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### **RADIOTHERAPY PLUS ADT BENEFIT CONFIRMED IN HIGH-RISK PROSTATE CANCER**

Radiotherapy (RT) should be part of the initial treatment for men with high-risk prostate cancer who are managed with long-term androgen-deprivation therapy (ADT), according to a major Scandinavian randomized trial presented at the 2014 Genitourinary Cancers Symposium (GUCCS) in San Francisco.

In the study, at a median follow-up of 10.7 years, 118/439 men treated with ADT alone died of prostate cancer, vs just 45/436 men treated with combination therapy ( $P < 0.0001$ ). Most of the combination therapy, which was significantly beneficial out to 15 years, consisted of adding RT to long-term oral antiandrogen therapy.

The 10-year prostate cancer-specific mortality (PCSM) rates were higher in the ADT group than in the combination therapy group (18.9% vs 8.3%), as were the 15-year rates (30.7% vs 12.4%). Thus, the men receiving only ADT were more than twice as likely to die of their disease over time, reported lead author Sophie Dorothea Fosså, MD, PhD, from the Department of Oncology at Oslo University Hospital in Norway.

These longer-term results come from the Scandinavian Prostate Cancer Group's Study VII, which started in 1996, and are based on mortality data from Danish, Norwegian, and Swedish death regis-

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### **LONG-TERM DATA SHOW THAT RADIUM-223 SAFE IN ADVANCED PROSTATE CANCER**

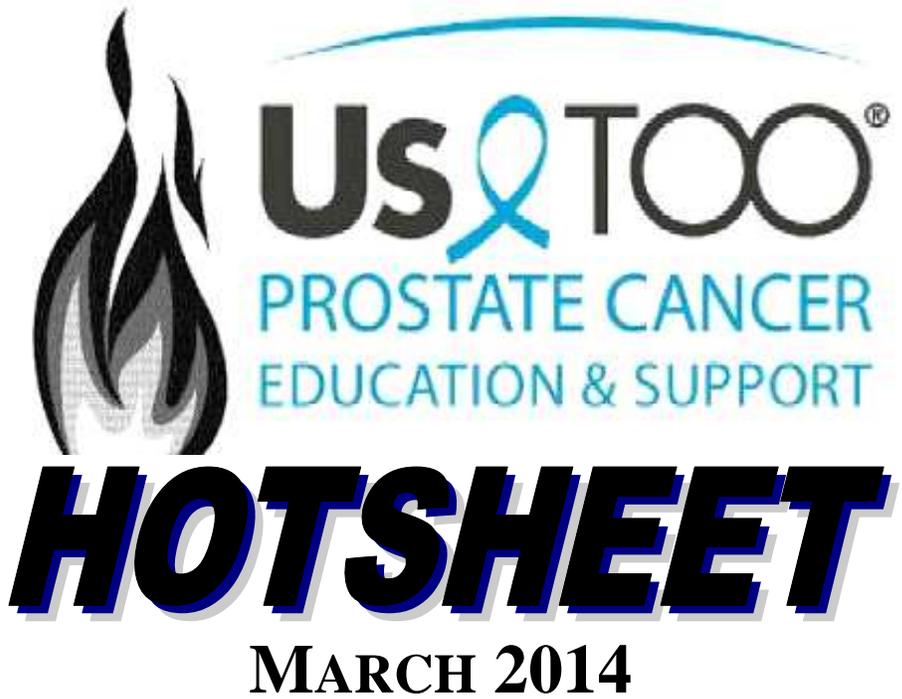
The novel radiopharmaceutical radium-223 (Xofigo®, Algeta/Bayer) appears to have long-term safety with minimal adverse events. In an updated report of the ALSYMPCA trial, no major safety issues were identified within ~1.5 years after the end of treatment in a population of men with castration-resistant prostate cancer (CRPC) and bone metastases. The updated results were presented here at the 2014 Genitourinary Cancers Symposium (GUCCS).

The drug, which has been approved in both the US and the European Union, extended survival in this population and addressed an "important unmet need," according to researchers who initially reported the results of the phase 3 trial that led to the product's approval.

"We found that it has a very benign safety profile, and that was shown in the earlier phase 1 and phase 2 trials," said lead author Sten Nilsson, MD, PhD, professor of oncology at the Karolinska Hospital, Stockholm, Sweden. "Now it is important that we try to follow the patients, and to see if any adverse events have developed and can be considered treatment related."

Dr. Nilsson told Medscape Medical News that they have been following both hematologic and nonhematologic side

*(Continued on page 6)*



### **ENZALUTAMIDE BEFORE CHEMOTHERAPY SLOWS METASTATIC PROSTATE CANCER**

The ability of the oral therapy enzalutamide (Xtandi®, Medivation/Astellas) to delay disease progression in men with metastatic castrate resistant prostate cancer (mCRPC) and extend their time to the treatment of last resort, chemotherapy, is "quite striking," said one of the drug's investigators at the 2014 Genitourinary Cancers Symposium (GUCCS).

Tomasz Beer, MD, from the Knight Cancer Institute at Oregon Health & Science University in Portland reported updated results from PREVAIL, a placebo-controlled phase 3 trial in which enzalutamide (ENZ) was used prior to chemotherapy in mCRPC.

The new data update the top-line results from this trial released in October 2013, when the trial was stopped early due to benefit. The manufacturer is planning to use these new data to apply for an extension of the indication, for use of ENZ prior to chemotherapy.

The drug is already approved for use in mCRPC, but its current indication is for second-line therapy in men previously treated with docetaxel. This indication was approved by the US FDA in August 2012, and was recently approved in the European Union.

Dr. Beer explained that the agent was

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## CLINICAL VARIABLES ASSOCIATED WITH PSA RESPONSE TO ABIRATERONE ACETATE IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Leibowitz-Amit R, et al

Ann Oncol 23 January 2014; Epub

**Background:** Abiraterone acetate (AA) prolongs overall survival (OS) in patients with metastatic castration-resistant prostate cancer (mCRPC). This study's objective was to retrospectively identify factors associated with PSA response to AA and validate them in an independent cohort. We hypothesized that the neutrophil/lymphocyte ratio (NLR), thought to be an indirect manifestation of tumor-promoting inflammation, may be associated with response to AA.

**Patients and Methods:** All patients receiving AA at the Princess Margaret (PM) Cancer Centre up to March 2013 were reviewed. The primary end point was confirmed PSA response defined as PSA decline  $\geq 50\%$  below baseline maintained for  $\geq 3$  weeks. Potential factors associated with PSA response were analyzed using univariate and multivariable analyses to generate a score, which was then evaluated in an independent cohort from Royal Marsden (RM) NHS foundation.

**Results:** A confirmed PSA response was observed in 44/108 assessable patients (41%, 95% confidence interval 31%-50%). In univariate analysis, lower pre-AA baseline levels of lactate dehydrogenase, an NLR  $\leq 5$  and restricted metastatic spread to either bone or lymph nodes were each associated with PSA response. In multivariable analysis, only low NLR and restricted metastatic spread remained statistically significant. A score derived as the sum of these two variables was associated with response to AA ( $P = 0.007$ ). Logistic regression analysis on an independent validation cohort of 245 patients verified that this score was associated with response to AA ( $P = 0.003$ ). It was also associated with OS in an exploratory analysis.

**Conclusions:** A composite score of baseline NLR and extent of mCRPC is associated with PSA response to AA and OS. Our data may help understand the role of systemic inflammation in mCRPC and warrant further research.

## PATIENT DEATHS CAUSE MEDIA STORM IN PROSTATE CANCER STUDY

A first-in-class targeted agent has demonstrated activity in men with very advanced castrate resistant prostate cancer (CRPC). In the phase 2 trial of the prostate-specific membrane antigen (PSMA) antibody drug conjugate (ADC), there was a reduction in several biomarkers. About 45 percent of men experienced a 30 percent reduction in PSA levels and a conversion from unfavorable to favorable circulating tumor cells counts (CTCs). Results were presented at the 2014 GUCCS.

Adverse events in this phase 2 study were similar to what had been observed in the initial phase 1 trial, except two men died of sepsis. These deaths sparked a media response, which culminated in the shares of Progenics, the developer of the agent, to drop by as much as 30 percent.

PSMA ADC is composed of PSMA antibody that is linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE). It binds PSMA and is internalized and cleaved by lysosomal enzymes releasing free MMAE, which causes cell-cycle arrest and apoptosis.

In their study, Dr. Israel and colleagues assessed the antitumor activity and tolerability of PSMA ADC in 80 men who had progressed on abiraterone and/or enzalutamide after failing taxane chemotherapy. In the study cohort, median age was 70.5 years, and ECOG performance status was 0, 1, or 2. All men had bone disease and 37 percent had visceral and soft tissue metastases. Safety, CTCs, imaging, biomarkers, and clinical progression were evaluated, and PSA was used to indicate tumor response.

Intravenous PSMA ADC was administered every three weeks for up to eight cycles. Dosing was initiated at 2.5 mg/kg and dose adjustment for tolerability was allowed. Of the 15 evaluable men, RECIST indicated that three (20%) had progressive disease and 12 (80%) had stable disease. Researchers found higher PSMA expression was associated with PSA and CTC responses ( $P = 0.019$ ). In addition, 78 percent of men with lower neuroendocrine markers experienced a reduction in CTCs of more than 50%.

(Continued on page 3)

## NEW AGENT MISSES THE MARK IN ADVANCED PROSTATE CANCER

A promising investigational agent for metastatic castration-resistant prostate cancer (CRPC) has failed to meet its primary end point in a phase 3 trial presented at the 2014 GUCS. There was no significant improvement in overall survival (OS) when orteronel (Takeda) was added to prednisone. Median OS with orteronel plus prednisone was similar to that with placebo plus prednisone. The study was terminated for failing to meet its primary end point.

However, orteronel “did lead to a notable improvement in radiographic progression-free survival (rPFS),” which was a secondary endpoint of the trial, reported lead author Robert Dreicer, MD, MS, professor of medicine at the Cleveland Clinic Lerner College of Medicine, and chair of the Department of Solid Tumor Oncology at the Cleveland Clinic Foundation.

In addition, he noted that there were regional differences in OS, and that a subgroup of men did achieve benefit. For men treated outside Europe and North America, survival was better with orteronel than with placebo. “This represented a little over a third of men in the trial,” Dr. Dreicer said.

Orteronel is an investigational oral, non-steroidal, selective inhibitor of 17,20-lyase, a key enzyme in the production of steroidal hormones, including androgens. Early-phase trials showed efficacy and safety, Dr. Dreicer pointed out. Phase 2 trials showed that the agent led to significant and durable declines in PSA levels in men with nonmetastatic CRPC.

The phase 3 Evaluation of the Lyase Inhibitor Orteronel in Metastatic Prostate Cancer (ELM-PC) 5 trial was conducted in 1099 men with metastatic CRPC that had progressed during or after docetaxel-based therapy. The manufacturer unblinded the study last July after a pre-specified interim analysis indicated that orteronel plus prednisone was unlikely to meet its primary end point. But this is the first time that the full results of the trial have been reported.

The trial was conducted in 260 centers in 42 countries. Men were randomized to 28-day cycles of oral orteronel 400

mg twice daily plus prednisone 5 mg twice daily, or to placebo plus prednisone, without regard to food. Men who had received previous orteronel, abiraterone or ketoconazole were excluded from the analysis.

For the entire cohort, median OS was similar in the orteronel and placebo groups (17.0 vs 15.2 months; hazard ratio [HR], 0.886;  $P = 0.1898$ ). However, geography had an effect. There was a difference in median OS between the orteronel and placebo groups in the 112 men treated in North America (20.9 vs. 16.9 months; HR, 0.889), the 590 men treated in Europe (18.3 vs. 17.8 months; HR, 1.048), and the 397 men treated in the rest of the world (15.3 vs 10.1 months; HR, 0.709). The secondary end point of median rPFS was significantly better in the orteronel group than in the placebo group (8.3 vs. 5.7 months; HR, 0.76;  $P = 0.00038$ ).

Grade 3/4 adverse events associated with orteronel included elevated serum levels of lipase (12%) and amylase (8%). Compared against placebo, the most common adverse events with orteronel were nausea (30% vs 16%), vomiting (23% vs 8%), fatigue (17% vs 11%) and diarrhea (16% vs 9%).

“One reason for the regional difference is that only 38 percent of the men in the non-European, non-North American population received subsequent therapy,” Dr. Dreicer explained. A higher percentage of men in Europe and North America received subsequent treatment. In addition, while orteronel was being investigated in this trial, abiraterone (Zytiga®) and enzalutamide (Xtandi®) became available. “Abiraterone was available in the US and Canada through an expanded-access program at the time of the study initiation,” Dr. Dreicer noted.

Overall differences in disease burden may also explain this finding. In an interview with GU Daily News, the official publication of the symposium, Jeff Michael Michalski, MD, MBA, professor of radiation oncology at the Washington University School of Medicine in St. Louis, MO, noted that men treated in

(Continued on page 8)

## PATIENT DEATHS

(Continued from page 2)

The media attention surrounding these deaths is perplexing. “I’m not sure why this got so much publicity,” said Robert Israel, MD, one of the study authors and executive vice president of medical affairs at Progenics. “Anytime you drop the white blood cell count, there is a risk associated with it.” Dr. Israel pointed out that both of the men who died had predisposing conditions. “One had an indwelling central line and the other had repeated urinary tract infections,” he said. “The patients were also heavily pretreated and didn’t have much in the way of other options.”

Overall, PSMA ADC is generally well tolerated. In fact, he said, “It is probably better tolerated than most chemotherapy drugs. It is more targeted to prostate cancer, but any cytotoxic agent carries a risk.” Dr. Israel also pointed out that the drug is still under development, so the “risk/benefit profile still needs to be written.” He also explained, “This very heavily pretreated group included patients with a performance status of two, which is pretty poor. There is no reason that those two deaths should affect the development of this drug.”

Another expert agrees. “The deaths were unrelated to treatment,” Susan Slovin, MD, PhD, a medical oncologist in the genitourinary oncology service at the Memorial Sloan-Kettering Cancer Center in New York City, told Medscape Medical News. “These are events that can occur during any other cancer treatment and, therefore, are of minimal concern.”

The researchers note that treatment after taxane and androgen-deprivation therapy is an area of unmet medical need, and that biomarker-guided patient selection could be more predictive of clinical benefit in CRPC

The men in this study are very representative of a “real-world” population, said Hagop Youssoufian, MD, executive vice president of research and development at Progenics. “We have identified the dose and schedule that is effective,” he said. “We believe that the 2.3 mg dose is safe and effective, and we have confirmed the results of the phase 1 trial.”

Presented at the 2014 GUCS, Abstract 8  
Medscape Medical News, 31 January 2014

## PROSTATE HEALTH INDEX MAY PROVIDE NEW TOOL TO IDENTIFY PATIENTS ASSIGNED TO WATCHFUL WAITING WHO REQUIRE IMMEDIATE TREATMENT

A simple tool called “phi” appears to be able to identify which patients assigned to active surveillance for prostate cancer are more likely to require treatment. Phi, or the prostate health index, is calculated from three serum measurements: PSA, free/total PSA, and a new measurement, [-2]proPSA, using the Beckman Coulter assay kit. In the study, phi gave a more accurate estimate of patients’ course of illness than either PSA alone or free/total PSA. The findings were presented at the 2014 GUCCS (Abstract 81).

“There are many patients who don’t need treatment even 10 years after diagnosis,” said lead author Andrew Eichholz, MD, of The Institute of Cancer Research, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom. Although he is quite enthusiastic about the applicability of the new tool, he said, “It is not ready for prime time. The phi index needs to be validated. We are the first group to study it, and another group is also studying it. If it is validated, it could massively change the way we manage these patients.”

The study was a retrospective analysis of frozen blood samples collected from men at diagnosis a median of 11.4 years ago. The investigators sought to determine the predictive value of phi. The study included 370 men with prostate cancer with T1/T2 tumors, Gleason scores of  $\leq 3+4$ , and PSA  $<15$  ng/mL. Ten years later, 37 percent of patients still did not require treatment, while about 20 percent needed treatment within the first two years.

Men were grouped into quartiles according to phi. Investigators determined that the cutoff point for phi was  $\leq 31.4$  for the lowest-risk quartile, and  $>58.5$  for the highest-risk quartile. Among lowest-risk patients, 95 percent would not need therapy within five years from diagnosis, while among highest risk, 54 percent would require treatment in five years.

“If validated, phi will be useful for advising patients. It will be an extra tool for our discussions,” Dr. Eichholz stated.

*The ASCO Post*, 3 February 2014

## DOC MOYAD’S WHAT WORKS & WHAT IS WORTHLESS COLUMN, ALSO KNOWN AS “NO BOGUS SCIENCE” COLUMN

### “The 2 for 1 Column: Testosterone or Exercise vs Drugs or both?!”

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:

First do no harm! So, we have to assume testosterone replacement therapy (TRT) might increase the risk of cardiovascular disease right now (CVD) even though it has not been proven because CVD is the number one cause of death in men. And, it is possible that exercise is as good as taking a prescription drug in many cases and in the worst case scenario makes most prescription drugs work better—even testosterone replacement therapy (TRT), which is not a bad case scenario folks!

Testosterone replacement therapy is an option some men choose after being treated for prostate cancer or if they watch enough TV and get convinced to use it from all those commercials! However, another new piece of research suggests that taking testosterone replacement therapy (TRT) might increase the risk of cardiovascular disease (CVD)/heart attacks in men with heart disease<sup>1</sup> and many health care professionals and patients have been asking my humble or not so humble opinion of the situation. And, I respond by saying “it does not matter” and they look stunned (kind of how I looked when the first girl I ever asked out on a date in high school told me she just wanted to be “friends”!).

What I mean is that since CVD is the number-one killer of men, and about 150,000 individuals 65 years of age and younger (overall over 800,000 men and women) died from this disease in the past year. So ALL MEN with diagnosed heart disease should NOT be treated as if they are already at high risk of CVD. So, if you want to go on TRT ALL NUMBERS and LIFESTYLE factors should be heart healthy (you should be losing weight/waist, normal to low cholesterol, glucose, blood pressure and should be EXERCISING daily and eat a primarily heart healthy diet) or you SHOULD NOT be allowed to go on TRT. I watched for decades “experts” tell women that hormone replacement therapy

(HRT) might reduce the risk of CVD and OOPS – they were really wrong!

In a separate (but in my opinion related) article, was one of the most extensive analyses ever conducted on the subject.<sup>2</sup> The authors concluded that “exercise and many drug interventions are often potentially similar in terms of their mortality benefits in the secondary prevention of coronary heart disease, rehabilitation after stroke, treatment of heart failure, and prevention of diabetes.” WOW! And, in a previous column in 2013, I mentioned that from Viagra to statins it appears that if someone exercises regularly it makes their prescription drugs work remarkably better! TRT would also work better with exercise, and in some cases men would never need TRT if they lost weight/waist and their testosterone would increase naturally and their risk of CVD would also decrease.

The message of the day is too many men (and women) have begun to rely on prescription drugs and supplements to solve many of the issues exercise and other lifestyle factors could solve. And, we already know exercise reduces the side effects of prostate cancer treatment, reduces fatigue and might even reduce the risk of prostate cancer recurrence. All of this new and old exercise research is nothing short of incredible and miraculous (similar to when my current wife told me she would marry me because I was sure I would get the same answer as that girl from back in high school)!!!

#### References:

1. Finkle WD, Greenland S, Ridgeway GK, et al. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One* 2014;9:e85805.
2. Naci H, Ioannidis J. Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study. *BMJ* 2013;347:f5577.

**RADIOTHERAPY PLUS ADT BENEFIT** *(Continued from page 1)*

tries. They update the eight-year results that were published in 2009 (Lancet Vol. 373, pp. 301–308, 2009). At that time, the researchers reported a 12 percent absolute reduction in PCSM in the men who received the combination therapy. The new results indicate an improvement in efficacy from 10 years to 15 years of follow-up.

“It’s very interesting to see that the results improve over time,” said Charles Ryan, MD, from the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, who was not involved with the study.

Dr. Ryan observed that the study involved lifelong use of an antiandrogen and not lifelong medical castration, which makes the trial “somewhat unique.” He was referring to the fact that other studies have used more potent long-term castration – either surgical or medical (a luteinizing hormone-releasing hormone agonist or a gonadotropin-releasing hormone antagonist) – alone or in combination with antiandrogens to interfere with the body’s production of testosterone.

When the trial started in 1996, lifelong medical castration was the standard of care for these men, explained Dr. Fosså. However, adverse effects are a concern with this approach, so the researchers used less potent lifelong antiandrogens as an alternative approach.

The study participants initially received 1 injection of a testosterone-blocking hormone (short-term castration that lasts for three months), followed by RT for two months and lifelong pill-based antiandrogen therapy. Antiandrogens for life are still the standard practice in Scandinavia. In other parts of Europe and in the United States, the standard is RT plus ADT (medical castration variety) for two or three years, Dr. Fosså noted.

All of the study participants were 75 years or younger, in good overall health, and had high-risk prostate cancer that was either locally advanced or histologically aggressive. Most cases (80%) were locally advanced, with tumor growth beyond the capsule.

In 1996, this type of extracapsular prostate cancer was considered inoperable, but that is no longer the case, Dr. Fosså explained. “Today, many urologists would operate on these patients,” she said. It is not known if such surgery improves survival, compared with radiotherapy plus ADT, because there have been no randomized trials to date.

However, Dr. Fosså did state that the 10-year prostate-cancer-specific mortality of 8 percent seen with the combination in this trial is “comparable” to results seen after prostatectomy in such patients in other studies.

Presented at the 2014 GUCS, Abstract 4  
*Medscape Medical News, 29 January 2014*

**FDA NOW INVESTIGATING  
CARDIOVASCULAR RISKS WITH TESTOSTERONE THERAPY**

The US FDA is now officially investigating the potential that FDA-approved testosterone products increase the risk of serious adverse cardiovascular outcomes.<sup>1</sup> FDA cites two studies, one of which was published just two days ago, that suggests men taking the testosterone supplements have an increased risk of death, myocardial infarction (MI), or ischemic stroke.

“We are providing this alert while we continue to evaluate the information from these studies and other available data and will communicate our final conclusions and recommendations when the evaluation is complete,” according to the FDA statement.

In the newest study, men treated with testosterone were significantly more likely to have an MI in the first 90 days after starting the drug. In the three months after the start of testosterone therapy, the risk of MI overall was increased by 36 percent and was even higher in older men. For those 65 years and older, the risk of MI was more than twofold higher in the 90 days after filling the prescription.

The second study, also an observational analysis of Veterans Affairs (VA) patients, found that testosterone therapy in men was linked with an increased risk of death, MI, or ischemic stroke.

*(Continued on page 8)*

**TREATMENT DECISIONS  
SIGNIFICANTLY MODIFIED BY  
MYRIAD’S PROLARIS TEST FOR  
PROSTATE CANCER**

Myriad Genetics, Inc. announced results from PROCEDE 500, a clinical utility study with its Prolaris test, at the 2014 ASCO GUCS in San Francisco, CA. The study demonstrated the significant clinical value of Prolaris to physicians who are treating men with prostate cancer. Prolaris is a prognostic test that accurately predicts prostate cancer-specific death and metastases and has been validated in 11 clinical studies with more than 5,000 patients.

“Prolaris has opened the door to a new era of personalized cancer treatment for men with prostate cancer,” said Michael Brawer, MD, vice president of medical affairs at Myriad Genetic Laboratories. “The Prolaris score is a stronger predictor of prostate cancer death and recurrence than either Gleason score or PSA (prostate specific antigen), and delivers clinically relevant information not provided by any other prognostic test.”

PROCEDE 500 is an ongoing prospective registry study designed to examine the clinical utility of Prolaris. Currently, 331 men have been enrolled and 150 clinicians have completed surveys in 305 cases to assess the influence of the Prolaris score on clinical decision making. Results for these interim data show that in 65 percent of cases, physicians changed their intended therapy and selected a different treatment based on the Prolaris test score. In 40 percent of cases, physicians reduced the therapeutic burden on men and opted for conservative management such as active surveillance and watchful waiting. In 25 percent of cases, physicians increased treatments including the use of surgery or radiation, and in 35 percent of cases, physicians did not change their treatment plans. Full results from PROCEDE 500 have been submitted to a peer-reviewed medical journal for publication.

Ashok Kar, MD of St. Joseph’s Hospital in Orange, CA stated “As a practicing physician, I must ask the same question for every patient; should I use surgery or radiation, or should I use active surveillance? Prolaris helps me answer this critical clinical question.”

*Medical News Today, 31 January 2013*

**LONG-TERM SAFETY OF XOFIGO***(Continued from page 1)*

effects, as well as the possible induction of secondary malignancies. Thus far, they have not seen any cases of myelogenous leukemia, myelodysplastic syndrome, or primary bone cancer.

The prognosis for this disease is poor, but radium-223 did extend survival. "The median survival was less than one year in placebo and 14.9 months in the active treatment arm, so the survival benefit was 3.6 months," Dr. Nilsson said. "That is a very robust finding." He noted that they will continue to follow the surviving patients, and updated study results will be presented in the spring, at the annual meeting of the American Society of Clinical Oncology.

The ALSYMPCA trial involved 921 men with CRPC and at least two bone metastases but no visceral metastases. Patients were enrolled whether or not they had received previous docetaxel therapy. The trial was halted early after an interim analysis showed that treatment with radium-223 significantly improved survival as compared with placebo. When these early results were originally presented, they were hailed by experts as practice-changing and were considered a new standard of care.

The ALSYMPCA safety population included 901 men (Ra-223, n = 600; placebo, n = 301). Overall,  $\geq 1$  treatment-related adverse event occurred in 25 (4%) men in the Ra-223 group and 8 (3%) men in the placebo group. During follow-up, primary cancer in other organs was reported in five men (Ra-223, n = 2; placebo, n = 3). However, none were deemed to be associated with Ra-223.

The most common hematologic event was anemia, reported in 11 patients who received radium-223 (five were grade 3/4) and in five patients in the placebo arm (one grade 3/4). There was also one case of aplastic anemia, in a patient who received active treatment.

"There is now safety data for a year and a half," commented Michael J. Morris, MD, a medical oncologist from Memorial Sloan-Kettering Cancer Center, who was a discussant for the paper. "For those concerned about long-term bone marrow toxicity, it looks like one can

*(Continued on page 8)***ENZALUTAMIDE BEFORE CHEMOTHERAPY** *(Continued from page 1)*

compared with placebo and not with chemotherapy in PREVAIL because the study population consisted of men with asymptomatic or minimally symptomatic advanced prostate cancer. "Such men 'typically' do not have chemotherapy at this point in their disease," he said.

The updated results show that ENZ delayed the radiographically detected progression of the disease by 81 percent (rPFS: hazard ratio [HR], 0.19; P <0.0001). The median rPFS for the placebo arm was 3.4 months but has not yet been reached in the treatment arm.

Additionally, ENZ stopped or slowed cancer growth in soft tissue in 59 percent of patients (20% complete responses and 39 percent partial responses) compared with five percent of patients on placebo.

This ultimately meant that, on average, chemotherapy was given about 17 months later in men treated with ENZ vs those treated with placebo (28 months vs 10.8 months; HR, 0.35; P <0.0001).

Dr. Beer also updated the survival data for the 1717 trial participants, who were randomized to ENZ (160 mg orally once daily) or placebo between September 2010 and September 2012. Men in both treatment arms also received standard hormone therapy.

At a median follow-up of 20.2 months, 28 percent of ENZ patients and 35 percent of placebo patients have died. This translated into a 29 percent reduction in risk for death (overall survival: HR, 0.71; P <0.0001). The estimated median overall survival (OS) was 32.4 months in the ENZ arm vs 30.2 months in the placebo arm, but the data are still maturing and the upper limits of survival have not yet been reached in either arm.

Currently in the US, the first-line treatment for mCRPC is limited to either chemotherapy regimens containing docetaxel or abiraterone (Zytiga®, Janssen), which had this extension to its indication approved in December 2012. Pending FDA approval for this extended indication, ENZ would become another systemic therapy option in this first-line setting.

The possibility of approval of ENZ as first-line treatment invites comparisons

with abiraterone in this setting. But Dr. Beer refused to indulge reporters' requests for such a summary, citing the inappropriateness of such cross-trial comparisons and the absence of an FDA approval for first-line ENZ.

However, he went on to say, "Some of the conveniences of ENZ may play a role in decision-making in the clinic. For instance, ENZ is not co-administered with steroids, as is abiraterone (with prednisone). Also, there are no diet restrictions with ENZ, as there are with abiraterone."

"Time will tell how ENZ and abiraterone are used in this patient population," stated Dr. Beer, saying that both drugs have "emerged very rapidly" and the clinical assessments and understandings of the pair are "just beginning."

Charles Ryan, MD, from the Helen Diller Family Comprehensive Cancer Center at the University of California, San Francisco, who was not involved with the study, moderated the session. "More than 50,000 men a year in the US live with CRPC. Although chemotherapy is held up as a benchmark for this disease, the reality is less than 50 percent of men with mCRPC receive chemotherapy," he commented.

ENZ was well tolerated in the study, with the same percentage (6%) of patients in both arms leaving the study because of side effects. There were more grade 3+ adverse events with enzalutamide vs placebo (43% vs 37%).

The most common side effects of all grades included fatigue (36% vs 26%), constipation (22% vs 17%), back pain (27% vs 22%) and joint discomfort (20% vs 16%).

The median time to reporting an adverse event was 17.1 months for ENZ and 5.4 months for placebo. Dr. Beer reported that one patient in each arm had a seizure. However, in both cases, the patients had a history of seizures.

ENZ is a second-generation androgen-receptor blocker and has proven more potent than the first generation of these agents such as bicalutamide, flutamide, and nilutamide.

*Medscape Medical News, 28 January 2014*

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

Gerald Chodak, MD Author, Winning the Battle Against Prostate Cancer, Second Edition <http://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** Treatment of locally advanced prostate cancer continues to evolve. Updated results were recently presented of a study in which men receive either an anti-androgen alone or in combination with external radiation therapy. The 10 and 15 years survival results showed a significant reduction in cancer mortality. The dose of radiation was approximately 70 Gy. Men received combined hormonal therapy for three months and then received the radiation over two months. Flutamide was given to patients three times a day until they had evidence of progression or they died. This is an unusual approach to managing this group of patients as most studies have used medical or surgical castration in combination with radiation. Since the side effects of the anti-androgen are less severe than with castration, this result could offer men a better alternative. That would need to be determined by a randomized study.

**The Bottom Line:** Men with locally advanced prostate cancer may consider combining radiation with an anti-androgen instead of combining it with medical or surgical castration.

**a2p1c2** The most recently approved treatment for men with advanced prostate cancer is Radium-223 (Xofigo). Since it involves radiation to the bones, a possible concern is the chance for long-term damage to the bone marrow. Patients can now be reassured that no new serious side effects were discovered for at least 18 months after treatment. This is based on updated analysis of the randomized study that resulted in the drug's approval.

**The Bottom Line:** Radium-223 appears to be well tolerated, without long-term side effects up to 18 months after treatment and it should be offered to men with symptomatic bone metastases.

**a3p1c3** New data from an ongoing randomized study of enzalutamide or placebo prior to chemotherapy in men with progressive metastatic disease has shown a significant benefit. This was a similar finding for abiraterone, which resulted in its approval prior to chemo-

therapy. Hopefully a similar approval will occur for enzalutamide. If that does occur, men will then have three options for treating this stage of disease and new studies will be needed to determine the best way to sequence these treatments.

**The Bottom Line:** Enzalutamide has shown positive results when administered before chemotherapy and could become another option for treating men with metastatic castrate resistant disease.

**a6p3c1** An important part of medical research is to report the results of both negative and positive research studies. Sadly, that is the case for what was thought to be the promising drug Orteronel. It had shown good results in preliminary studies but in the most recent study it failed to improve survival in men with advanced disease. There were some positive findings and also some reasons that could explain the results. For now, however, it is unclear if this drug will gain approval.

**The Bottom Line:** Orteronel failed to show an improvement in survival in men with progressive metastatic disease.

**a7p6c1** One of the more important questions for men with newly diagnosed disease is who needs treatment? The study on the prostate health index provides additional data to help answer this question. The test makes three measurements, the total PSA, free/total PSA ratio, and a new free PSA isoform called [-2]proPSA. The lower the PHI value, the higher the chance the cancer is not life threatening. The test is FDA approved although its true value is still evolving. Like all tests, the cutoff value chosen must balance the false negatives against the false positive results. Ultimately the value of this test must be measured based on the long-term outcome. This means can the test identify which patients do well with no treatment many years after diagnosis. The authors acknowledge that a prospective study is needed to validate these findings.

**The Bottom Line:** The Prostate health index may eventually be useful for identifying men for active surveillance pend-

ing data from a prospective trial.

**a9p5c2** Are men who take testosterone supplementation at increased risk for heart attacks? That question is being raised by the FDA after new reports have found higher than expected mortality within a few months of starting treatment. Around the United States, these drugs are being marketed to men who do not necessarily meet the requirements of having symptoms related to a low testosterone level. Many more details are needed to understand which men should and should not use this drug and hopefully the information will be forthcoming soon.

**The Bottom Line:** Until more information is available, men taking testosterone replacement should consult with their doctor.

**a10p5c3** Another test that offers promise for helping men decide whether a tumor needs aggressive treatment is the Prolaris test. It measures 46 gene products and the number generated helps to separate patients into groups with a low or high risk for progression. Data continues to accumulate; however, as yet the test has not shown the long term outcomes of men for whom treatment was based on the test result. This most recent study suggests that the result might lead doctors to recommend a different therapy. More data still are needed to define its true value.

**The Bottom Line:** The Prolaris test may soon provide enough valuable information to help guide treatment of localized disease.



**LONG-TERM SAFETY OF XOFIGO**

*(Continued from page 6)*

rest easy and there are no surprises coming down the pipe,” he said. “It prolongs survival and with a side effect profile that is tantalizingly close to zero.”

But he noted that now that 1.5 years have passed, it is time to delve more deeply and find out how the drug works, as much remains unclear. “One can go much higher on the dose and still not risk toxicity,” he said. “We don’t know how to leverage the gains with this drug as monotherapy into combinations with other treatments.

“We also don’t know how to identify a responder or progresser on this drug,” Dr. Morris continued. “And perhaps the most frustrating aspect, from a scientific standpoint, is that we don’t know what the target is.

“What we do know is that it prolongs survival and we do know that at least at one and a half years out it is relatively safe. But there are many questions that need to be answered,” he said.

Presented at the 2014 GUCS, Abstract 9  
*Medscape Medical News, 31 January 2014*

**TESTOSTERONE RISKS**

*(Continued from page 5)*

The agency stresses that testosterone products are approved for use in men with low levels and an associated medical condition. Other medical conditions include problems with the hypothalamus or pituitary gland that result in low testosterone levels. The FDA says that these testosterone therapies are not approved for men with low levels without the associated medical condition.

FDA says that men should not stop taking testosterone therapy unless first consulting their physician but adds all physicians need to consider the risk/benefit profile when prescribing this drug. “The prescribing information in the drug labels of FDA-approved testosterone products should be followed,” they write.

Reference

1. FDA Drug Safety Communications: FDA evaluating risk of stroke, heart attack, and death with FDA-approved testosterone products. 31 Jan.. 2014.

*Medscape News Alerts – Heartwire  
31 January 2014*

**ORTERONEL MISSES MARK**

*(Continued from page 3)*

North America had very early stages of metastatic disease (average PSA, 50 ng/mL), compared with men treated elsewhere (average PSA, 150 ng/mL).

Also, men from other countries were “more often heavily treated and had worse performance status—just worse overall disease,” he said. “It may appear that men with earlier stages of [metastatic] disease do not benefit from these newer agents, compared with men who have a greater burden of illness.”

The trial did demonstrate that orteronel has activity, as evidenced by the rPFS, Dr. Michalski said. “Also, the PSA progression rate was improved with the use of orteronel.” Although this probably isn’t going to be the trial that leads to approval by the US Food and Drug Administration, “we are encouraged to continue the existing/ongoing trials that are using orteronel,” he added.

Presented at the 2014 GUCS, abstract 7.  
*Medscape Medical News, 4 February 2014*

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