|  |
| --- |
| **Trascript** |
| **Redefining Care For Advanced Ovarian Cancer Patients:****Clinical Perspectives on the Impact of SOLO-1 and PAOLA-1****An Interview with Dr Bradley Monk**Bradley Monk, MD, FACOG, FACS is a board-certified gynecologic oncologist with Florida Cancer Specialists & Research Institute and a co-founder of the GOG-Partners Foundation®Dr Monk has been compensated by AstraZeneca for his participation.**Select Safety Information**LYNPARZA is associated with serious and potentially fatal adverse events including myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), pneumonitis, and venous thromboembolism (VTE). Monitor patients for signs and symptoms and discontinue LYNPARZA if MDS/AML or pneumonitis is confirmed. Monitor patients for signs and symptoms of VTE and treat as medically appropriate. LYNPARZA can cause fetal harm.Please see full Important Safety Information at the end of the video.  |

|  |
| --- |
| **Screen 1** |
| Greetings and welcome. My name is Brad Monk and I'm a gynecologic oncologist here in West Palm Beach, Florida. I spent the better of my adult life trying to learn about maintenance treatment, keeping patients in remission, because the risk of recurrence, particularly in ovarian cancer, is very high. We're here to celebrate the 10 year evolution of what olaparib has achieved for patients. More than being active in four tumor types, ovarian, breast, pancreatic, and prostate, it has helped patients. |
| **Screen 2** |
| In 1991, Dr. Mary Claire King coined the term breast cancer 1, or *BRCA1*, for what was the hypothetical gene. And then in February 1994, the location and sequence of the *BRCA1* gene was reported. And then in September, in 1994, the *BRCA2* gene was identified and located.2  |
| **Screen 3** |
| The first pivotal observation was in 2009, a phase 1 study published in the New England Journal of Medicine, showing that olaparib, an oral poly ADP-ribose polymerase inhibitor, or PARP inhibitor, had activity in *BRCA*-associated cancers.3 We continued. That wasn't enough. More studies continued looking at olaparib until we broke through in 2014 with FDA approval.4 |
| **Screen 4** |
| And that's why we're here. Ten year celebration from 2014 to 2024. Celebrating the FDA approval of olaparib for a specific type of ovarian cancer.4  |
| **Screen 5** |
| The next milestone was SOLO-1. This was the third trial that we had done within the GOG.5 This was a study that enrolled 391 patients with newly diagnosed advanced ovarian cancer with a *BRCA* mutation who responded to platinum with either a complete or partial response in the first line. Based on the statistically significant improvement in investigator initiated progression free survival or death for LYNPARZA compared to placebo, SOLO1 ultimately led to the next FDA approval in December 2018 in this setting, a first line maintenance treatment of *BRCA*-associated mutated ovarian cancers.1,6 |
| **Screen 6** |
| The post hoc five year, now more mature, progression free survival showed that the primary endpoint in SOLO-1 was approximately 4.7 years with LYNPARZA compared to 1.2 years with placebo, with a hazard ratio of 0.33. That's a 67 percent reduction.7 |
| **Screen 7** |
| At the seven year interim overall survival follow up of SOLO-1, 67 percent of patients on LYNPARZA were alive versus 47 percent with placebo, with a hazard ratio for survival of 0.55.8  |
| **Screen 8** |
| Now earlier that year, also in 2018, the treatment of newly diagnosed advanced ovarian cancer had changed with the FDA approval of bevacizumab in combination with chemotherapy followed in maintenance based on another GOG trial, GOG 2018, published in the New England Journal by Robert Berger. There's another study, a confirmatory trial called ICON7, authored by Tim Perren, published in the same issue of the New England Journal of Medicine.9-11 |
| **Screen 9** |
| So, in the timeline of the development of ovarian cancer treatments, the first novel agent was paclitaxel, dating way back to 1992. The second was bevacizumab, approved in the front line in 2018. And then the third was olaparib. Olaparib was approved for the maintenance treatment of *BRCA*-associated cancers in December of 2018. And number four, the combination of bevacizumab plus olaparib in the maintenance phase in HRD-positive patients, approved in May of 2020.9,12-14 |
| **Screen 10** |
| The good news is, we can give all three of these agents together, paclitaxel, bevacizumab, continued in maintenance, and then in the maintenance phase, olaparib in the HRD-positive patients.15PAOLA-1 randomized patients 2 to 1 with stratification according to first-line treatment outcomes and *BRCA* status. 15 |
|  **Screen 11** |
| It was an interesting study because it enrolled allcomers, not only patients with *BRCA* mutations, but also patients who had *BRCA*-like findings, defined as homologous recombination repair deficiency, sometimes termed genomic instability. When genes such as *BRCA* that are involved in this homologous recombination repair process are mutated, it results in changes in chromosomal structure.16-18In PAOLA-1 showed that by using a biomarker such as HRD, we can interrogate the molecular signature when double stranded DNA repairs were not repaired or recombined based on the sister chromatid template.15 |
| **Screen 12** |
| In terms of efficacy, PAOLA-1 showed that progression free survival was improved in a clinically significant way with the median progression free survival of 3.1 years with olaparib and bevacizumab versus 1.5 years with placebo and bevacizumab, with a hazard ratio of 0. 33 in the HRD-positive subgroup.15In terms of overall survival, one of the most important endpoints in the HRD-positive subgroup, a select secondary endpoint, patients treated with LYNPARZA + bevacizumab had a five year overall survival rate of 65.5% versus 48.4% with placebo + bevacizumab. 65.5% versus 48.4% at five years.19 This data was based on a pre-specified, exploratory subgroup analysis, it was not controlled for type 1 error, and HRD was not a stratification factor.15The results of PAOLA-1 were truly clinically significant. |
| **Screen 13** |
| Despite the positive results and impact of LYNPARZA, in my experience treating many, many patients with ovarian cancer, it's not the survivors that I dwell on. It's the non-survivors. It's the patients that died. That's what affects me in my practice. That's why I keep doing clinical trials, because I want to help even more women live longer. We know there's no such thing as low risk advanced ovarian cancer. However, in a post hoc exploratory subgroup analysis of progression free survival by clinical risk of relapse. PAOLA-1 showed that the median progression free survival in the higher-risk HRD-positive subgroup was 3 years with bevacizumab and approximately 1.3 years with placebo plus bevacizumab, 3 vs 1.3 with a hazard ratio of 0.39.20There's no official consensus on what is considered higher or lower risk. However, in this analysis, higher risk was defined as FIGO stage 4, stage 3 with residual disease or neoadjuvant and interval debulking surgery.20The point is that we as oncologists need to test. We need to do germline testing and somatic testing, genetic and genomic testing early for all patients with epithelial ovarian cancer to ensure we have the right information to make the right decision and inform the treatment plan. |
| **Screen 14** |
| The companion diagnostic that was attached to olaparib approval was Myriad MyChoice, as well as the inclusion of biomarker testing in treatment guidelines, encouraged oncologists to order biomarker testing at the time of diagnosis to determine the appropriate maintenance treatment for patients with advanced ovarian cancer.14,21There are 2 other companion diagnostics approved for LYNPARZA.22 |
| **Screen 15** |
| In terms of biomarker testing, once a patient has been diagnosed with ovarian cancer, I immediately order Myriad MyChoice genomic testing and germline *BRCA* testing, knowing the germline mutational signature and the somatic HRD result. These tests provide comprehensive information, that includes in the somatic test Myriad Mychoice, loss of heterozygosity, telomeric allelic imbalance, and large-scale state transitions.23It also shows if the patient has a germline *BRCA* mutation or another pathogenic variant. And if they do, I refer them to a genetic counselor for surveillance, risk reducing surgery, and also interrogation of their family. |
| **Screen 16** |
| In addition to the approval of LYNPARZA for the treatment of certain types of advanced ovarian cancer, there are opportunities for using LYNPARZA to treat certain types of breast, prostate, and pancreatic cancer. Together, across four tumor types and eight indications, olaparib has transformed the landscape of treating women and men.1 In my opinion, the number of individuals whose lives have been transformed by olaparib is truly significant.  |
| **Screen 17** |
| For the last decade, at this 10-year celebration, LYNPARZA has had a meaningful impact in patients’ lives, in ovarian cancer and other cancers with BRCA mutations, including homologous recombination repair genes or the HRD signature. And the combination of olaparib and bevacizumab has now been the standard of care since its FDA approval in May of 2020, over four years. I'd like to point out that, in my opinion, we're still in the implementation phase of expanding the use of LYNPARZA for appropriate patients. So, I'm looking forward to seeing its continued impact over the next 10 years, in the community and helping more patients of mine and yours live longer. |
| **Important Safety Information****CONTRAINDICATIONS**There are no contraindications for LYNPARZA.**WARNINGS AND PRECAUTIONS****Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML):** Occurred in approximately 1.2% of patients with various *BRCA*m, g*BRCA*m, HRR gene-mutated or HRD-positive cancers  who received LYNPARZA as a single agent or as part of a combination regimen, consistent with the approved indications, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was approximately 2 years (range: <6 months to >4 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.In SOLO-1, patients with newly diagnosed advanced *BRCA*m ovarian cancer, the incidence of MDS/AML was 1.9% (5/260) in patients who received LYNPARZA and 0.8% (1/130) in patients who received placebo based on an updated analysis. In PAOLA-1, of patients with newly diagnosed advanced ovarian cancer with HRD-positive status, the incidence of MDS/AML was 1.6% (4/255) in patients who received LYNPARZA and 2.3% (3/131) in the control arm.In SOLO-2, patients with *BRCA*m platinum-sensitive relapsed ovarian cancer, the incidence of MDS/AML was 8% (15/195) in patients who received LYNPARZA and 4% (4/99) in patients who received placebo. The duration of LYNPARZA treatment prior to the diagnosis of MDS/AML ranged from 0.6 years to 4.5 years. Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.**Pneumonitis:** Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.**Venous Thromboembolism (VTE):** Including severe or fatal pulmonary embolism (PE) occurred in patients treated with LYNPARZA. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.**Embryo-Fetal Toxicity:** Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating treatment. *Females*Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.**ADVERSE REACTIONS—First-Line Maintenance *BRCA*m Advanced Ovarian Cancer**Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA in the **first-line maintenance setting** for **SOLO-1** were: nausea (77%), fatigue (67%), abdominal pain (45%), vomiting (40%), anemia (38%), diarrhea (37%), constipation (28%), upper respiratory tract infection/influenza/nasopharyngitis/bronchitis (28%), dysgeusia (26%), decreased appetite (20%), dizziness (20%), neutropenia (17%), dyspepsia (17%), dyspnea (15%), leukopenia (13%), urinary tract infection (13%), thrombocytopenia (11%), and stomatitis (11%).Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the **first-line maintenance setting** for **SOLO-1** were: decrease in hemoglobin (87%), increase in mean corpuscular volume (87%), decrease in leukocytes (70%), decrease in lymphocytes (67%), decrease in absolute neutrophil count (51%), decrease in platelets (35%), and increase in serum creatinine (34%).**ADVERSE REACTIONS—First-Line Maintenance Advanced Ovarian Cancer in Combination with Bevacizumab**Most common adverse reactions (Grades 1-4) in ≥10% of patients treated with LYNPARZA/bevacizumab and at a ≥5% frequency compared to placebo/bevacizumab in the **first-line maintenance setting** for **PAOLA-1** were: nausea (53%), fatigue (including asthenia) (53%), anemia (41%), lymphopenia (24%), vomiting (22%), and leukopenia (18%). In addition, the most common adverse reactions (≥10%) for patients receiving LYNPARZA/bevacizumab irrespective of the frequency compared with the placebo/bevacizumab arm were: diarrhea (18%), neutropenia (18%), urinary tract infection (15%), and headache (14%). In addition, venous thromboembolism occurred more commonly in patients receiving LYNPARZA/bevacizumab (5%) than in those receiving placebo/bevacizumab (1.9%). Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients for LYNPARZA in combination with bevacizumab in the **first-line maintenance setting** for **PAOLA-1** were: decrease in hemoglobin (79%), decrease in lymphocytes (63%), increase in serum creatinine (61%), decrease in leukocytes (59%), decrease in absolute neutrophil count (35%), and decrease in platelets (35%).**ADVERSE REACTIONS—Maintenance g*BRCA*m Recurrent Ovarian Cancer**Most common adverse reactions (Grades 1-4) in ≥20% of patients who received LYNPARZA in the **maintenance setting** for **SOLO-2** were: nausea (76%), fatigue (including asthenia) (66%), anemia (44%), vomiting (37%), nasopharyngitis/upper respiratory tract infection (URI)/influenza (36%), diarrhea (33%), arthralgia/myalgia (30%), dysgeusia (27%), headache (26%), decreased appetite (22%), and stomatitis (20%).Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA in the **maintenance setting** for **SOLO-2** were: increase in mean corpuscular volume (89%), decrease in hemoglobin (83%), decrease in leukocytes (69%), decrease in lymphocytes (67%), decrease in absolute neutrophil count (51%), increase in serum creatinine (44%), and decrease in platelets (42%).**DRUG INTERACTIONS****Anticancer Agents:** Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.**CYP3A Inhibitors:** Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.**CYP3A Inducers:** Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.**USE IN SPECIFIC POPULATIONS****Lactation:** No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose. **Pediatric Use:** The safety and efficacy of LYNPARZA have not been established in pediatric patients.**Hepatic Impairment:** No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).**Renal Impairment:** No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).**INDICATIONS**LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated: **First-Line Maintenance *BRCA*m Advanced Ovarian Cancer**For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.**First-Line Maintenance HRD-Positive  Advanced Ovarian Cancer in Combination with Bevacizumab** In combination with bevacizumab for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with homologous recombination deficiency (HRD)-positive status defined by either a deleterious or suspected deleterious *BRCA* mutation, and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.**Maintenance *BRCA*-mutated Recurrent Ovarian Cancer**For the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated (g*BRCA*m or s*BRCA*m) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.**Please see complete Prescribing Information, including Medication Guide, at** [**www.lynparzahcp.com**](http://www.lynparzahcp.com) **Or at the link on this website.**You are encouraged to report negative side effects of AstraZeneca prescription drugs by calling 1-800-236-9933. If you prefer to report these to the FDA, call 1-800-FDA-1088.LYNPARZA is a registered trademark of the AstraZeneca group of companies.©2024 AstraZeneca. All rights reserved. US-91304 Last Updated 8/24 |

|  |
| --- |
|  |
| **References**1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023.
2. Hurst JH. Pioneering geneticist Mary-Claire King receives the 2014 Lasker~Koshland Special Achievement Award in Medical Science. *J Clin Invest*. 2014;124(10):4148-4151.
3. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly (ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N Engl J Med*. 2009;361(2):123-134.
4. AstraZeneca. LYNPARZA approved by the US food and drug administration for the treatment of advanced ovarian cancer in patients with germline BRCA-mutations. Published December 19, 2014.
5. GOG Partners. Clinical Trials. Accessed Aug 6, 2024. Available at: https://www.gog.org/gog-partners/trial-search/?
6. AstraZeneca. LYNPARZA approved by US FDA for 1st-line maintenance therapy in BRCA-mutated advanced ovarian cancer. Published December 19, 2018.
7. Banerjee S, Moore KN, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2021;22(12):1721-1731.
8. DiSilvestro P, Banerjee S, Colombo N, et al. Overall survival with maintenance olaparib at a 7-year follow-up in patients with newly diagnosed advanced ovarian cancer and a *BRCA* mutation: The SOLO1/GOG 3004 Trial. *J Clin Oncol*. 2023;41(3):609-617.
9. US Food and Drug Administration (FDA). FDA approves bevacizumab in combination with chemotherapy for ovarian cancer. Published June 13, 2018.
10. Burger RA, Brady MF, Bookman MA, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365:2473-2483.
11. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med*. 2011;365:2484-2496.
12. Awosika AO, Farrar MC, Jacobs TF. Paclitaxel. Updated Nov 18, 2023. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available at: https://www.ncbi.nlm.nih.gov/books/NBK536917/
13. US Food and Drug Administration (FDA). FDA-approved olaparib (LYNPARZA, AstraZeneca Pharmaceuticals LP) for the maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic BRCA-mutated (gBRCAm or sBRCAm) advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Published December 26, 2018.
14. US Food and Drug Administration (FDA). FDA approves olaparib plus bevacizumab as maintenance treatment for ovarian, fallopian tube, or primary peritoneal cancers. Published May 8, 2020.
15. Ray-Coquard I, Pautier P, Pérol D, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer: *N Engl J Med*. 2019;381(25):2416-2428.
16. Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. Supplementary Appendix. *N Engl J Med*. 2019;38(25):2416-2428.
17. Lozano R, Castro E, Aragón IM, et al. Genetic aberrations in DNA repair pathways: a cornerstone of precision oncology in prostate cancer. *Br J Cancer.* 2021;124:552–563.
18. Mangogna A, Munari G, Pepe F, et al. Homologous recombination deficiency in ovarian cancer: from the biological rationale to current diagnostic approaches. *J Pers Med*. 2023;13:284.
19. Ray-Coquard I, Leary A, Pignata S, et al. Olaparib plus bevacizumab first-line maintenance in ovarian cancer: final overall survival results from the PAOLA-1/ENGOT-ov25 trial. *Ann Oncol*. 2023;34(8):681-692.
20. Harter P, Mouret-Reynier MA, Pignata S, et al. Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial. *Gynecol Oncol*. 2022;164(2):254-264.
21. Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and somatic tumor testing in epithelial ovarian cancer: ASCO Guideline. *J Clin Oncol*. 2020;38:1222-1245.
22. US Food and Drug Administration (FDA). List of cleared or approved companion diagnostic devices (in vitro and imaging tools). Published May 1, 2024.
23. Myriad Genetics, Inc. MyChoice® CDx Myriad HRD Companion Diagnostic Test. 2024. https://myriad.com/genetic-tests/mychoicecdx-tumor-test/.
 |