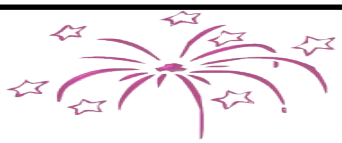
Newsletter

Prostate Cancer 101, Inc.

http://prostatecancer101.org

December, 2020

The Prostate Cancer Information and Support Group of the Mid-Hudson



Our 25th Anniversary

We all know this year of 2020 has been one for the books, but in the midst of all the chaos our prostate cancer group attained the 25th year of its first meeting in February of 1995. We had hoped to have a gathering to celebrate that milestone, but the virus had other plans in store for us all. Here's hoping we can celebrate in 2021 and that we all stay healthy.

Our first meeting came about because Ron Koster, our founder, having been diagnosed and treated for prostate cancer, saw the need for a group in the Kingston area to help men battling this disease. John Breithaupt and John Decker put their heads together with Ron and the rest is our history. Fred Bell and Gene Groelle came soon after and served well for many, many years. Our thanks to all of these good men for all they did to help hundreds during their tenure.

In 2003, after operating under the auspices of the American Cancer Society and being unable to settle a number of differences in policy, we formed our 501-c -3 organization officially known as Prostate Cancer 101 and continued serving the community. The title came from the First Tuesday meetings of years past. Sadly, Ron passed away in 2003 and John Breithaupt a couple of years after. Good people leave us too soon, no matter their age.

All, past and present, in the core group have served as volunteers. It all takes a lot of time, effort and keeping up with information plus organizing meetings. A second meeting during the month with a knowledgeable speaker takes a lot of coordinating and further time and effort. The elves don't magically do the work while we sleep.

Since 2005, Fred Bell, Gene Groelle, Arlene Ryan, Walt Sutkowski and I have done our best to continue the outreach along with the good men and women who continue to come to meetings to help others who are new to the prostate game and give them hope, encouragement and to leave with a smile knowing their education has been started. They learn that this is a journey, not a destination and can look at those who have survived well for 5, 10 and more than 20 years with a good quality of life and are still getting PSA results that are undetectable.

We wish you all good health and hope we can continue our outreach for years to come.

Diane

Dr. Catalona Featured at the AUA Conference

Dr. Catalona Argues that Biopsies are Still Necessary in Active Surveillance

Dr. Catalona participated in a plenary session at the conference entitled Crossfire: Controversies in Urology: Prostate Cancer Active Surveillance Can be Done with mpMRI and Biomarkers; Biopsies are No Longer Necessary. The debate centered on the question of whether patients with low-risk disease on active surveillance still need a biopsy every two years, or whether the use of non-invasive biomarker tests or a multiparametric MRI can determine if they can skip these standard surveillance biopsies.

The panel included a debate with Mark Emberton, M.D., Eric A. Klein, M.D. arguing in favor of biomarkers to reduce biopsies. William Catalona, M.D., and Samir Taneja, M.D. argued that biopsies are still necessary. The panel was moderated by Christopher Evans, M.D.

Current active surveillance protocols vary, but generally include routine PSA testing and surveillance biopsies. There is not a clear consensus on the use of multiparametric MRI and genomic biomarkers in the setting of active surveillance.

In his portion of the presentation Dr. Catalona argued that biomarkers are not sufficient substitutes for surveillance biopsies at this time, as surveillance biopsies are more accurate than biomarkers. He noted that an ideal substitute for surveillance biopsies would have a very high positive and negative predictive value, add independent predictive information about risk, work for all different subtypes of prostate cancer, detect alterations in tumor status over time, and yield reproductive results across institutions and populations. It would also be convenient and cost-effective.

Most of the predictive biomarkers were developed in men with high-risk disease. Although some have been shown to add prognostic information in low-risk cohorts, they were largely in company-driven, non-randomized studies. Therefore, they were subject to potential biases. Genes and pathways that are correlated with high-risk disease may be different for men with lower-risk disease. In addition, different biomarkers may operate differently in men with different racial and ethnic backgrounds.

Dr. Catalona pointed out that biopsies work for all subtypes of prostate cancer—low- and high-risk—and across all populations. Biopsies also provide predictive information regarding the aggressiveness of the disease, which is better than MRI and all biomarkers. Furthermore, Dr. Catalona pointed out statistics showing that men are less likely to comply with active surveillance biopsies over time, which can lead to a higher risk of treatment failure and developing metastatic disease.

Detailed coverage of the debate session appeared in UroToday. Visit the Media Coverage page on URF website at for a link to the article.

Prostate Cancer Update Course

Dr. Catalona and his colleagues also led their annual AUA Prostate Cancer Update course, which reviews the prostate cancer scientific literature for the past year, selecting articles and topics that have immediate or possible near- term relevance for clinical practice. Many studies covered in QUEST were included in the Prostate Cancer Update course.

Ramon Guiteras Award Recipient

As reported in the Spring 2020 QUEST, Dr. Catalona was awarded this year's Ramon Guiteras Award for outstanding leadership in demonstrating the value of PSA testing and surgical management of prostate cancer. This is the association's most prominent award, which is presented annually to an individual who is deemed to have made outstanding contributions to the art and science of urology.

Source URL: *https://drcatalona.com/quest/dr-catalona-featured-at-the-aua-conference/*

Contributions

Our thanks to those who help us continue our outreach

Charles & Jean Cunningham
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We need your donations to help continue our meetings and newsletters.

Genomic Differences May Be Key to Overcoming Prostate Cancer Disparities Among African American Men

October 21, 2020

TAMPA, Fla. — Prostate cancer is the most common type of cancer among American men after skin cancer, but the disease does not affect all races equally. African American men are nearly two times more likely to develop prostate cancer, and more often have an aggressive form of the disease that grows and spreads quickly. They are also two times more likely to die from prostate cancer compared to white men. While the health care community is aware of this disparity, little is known about why prostate cancer affects African American men differently. It has become increasingly evident that both socio-economic and biological factors may contribute to the disparity.

Moffitt Cancer Center researchers are taking a closer look at the genomic features of prostate cancer tumors among men of different races in hopes of better understanding why African Americans are more susceptible to the disease. In a new article published in Clinical Cancer Research, the research team describes the immune-oncologic differences in prostate cancer tumors of African American men and how those variations may be exploited to develop more personalized treatment approaches for this population.
"Previous studies have looked at the immune landscape of prostate cancer in white or European American men but have lacked validation among their African American counterparts," said Kosj Yamoah, M.D., Ph.D., associate member and director of cancer disparities research in the departments of Radiation Oncology and Cancer Epidemiology at Moffitt. "Our genomic analysis, the largest of its kind, revealed there are major immune pathways that are significantly elevated in African American men, which can correlate with risk of cancer recurrence and poor outcomes."

The Moffitt researchers analyzed whole transcriptome data from nearly 1,200 proctectomy samples in the Decipher Genomic Resource Information Database registry. Transcriptomic data provides a complete look at all the RNA sequences within a cell, which in turn can show when and where each gene is turned on or off. The team focused on 1,260 immune specific genes to determine differences between prostate cancer tumor cells in African American and European American men.

They discovered striking differences between the two races. Major immune pathways, including cytokine, interferon and interleukin signaling, are elevated in African American prostate tumors. These pathways can contribute to and escalate the growth and spread of cancer cells. The immune biologic signatures suggest prostate cancer tumors in African American men may be more sensitive to

radiotherapy and could have a better response to immunotherapy.

"Currently there are only two immunotherapy options for prostate cancer patients: the sipuleucel-T cell vaccine and pembrolizumab. However, not everyone responds to those therapies," said Yamoah. "Our study shows that African American men have higher overall immune content within their tumor microenvironment and higher expression of T lymphocytes. We can use that information to select a therapy that better targets their tumor and therefore improve their outcome."

The team also discovered six genes that expression levels were consistently different between African American and European American men. One gene, IFITM3, is often an indicator that a patient has a significantly higher risk of biochemical recurrence, meaning their prostate antigen score continues to rise despite surgery or radiation. In addition to cancer progression, this gene also plays an important role in metastasis.

The researchers say further study will be needed to determine if their findings can have positive implications on the treatment and management of prostate cancer in African American men.

Their work was supported by the Moffitt George Edgecomb Society, Prostate Cancer Foundation and the Department of Defense (CDMRP-PC181013).

About Moffitt Cancer Center
Moffitt is dedicated to one lifesaving mission: to contribute to the prevention and cure of cancer. The Tampa-based facility is one of only 51 National Cancer Institute-designated Comprehensive Cancer Centers, a distinction that recognizes Moffitt's scientific excellence, multidisciplinary research, and robust training and education. Moffitt is the No. 11 cancer hospital and has been nationally ranked by U.S. News & World Report since 1999. Moffitt's expert nursing staff is recognized by the American Nurses Credentialing Center with Magnet® status, its highest distinction. With more than 7,000 team members, Moffitt has an economic impact in the state of $2.4 billion. For more information, call 1-888-MOFFITT (1-888-663-3488), visit MOFFITT.org, and follow the momentum on Facebook, Twitter, Instagram and YouTube.

Source URL https://moffitt.org/newsroom/press-release-archive/2020/genomic-differences-may-be-key-to-overcoming-prostate-cancer-disparities-among-african-american-men

Merry Christmas

Darolutamide, an androgen receptor antagonist

Newswire (Published: Thursday, October 8, 2020, Received: Thursday, October 8, 2020, 6:54:09 PM CDT)
2020 OCT 08 (NewsRx) -- By a News Reporter-Staff News Editor at Clinical Trials Daily -- Fresh data on Cancer are presented in a new report. According to news reporting originating in Myrtle Beach, South Carolina, by NewsRx journalists, research stated, "Darolutamide, an androgen receptor antagonist with a distinct molecular structure, significantly prolonged metastasis-free survival versus placebo in the phase III ARAMIS study in men with nonmetastatic castration-resistant prostate cancer (nmCRPC). In this population, polypharmacy for age-related comorbidities is common and may increase drug-drug interaction (DDI) risks."
Financial supporters for this research include Bayer HealthCare, Orion Pharma.
The news reporters obtained a quote from the research from Carolina Urologic Research Center, "Preclinical/phase I study data suggest darolutamide has a low DDI potential-other than breast cancer resistance protein/organic anion transporter protein substrates (e.g., statins), no clinically relevant effect on comedications is expected. Our objective was to evaluate the effect of commonly administered drugs on the pharmacokinetics of darolutamide and the effect of comedications potentially affected by darolutamide on safety in patients with nmCRPC. Comorbidities and comedication use in the 1509 ARAMIS participants treated with darolutamide 600 mg twice daily or placebo were assessed. A population pharmacokinetic analysis evaluated whether comedications affected the pharmacokinetics of darolutamide in a subset of

388 patients. A subgroup analysis of adverse events (AEs) in statin users versus nonusers was conducted. Most participants (median age 74 years) had at least one comorbidity (98.4% in both arms) and used at least one comedication (98.7% with darolutamide vs. 98.0% with placebo); these were similar across study arms. Despite frequent use of comedications with DDI potential, no significant effects on darolutamide pharmacokinetics were identified. Comedications included lipid-modifying agents (34.5%), beta-blockers (29.7%), antithrombotics (42.8%), and systemic antibiotics (26.9%). AE incidence was similar across study arms in statin users and nonusers. Study limitations include the small sample size for sub-analyses. These analyses suggest the pharmacokinetic profile of darolutamide is not affected by a number of commonly administered drugs in patients with nmCRPC. Although pharmacokinetic data have indicated that darolutamide has the potential to interact with rosuvastatin, used to assess DDI in these studies, this finding did not seem to translate into increased AEs due to statin use in the ARAMIS trial. Clinicaltrials.gov identifier: NCT02200614. Plain Language SummaryBackground Darolutamide is a medicine used to treat men with prostate cancer that has not spread to other parts of the body (nonmetastatic). Often, these patients are taking other medicines for common age-related illnesses. Taking more than one medicine at the same time increases the chances of what is known as drug-drug interactions. Drug-drug interactions can decrease how well the medicines work or may sometimes increase side effects. To test for possible drug-drug interactions in men with prostate cancer who take darolutamide alongside other medicines. Participants Men with nonmetastatic prostate cancer who were being treated with a medicine that lowers testosterone, a chemical in the body that causes prostate cancer tumors to grow. Participants took two darolutamide 300 mg tablets, or an inactive placebo, twice a day. What Did the Researchers Measure? The researchers documented the number of medicines taken by each participant and the number of other medical conditions that they had. Tests were done to find out whether other medicines affected the way that darolutamide works in the body and whether patients taking darolutamide alongside other medicines experienced more side effects. As would be expected, based on the typical age of patients with prostate cancer, more than 90% of participants in this study used medicines other than darolutamide to manage common age-related illnesses or medical conditions. Taking medicines alongside darolutamide did not impact how darolutamide worked in the body and did not increase the number of side effects experienced by patients. Darolutamide is known to interact with rosuvastatin, a cholesterol-lowering drug. However, in this study, there was no overall increase in side effects among darolutamide-treated patients who took this type of drug compared with in those who did not."

According to the news reporters, the research concluded: "In this study of patients with nonmetastatic prostate cancer, limited drug-drug interactions were seen when taking darolutamide alongside other medicines given to these patients to manage age-related medical conditions."

This research has been peer-reviewed.

For more information on this research see: Evaluation of Clinically Relevant Drug-drug Interactions and Population Pharmacokinetics of Darolutamide In Patients With Nonmetastatic Castration-resistant Prostate Cancer: Results of Pre-specified and Post Hoc Analyses of the Phase Iii Aramis Trial. *Targeted Oncology*, 2019;14(5):527-539. *Targeted Oncology* can be contacted at: Springer, Van Godewijckstraat 30, 3311 Gz Dordrecht, Netherlands. (Springer - www.springer.com; Targeted Oncology - http://www.springerlink.com/content/1776-2596/)

Our news correspondents report that additional information may be obtained by contacting Neal Shore, Carolina Urologic Research Center, 823 82ND Pkwy, Suite B, Myrtle Beach, SC 29572, United States. Additional authors for this research include Christian Zurth, Robert Fricke, Hille Gieschen, Kristina Graudenz, Bart Ploeger, Olaf Prien, Gustavo Borghesi, Oana Petrenciuc, Iris Kuss, Frank Verholen, Mikko Koskinen, Jonathan Moss, Teuvo L. Tammela, Matthew R. Smith and Karim Fizazi.

The direct object identifier (DOI) for that additional information is: https://doi.org/10.1007/s11523-019-00674-0. This DOI is a link to an online electronic document that is either free or for purchase, and can be your direct source for a journal article and its citation.

(Our reports deliver fact-based news of research and discoveries from around the world.)

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Identifying Genomic Drivers of Prostate Cancer Progression

Wassim Abida, M.D., Ph.D., Memorial Sloan Kettering Cancer Center

Despite significant advances in therapy, metastatic

prostate cancer (PCa) remains a lethal disease. A better understanding of the biological basis of PCa is needed in order to develop new treatment approaches and improve outcomes for patients. Recently, large studies have reported DNA changes, known as genomic alterations, which occur in early and advanced PCa. Some genomic alterations drive the clinical progression of prostate cancer and may serve as clinical targets. An important group of genomic drivers are genes that are involved in DNA repair, which are altered in up to 25% of PCa.

Dr. Wassim Abida at **Memorial Sloan Kettering Cancer Center** studies tumors that harbor alterations in DNA repair genes. His approach has been to focus on molecularly defined subsets of PCa, determine their clinical behavior, and bring these findings into the clinic through exploring new therapies that may target their specific vulnerabilities.

With funding from an **FY16 Physician Research Award**, Dr. Abida and his research team studied matched primary and metastatic tumors from PCa patients to identify drivers of disease progression. Through this, they found that 3-4% of PCa tumors harbor deficiencies in DNA mismatch repair and display a feature called microsatellite instability. In some cases, microsatellite instability is identified only in the tumor obtained later in the course of disease. Approximately half of prostate cancers with microsatellite instability responded to a class of drugs called immune checkpoint inhibitors. They next explored the association of genomic alterations in several genes associated with DNA damage repair with the response to inhibitors of the PARP protein, which have been shown to effectively kill PCa cells with mutations in the DNA repair genes BRCA1 and BRCA2. Additional studies of BRCA1 and BRCA2 found that unlike other solid tumors, alterations in these genes in PCa occur evenly as inherited and somatic (tumor acquired) alterations and about 40-50% respond to PARP inhibition. Furthermore, they were able to identify positive response rates to PARP inhibition in patients with other altered DNA repair genes, such as PALB2 and FANCA.

Dr. Abida has provided insight into the genes that drive the progression of PCa and has identified drugs that can specifically target these tumors. His research on BRCA1 and BRCA2 genes, helped contribute to the clinical trial which led to the FDA approval of PARP inhibitor rucaparib for metastatic PCa in May, 2020. He hopes that his work will help to identify additional drug targets and lead to approval of more therapeutic options for men with PCa.

Response to immunotherapy (PSA and radiographic) in a patient with microsatellite instability-high (MSI-H) prostate cancer treated with immune checkpoint blockade. (Adapted from Abida et al, JAMA Oncology 2019)

Publications:

Abida W, Armenia J, Gopalan A, et al. 2017. Prospective Genomic Profiling of Prostate Cancer Across Disease States Reveals Germline and Somatic Alterations that May Affect Clinical Decision Making. JCO Precision Oncol. 1: 1-17. doi: 10.1200/PO.17.00029.

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Abida W*, Campbell D, Patnaik A, Shapiro JD, Sautois B, Vogelzang NJ, Voog EG, Bryce AH, McDermott R, Ricci F, Rowe J, Zhang J, Piulats JM, Fizazi K, Merseburger AS, Higano CS, Krieger LE, Ryan CJ, Feng FY, Simmons AD, Loehr A, Despain D, Dowson M, Green F, Watkins SP, Golsorkhi T, Chowdhury S. Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study. Clin Cancer Res. 2020 Jun 1;26 (11):2487- 2496. doi: 10.1158/1078-0432.CCR-20-0394. Epub 2020 Feb 21. PubMed PMID: 32086346.

Link:

Identifying Genomic Drivers of Prostate Cancer Progression and Drug Resistance in Tumors and Circulating DNA

Source URL: https://cdmrp.army.mil/pcrp/research_highlights/20abida_highlight.aspx

Hanukkah Sameach

Blood cell mutations confound prostate cancer liquid biopsy

Leila Gray - 206.475.9809, leilag@uw.edu contact

A set of photos shows the workflow for cell-free DNA testing, or liquid biopsy, for advanced prostate cancer. The special blood collection tubes have been spun. The yellow plasma is at the top.

Unrelated mutations, when present in the blood, can lead to false positive results in men with advanced prostate cancer who are undergoing liquid biopsies. Such tests, which look for variants in the cell-free DNA that tumors shed into the blood plasma, help determine suitable treatment options.

"You can actually measure what's happening with a patient's tumor by taking a blood draw," said Dr. Colin Pritchard, associate professor of laboratory medicine and pathology at the University of Washington School of Medicine. The testing can guide therapy for already-diagnosed cancers by finding mutations that can suggest precision medicine choices. Cell-free DNA testing offers the ease and convenience of testing a blood sample for patients with advanced cancer.

Nonetheless, Pritchard and his team point to the urgency of evaluating the performance of cell-free DNA testing in actual practice and understanding sources of potential interferences with the accuracy of test results.

Two cancer treatment medications, recently approved by the U.S. Food and Drug Administration, or FDA, in fact, are indicated for possible use if certain cell-free DNA mutations appear in the plasma of men whose prostate cancer has spread.

However, other kinds of non-cancer DNA mutations can exit blood cells and get into the plasma. Pritchard said that precision medicine scientists are learning more about a phenomenon called "clonal hematopoiesis" that can often interfere with cancer liquid biopsy findings. Mutations in some DNA repair genes – *BRCA1*, *BRCA2*, and *ATM* – are associated with male and female cancers.

"Unfortunately, these same genes are also commonly mutated as a result of clonal hematopoiesis," Pritchard said. He and his research team at UW Medicine and the Brotman Baty Institute for Precision Medicine, a partnership among UW Medicine, Seattle Children's and Fred Hutchinson Cancer Research Institute, looked at the degree to which clonal hematopoiesis was interfering with prostate cancer liquid biopsy results. They examined both the prevalence and the gene spectrum of this interference in patients undergoing cell-free DNA testing.

Their research paper appears today in the Nov. 5 edition of the medical journal, JAMA Oncology.

The researchers discovered that CHIP (clonal hematopoiesis of indeterminant potential) variants accounted for almost half of the somatic DNA repair mutations that the liquid biopsy detected. The presence of these CHIP variants became exponentially more common with advancing age of the patients.

False positives have become an even greater concern as two new classes of PARP inhibitors for prostate cancer became approved in May of 2020 – rucaparib and olaparib. People with a positive liquid biopsy test can be candidates for these drugs. A false positive for these biomarker-guided treatments can lead to misdiagnosis and to patients receiving unnecessary, unhelpful therapy.

About half the time when the plasma is thought to contain a mutation that would guide therapy with these drugs, it actually contains CHIP variants, not prostate cancer DNA variants. That means that in about half of those tested, a patient could be told that he should be administered a drug that is not indicated to treat to his cancer, Pritchard explained.

Solving this problem of potential misdiagnosis and misguid-

ed treatment is fortunately quite simple. Pritchard said that at UW Medicine and at Brotman Baty Institute for Precision Medicine, the laboratory medicine staff examine a sort of paired control: the whole blood cells where the clonal hematopoiesis is and the plasma.

"The good news is that, by looking at the blood cellular compartment, you can tell with pretty good certainty whether something is cancer or something is hematopoiesis," he said.

The research team noted that some of the limitations of their study were the small sample size (69 men), its retrospective approach, and the similarities within their patient population, including the men's prior therapies.

The lead author of the study is Dr. Kendal Jensen, a recent graduate of the molecular genetic pathology fellowship program at the UW School of Medicine.

The work was funded by a U.S. Department of Defense Award, the Brotman Baty Institute for Precision Medicine, the Pacific Northwest Prostate Cancer SPORE, the UW Medicine/Fred Hutchinson Cancer Research Institute for Prostate Cancer Research, and the National Cancer Institute at the National Institutes of Health.
The authors' potential conflicts of interests are declared within their JAMA Oncology paper.

Source URL: ***https://newsroom.uw.edu/news/blood-cell-mutations-confound-prostate-cancer-liquid-biopsy***

Reserve PARP Inhibitors for mCRPC with BRCA Mutations

For men with metastatic castration-resistant prostate cancer (mCRPC), any new therapy that offers the chance of a higher response rate or longer survival vs. with the standard of the care would be welcome. The USFDA recently approved 2 such drugs for use in men with mCRPC: the poly (ADP-ribose) polymerase (PARP) inhibitors rucaparib and olaparib.

Both were approved for treating men with advanced prostate cancer (PCa) with deleterious germline and/or somatic BRCA [genetic] mutations following androgen receptor-directed therapy and taxane-based chemotherapy. But there was difference in the wording of the indication that was approved, as noted by Michael T. Schweizer, MD, and colleagues from the Fred Hutchinson Cancer Research Center and the University of Washington in a recent commentary published in the Journal of Clinical Oncology. Olaparib received wider approval for treatment of "deleterious or suspected deleterious germline or somatic homologous recombination repair gene (HRR)-mutated mCRPC" with disease progression following therapy with either enzalutamide or abiraterone. It's the "deleterious or suspected deleterious" part of that indication that concerns these experts that this may lead to injudicious treatment of men who may best be treated by other approaches.

"Using standard-of-care PARP inhibitors in those with uncertain or little chance of benefit could mean missing a window of opportunity for more effective therapy. This may result in decreased survival and hamper clinical trial enrollment to the very studies that could define the predictive utility of individual genes," they write. Elaborating in an interview with Medscape Medical News, Schweizer said: "The issue is that olaparib has a long list of genes that would make you eligible to receive it, but it's not clear that many of these genes are good biomarkers for response to that drug. "For men who have "one of the less common HRR genes, maybe without high level of evidence that they are really predictive of response, I would still give careful consideration to

some of the other drugs that have been around for a while and that we know have a track record of working well for PCa, such as taxane-based chemother-apy,"
Schweizer commented. Mark Pomerantz, MD, a geneticist and specialist in genitourinary oncology at the Dana-Farber Cancer Institute in Boston, who was not involved in the study, stated Schweizer and colleagues are "exactly right." "The landmark studies leading to the approval of the two PARP inhibitors for PCa were critical studies," Pomerantz said in an interview. "However, they do not address, the full expanse or limitation of men who bene-fit most from these drugs.

""The editorial is a call to action for additional studies of specific mutations to see which may be sensitive to PARP inhibitors," he said. In their commentary, Schweizer and colleagues note that the approval of olaparib includes several genes that have not been shown in clinical studies to be predictive of response to PARP inhibitors. "The unintended consequence of using this permissive biomarker strategy for selecting men for PARP inhibitor treatment may be that men having an unclear chance of benefit are exposed to toxicities and delays in utilizing more effective therapies," they write. In the pivotal phase 2 TRITON2 trial, which led to rucaparib's accelerated approval for mCRPC, a preliminary analysis showed that the objective radiographic response rate among men with BRCA-mutated mCRPC and measurable disease was 44%; for slightly more than half of the men responding, the duration of response was at least six months. But as the TRITON2 investigators also reported in a separate analysis, "we found limited radiographic/PSA responses to PARP inhibition in men with alterations in ATM, CDK12, or CHEK2.

How-ever, patients with alterations in other DDR-associated genes (e.g., PALB2) may benefit from PARP inhibition. "Olaparib was approved for mCRPC on the basis of the phase 3 randomized PROfound study. The trial had two cohorts: one for men with at least one alteration in BRCA1, BRCA2, and/or ATM, and one for men with alterations in any of 12 other pre-specified genes. The investigators reported in The New England Journal of Medicine in May 2020 that the trial met its primary progression-free survival (PFS) endpoint for the BRCA/ATM mutation population, with a median of 7.4 vs. 3.6 months for control patients (men assigned to receive the physician's choice of abiraterone or enzalutamide). But as more recently reported, overall survival was significantly improved with olaparib for men in the BRCA/ATM cohort, but there was no significant survival benefit among men with other HRR gene mutations. Schweizer's editorial was published a few weeks be-fore these final PROfound results were reported at the European Society of Medical Oncology 2020 Virtual Congress. But even before these additional data were reported, they wrote the following:"On the basis of published studies, there are limited data to support use of olaparib in the absence of BRCA1/2 mutations, and without other indications of HR repair deficiency, these men would be better served by participating in clinical trials or receiving a therapy that is beneficial in unselected patients (e.g., taxane-based chemotherapy)."Pomerantz said that his center tries whenever possible to perform genetic profiles of mCRPC tumors, in

addition to assessing the patient's genetic background. "Cancer is a disease of two genomes," he explained. "We're always dealing with two genomes: the germline genome –the genome inherited from your parents –and the somatic genome, the deranged, mutated genome of the tumor. "He said some germline and somatic DNA-damage repair mutations can make prostate tumors susceptible to PARP inhibition, but further trials are needed to determine the ultimate role of PARP inhibitors in advanced PCa. "I think there's still a big knowledge gap here," Schweizer said. "We need to really focus on clinical trials to better delineate which biomarkers are really appropriate for selecting patients for these drugs.

"Medscape Medical News08 October 2020

Source URL: https://www.ustoo.org/PDFs/HotSheets/Us-TOO-HotSHEET-November-2020.pdf

HAPPY NEW YEAR!

Prolonged androgen deprivation therapy (ADT) can impair cardiorespiratory fitness

The American College of Cardiology issued the following news release:
Prolonged androgen deprivation therapy (ADT) can impair cardiorespiratory fitness and increase risk of cardiovascular death in prostate cancer patients with high risk of cardiovascular disease, according to a study in JACC: CardioOncology. The findings contribute further data supporting the need for cardiovascular disease (CVD) monitoring in patients who are living longer after successful cancer treatment.

Approximately 1 in 9 men will be diagnosed with prostate cancer during their lifetime, and it is the second leading cause of cancer death for men in the United States. Furthermore, CVD is a leading cause of death in men who have a history of prostate cancer.
ADT with radiation therapy is a standard primary treatment for prostate cancer as an alternative to surgery and is frequently used in patients with metastatic, recurrent and localized high-risk tumors. More prolonged use of ADT in certain patients with prostate cancer is increasingly employed following studies that demonstrated improved cancer outcomes compared to short-term ADT exposure. However, whether ADT is associated with increased CV mortality remains controversial. Authors of this study set out to study the association between ADT exposure and CV mortality and cardiorespiratory fitness (CRF), which is a known independent predictor of CV mortality, in patients with prostate cancer.

Researchers of this study evaluated 616 patients from a single center, retrospective cohort who underwent an exercise treadmill test for clinical indications a median of 4.8 years after their prostate cancer diagnosis. CV risk assessment was determined by a patient's demographics, indication for exercise treadmill test (such as chest pain), medical history and medication usage at the time of the treadmill test. Prostate cancer treatment regimens used before and after a patient's exercise treadmill test were looked at. Researchers also examined ADT treatment, including the therapy used and duration of ADT exposure prior to the treadmill test. ADT exposure was categorized as short-term (less than or equal to six months) versus prolonged (greater than six months). CRF was calculated from peak treadmill speed and grade achieved during a patient's exercise treadmill test.

Almost one-quarter of the patients (150) received ADT prior to their treadmill test, with 51 patients exposed to long-term ADT use. There were 504 patients (81.8%) out of the study cohort who had two or more CV risk factors, such as diabetes mellitus and hypertension. Most patients with prolonged exposure to ADT (92.2%) had two or more CV risk factors.

The rate of reduced CRF was considerably higher among patients with ADT exposure compared to those without the treatment (48.7% versus 32.6%). Prolonged ADT exposure was significantly linked to reduced CRF. Long-term ADT exposure was associated with an almost four-fold increased adjusted risk of CV mortality.

"This study highlights that patients with prostate cancer and high baseline CV risk are at increased risk of reduced CRF and CV mortality when exposed to prolonged ADT regimens," said John D. Groarke, MBBCh, MSc, MPH, cardiologist and author of this study. "While prolonged ADT certainly plays a role in the treatment of prostate cancer, these findings emphasize the need to consider CV surveillance/risk modification during and after ADT exposure."

In an accompanying editorial comment, Vivek K. Narayan, MD, MS, Assistant Professor of Medicine and genitourinary medical oncologist at the Abramson Cancer Center at the University of Pennsylvania in Philadelphia, said this study adds value to our existing clinical knowledge base, but cautions that further attention to the cardiovascular complications of varying ADT exposure durations is critical as oncologic treatment strategies evolve. "By improving our understanding of the patient- and treatment-related factors contributing to ADT-related cardiac toxicity, oncology and cardiology providers can work collaboratively to optimally employ therapy modifications and cardiovascular risk mitigation strategies," Narayan said.

Study limitations include the high baseline CV risk of the patient cohort, reflecting selection bias; and the relatively small sample size that may have limited the ability to find significant independent associations between short-term ADT use and either reduced CRF or CV mortality.

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