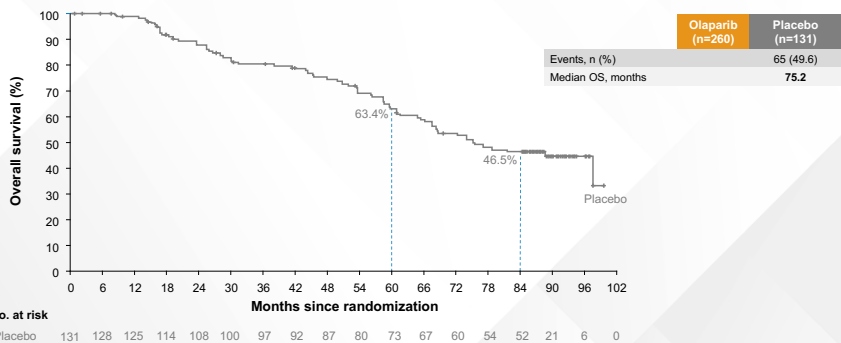
► Now, when we presented this in 2018, you can see here, this is with 41 months of follow-up, the hazard ratio again is 0.3 and you can see the 2-year treatment cap after which assigned therapy is discontinued, and really the plateauing of those curves. And at 3 years, we had 60 versus 27% of patients alive and without progression, which was fairly remarkable at the time. And again, I'll point out that these curves are not coming back together, we do not see a banana sign in terms of the progression-free survival curve.

SOLO-1: PFS Benefit of Maintenance Olaparib Was Sustained Beyond the End of Treatment

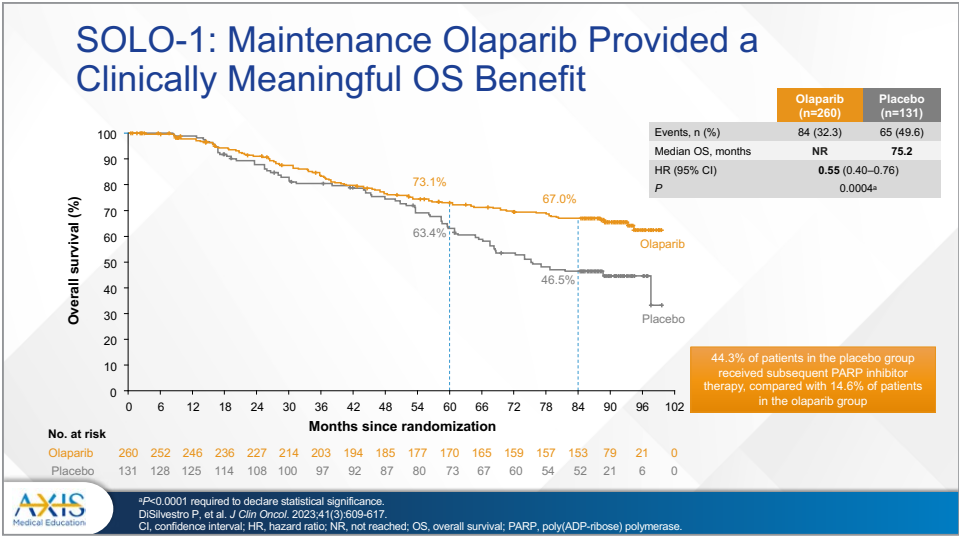


► And this held as we continued to follow these patients. This is the report out to now 60 months, where we're sitting at 48% versus 21% of patients who are progression free. And you can still see that 2-year treatment cap there. All of these patients have been off therapy at this point now for 3 years, 21% on placebo, so there's your cure fraction, at least at 5 years, and we're rescuing about 27% more with olaparib.

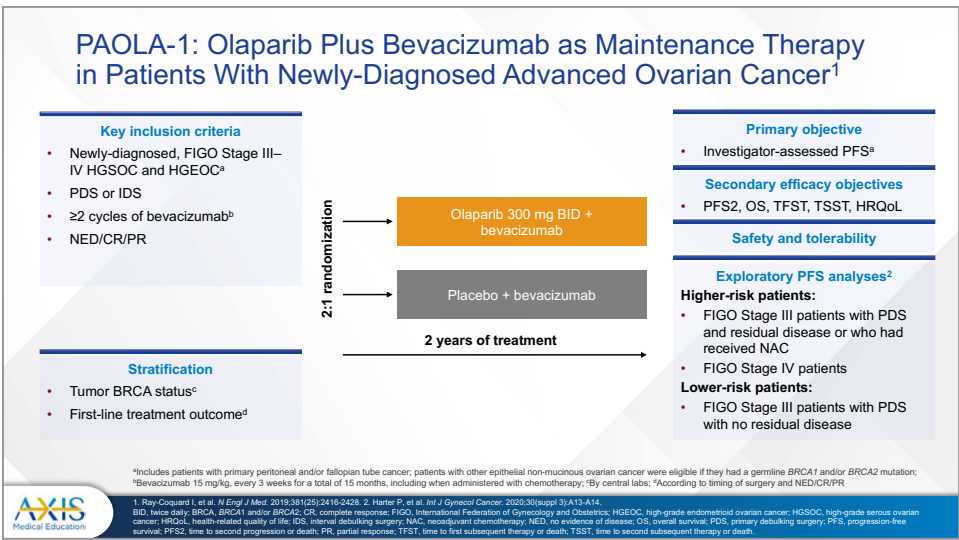
SOLO-1: Descriptive OS Analysis



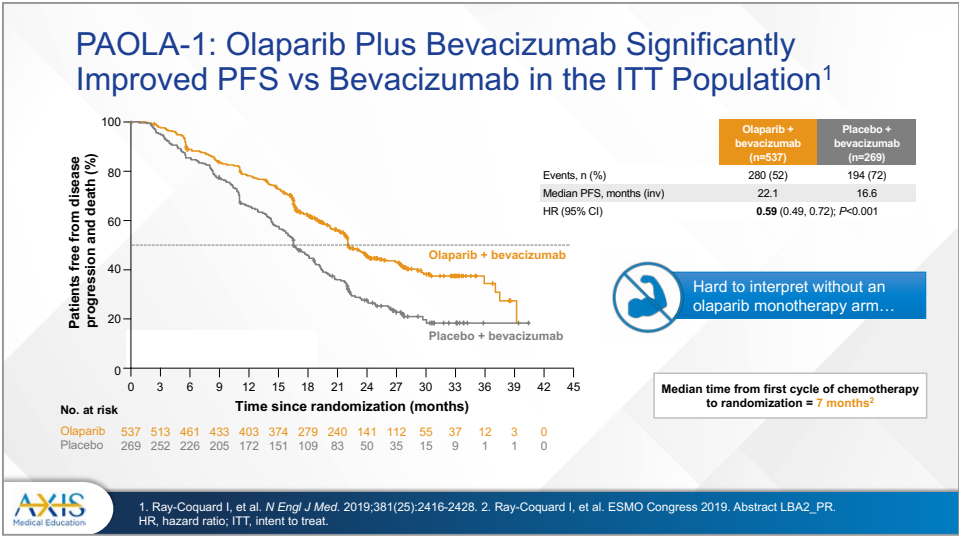
► Now, we have demonstrated some early signals of overall survival. It's not quite mature yet from SOLO-1. But we have we relooked at the progression-free survival in SOLO-1 at 7 years, and we're still sitting right about the same.



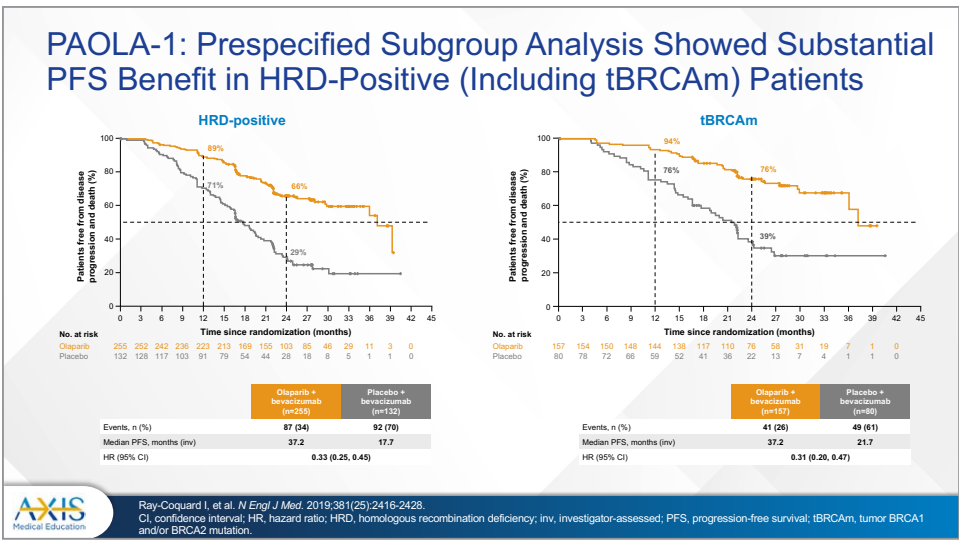
► And so, it looks like we've converted from a cure fraction of about 20% for placebo, up to 45% at 7 years, most of those patients are likely cured. And so, I do think we are making an impact in overall survival, but really in a biomarker selected population.



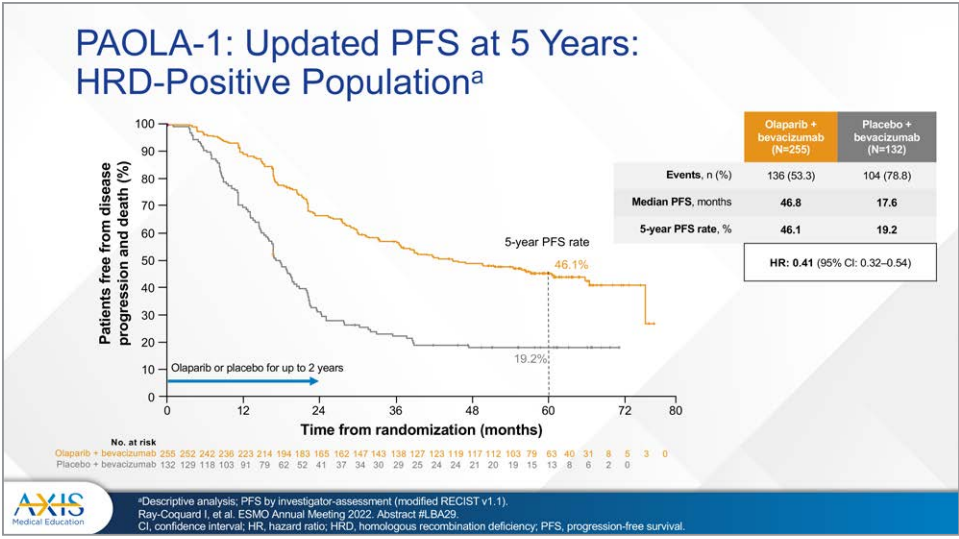
► And so, the next question would be, what about everyone else? What about patients that don't have BRCA? Well, the first study, there's a couple I'm going to show you that we're going to talk about, is PAOLA-1, which I've already mentioned once. This is a study where everybody gets chemo plus bevacizumab, and then at the conclusion of chemo and bevacizumab, once you're in response, patients were randomized 2:1 to layer on olaparib, again for 2 years versus just continuing with bevacizumab for maintenance. And the primary endpoint was progression-free survival in the intention-to-treat arm, in the entire arm. And this study was stratified by BRCA, but the primary endpoint was just in the intention-to-treat arm.



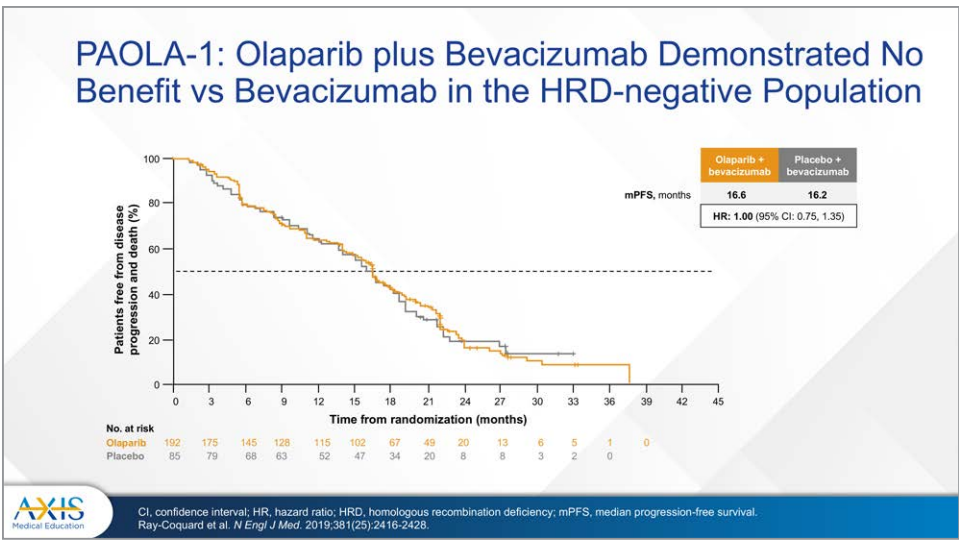
▶ And they met that. So, here is the intention-to-treat arm. Olaparib/bevacizumab versus bevacizumab with a hazard ratio of 0.59. So, 41% reduction in the hazard of progression or death with use of olaparib and bevacizumab, versus bevacizumab, which is a great primary endpoint. But we would all design the study differently now if we could. And it's hard to interpret this study with what we now know is a missing arm, which is olaparib alone. So, do you need the bevacizumab with the olaparib? Or do you just need the olaparib? We just don't really know. And so, that is the limitation to this study.



▶ Now, they did show us some subset analyses from PAOLA-1. I will remind you that these are non-analytic. The analytic endpoint was in the intention-to-treat arm but these are in some exploratory subsets you can think about. On the left-hand side is the HRD-positive subset, and on the right-hand side is just the tumor BRCA-positive. And if you remember from the earlier pie charts I showed you, 30% of the patients on PAOLA were BRCA and 50% were HRD-positive. So, this HRD-positive subset is largely influenced by BRCA, and you can see the hazard ratio is 0.33 really in both arms, just reinforcing the power of olaparib. But again, we asked the question of do you need the bevacizumab or not, which we really can't answer.



► Now, they have shown updated progression-free survival data from PAOLA in the HRD-positive population, again, largely driven by BRCA. But you can see here, it looks very similar to what I showed you at 5 years with SOLO-1. You have about 19% of patients who have not recurred on that bevacizumab/placebo arm. Bevacizumab was only given for 15 cycles, so they've been long off of this, versus the olaparib arm where you're sitting at 46%. Very similar to what we saw with SOLO-1, and so it reinforces the power of PARP inhibitor in this population.



► As I've already discussed once, there was no signal of benefit, albeit in a non-analytic subgroup of olaparib/bevacizumab versus bevacizumab, in the HRD test-negative population. This somewhat a little controversially, because it wasn't an analytic endpoint, but did influence the regulatory agencies to say, "Well, you can't use this regimen in an HRD test-negative population," so the PAOLA regimen is only approved in HRD-positive tumors, either BRCA or BRCA wild-type HRD, but not in HRD test-negative population.

PRIMA: Maintenance Niraparib for Patients With Newly-Diagnosed Ovarian Cancer, Regardless of BRCAm Status

- Key inclusion criteria**
- FIGO Stage III–IV HGSOC or HGEOC^a
 - Tissue for HRD testing required at screening (Myriad myChoice[®])
 - CR or PR (<2 cm^b) and normalization of CA-125 levels^{c,2}

- Key exclusion criteria**
- Stage III disease with complete cytoreduction after PDS

2:1 randomization

Niraparib

Placebo

Stratification

- CR or PR
- NACT
- HRD-positive or HRD-negative/unknown

Body weight ≥77 kg and platelets ≥150,000/μL started with 300 mg QD

Body weight <77 kg and/or platelets <150,000/μL started with 200 mg QD

35% of patients received a modified starting dose after a protocol change; of these, 72% received 200 mg QD³; initial dose for everyone regardless of weight or platelets was 300 mg/day

Primary endpoint

- PFS (BICR)

Secondary endpoints

- OS
- PFS2
- TFST
- PRO
- Safety

Hierarchical PFS testing

- Patients with HRD-positive disease, then ITT population

3 years treatment if no evidence of disease

Patients were treated with niraparib or placebo once daily for 36 months or until disease progression.

^aIncludes patients with primary peritoneal and/or fallopian tube cancer; ^bBased on protocol modification; ^cNormal or >90% decrease in CA-125 with front-line treatment.



1. González-Martín A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 2. ClinicalTrials.gov. <https://clinicaltrials.gov/ct2/show/NCT02655016>. 3. Mirza MR, et al. ASCO Virtual Scientific Program 2020. Abstract 6050. BICR, blinded independent central review; BRCAm, *BRCA1* and/or *BRCA2* mutation; CA-125, cancer antigen 125; CR, complete response; FIGO, International Federation of Gynecology and Obstetrics; HGEOC, high-grade endometrioid ovarian cancer; HGSOC, high-grade serous ovarian cancer; HRD, homologous recombination deficiency; ITT, intention-to-treat; NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; PFS, progression-free survival; PFS2, time to progression on subsequent therapy; PR, partial response; PRO, patient-reported outcome; QD, once daily; TFST, time to first subsequent therapy.

► And so, moving forward, I also already mentioned the PRIMA study to you. So, I want to talk about that now, because it's a very similar but a different study. PRIMA is niraparib, and it enrolled patients with advanced ovarian cancer, all-comers who were in response to their primary chemotherapy, and then they were randomized 2:1 just like the others, to niraparib or placebo. Initially, it was for 3 years and then they adjusted

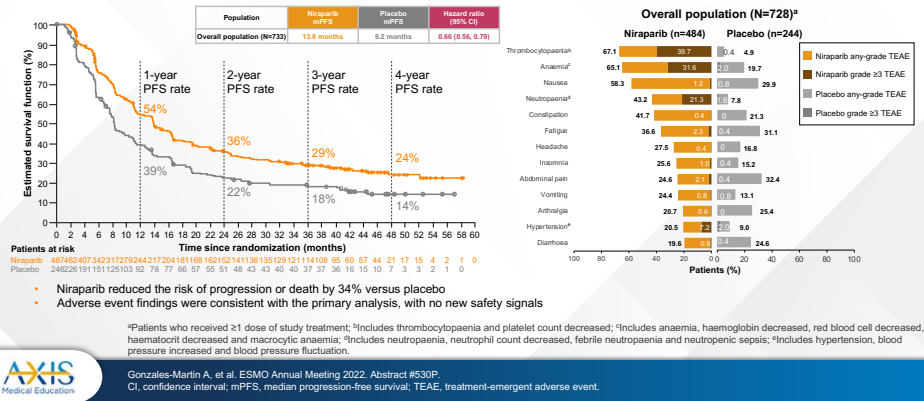
it throughout the study to be as long as the investigator wanted to treat. So, this one does not have a predefined endpoint to the length duration of therapy. But PRIMA is unique in that it enrolled purposefully a population of patients at very high clinical risk for progression, and so almost 70% of the participants were those dispositioned to neoadjuvant chemotherapy, almost 40% were stage 4, 35% came on to the study with a

partial response as opposed to a complete response. So, a clinically very high-risk group that were then randomized to niraparib or placebo. The primary endpoint is progression-free survival, first in the HRD test-positive group. And then if that's positive, they looked at the intention-to-treat population. And then there's a lot of subsets that we could look at as well.

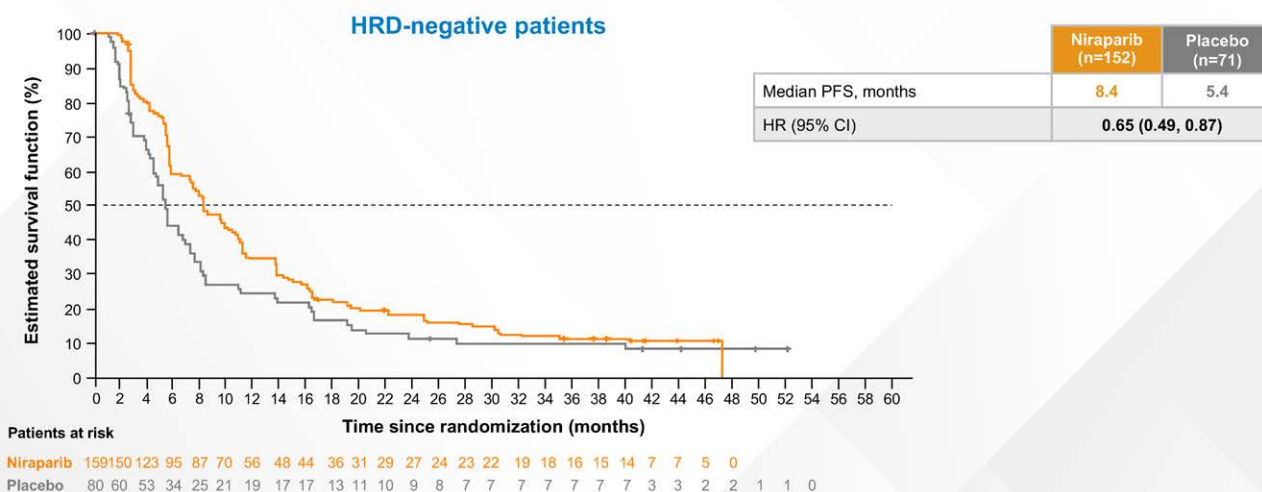
PRIMA: Niraparib Maintenance Therapy Significantly Improved PFS vs Placebo in the Overall Population

Investigator-assessed PFS in the overall population

TEAEs reported in ≥20% of patients



PRIMA: Niraparib Maintenance Therapy Demonstrated Limited PFS Benefit vs Placebo in the HRD-Negative Population



Gonzales-Martin A, et al. ESMO Annual Meeting 2022. Abstract #530P.
 CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; PFS, progression-free survival.

► Now, just like the other studies, we saw subset analyses, and I don't have time to show all of them to you, but I want to show you one that's very different than PAOLA, and that is the HRD test-negative population, which I'm showing you here. Here, this is niraparib versus placebo, so not versus bevacizumab. And we do see a statistically and, many would argue, clinically relevant improvement in the progression-free survival with

a hazard ratio of 0.65, so a 35% reduction in the hazard of progression or death with use of niraparib, as opposed to placebo in this population. And this is why when the regulatory authorities looked at PRIMA, they awarded an all-comer indication for niraparib, because even though the magnitude of benefit is nowhere near as high as the HRD subset, fully powered cohort, it's not negative, there is a benefit here. And so, the

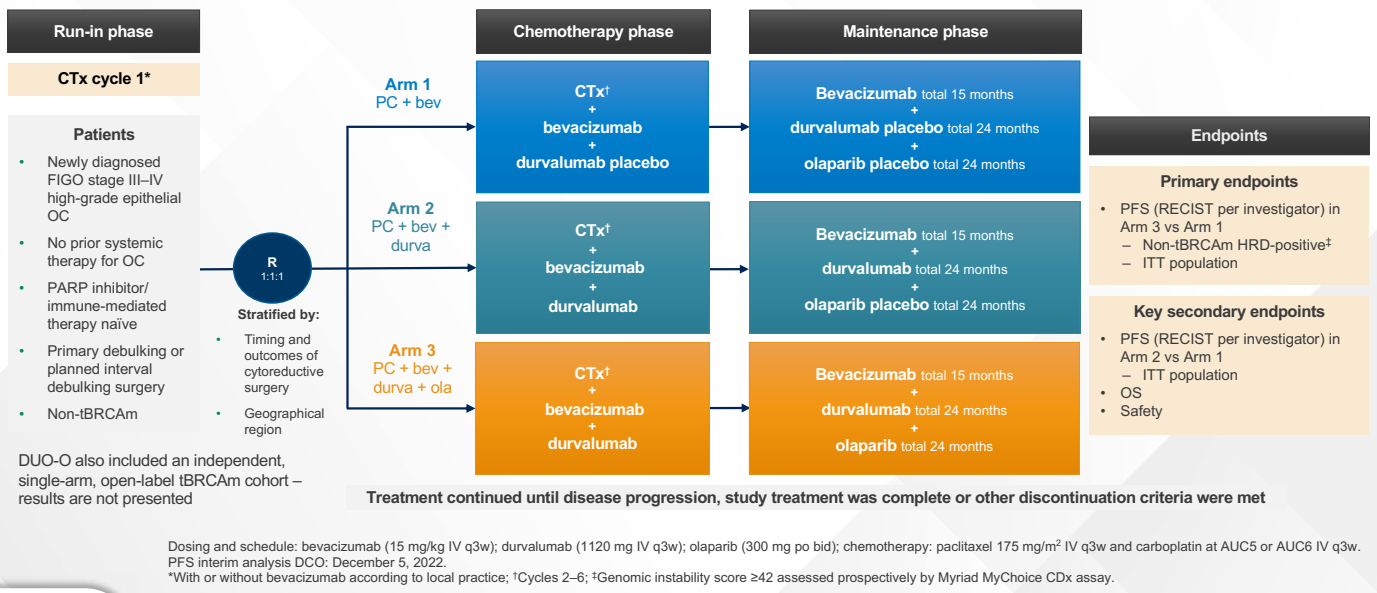
HRD test didn't tell you who shouldn't receive niraparib, and so it is an option for patients with HRD test-negative tumors who were in response to their frontline chemotherapy.

And we don't have time to talk about some of the other studies such as ATHENA, but they're all very consistent. Very consistent hazard ratios and efficacy across subgroups. So, this isn't sort of a one-off, this really is, I think, consistent across the board.

DUO-O Study Design



The continuing saga of missing study arms...

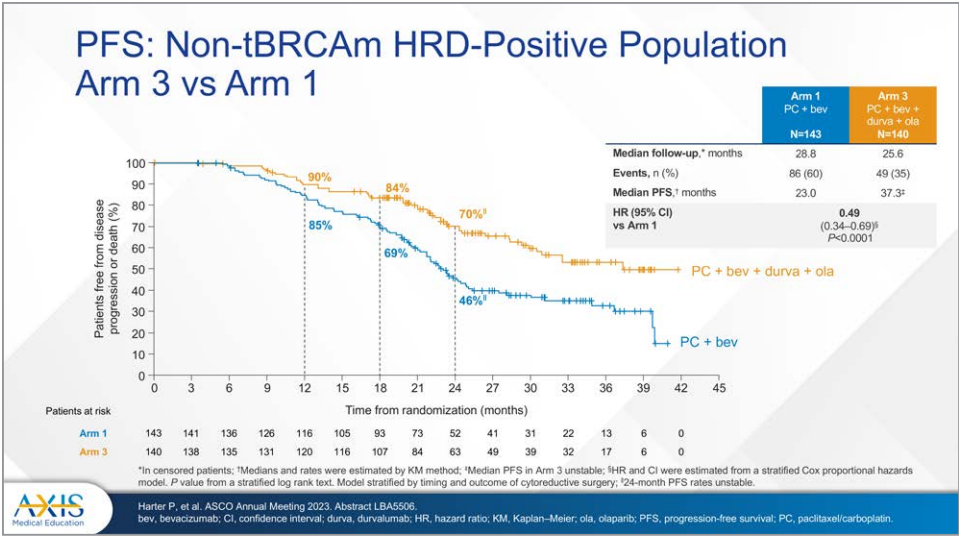


Harter P, et al. ASCO Annual Meeting 2023. Abstract LBA5506.
AUC, area under the curve; bev, bevacizumab; bid, twice daily; CTx, chemotherapy; DCO, data cutoff; durva, durvalumab; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency; ITT, intent-to-treat; IV, intravenous; OC, ovarian cancer; ola, olaparib; OS, overall survival; PARP, poly(adenosine diphosphate ribose) polymerase; PC, paclitaxel/carboplatin; po, by mouth; q3w, every 3 weeks; R, randomization; RECIST, Response Evaluation Criteria for Solid Tumors; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

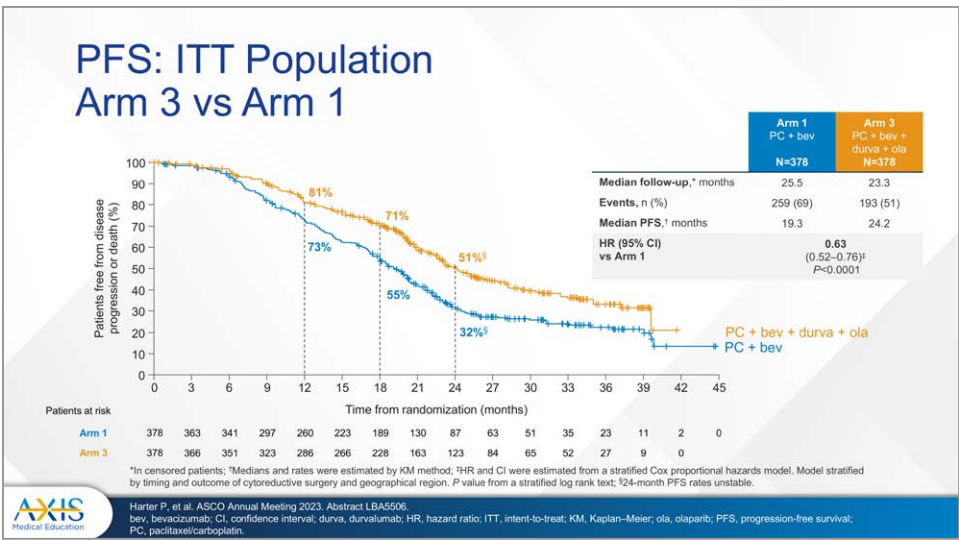
► And so, you might be asking, well what's the next big thing? Well, I don't know yet. But it might be immunotherapy, but also might not be, we don't know yet. There's 4 studies which I'll outline in a few slides for you. This was the first to report, DUO-O, which tried to add immune checkpoint inhibitors to this backbone of bevacizumab and PARP inhibitor. DUO-O, though, was distinct, so you have to really think about it a little bit differently than the other data I've shown you. And it's going to be distinct from the studies that are

going to result out in 2024, in that this is only focused on BRCA wild-type. There are no patients with BRCA on this particular analysis, so already your curves are going to look different and your hazard ratios to PARP inhibitor are going to look different, so keep that in mind. But this was really a study of chemotherapy and bevacizumab, bevacizumab maintenance, that's arm 1 in blue. Chemotherapy, bevacizumab, durvalumab, durvalumab/bevacizumab maintenance that's green. And then in orange, chemotherapy, bevacizumab, durvalumab,

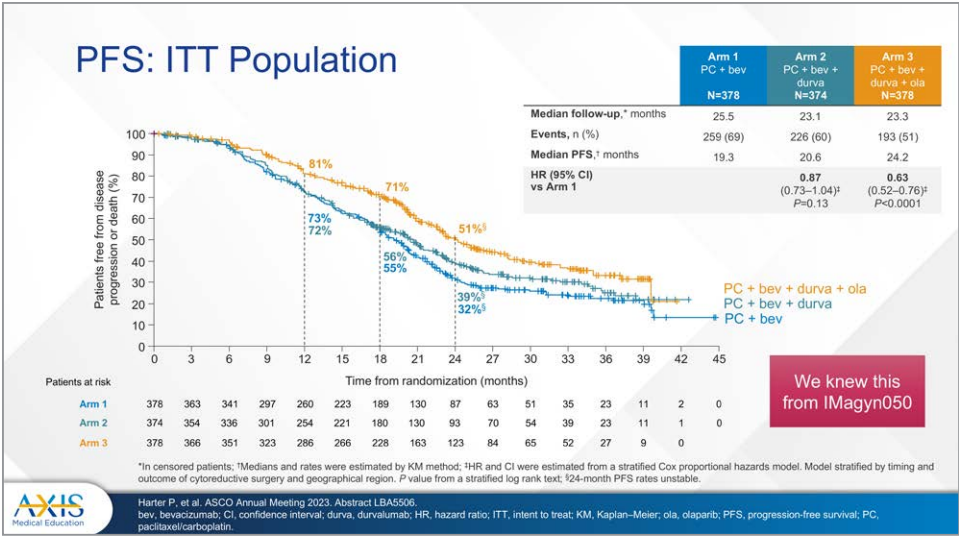
followed by the triplet maintenance, bevacizumab, durvalumab, olaparib. The primary endpoint that was presented thus far is the orange box versus the blue box, arm 3 versus arm 1. That was the statistical analysis, triplet versus singlet of bevacizumab. So, you can already see why we have the missing arm, we have this continuing saga, unfortunately, of the missing arm because we want to know what olaparib/bevacizumab would have done, and that arm just isn't here.



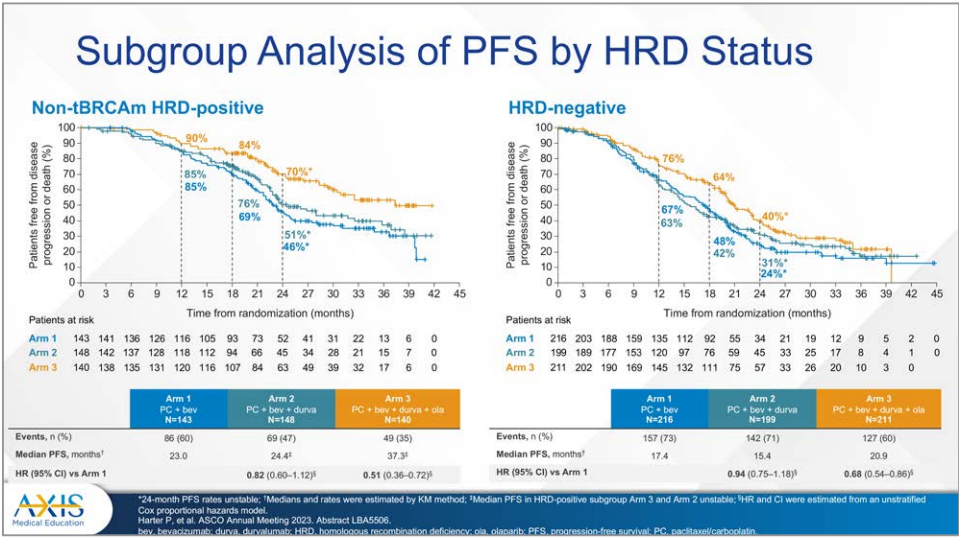
▶ But, be that as it may, we have some results that I can show you. Here is and it was done in HRD-positive and then ITT; those are the two primary endpoints. So, here's HRD-positive. Remember, this is BRCA wild-type. So, no BRCA here. And it includes the time on chemo. So, it's a totally different start point for these curves than everything else I have shown you. But it's positive. So, olaparib, bevacizumab, durvalumab looks better than bevacizumab maintenance. That is clear. You know, our hazard ratio is 0.49, so a 51% reduction in the hazard of progression with triplet versus singlet.



▶ So that was positive, so then they moved to the intention-to-treat population, all-comers, all BRCA wild-type. And again, hazard ratio is 0.63, so that looks pretty good as well.



► Here, what I'm showing you is that same slide, the progression-free survival in the intention-to-treat population, but we layered in that arm 2, which is the durvalumab/bevacizumab arm as compared to both. But what you can see here is that there's no statistical or really clinical improvement in the progression-free survival with the addition of durvalumab to bevacizumab, which shouldn't come as a surprise. We did an entire clinical trial called IMagyn050, which was atezolizumab/bevacizumab versus bevacizumab, and that was not statistically significant either. So, we shouldn't be surprised about this finding. The question really is with this study is: What's the benefit? What's the add-on of durvalumab to the olaparib in arm 3? And that's really what we can't answer because of the missing arm, which is a little frustrating.



► I'm going to show you the subgroup analysis of progression-free survival by HRD status. So, on the left, again, BRCA wild-type, the HRD-positive, this is that 20% of the pie I talked to you about earlier, but again starting during chemo, not after, so it is a different population. And you can see here, the hazard ratio for arm 1 versus arm 3 is 0.51, which is about what you would expect for PARP, bevacizumab versus bevacizumab, that's just like what we saw with PAOLA, very similar hazard ratio. And then on the right-hand side, you can see the HRD test-negative group where surprisingly, arm 3 versus arm 1, you see a benefit of 0.68. But I'll remind you, this is not an analytic subgroup and so, this is hypothesis-generating only and I'll show you what I mean that in a moment.

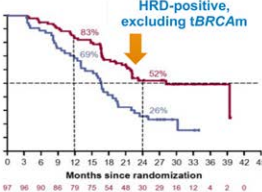
DUO-O vs PAOLA-1: PFS in BRCAwt/HRD

Non-tBRCAm HRD-positive



You might be tempted to say that this

Looks better than this



Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
Events, n (%)	86 (60)	69 (47)	49 (35)
Median PFS, months ¹	23.0	24.4 [†]	37.3 [†]
HR (95% CI) vs Arm 1		0.82 (0.60-1.12) [‡]	0.51 (0.36-0.72) [‡]

	Olaparib + Bevacizumab (N = 97)	Placebo + Bevacizumab (N = 55)
Events	43 (44)	40 (73)
Median PFS, months ¹	28.1 [*]	16.6
HR (95% CI)	0.43 (0.28, 0.66)	

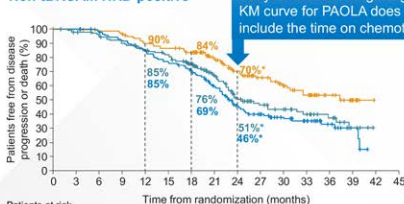


Harter P, et al. ASCO Annual Meeting 2023, Abstract LBA5506; Ray-Coquard I, et al. ESMO Congress 2019, Abstract LBA2_PR. bev, bevacizumab; BRCAwt, BRCA wild type; CI, confidence interval; durva, durvalumab; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent to treat; KM, Kaplan-Meier; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

► So, how do we interpret DUO-O? Because we were all waiting for this, will immune checkpoint inhibitors be transformative in frontline ovarian cancer? And unfortunately, this study has more questions than answers. So, you might compare like I just did, DUO-O to PAOLA, because PAOLA is bevacizumab/olaparib, and DUO-O is also olaparib/bevacizumab with durvalumab. So, let's do it. Let's just do some cross-trial comparison, and we'll just own that we're doing it. So, you might be tempted to put these two progression-free survival curves up next to each other. And you might be tempted to say, alright, well, at 24 months in DUO-O, the percentage of patients on the triplet who hadn't recurred is 70%, versus only 52% on the PAOLA arm, so even though it's cross-trial comparison, I'm tempted to say this is superior, that the durvalumab must have done something.

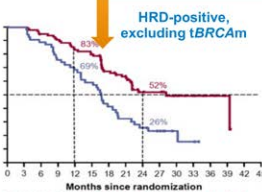
DUO-O vs PAOLA-1: PFS in BRCAwt/HRD

Non-tBRCAm HRD-positive



But you would be forgetting that the KM curve for PAOLA does NOT include the time on chemotherapy

So 24 months in DUO-O is around 18 months in PAOLA



Patients at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Arm 1	143	141	136	126	116	105	93	73	52	41	31	22	13	6	0	0
Arm 2	148	142	137	128	118	112	94	66	45	34	28	21	15	7	0	0
Arm 3	140	138	135	131	120	116	107	84	63	49	39	32	17	6	0	0

	Arm 1 PC + bev N=143	Arm 2 PC + bev + durva N=148	Arm 3 PC + bev + durva + ola N=140
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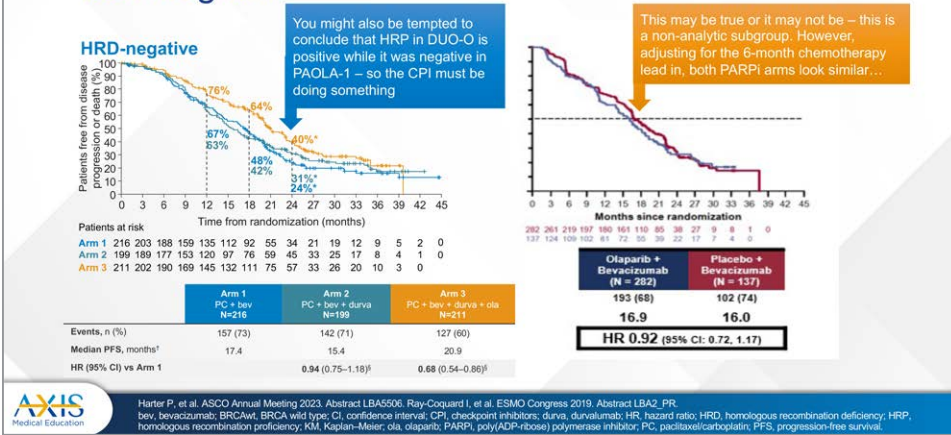
	Olaparib + Bevacizumab (N = 97)	Placebo + Bevacizumab (N = 55)
Events	43 (44)	40 (73)
Median PFS, months ¹	28.1 [*]	16.6
HR (95% CI)	0.43 (0.28, 0.66)	



Harter P, et al. ASCO Annual Meeting 2023, Abstract LBA5506; Ray-Coquard I, et al. ESMO Congress 2019, Abstract LBA2_PR. bev, bevacizumab; BRCAwt, BRCA wild type; CI, confidence interval; durva, durvalumab; HR, hazard ratio; HRD, homologous recombination deficiency; ITT, intent to treat; KM, Kaplan-Meier; ola, olaparib; PFS, progression-free survival; PC, paclitaxel/carboplatin; tBRCAm, tumor BRCA1 and/or BRCA2 mutation.

► But what we have to remember is that these timepoints for this curve start differently. DUO-O starts with chemo, and PAOLA starts at the end of chemo. And so, if you correct that survival curve for PAOLA, 24 months in DUO-O equals about 18 months-ish on PAOLA, adjusting for that time on chemo. And then the percentage of patients who haven't recurred looks about the same, roughly. So, you can't really say that you have a sense that the durvalumab is adding something here.

DUO-O vs PAOLA-1: PFS in BRCAwt/HRD Test Negative



▶ Similarly, let's just look at the HRD test-negative population in DUO-O, which was non-analytic, just like it was in PAOLA, so putting up two non-analytic inputs. And again, you might be tempted to say, well, at 24 months, 40% of the

patients on DUO-O who were HRD test-negative didn't have recurrence. And at 24 months on PAOLA it was a lot less than that. If you do that correction, you're sitting right about 50%. But the true truth is, it might be true that the durvalumab

adds something here and that it's important or it might not be. These are non-analytic endpoints, we cannot make statements about either one of these two studies in this subset, because they're both non-analytic endpoints, one may be true and one is false. And until we do a fully powered trial in this population, testing a hypothesis, we will not know what the truth is. And so, that's what I'd say; it may be true, it may not be true. Unfortunately, we cannot tell based on this.

Addition of CPI Will Have to Wait for One of These to Result...

Trial	Size	Anti-angiogenic	PARPi	CPI	Start	Estimated Primary Completion
FIRST ¹ ENGOT OV-44	1405	± Bevacizumab	Niraparib	Dostarlimab	Oct 2018	Jan 2023
DUO-O ² ENGOT OV-46	~1204	Bevacizumab	Olaparib	Durvalumab	Jan 2019	June 2023
ATHENA ³ GOG-3020 ENGOT OV-45	~1000	-	Rucaparib	Nivolumab	May 2018	Dec 2024
ENGOT OV-43 ⁴ KEYLYNK-001	~1086	± Bevacizumab	Olaparib	Pembrolizumab	Dec 2018	Aug 2025

are biomarker powered around the IO, some are around HRD. And so, they're very different studies. And I think we're going to have to wait for each one of them to read out in their specific population with their specific endpoint to really make any definitive statements about whether or not checkpoint inhibitor has a role for frontline ovarian cancer or not. Fortunately, these should read out this year, and we may have an answer.

▶ And so, for now, our addition of a checkpoint inhibitor to frontline chemotherapy is going to have to wait for some of these other studies to read out, first ATHENA-COMBO or KEYLYNK-001, which are all combinations; two of them have bevacizumab,

one does not, but all PARP immune checkpoint inhibitor combinations. But I will caution you, these are not 3 versions of the same study; they're all different. They have different endpoints, they have different biomarkers, and different stratification; some

PAOLA-1, PRIMA and ATHENA-MONO: Clinical Context of Trial Populations

PAOLA-1 ^{1,2} Olaparib + bevacizumab	PRIMA ^{3,4} Niraparib	ATHENA-MONO ^{5,6} Rucaparib
Chemotherapy + bevacizumab → Olaparib + bev	Chemotherapy → Niraparib monotherapy	Chemotherapy → Rucaparib monotherapy
Primary endpoint: • Investigator-assessed PFS (ITT)	Primary endpoint: • PFS by BICR (HRD → ITT)	Primary endpoint: • Investigator-assessed PFS
HRD status: • Determined by Myriad MyChoice CDx (BRCA mutations and LOH, TAI and LST)	HRD status: • Determined by Myriad MyChoice CDx (BRCA mutations and LOH, TAI and LST)	HRD status: • Determined by FoundationOne CDx (BRCA mutations and LOH)
No selection for higher risk of relapse: • PDS or IDS with residual / no residual disease	Selection for higher risk of relapse: • Stage III PDS with residual disease • Stage III IDS / Stage IV	No selection for higher risk of relapse: • PDS or IDS with residual / no residual disease
Weak selection for evaluable response to platinum: • CR/PR (investigator) • ~50% PDS of which 60% had no residual tumor • Response partially based on bevacizumab • Selection for response to bevacizumab in HRD-negative population	Strong selection for evaluable response to platinum: • CR/PR (investigator) • All Stage III PDS patients had measurable disease to assess platinum response • Normal or >90% \downarrow CA-125	Weak selection for evaluable response to platinum: • CR/PR (investigator) • ~49% of patients had PDS • ~75% had no residual tumor

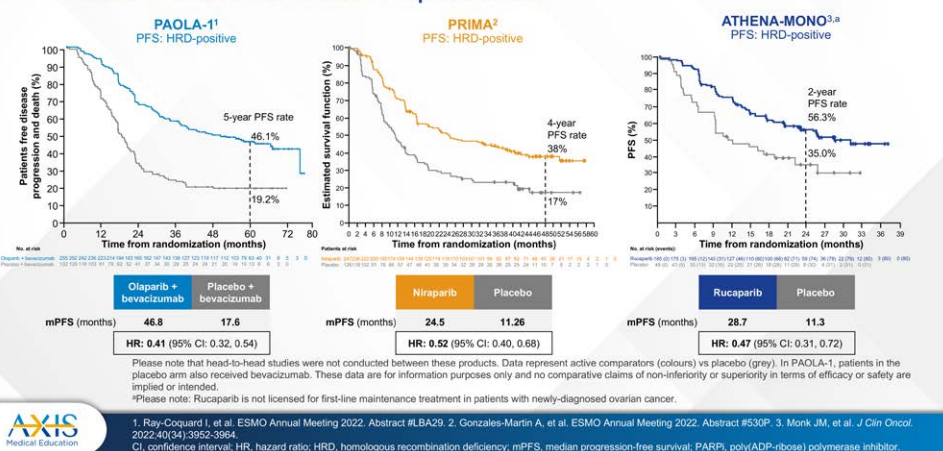
Head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.
*Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.



Ray-Coquard J, et al. *N Engl J Med*. 2019;381(25):2416-2428. 2. Gonzalez-Martin A, et al. ESMO Virtual Congress 2020. Abstract LBA33. 3. Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(23):2402-4. *ClinicalTrials.gov*. <https://clinicaltrials.gov/ct2/show/NCT02685016>. 5. Monk JM, et al. *J Clin Oncol*. 2022;40(34):3952-3964. bev, bevacizumab; BICR, blinded independent central review; BRCA, BRCA1 and/or BRCA2; CA-125, cancer antigen-125; CR, complete response; HRD, homologous recombination deficiency; IDS, interval debulking surgery; ITT, intention-to-treat; LOH, loss of heterozygosity; LST, large-scale state transition; NED, no evidence of disease; PDS, primary debulking surgery; PFS, progression-free survival; PR, partial response; TAI, telomeric allelic imbalance.

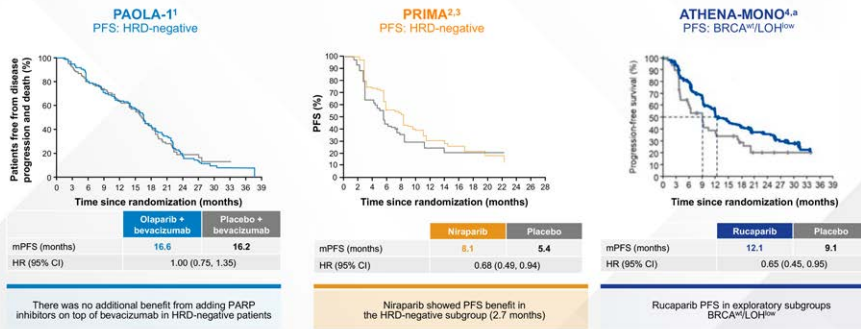
► And so, this is circling back to the data that we have, if we look at PAOLA, PRIMA, and, here will be our one little reference to ATHENA-MONO with rucaparib, which is a very important study, and it is NCCN listed, but just not FDA approved as of this point. But very consistent data. But these are all a little different. PAOLA was a much smaller study, it had an intention-to-treat population was its primary endpoint. And PRIMA, it was progression-free survival for HRD and then ITT. And ATHENA was the same but had a different biomarker for HRD here, the FoundationOne test. So, even though I had said these results are all very consistent, they're different studies, they do have to be looked at in the context of each individual study and each individual population, because they're a little bit different.

A Significant PFS Benefit From PARPi Was Observed in HRD-Positive Patient Populations



► Even though I've said that, I'm showing you the results that are all relatively consistent, here's the patient population that are HRD-positive in each of these studies. Again, just reminding you that HRD does include the BRCA population as well as HRD test-negative, and so these hazard ratios are in like 0.4 to 0.5 range, very striking and justifies use of PARP inhibitor in this population.

What About Patients With HRD-Negative Tumors? PFS Analyses from PAOLA-1, PRIMA, and ATHENA-MONO



There was no additional benefit from adding PARP inhibitors on top of bevacizumab in HRD-negative patients

Niraparib showed PFS benefit in the HRD-negative subgroup (2.7 months)

Rucaparib PFS in exploratory subgroups BRCA^{wt}/LOH^{tw}

Head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

*Please note: Rucaparib is not licensed for first-line maintenance treatment in patients with newly-diagnosed ovarian cancer.



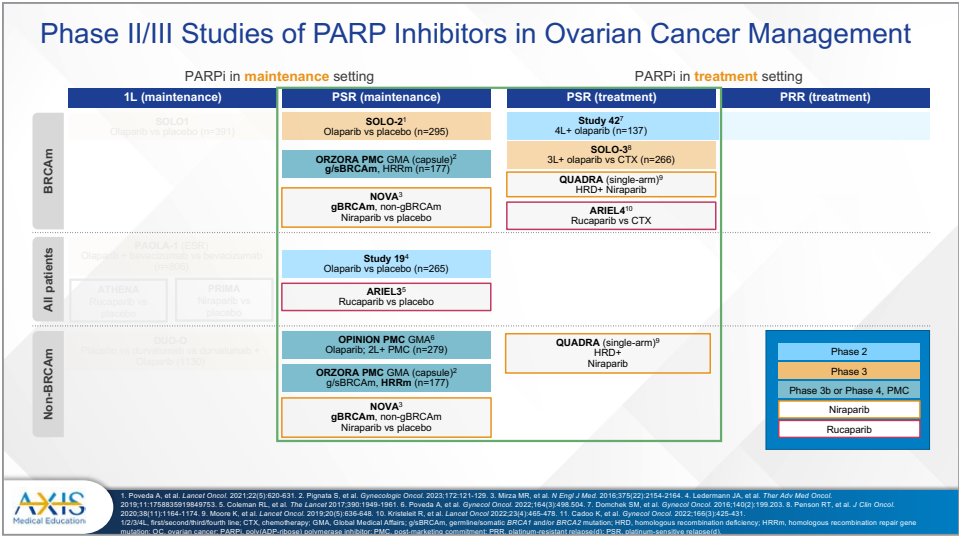
1. Ray-Coquard I, et al. *N Engl J Med*. 2019;381(25):2416-2423. 2. Gonzalez-Martin A, et al. *N Engl J Med*. 2019;381(25):2391-2402. 3. Monk BJ, et al. *SGO 2020*. Abstract 31. 4. Monk BJ, et al. *ASCO Annual Meeting 2022*. Abstract LBA5500. BRCA, BRCA1 and/or BRCA2, CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; LOH, loss of heterozygosity; (m)PFS, (median) progression-free survival; PARP, poly(ADP-ribose) polymerase; wt, wild-type.

► And then here's the HRD test-negative population, PAOLA on the left with no benefit, and we do not have an indication here. But PRIMA and ATHENA – so, I'm glad to show ATHENA here just to show the consistency of that PRIMA signal, it's really similar, 0.68 and 0.65 are the PRIMA and ATHENA hazard ratios, respectively. And so, these do show a consistent, not modest, but it's clinically and statistically relevant improvement in progression-free survival with use of PARP in this biomarker-negative population. And I say statistically which I shouldn't have, because it's non-analytic. So, clinically relevant, consistent signal in both populations, which justifies the all-comer indication for PRIMA. And we'll see what happens with rucaparib over time.

PARP Inhibitors as Maintenance Therapy and Treatment for Relapsed/Recurrent Advanced Ovarian Cancer

► There have been many studies of platinum-sensitive recurrence and platinum-resistant recurrence, where we've used PARP inhibitors either as maintenance or as treatment instead of chemotherapy.





Now I showed you this at the beginning, I focused on frontline, and when we use it as treatment, we're mainly in biomarker selected populations such as BRCA. And all of this was done, I'll remind you, in a PARP inhibitor-naive setting. So, if we were in the platinum-sensitive or the platinum-resistant setting, these patients had not seen prior PARP inhibitor. And these studies were all very positive.

PARPi Maintenance Treatment Clinical Trials in Relapsed OC

	Phase	PARPi	Comparator	OS (HR)			PFS (HR)		
				ITT	BRCAm	Non-BRCAm	ITT	BRCAm	Non-BRCAm
Study 19 ¹⁻³	2	Olaparib	Placebo	0.73	0.62	0.84	0.35	0.18	0.54
SOLO-2 ^{4,5}	3	Olaparib	Placebo	-	0.74	-	0.30	0.33	-
NOVA ^{6,7}	3	Niraparib	Placebo	-	0.85	1.06	-	0.27	0.45
ARIEL3 ^{8,9}	3	Rucaparib	Placebo	0.995	0.83	1.280 (LOH-high) 1.153 (LOH-low)	0.36	0.23	0.44 (LOH-high) 0.58 (LOH-low)

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

AXIS Medical Education

1. Ledermann JA, et al. N Engl J Med. 2012;366:1302-1310. 2. Ledermann JA, et al. Lancet Oncol. 2014;15(8):852-861. 3. Friedlander M, et al. Br J Cancer. 2014;110:1075-1085. 4. Poveda A, et al. Lancet Oncol. 2021;22(5):520-531. 5. Pignata S, et al. Lancet Oncol. 2023;24(10):1274-1284. 6. Markovits S, et al. SOG Annual Meeting 2022. Abstract LBA 6. 7. Mirza MR, et al. N Engl J Med. 2016;375(22):2154-2164. 8. Coleman RL, et al. J Clin Oncol. 2020;38(11):1156-1174. 9. Coleman RL, et al. Lancet. 2017;390:1948-1961. HRD, homologous recombination deficiency, HRRm, homologous recombination repair gene mutation, OC, ovarian cancer, PARPi, poly(ADP-ribose) polymerase inhibitor, PRR, platinum-resistant recurrence, PSR, platinum-sensitive relapse

And so, these are just the results of PARP inhibitor treatment clinical trials in the platinum-sensitive maintenance. Study 19 is a phase 2 very important study, SOLO-2, NOVA, and ARIEL3 were all phase 3s, and you can see the very strong signals of benefit in terms of progression-free survival, hazard ratios, and they're outlined on the kind of the right-hand side of this screen, when we use PARP inhibitor maintenance across biomarkers in this platinum-sensitive recurrent setting. So, this is the first place where we had actually phase 3 data for use of PARP inhibitors in ovarian cancer. It started in platinum-sensitive recurrent disease.

PARPi Treatment Clinical Trials in Later-Line Relapsed OC

	Phase	PARPi	Comparator	OS (HR)			PFS
				BRCAm	HRD-positive	HRD-negative	BRCAm
SOLO-3 ^{1,2}	3	Olaparib	Chemotherapy	(≥2 prior lines of chemo) 1.07 (≥3 prior lines of chemo) 1.33	-	-	0.62
ARIEL4 ^{3,4}	3	Rucaparib	Chemotherapy	1.31 ^a	-	-	0.67 ^a
QUADRA ⁵	2 (single-arm)	Niraparib	-	mOS: 26.0 months	mOS: 19.0 months	mOS: 15.5 months	-

Please note that head-to-head studies were not conducted between these products. These data are for information purposes only and no comparative claims of non-inferiority or superiority in terms of efficacy or safety are implied or intended.

^aIntention-to-treat population.



1. AstraZeneca. <https://www.lynpazhpc.com/content/dam/physician-services/us/590-lynpazhpc-branded/hcp-global/pdf/solo3-dhpc-final-signed.pdf>. 2. Penson RT, et al. *J Clin Oncol*. 2020;38:1164-1174. 3. Clovis Oncology. https://clovisoncology.com/pdfs/US_DHCP_L_final_signed.pdf. 4. Kristeleit R, et al. *Lancet Oncol*. 2022;23(4):465-478. 5. Moore KN, et al. *Lancet Oncol*. 2019;20(5):636-648. BRCAm, BRCA1 and/or BRCA2 mutation; HR, hazard ratio; OC, ovarian cancer; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

▶ Then, we also studied this as I said, instead of chemotherapy in platinum-sensitive settings, but ARIEL4 actually in platinum-resistant settings as well. But these were in PARP-naive, BRCA tumors that were recurrent using an effective drug versus standard-of-care chemotherapy. And so, all of these looked superior and this is really where, again, we saw some of our early indications for incorporation of PARP inhibitors into the treatment paradigm for ovarian cancer, was in these later line settings, which really don't exist anymore because we don't have these PARP-naive tumors in the third and fourth line.

OS Results in Non-BRCAm Patients From ARIEL3 and NOVA Has Led to Restriction of the PSR Label in the US

Olaparib FDA-approved indication¹

For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy

Rucaparib FDA-approved indication²

For the maintenance treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy

Niraparib FDA-approved indication³

For the maintenance treatment of adult patients with gBRCAm recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy

EMA label for olaparib, rucaparib, and niraparib remain unchanged in this setting



1. LYNPENZA (olaparib). Prescribing Information. AstraZeneca; 2023. 2. RUBRACA (rucaparib). Prescribing Information. Clovis Oncology; 2022. 3. GSK. [https://www.zeljehpc.com/content/dam/cf-pharma/hcp-zeljehpc-v2/en_US/pdf/ZEJULAY%20\(niraparib\)%20Dear%20HCP%20Letter%20November%202022.pdf](https://www.zeljehpc.com/content/dam/cf-pharma/hcp-zeljehpc-v2/en_US/pdf/ZEJULAY%20(niraparib)%20Dear%20HCP%20Letter%20November%202022.pdf). EMA, European Medicines Agency; FDA, Food and Drug Administration; gBRCAm, germline BRCA1 and/or BRCA2 mutation; OC, ovarian cancer; PARPi, poly (ADP-ribose) polymerase inhibitor; PSR, platinum-sensitive relapsed.

▶ But more, probably, important than that is the fact that the indications for use of PARP inhibitors have expanded. All of those were positive FDA approved indications, everything I just showed you in the recurrent setting, but they've almost all entirely been retracted. So, in the recurrent setting, the only places you can use PARP right now are in the platinum-sensitive recurrent maintenance setting for BRCA. That's it. So, platinum-sensitive recurrent HRD test-positive, even if that patient is PARP naive, is no longer on label

to use a PARP inhibitor. And why this is, is a very complex discussion that probably deserves more than one slide. But the truth is, in these studies of platinum-sensitive recurrent maintenance, which weren't designed to show overall survival. So, there's all sorts of caveats here of how well the patients were followed, and how well crossover was ascertained, and data completion, all those things notwithstanding, there was a very consistent signal of detriment to overall survival across these studies

in BRCA wild-type, especially BRCA wild-type HRD. The hazard ratios were like 1.2 to 1.3, all of them crossed 1, so the confidence intervals were not significant. But the point estimate was on the wrong side of 1. And so, in an abundance of caution, the U.S. regulatory agency withdrew the approvals in these recurrent settings, again, outside of platinum-sensitive recurrent maintenance for BRCA. There, you can still use it; all the other indications had been withdrawn.

Key Takeaways and Considerations

- Most patients with advanced ovarian cancer relapse following first-line multimodality therapy
- Multiple lines of chemotherapy is associated with cumulative toxicity while remission periods decrease
- First-line treatment for advanced ovarian cancer is the optimal setting to achieve a potential cure
- Significant progress has been made in the management of ovarian cancer over the past decade
 - Bevacizumab
 - PARP inhibitors for BRCA-mutated ovarian cancer
 - PARP inhibitors beyond BRCA mutation
- PARP inhibitors as first-line maintenance:
 - SOLO-1: olaparib (BRCAm)
 - PAOLA-1: olaparib + bevacizumab (HRD+)
 - PRIMA: niraparib (all patients)
 - ATHENA-MONO: rucaparib (investigational)
- Earlier introduction of PARP inhibitors may benefit significant numbers of patients
- Benefits of delaying chemotherapy in some patients and use of PARP inhibitors in maintenance regimens
- Considerations when selecting therapy:
 - Patient response to platinum therapy
 - BRCA and HRD testing and biomarker status
 - Route of administration
 - Guideline recommendations
 - Shared decision-making
- Importance of consultation and referral to gynecologic oncologists



HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival.

► And right or wrong, I hope I convinced you at the beginning of this talk, that the best place to use a PARP inhibitor is frontline, in any, irrespective of biomarker. And so, that's really where we need to be focused is making sure the right patients get PARP inhibitors at the right time, which is frontline while we sort out sort of use in later lines of therapy with upcoming clinical trials, and they are being planned. But for right now, it's important you know where you have indications and where you don't.

So, in conclusion, or I guess key takeaways for this talk is, I've shown you some signals that we are curing more patients, especially with BRCA, but not all. I showed you 45% or maybe I told you our progression-free at 7 years, but that means 55% have recurred. And so, that's still an unmet need. And those rates are even higher for our BRCA wild-type. So, the majority of patients are still recurring. And once recurrent, we have many, many things to treat them with but we can no longer cure. So, we really want to put all of our efforts into these frontline, good surgery,

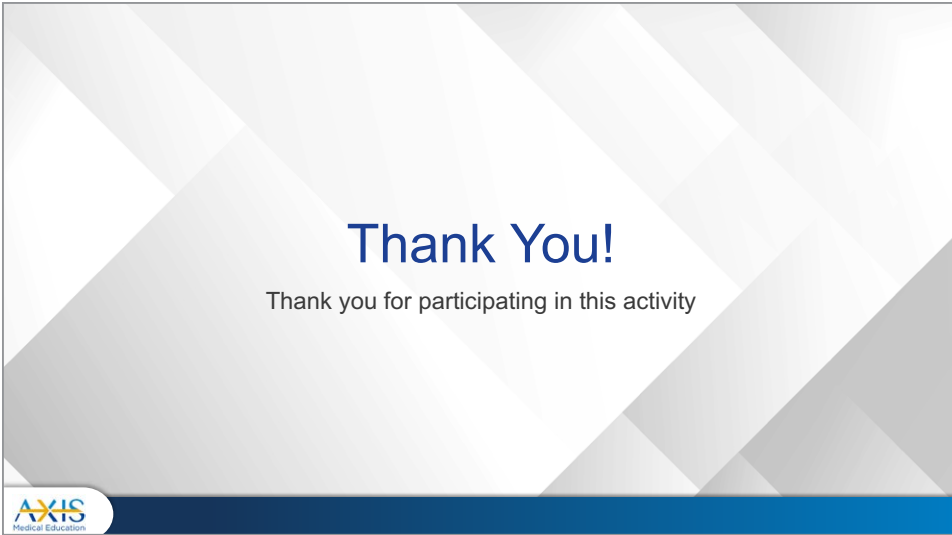
good chemotherapy, and maintenance as appropriate to try and move as many patients as possible into that cure fraction.

Once patients have recurred, again, they're no longer curable and the multiple lines of chemotherapy start to add up, cumulative toxicity, additive toxicity just from disease burden that grows with each line of therapy as the disease becomes more resistant and then less robust responses to those subsequent lines of therapies as these tumor clones become more heterogeneous. So, everything we can do to sort of move more patients to cure in the frontline, use maintenance where appropriate to sort of spread out the cycles of chemotherapy and recurrent different types of chemotherapy our patients are getting, will help them live longer in the end.

PARP inhibitors are approved as first-line maintenance. We have olaparib monotherapy for BRCA. We have olaparib plus bevacizumab for HRD-positive, inclusive of BRCA. We have niraparib for all-comers. Those are all FDA approved. And

then we have rucaparib from the ATHENA-MONO study that is not FDA approved, but is NCCN listed. So, you basically have four options for consideration for PARP inhibitor in the frontline.

So considerations for when selecting therapy really comes down to that patient's response to that frontline chemotherapy, their biomarker status either BRCA or HRD. Kind of the patient shared decision about what she holds important, you know, in terms of maybe combining with bevacizumab or not. Is she okay with coming in for infusions? Or does she want something completely oral once daily versus twice daily? So, a lot of shared decision-making that goes into selections for frontline maintenance. But if we do this well, we can do this for the best benefit for all of our patients.



- ▶ And with that, I thank you for participating in this activity. Please join me for Part 2, where I'll review adverse events associated with PARP inhibitor-based therapy, shared decision-making strategies, and case study examples that highlight the integration and management of first-line maintenance treatment with PARP inhibitors in advanced ovarian cancer. See you then.

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