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US TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

JULY 2013

XOFIGO® (RADIUM-223) APPROVED FOR PROSTATE CANCER WITH BONE METS

A novel radiopharmaceutical agent has been approved by the US Food and Drug Administration (FDA) for use in the treatment of prostate cancer.

The product, radium-223 dichloride (formerly known as alpharadin), will be marketed as Xofigo by Algeta and Bayer for use in men with symptomatic metastatic castration-resistant prostate cancer that has spread to the bone but not to other organs. It is intended for men whose cancer has spread after medical or surgical therapy to lower testosterone, according to the FDA.

The FDA reviewed the product under its priority program, which provides for an expedited review of drugs that appear to provide safe and effective therapy when no satisfactory alternative therapy exists or offer significant improvement over products on the market. It was approved more than 3 months ahead of schedule.

Radium-223 dichloride "binds with minerals in the bone to deliver radiation directly to bone tumors, limiting the damage to the surrounding normal tissues," said Richard Pazdur, MD, director of the Office of Hematology and Oncology Products at the FDA Center for Drug Evaluation and Research.

The product, administered once a month

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PROSTATE CANCER WITH FAULTY BRCA2 GENE SPREADS MORE QUICKLY

A new study finds that prostate cancer spreads more quickly and is more likely to be fatal in men who inherit a faulty BRCA2 gene. Researchers say such patients should be treated straight away with radical prostatectomy (RP) or radiotherapy (RT) rather than monitored.

Research has already established that men who inherit a faulty BRCA2 gene have a higher risk of developing prostate cancer, but this, the largest study of its kind, is the first to show that the faulty gene also means carriers are more likely to experience more rapid spread of the disease and poorer survival.

The study, reported in the *Journal of Clinical Oncology*, poses a potential challenge to health systems like the UK's NHS where carriers of the faulty gene are offered the same prostate cancer treatment options as non-carriers.

Senior author Ros Eeles, Professor of Oncogenetics at The Institute of Cancer Research (ICR) in the UK, says in a statement that the study clearly shows prostate cancers linked to inheritance of the faulty BRCA2 cancer gene are more deadly than other types. It is not easy to tell at the diagnosis stage whether a man with prostate cancer has the more aggressive type, so while treatment options in the early stage include RP and RT, the tendency is to place many patients

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HOW LIKELY IS PROSTATE CANCER TO KILL?

Older, sicker men with non-aggressive prostate cancer had a significantly greater risk of dying of causes other than prostate cancer, a risk that increased with age at diagnosis and comorbidities, data from a large cohort study affirmed. During 14 years of follow-up, other-cause mortality ranged from 24% for men with no comorbid conditions at diagnosis to 57% for men with three or more comorbidities. For men who were 65 at diagnosis, the mortality hazard versus no baseline comorbidities increased with the number of comorbid conditions from 1.2 to 2.6.

The impact of comorbidity burden on other-cause mortality increased with age ranges from younger than 60 to older than 75 at diagnosis but was greater in older ages, as reported online in Annals of Internal Medicine. Yet use of aggressive therapy predominated, regardless of comorbidity burden, including for 60% of men with three or more comorbidities, David F. Penson, MD, of Vanderbilt University in Nashville, Tenn., and co-authors concluded.

Although estimated life expectancy should figure prominently in treatment decisions, available data suggest physician skill in this area is lacking, often leading to inappropriate treatment. Several factors may contribute to inappro-

(Continued on page 4)

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REPURPOSING ITRACONAZOLE AS A TREATMENT FOR ADVANCED PROSTATE CANCER: A NONCOMPARATIVE RANDOMIZED PHASE II TRIAL IN MEN WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Antonarakis ES, Heath EI, Smith DC, et al

The Oncologist 18: 163–173, 2013

Background: The antifungal drug itraconazole inhibits angiogenesis and Hedgehog signaling and delays tumor growth in murine prostate cancer xenograft models. We conducted a noncomparative, randomized, phase II study evaluating the antitumor efficacy of two doses of oral itraconazole in men with metastatic prostate cancer.

Patients and Methods: We randomly assigned 46 men with chemotherapy-naïve metastatic castration-resistant prostate cancer (CRPC) to receive low-dose (200 mg/day) or high-dose (600 mg/day) itraconazole until disease progression or unacceptable toxicity. The primary endpoint was the prostate-specific antigen (PSA) progression-free survival (PPFS) rate at 24 weeks; a 45% success rate in either arm was prespecified as constituting clinical significance. Secondary endpoints included the progression-free survival (PFS) rate and PSA response rate (Prostate Cancer Working Group criteria). Exploratory outcomes included circulating tumor cell (CTC) enumeration, serum androgen measurements, as well as pharmacokinetic and pharmacodynamic analyses.

Results: The high-dose arm enrolled to completion (n =29), but the low-dose arm closed early (n=17) because of a prespecified futility rule. The PPFS rates at 24 weeks were 11.8% in the low-dose arm and 48.0% in the high-dose arm. The median PFS times were 11.9 weeks and 35.9 weeks, respectively. PSA response rates were 0% and 14.3%, respectively. In addition, itraconazole had favorable effects on CTC counts, and it suppressed Hedgehog signaling in skin biopsy samples. Itraconazole did not reduce serum testosterone or dehydroepiandrostenedione sulfate levels. Common toxicities included fatigue, nausea, anorexia, rash, and a syndrome of hypokalemia, hypertension, and edema.

Conclusion: High-dose itraconazole (600 mg/day) has modest antitumor activity in men with metastatic CRPC that is not mediated by testosterone suppression.

Implications for Practice: This study investigated two doses of an oral antifungal drug, itraconazole, to determine whether it has antitumor activity in men with metastatic castration-resistant prostate cancer. The results showed that while low-dose itraconazole (200 mg/day) did not have significant antitumor effects, high-dose itraconazole (600 mg/day) did have some activity in these patients. Moreover, the effects of itraconazole appeared to be associated with inhibition of Hedgehog signaling in skin biopsies, and were not caused by testosterone suppression. Therefore, itraconazole may be a non-hormonal treatment option for patients with castration-resistant prostate cancer who wish to prevent or delay the use of chemotherapy. While itraconazole is not as effective as other novel agents for advanced prostate cancer (e.g., abiraterone, enzalutamide), it is a generic drug that may be considered if the cost of these newer agents is prohibitive, or in parts of the world where abiraterone and enzalutamide may not be available.

GENE TEST PREDICTS PROSTATE CANCER OUTCOME BUT THEN WHAT?

A commercially available prostate cancer test (Prolaris, Myriad Genetics) is highly predictive of biochemical recurrence and death, but experts say it is not clear how this affects clinical decision-making. A discussion followed the presentation of 5 retrospective studies at the 2013 American Society of Clinical Oncology (ASCO) annual meeting.

The Prolaris test, launched in 2010, has recently seen competition from several newer prostate cancer tests, including OncoType DX (Genomics Health), which was launched last month. "With the demand for individualized treatment, there's a huge market for this," said Scott Tomlins, MD, PhD, assistant professor of pathology and urology at the University of Michigan , who served as discussant for the study.

(Continued on page 3)

PREDICTIVE GENE TEST

(Continued from page 2)

However, Dr. Tomlins, who is not involved with the test, stated that "the challenge for us looking at the presented data is that we haven't seen how it affects clinical decision-making."

"There are many potential uses for this test that clinicians need to get comfortable with," said Jack Cuzick, PhD, from Queen Mary College University of London, United Kingdom, after he presented the company's data. "I believe the main use will be to help in deciding which patients should be managed with active surveillance. In addition, in those who've had a radical prostatectomy, it will aid in deciding whether to use adjuvant chemo or hormones," Dr. Cuzick noted.

However, Dr. Tomlins pointed out that, for the majority of patients, standard pathology parameters can be used to arrive at the same prognosis prediction as the test. "So we're not really moving men across large categories [with the test]," he told Medscape Medical News.

The Prolaris test, which measures the activity of cell cycle progression (CCP) genes in prostate cancer biopsy samples, was evaluated for its ability to predict either death from prostate cancer or biochemical recurrence in 5 company-sponsored studies, Dr. Cuzick reported. In the studies, formalin-fixed prostate tissue from men with prostate adenocarcinoma was analyzed. A CCP score was calculated by measuring the average RNA expression of 31 CCP genes normalized by the average expression of 15 housekeeping genes as quantitated with reverse-transcriptase polymerase chain reaction., explained Dr. Cuzick.

A hazard ratio (HR) was then calculated for every unit change in CCP score for the risk for either biochemical recurrence or death from prostate cancer. "A unit change is essentially a doubling in the expression of these cell cycle genes," he explained.

On multivariate analysis – variables ranged in the different studies but all included Gleason score and PSA level – the predictive value of the CCP score for either outcome was "dominant" (HR, 2.6; $P < 10^{-10}$), said Dr. Cuzick. "PSA retained a fair amount of its predictive

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DOC MOYAD'S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS "NO BOGUS SCIENCE" COLUMN

"Vitamin C dietary supplements in high doses have not been found to impact prostate cancer and could increase the risk of a kidney stone-OUCH!"

Mark A. Moyad, MD, MPH, Univ. of Michigan Medical Center, Dept. of Urology

Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

Bottom Line: A large study of men followed for over a decade suggested a higher risk of kidney stones for men ingesting high doses of vitamin C supplements.[1] This information along with the finding in a large randomized trial of daily vitamin C versus placebo showing no reduced risk of prostate cancer suggest men (and probably women) should be carefully about continuously taking high-dose (especially 1000 mg or more daily) vitamin C supplements.

A recent population-based, prospective study of over 23,000 men aged 45–79 compared users vs. non-users of vitamin C supplements. A total of 11-year of follow-up identified 436 first time cases of kidney stones, and vitamin C was correlated with a dose-dependent 2-fold significant increased risk! The authors believe the majority of men in this study ingested 1000 mg per day. A commentary following the article estimated 1 kidney stone could occur per 680 high-dose vitamin C users per year if this data is accurate. It has been known since I was just a little baby boy that vitamin C supplements at dosages of 1000 mg or more increases significantly the amount of a compound called "oxalate" in the urine and very high levels of oxalate could theoretically bind to calcium in the urinary tract and BAM! A kidney stone could theoretically occur.

So, why is this recent news a big deal? It is because although researchers disagreed on whether or not this increase in oxalate was significant enough to really and truly cause a kidney stone over time. It appears based on this latest information and some past studies the answer has gone from "maybe" to "probably." Recently vitamin C supplements were also NOT found to reduce the risk of prostate cancer from the largest study ever done to address this issue. So, what to do? If you like to take vitamin C for a few days to prevent a cold I am not as worried. If vitamin C is in the pill you take for vision health I am also not as worried (usually a low dose). And, it is possible that taking non-acidic vitamin C (buffered vitamin C) does not have the same kidney risk as plain vitamin C. Regardless, when I get the feeling of a cold coming at me (like when a little kid decides to hurl a hurricane-like sneeze at me and my big nose for no apparent reason the moment I bend down to say ("Hi") I use vitamin C or buffered vitamin C for a few days but otherwise I do not take it day in and day out. Intravenous vitamin C is being studied in cancer patients to determine if it impacts prostate cancer but the verdict is not out on this.

Regardless, this just means you should always weigh the benefit versus the risk of your pills, and for some folks for example that may have already had a kidney stone the risk could outweigh the benefit. And, if you have never had a kidney stone and you are wondering what it feels like….well think about some of the worst pain you could ever imagine, along with the use of a lot of screaming 4 letter words (like "Ouch!" or "Darn!" or "Dang!" or "Heck!") while begging someone to take you immediately to urgent care or the emergency room ASAP because it feels like you are giving birth (it is not like men know what it is like to give birth but we are always looking for ways to relate to that situation-because we are men). Now you have a picture of what it is like to have a really bad kidney stone! OUCH! DARN! DANG! HECK!

Reference

1. Thomas LD, Elinder CG, Tiselius HG, et al. JAMA Intern Med 173: 386-388, 2013

RADIUM-223 APPROVED

(Continued from page 1)

by intravenous injection, contains the isotope radium-223, which is taken up by osteoblasts and then emits alpha radiation. This causes double-strand DNA breaks that are lethal to the prostate cancer cell at the site of increased bone turnover induced by the cancer.

In a Medscape video commentary, Johann de Bono, MBChB, PhD, MSc, from the Royal Marsden NHS Foundation Trust in Sutton, United Kingdom, explained that radium-223 dichloride has minimal myelosuppression, is very well tolerated, and shows an impressive overall survival benefit.

The survival data come from the pivotal phase 3 ALSYMPCA trial, which involved 809 prostate cancer patients who were resistant to hormone treatment and had developed 2 or more bone metastases. All of the participants received standard treatment, but the men who also received radium-223 lived significantly longer. An interim analysis revealed a median overall survival of 14.0 months, compared with 11.2 months (hazard ratio, 0.695; P=0.00185), and the trial was stopped because of clear evidence of the drug's benefit.

An exploratory updated analysis confirmed the product's ability to extend overall survival, according to the FDA.

The most common adverse effects of radium-233 seen during clinical trials were nausea, diarrhea, vomiting, and swelling of the leg, ankle, or foot.

Radium-223 dichloride is highly targeted for bone metastases, so it is possible that it could be used in many different cancers that have spread to the bone, regardless of primary site, said lead investigator Chris Parker, MD, consultant clinical oncologist at the Royal Marsden Hospital in London, United Kingdom. Prostate cancer patients were studied in the first instance because this cancer has a high tendency to metastasize to the bone, Dr. Parker explained. About 90% of patients with advanced prostate cancer will develop bone metastases and, in many cases, there will not be any detectable metastases elsewhere in the body, he said.

Medscape, 15 May 2013

HOW LIKELY IS PROSTATE CANCER TO KILL? *(Continued from Page 1)*

priate treatment, the authors continued. Available data on other-cause mortality associated with comorbidity came from single-institution case series or involved only one treatment option.

Penson and colleagues queried the Prostate Cancer Outcomes Study (PCOS) database, a population-based cohort study of men with newly diagnosed prostate cancer. The cohort was derived from a subset of patients in the NCI Surveillance, Epidemiology, and End Results (SEER) program.

The PCOS cohort included men with nonmetastatic prostate cancer diagnosed from Oct. 1, 1994 through Oct. 31, 1995. All participants completed a baseline survey within 6 months of diagnosis, and each patient's medical record was reviewed 1 and 5 years after diagnosis. The PCOS cohort was stratified by clinicopathologic characteristics using D'Amico criteria: Gleason score, and PSA and clinical stage at diagnosis.

The analysis comprised 3,183 men: 1,221 with no comorbidities, 1,020 with one, 523 with 2, and 419 with 3 or more. In general, aggressive treatment was employed less often in men with a greater comorbidity burden. Even so, investigators found that 256 of 419 (61%) of men with 3 or more comorbid conditions received aggressive therapy.

During the 14 year followup, estimated non-prostate cancer mortality was 24% among men with zero comorbidities at baseline, 33% for men with one comorbidity, 46% for 2 comorbidities, and 57% for 3 or more comorbidities. After adjustment for age, race, SEER geographic area, tumor risk, and treatment, the hazard ratios for other-cause mortality vs. men with no comorbidities were 1.2, 1.7, and 2.4 for men with one, 2, or 3 or more comorbidities.

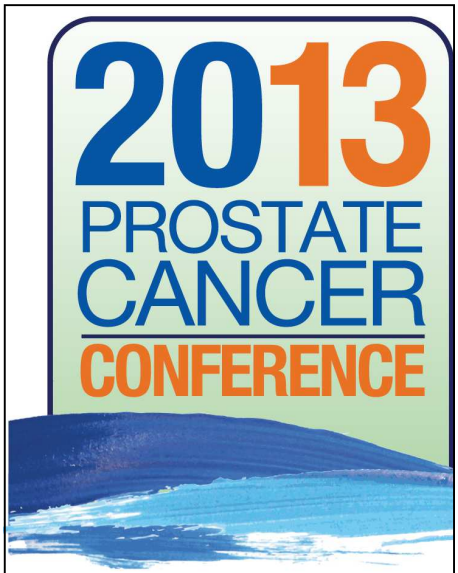
Advancing age added to the other-cause mortality hazard conferred by comorbidity burden. For example, men with three or more comorbidities had an estimated 10-year other-cause mortality of 26% if they were younger than 60 at diagnosis. The mortality increased to 40% for men 61 to 74 and to 71% for men 75 or older.

The investigators found that 29% of men with zero comorbidities received nonaggressive treatment (ADT or watchful waiting), as did 33% of men with one comorbidity, 18% of men with 2 comorbidities, and 20% of men with 3 or more comorbid conditions.

The author of an accompanying editorial emphasized the complexities of integrating comorbidity and life expectancy into clinical decision making. "Patients should be aware that the cumulative incidence of prostate cancer mortality and other-cause mortality in men aged 70 years or older is similar for those with three or more comorbid conditions and those at high risk for tumor aggressiveness," Lazzaro Repetto, MD, of Sanremo Hospital in Italy and colleagues wrote.

"Furthermore, the study showed that in the overall population, patients with zero or one comorbid condition who were receiving nonaggressive treatment had a statistically significantly higher risk for prostate cancer death than did those treated aggressively." The data generated by Penson and colleagues make a good case for using age, tumor grade, and comorbidity to identify men who are unlikely to benefit from aggressive therapy," the editorialist added.

MedPage Today, 21 May 2013



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PROSTATE CANCER WITH FAULTY BRCA2 GENE SPREADS MORE QUICKLY *(Continued from page 1)*

under active surveillance to see how the disease develops.

Normal BRCA1 and BRCA2 genes help to suppress tumors and protect DNA. Mutations of these genes (spelling mistakes in their DNA code) hamper them carrying out these potentially life-saving functions. Mutations in BRCA1 and BRCA2 genes were originally spotted in women with breast cancer. We now know that these faulty genes not only raise the risk of developing breast cancer, but also of ovarian and prostate cancers.

1.2% of men with prostate cancer carry the BRCA2 mutation (BCRA2m) and 0.44% carry the BRCA1m. BRCA2m carriers have an 8.6 times higher risk of developing prostate cancer compared to a non-carrier. If a man carries the BRCA1m, he has a 3.4-fold higher risk.

For their study, Eeles and colleagues examined the medical records of over 2,000 prostate cancer patients. 61 of the patients carried mutations in BRCA2, 18 had mutations in BRCA1, and 1,940 had neither BRCA1 nor BRCA2 mutations.

They found that compared to non-carriers, men carrying the faulty genes were more likely to be diagnosed with advanced prostate cancers (37% vs. 28%), or with cancer that had already spread (18% vs. 9%). Also, for those patients whose diagnosis showed the cancer had not yet spread, during the five years after diagnosis, it started to spread in 23% of the mutation carriers compared with only 7% of the non-carriers.

Carriers of faulty BRCA2 genes were also significantly less likely to survive. While non-carriers lived an average of 12.9 years after diagnosis, BRCA2 carriers only survived an average of 6.5 years. The analysis for BRCA1 carriers showed while those patients had a shorter survival average (living 10.5 years after diagnosis) than non-carriers, this was not statistically significant, say the authors. The study concludes that "BRCA mutations are associated with poor survival outcomes and this should be considered for tailoring clinical management of these patients."

"It must make sense to start offering affected men immediate surgery or radiotherapy, even for early-stage cases that would otherwise be classified as low-risk," says Eeles, who is also Honorary Consultant in Clinical Oncology at The Royal Marsden in London. However, she also cautions that "We won't be able to tell for certain that earlier treatment can benefit men with inherited cancer genes until we've tested it in a clinical trial, but the hope is that our study will ultimately save lives by directing treatment at those who most need it."

It is not routine in the UK for all men diagnosed with prostate cancer to be offered a test for these faulty genes, but it may be offered more routinely as the test becomes cheaper. The researchers would like to see BRCA2 offered to all men under age 65 who develop disease.

Reference:

Castro E, Goh C, Olmos, D, et al. J Clin Oncol, 8 April 2013 [Epub]

Medical News Today, 10 April 2013

AUA ISSUES NEW GUIDELINES ON PSA SCREENING

New guidelines on prostate cancer screening, issued by the American Urological Association (AUA), support routine use of the PSA test in healthy men, but only for a specified age group, and only after discussion between a man and his physician. Specifically, the new guidelines state that men aged 55–69 years **who are at average risk** and asymptomatic can consider PSA screening. They should speak to their physician about the benefits and harms of testing to determine the best course of action.

This is a major difference from the US Preventative Services Task Force (USPSTF) guidelines issued last year recommending against routine use of the PSA test, concluding that any benefit is outweighed by harm. "We recognize that there are some men who could benefit from screening," said Ballentine Carter, MD, professor of urology and oncology at the Johns Hopkins School of Medicine and director of adult urology at the Brady Urological Institute in Baltimore, MD, who chaired the guideline committee.

"In the age group that we identified – 55 to 69 – there is evidence that there may be more benefit than harm," Dr. Carter said. But only in that age range, he emphasized; for other age groups, the panel could not recommend routine screening.

AUA guidelines also differ in that they reviewed evidence from an individual rather than a public health perspective, Dr. Carter explained. "The point of the guidelines is to help urologists inform an average-risk man who is asymptomatic."

AUA guidelines are "not a response" to the USPSTF or any other guidelines, he noted. The process for drawing up the AUA guidelines began 2 years ago. It was based on a rigorous systematic literature review by a multidisciplinary team, involving medical and radiation oncologists, general internists, epidemiologists, and urologists, he said.

The AUA guidelines state that PSA screening is not recommended for men younger than 40 years, age 40–54 years at average risk, age 70 years and older, and those with a life expectancy of less than 10 –15 years. It is recommended that men in these age groups who are at a higher risk for prostate cancer (e.g., due to family history or by virtue of their race) speak to their physician about the benefits and risks of PSA testing.

"There is less evidence here of benefit," Dr. Carter said, but these men who are at higher risk need to know the benefits and harms of screening, he added.

The new AUA guidelines supersede and replace the prostate cancer detection section in the 2009 AUA Best Practices, which recommended that screening start at age 40. That document was based on opinion and clinical evidence, whereas these new clinical guidelines are based on evidence from a systematic literature review, Dr. Carter explained.

In the new guidelines, "our statements do not go beyond the evidence," he said. The quality of the evidence for benefit was moderate (grade B), whereas the quality of the evidence for harm was high (grade A)," he noted. "The panel felt that it would not be reasonable to go beyond the evidence and make statements based on opinion."

Medscape Medical News, 8 May 2013

SULFORAPHANE IN PROSTATE CANCER FOUND WORTHY OF FURTHER INVESTIGATION

Treatment with 200 µmol per day of sulforaphane for 20 weeks was "feasible, safe," and inhibited histone deacetylase (HDAC) function in a single-arm study of 20 patients who had non-castrate biochemical recurrence (BCR) of prostate cancer despite surgery or radiation (Abstract 5017). Findings were reported by Joshi J. Alumkal, MD, of the Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon. Sulforaphane is a constituent of cruciferous vegetables such as broccoli, which are "strongly associated with lower prostate cancer risk," explained Alumkal. In preclinical studies sulforaphane has exhibited antineoplastic effects in multiple tumor models.

"Our own preclinical work demonstrated that sulforaphane inhibits HDAC function and suppresses androgen receptor signaling in prostate cancer cells," he continued. "A variety of mechanisms have been implicated for these effects. The antitumor efficacy and safety of sulforaphane in men with prostate cancer, however, was unknown."

The primary endpoint was PSA response rate (>50% decline in PSA). Other efficacy endpoints included maximal PSA decline and PSA doubling time changes using a mixed effects model. Genotyping for the GSTM1 gene, which contributes to sulforaphane metabolism; sulforaphane pharmacokinetics, and pharmacodynamic measures of HDAC inhibition in peripheral blood mononuclear cells were also performed.

Of 20 men enrolled, 16 (80%) completed the preplanned 20 week treatment. One man experienced a PSA decline >50%. Thirty-five percent of men had lesser PSA declines (3% to 20%), and 15% had a final PSA below baseline.

"There was a significant reduction in PSA doubling time (6 months pre-study vs 9.4 months on-study, P = 0.013)," said Alumkal. "Of note, testosterone levels remained non-castrate in all subjects." Pharmacodynamic assays showed increased histone acetylation with sulforaphane treatment. "Finally, no grade 3 adverse events were seen, and only one patient discontinued study treatment

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JUNE IS MEN'S HEALTH MONTH

Get Active – Stay Active

With Father's Day, Men's Health Week, and Men's Health Month in June, it's a perfect time to focus on the many different ways that we can be active participants promoting men's health and wellness. We all know the important role that diet and exercise play, but there are other ways that we can be active that are as important as taking care of our bodies to fight off disease and illness.

Being an active participant in our community by raising awareness about disease, educating about healthy living, and yes – advocating for the cause of men's health is rewarding and will save lives.

Prostate cancer will take the lives of more than 29,000 men in 2013. If detected early (before the cancer spreads beyond the tissue and organs around the prostate), a man has over a 99 percent chance of surviving. However, once the cancer spreads to other parts of the body, that chance of survival drops to only 28 percent. Why then is the government task force charged for making decisions about preventing chronic illness and disease recommending that men NOT be tested for prostate cancer?

Why is this so important? The recommendations by the US Preventive Services Task Force (USPSTF) make up the list of preventive services (tests and screenings) that insurance companies under the Affordable Care Act must cover. Because prostate cancer testing is not recommended by the USPSTF, insurance companies and Medicare will not be required to cover the cost of testing for prostate cancer using the PSA test. The PSA test is currently the only way a man in conjunction with his doctor can decide what steps need to be taken to fight prostate cancer.

What action can you take against the task force? You can volunteer to educate men at health fairs or other appropriate venues about the importance of early detection and the PSA test, write a letter to the editor at your local or community newspaper, or write your Representative and Senators to ask that they stand up this Father's Day to urge men to educate themselves about prostate cancer and get tested.

So please do take a 30 minute walk, eat more broccoli, play tennis and be more physically active – a healthy body and immune system will fight off cancer, but also consider joining the cause to make an even broader impact now and in the future. Policies being set by others are changing how we as a society can access healthcare, and now is the time to stand up and be heard.

For more information, Contact Kevin at ZERO (kevin@zerocancer.org) and learn how you can get more involved.

ENZALUTAMIDE MONOTHERAPY ACHIEVES 'HIGH RESPONSE RATE'

Monotherapy with enzalutamide (Xtandi®) achieved a "high PSA response rate and marked PSA decline" in men with hormone-naïve prostate cancer (HNPC) after 6 months in a single-arm, multicenter phase II study, reported Matthew Raymond Smith, MD, PhD, of the Massachusetts General Hospital (MGH) Cancer Center in Boston, MA. Efficacy was similar to castration, but in contrast with castration, bone mineral density (BMD) remained stable and there was no major impact on metabolic variables, including fat body mass, lipid, and glycemic profiles by enzalutamide over the 6-month study.

Xtandi monotherapy was assessed in 67 men with hormone-naïve prostate cancer (HNPC) and noncastrate testosterone levels. Median age of men was 73 years (range, 48-86). Thirty-nine percent of men had metastases, 36% had prior prostatectomy, and 24% had prior radiotherapy. Men with any stage HNPC requiring androgen deprivation therapy (ADT) received Xtandi at the approved dose of 160 mg daily for 25 weeks. The primary endpoint was PSA response (≥80% post-treatment decline at week 25).

At week 25, PSA response was 93% (95% confidence interval [CI], 86–99%); and median PSA decrease was 99.6%. Declines were similar for men with and without metastases. Of 16 men evaluable for objective response at week 25, 3 had a complete and 5 achieved a partial response, for a 50% overall response rate.

(Continued on page 8)

DOCTOR CHODAK'S BOTTOM LINE *(Ref Key: article #, page #, column #)*

Gerald Chodak, MD www.prostatevideos.com

Editors' note: Us TOO has invited certain physicians and others to provide information and commentary for the *HotSheet* to enrich its content to empower the reader. This column contains the opinions and thoughts of its author and is not necessarily those of Us TOO International.

a1p1c1 This month's *HotSheet* contains yet another new treatment that has been approved for men castrate resistant prostate cancer (CRPC) with symptomatic metastatic disease to the bones and who have not received chemotherapy. The new agent called Radium-223 (Xofigo®) is injected monthly for up to 6 months. Unlike other bone targeted radiation treatments that prolong the time until a skeletal related event, Xofigo showed a 2.8-month increase in overall survival. The incidence of serious side effects was very low. This becomes the third treatment for CRPC prior to docetaxel chemotherapy. Others are Provenge® (Sipuleucel-T) and Zytiga® (abiraterone). For now, the decision about which treatment to recommend should be easy. It will depend on patient's symptoms; asymptomatic men should be offered Provenge or Zytiga and Xofigo offered to symptomatic men.

The Bottom Line: Xofigo is another important advance for symptomatic men with bone metastases due to CRPC.

a2p1c2 Another test offering prognostic information measures mutations in the BRCA1 and BRCA-genes. The study by Eeles et al found that men with these alterations have a poorer prognosis, a higher chance of Stage T3/T4 disease, and a higher chance of Gleason 8 disease. Fortunately, these mutations occur in only 3% of newly diagnosed cancers. This finding raises a number of questions. First, with such a low likelihood of these mutations, should all newly diagnosed cases be tested, which would be very expensive? Another question I was unable to answer is how often men with apparently low risk disease (PSA <10 ng/mL and Gleason score <7) have these mutations. If that is a very rare event and the test invariably is abnormal when other indicators of life-threatening disease such as a high PSA, Gleason score or tumor stage, it would make little sense to test those men because they will almost always be treated aggressively regardless of the test result.

The Bottom Line: BRCA mutations, particularly BRCA2 are associated with more aggressive prostate cancer but fortunately they are very uncommon. More information is needed to determine who should be tested before the test is routinely recommended.

a3p1c3 The study by Penson et al provides further evidence for overtreatment of many men who are unlikely to be harmed by their disease. They evaluated the outcomes of men with varying levels of co-morbid disease and observed that death from other causes increased as the number of comorbid illnesses increased and was far greater than the risk of dying from prostate cancer. Unfortunately a high percentage of these men were treated aggressively for their cancer. This presents a real challenge for physicians counseling men about prostate cancer. Unless comorbidity is incorporated into the decision process, too many men are likely to get a treatment that has little, or no chance of helping them.

The Bottom Line: Overall health and the presence of co-morbid illnesses are important but underused factors in determining whether a man should undergo aggressive therapy. Tools are needed to improve our ability to convey this information to patients when they are informed about their options.

a5p2c3 Improving the ability to determine a man's risk from his prostate cancer is the focus of two new commercially available gene tests, Prolaris and the Genomic Prostate Score or GPS. Both measure the presence of about 17 genes in biopsy samples. The tests are intended to assess tumor aggressiveness and help a man decide if his tumor can be treated with active surveillance (AS). More results are likely to be forthcoming but presently it is unclear how helpful either test may be. The GPS test only provides information about pathological findings of men who undergo surgery. It does not provide any information yet about what happens to the men who have chosen therapy based on the test results. To be truly helpful, more data is needed. Some of it must show how often men treated by AS due to the test develop progressive disease. Also needed are how often men thought to have aggressive disease based on pathologic risk and then undergo AS do poorly. The Prolaris test also needs more data to be able to assess how many men are helped by this costly test.

The Bottom Line: Progress is being made in helping men decide who should choose AS but presently, the data is not sufficient to recommend these tests.

a7p5c1 Lastly, there is new guidance from the AUA about screening for prostate cancer. Their position has changed significantly and now is more in line with other organizations. Their recommendations include:

- They do not recommend routine screening of men under age 40, over age 70 or those with a life expectancy less than 15 years.
- They do not recommend routine screening in men 40–54 if they have average risk.
- For men between 55-69, they recommend a shared decision after informing men of the pros and cons of screening and treatment.
- For high-risk men, they recommend that men be informed and then they can make a shared decision.

This is a marked improvement in their message and more closely represents the currently known information. Undoubtedly, many men are going to argue this message is incorrect. However, it truly reflects the best information available, and while that might change with longer follow-up in certain studies, for now it most closely reflects the facts as we know them. However, many men are likely to be confused when they try to determine the difference between "recommending against" screening compared to "not recommending screening."

The Bottom Line: AUA has greatly modified their position on routine prostate cancer screening that more closely reflects currently available information . The net impact is some men will be worse off but many more men will be better off by avoiding the harms of the diagnosis and treatment when they have such a small chance of benefitting.

CCP SCORE

(Continued from page 3)

value, but the predictive value of the Gleason score 'diminished' against the CCP score." he said.

"Overall, the CCP score was a highly significant predictor of outcome in all of the studies," said Dr. Cuzick. "It was the dominant predictor in all but 1 of the studies in the multivariate analyses, and typically a unit change in the score was associated with a remarkably similar 2- to 3-fold increase in either death from prostate cancer or biochemical recurrence, indicating that this is a very robust predictor, and seems to work in a whole range of circumstances."

"Exactly how you use it is still something that's being developed," Cuzick acknowledged, "but particularly for those with low-grade (Gleason score ≤6) low-risk cancers, you can get a clear indication of which patients are truly low risk and which need more aggressive therapy."

Presented at the 2013 Annual meeting of ASCO, abstract 5005

Medscape Medical News, 5 June 2013

SULFORAPHANE

(Continued from page 6)

for toxicity (grade 1 GI discomfort)."

These findings, combined with the preliminary observation of PSA modulation possibly indicative of biologic activity, "provides the basis for dose-escalation studies of sulforaphane in men with prostate cancer," concluded Dr. Alumkal.

Additional work is required before dose-escalation studies are undertaken, Alumkal explained. "The compound we used is limited by not having several species toxicity, which will be necessary prior to dose escalation….Groups are working on developing a synthetic version with druglike properties.

Silke Gillessen, MD, of Kantonsspital St. Gallen, Switzerland, commented, "A strength of the study is that it addresses the new field of epigenetic therapy and patients do like natural therapies." While clinical effects of sulforaphane were modest at the dose studied, she stated, "Even a slowing down of the disease in this setting can be helpful for patient and physician satisfaction, especially when the treatment is well tolerated."

Cancer Network, 3 June 2013

ENZALUTAMIDE

(Continued from page 6)

The most common treatment-emergent adverse events (AEs) were grade 1 and included gynecomastia (36%), fatigue (34%), nipple pain (19%), and hot flush (18%). Five men had serious AEs (none of which were deemed drug related).

"In contrast with castration, enzalutamide monotherapy was associated with stable BMD and only modest changes in serum cholesterol and triglycerides," noted Smith. "These results compare favorably with ADT. We believe the results of this phase II study support the further evaluation of enzalutamide as monotherapy in prostate cancer."

Michael A. Carducci, MD, of the Johns Hopkins Kimmel Cancer Center in Baltimore, observed that the study design "limits discussion of the durability of PSA declines and clinical benefits." He also expressed concern about the "significant frequency of side effects," albeit mostly grades 1 and 2.

Presented at the 2013 Annual ASCO meeting, abstract 5001

Cancer Network, 4 June 2013

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