|  |
| --- |
|  |
| **Redefining Care for Prostate Cancer Patients:**  **Clinical Perspectives on the Impact of PROfound and PROpel.**  **An Interview with Dr Eleni Efstathiou**  efstathiou-eleni  Eleni Efstathiou, MD, PhD, is a Professor of Cancer Medicine and the Section Chief of Genitourinary Medical Oncology at the Houston Methodist Cancer Center.  Dr Efstathiou has been compensated by AstraZeneca for her 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** | | |
| Hello I am Eleni Efstathiou and I am a GU medical oncologist.  Over the past 20 years, our comprehension of prostate cancer has advanced significantly, yet we acknowledge that we are still exploring its depths. A critical area where our understanding falls short is in identifying effective biomarkers. The significance of biomarkers lies in their ability to accurately predict prognosis and their connection to therapies that are designed to enhance patient outcomes.1  For some time, we’ve understood from other tumor types that patients with DNA damage response mutational events, whether germline or somatic, typically have poorer outcomes. We had a lot of retrospective data based on the available agents and we knew from other disease spaces that you could consider these events as not only drivers of carcinogenesis, but also of disease progression. However, we did not know this for prostate cancer.2 | | |
| **Screen 2** | | |
| Looking back, germline *BRCA* mutations were first reported in prostate cancer in 1997 by doctor Rosalind Eeles.3 12 years later, with the publication of the phase 1 study of LYNPARZA in 2009 in the New England Journal of Medicine, evidence began to emerge linking these mutations to cancer progression in prostate cancer.2  The 2020 approval of LYNPARZA for the treatment of adult patients with deleterious or suspected deleterious germline or somatic DDR gene-mutated metastatic castration resistant prostate cancer who have progressed following prior treatment with enzalutamide or abiraterone contributed to the recognition of the significance of these DDR pathway mutations in patients with prostate cancer.4,5  It's noteworthy that only in recent years, publications started shedding light on the significance of somatic events in prostate cancer, which are now recognized to be equally crucial as germline events. Allelic loss, a common occurrence in prostate cancer, underscores this point. Interestingly, the impact of these mutations is not as extensively understood as in breast and ovarian cancers.6 | | |
| **Screen 3** | |
| One of the biggest challenges in treating prostate cancer was determining whether DDR mutations drive cancer progression. When the PROfound study results were published, they demonstrated this connection. This trial wasn't just about introducing LYNPARZA for prostate cancer; it contributed to the growing body of evidence that DDR mutations drive progression in prostate cancer, and demonstrated that LYNPARZA increased progression-free survival compared to investigator’s choice of enzalutamide or abiraterone. PROfound was pioneering in placing biomarkers as predictive indicators in prostate cancer research.7 | |
| **Screen 4** | |
| In PROpel, we explored the effectiveness of combining a PARP inhibitor with an androgen signaling inhibitor in the first-line treatment setting in mCRPC.8 This study demonstrated for the first time that adding LYNPARZA to abiraterone enhances outcomes for patients with the mutated DDR phenotype.8 Previously, it was known that men with mCRPC carrying germline or somatic DDR mutations, particularly *BRCA* mutations, faced rapid disease progression and poor survival.6 However, PROpel's findings completely changed this outlook by showing the significant impact of starting this combination therapy early in the treatment sequence. For men with *BRCA*-mutated mCRPC, initiating this combination upfront offered a substantial improvement in their prognosis compared to previous standard of care, abiraterone, allowing them to live longer with the disease.5  In 2023, LYNPARZA was approved in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*m mCRPC.5,9 | |
| **Screen 5** | |
| Taken together, the LYNPARZA clinical trials made a strong case for the use of precision medicine in prostate cancer, and also changed the view of the community that not all prostate cancer is the same, not all metastatic CRPC is the same, and not all locally advanced prostate cancers are the same. | |
| **Screen 6** | |
| I'd like to share a story about a man with mCRPC whom I treated with LYNPARZA and who continues on it today.  A 42-year-old man, diagnosed with mCRPC, came to see me at my Houston clinic, accompanied by his wife. They had two young children at home. Originally, he was misdiagnosed with locally advanced prostate cancer at the age of 41, he underwent androgen deprivation therapy and radiation and unfortunately progressed rapidly within six months. Subsequent chemotherapy with docetaxel also proved ineffective. He had not received germline testing at this point  With limited insurance coverage, we could only conduct CT scans which revealed bone, liver, and lymph node metastases. Despite initial setbacks, we came to secure support for germline and somatic testing and initiated treatment with abiraterone. However, his PSA continued to rise. The man’s genetic testing results came back, revealing that he had a hereditary *BRCA2* gene mutation.  At this stage, traditional treatments like hormone therapy and chemotherapy weren't working anymore. Amidst AstraZeneca's PROpel trial announcement combining abiraterone with LYNPARZA in first line for patients with mCRPC,10 I discussed the potential benefits with the patient and his wife, and we embarked on combination therapy. Although his PSA initially continued to climb for several months, by the sixth month, it dramatically dropped to below one from a peak of 150.  This patient is still on abiraterone plus LYNPARZA today, maintaining a lifestyle as a full-time truck driver, albeit managing fatigue. While his aggressive prostate cancer remains metastatic and castration-resistant, the combination of LYNPARZA plus abiraterone has significantly stabilized his disease.  This man's journey has been remarkable because the phenotype of his cancer has been changed. Despite having a very aggressive and advanced form of prostate cancer that's difficult to treat, he's experienced a significant benefit of LYNPARZA combined with abiraterone. While we can't predict the long-term, he's had a remarkable period of improvement and stability in his life. This case underscores the importance of genetic testing for men with prostate cancer, helping us choose the most effective treatments available. | |
| **Screen 7** |
| There's a pressing need to increase awareness about the importance of biomarkers and testing in prostate cancer. While some providers are beginning to grasp its significance, more can be done. This isn't a critique of medical professionals but rather a call for enhanced education, awareness, and support among oncologists and urologists alike.  We must also work toward reducing the administrative complexities and streamlining the testing process—from obtaining results and connecting patients with genetic counselors to navigating insurance coverage. Testing, whether germline or somatic, should become a seamless and systematic part of our daily practice.  Our aim should be to maximize the effectiveness of PARP inhibition in prostate cancer by identifying every patient who could potentially benefit, ensuring no one is overlooked. Currently, LYNPARZA is only approved for mCRPC patients with specific mutations.  So, in the future, part of the focus should be to target DDR events and evaluate how we maximize their impact, whether it's with LYNPARZA or any PARP inhibitor or any other evolving agent.  Another crucial focus should involve advancing precision medicine by delving into secondary DDR events. This extends beyond single gene mutations, potentially involving combinations or undiscovered factors. This pursuit urges us to intensify our efforts in identifying additional patients who could benefit from PARP therapy. |
| **Screen 8** |
| I’ve had a really positive experience treating my eligible prostate cancer patients with LYNPARZA and I’m looking forward to helping more of my patients. |
| **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.  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. In the combined data of two randomized, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received LYNPARZA, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5%, including pulmonary embolism in 1.5%.  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.  *Males*  Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.  **ADVERSE REACTIONS—HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer**  Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA for **PROfound** were: anemia (46%), fatigue (including asthenia) (41%), nausea (41%), decreased appetite (30%), diarrhea (21%), vomiting (18%), thrombocytopenia (12%), cough (11%), and dyspnea (10%).  Most common laboratory abnormalities (Grades 1-4) in ≥25% of patients who received LYNPARZA for **PROfound** were: decrease in hemoglobin (98%), decrease in lymphocytes (62%), decrease in leukocytes (53%), and decrease in absolute neutrophil count (34%).  **ADVERSE REACTIONS—Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone**  Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA/abiraterone with a difference of ≥5% compared to placebo for **PROpel** were: anemia (48%), fatigue (including asthenia) (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%).  Most common laboratory abnormalities (Grades 1-4) in ≥20% of patients who received LYNPARZA/abiraterone for **PROpel** were: decrease in hemoglobin (97%), decrease in lymphocytes (70%), decrease in platelets (23%), and decrease in absolute neutrophil count (23%).  **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:  **HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer** For the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.  ***BRCA*m Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone** In combination with abiraterone and prednisone or prednisolone (abi/pred) for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). 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)**.**  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-91715 Last Updated 8/24 | |

|  |
| --- |
|  |
| **References**   1. Mateo J, Carreira S, Sandhu S, et al. DNA-repair defects and olaparib in metastatic prostate cancer. *N Engl J Med*. 2015;373:1697-1708. 2. 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. 3. Eeles RA, Dearnaley DP, Ardern-Jones A, et al. Familial prostate cancer: the evidence and the Cancer Research Campaign/British Prostate Group (CRC/BPG) UK Familial Prostate Cancer Study. *Br J Urol*. 1997;79 Suppl 1:8-14. 4. US Food and Drug Administration (FDA). FDA approves olaparib for HRR gene-mutated metastatic castration-resistant prostate cancer. Published May 19, 2020. Accessed August 14, 2024. Available at: <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-olaparib-hrr-gene-mutated-metastatic-castration-resistant-prostate-cancer> 5. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. 6. Shah S, Rachmat R, Enyioma S, Ghose A, Revythis A, Boussios S. *BRCA* mutations in prostate cancer: assessment, implications and treatment considerations. *Int* *J Mol Sci*. 2021;22(23):12628. 7. de Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. *N Engl J Med*. 2020;382:2091-2102. 8. Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid*. 2022;1(9). 9. US Food and Drug Administration (FDA). FDA approves olaparib with abiraterone and prednisone (or prednisolone) for *BRCA*-mutated metastatic castration-resistant prostate cancer. Published May 31, 2023. Accessed August 14, 2024. Available at: <https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-olaparib-abiraterone-and-prednisone-or-prednisolone-brca-mutated-metastatic-castration> 10. AstraZeneca. LYNPARZA® (olaparib) in combination with abiraterone significantly delayed disease progression in all-comers in PROpel Phase III trial in 1st-line metastatic castration-resistant prostate cancer. Published September 24, 2021. Accessed August 14, 2024. Available at: <https://www.astrazeneca-us.com/media/press-releases/2021/lynparza-olaparib-in-combination-with-abiraterone-significantly-delayed-disease-progression-in-all-comers-in-propel-phase-iii-trial-in-1st-line-metastatic-castration-resistant-prostate-cancer-09242021.html> |