Us TOO® PROSTATE CANCER EDUCATION & SUPPORT

HOTSHEET

NOVEMBER 2014

ZYTIGA® Plus Prednisone Demonstrates Statistically Significant Overall Survival After 49-Month Follow-Up Analysis in Chemotherapy-Naive Men with Metastatic Castration-Resistant Prostate Cancer

A final analysis of the Phase 3 COU-AA -302 trial presented at the European Society for Medical Oncology (ESMO) 2014 Congress in Madrid, Spain showed that ZYTIGA® (abiraterone acetate) plus prednisone significantly prolonged overall survival (OS), compared to an active control of placebo plus prednisone, in men with chemotherapy-naive metastatic castration-resistant prostate cancer (mCRPC). The Janssen Research & Development, LLC ("Janssen")-sponsored registration study demonstrated a 19 percent reduction in risk of death in this study population (median OS, 34.7 vs. 30.3 months, respectively; HR 0.81 [95% CI, 0.70–0.93]; p=0.0033), after a median follow-up of more than four years (49.2 months).

The final analysis presented today is the first to demonstrate a statistically significant improvement in OS in this study. "OS is particularly noteworthy in COU-AA-302, because 67 percent of men in the ZYTIGA plus prednisone arm and 80 percent in the control arm received subsequent therapy. This includes 44 percent of men in the control arm who subsequently received ZYTIGA plus prednisone," said Charles Ryan, MD,

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PSA Bounce after Radiotherapy May Be Associated with Outcomes in Patients with Prostate Cancer

A temporary rise in PSA levels after radiotherapy (RT) may have an association with outcomes in men with prostate cancer, according to study findings presented by Naghavi et al in the International Journal of Clinical Oncology. Experiencing a PSA bounce was associated with improved biochemical disease -free survival (bDFS).

A PSA bounce is often seen after patients receive RT and is indicated by a temporary rise in the PSA level by at least 0.1 to 0.5 ng/mL without evidence of prostate cancer recurrence post-RT. Although clinicians are familiar with this occurrence, there is still uncertainty regarding whether these rises in PSA levels are of any benefit in continued management of men with prostate cancer. There is great interest among researchers on whether a PSA bounce is predictive of recurrent cancer or cancer in remission. With that in mind, Naghavi and colleagues set out to determine whether a PSA bounce seen after RT was a predictor of cancer recurrence or an indication of RT success.

The investigators analyzed the medical records of 691 prostate cancer patients without regional or distant metastases who were treated with external-beam RT and/or brachytherapy. The median patient age was 69 years (range, 49–87 years). Men were categorized as being

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Radical Prostatectomy Rates Rising

Use of radical prostatectomy (RP) for localized prostate cancer (PCa) increased significantly from 2004 to 2011, whereas the use of radiotherapy (RT) decreased during that period, according to study findings presented at the 56th annual meeting of the American Society for Radiation Oncology in San Francisco.

Using the national cancer database, Phillip J. Gray, MD, of Massachusetts General Hospital, and colleagues identified 823,977 men diagnosed with PCa from 2004 to 2011. Of these, 38.5%, 42.7%, and 18.9% had low-, intermediate-, and high-risk disease, respectively, according to National Comprehensive Cancer Network guidelines.

In low-risk patients, active surveillance (AS) rates increased from 12.4% to 18.5% from 2004 to 2011 and RP rates rose from 40.3% to 54.4%. During the same period, brachytherapy (BT) rates decreased from 24.4% to 11.4% and the rates of external beam RT (EBRT) alone decreased from 18.2% to 13.4%.

Among men with intermediate-risk disease, AS rates increased from 6.1% to 7.3% and RP rates increased from 48.1% to 58.5%, whereas BT rates dropped from 12.1% to 6.4%. Rates of combined therapy with EBRT and androgen deprivation therapy (ADT) declined from 14.7% to 8.7%.

In the high-risk group, AS rates and EBRT monotherapy rates remained sta-

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CAN WE EXPAND ACTIVE SURVEILLANCE CRITERIA TO INCLUDE BIOPSY GLEASON 3+4 PROSTATE CANCER? A MULTI-INSTITUTIONAL STUDY OF 2,323 PATIENTS

Ploussard G, Isbarn H, Briganti A, et al

Urol Oncol 14 August 2014; Epub

Objective: To test the expandability of active surveillance (AS) to Gleason score 3+4 cancers by assessing the unfavorable disease risk in a large multi-institutional cohort.

Materials and Methods: We performed a retrospective analysis including 2,323 patients with localized Gleason score 3+4 prostate cancer who underwent a radical prostatectomy between 2005 and 2013 from six academic centers. We analyzed the rates of biopsy downgrading/upgrading and advanced stage in the overall cohort by employing standardized AS criteria (using biopsy Gleason score 3+4=7).

Results: The final pathologic Gleason score was 3+3=6 in 8%, 3+4=7 in 67%, 4+3=7 in 20%, and 8 to 10 in 5% of the cases. The overall rate of unfavorable disease (upgrading or advanced stage or both) was 46%. In multivariable analysis, prostate-specific antigen (PSA) level >10 ng/mL, PSA density (PSAD) >0.15 ng/mL/g, clinical stage >T1, and >2 positive cores were predictors of unfavorable disease. According to the AS criteria used, the risk of unfavorable disease ranged from 30% to 42%. In patients without any risk factor (PSA level ≤10 ng/mL, PSAD ≤0.15 ng/mL/g, T1c, and ≤2 positive cores), the unfavorable disease rate was 19%. The main limitations of this study are the retrospective design and nonstandardization of pathologic assessment between centers.

Conclusions: Approximately half of patients with biopsy Gleason score 3+4 cancer have unfavorable disease at final pathology. Nevertheless, expanding AS eligibility to these patients may be acceptable provided adherence to strict selection criteria leading to a <20% risk of unfavorable disease. Future tools for selection such as magnetic resonance imaging, early rebiopsy, and serum markers may be especially beneficial in this group of patients.

^{89}ZR-HUJ591 IMMUNO-PET IMAGING IN PATIENTS WITH ADVANCED METASTATIC PROSTATE CANCER

Pandit-Taskar N, O'Donoghue JA, Beylergil V, et al

Eur J Nucl Med Mol Imaging 21 August 2014; Epub

Purpose: Given the bone tropism of prostate cancer, conventional imaging modalities poorly identify or quantify metastatic disease. ^{89}Zr-huJ591 positron emission tomography (PET) imaging was performed in patients with metastatic prostate cancer to analyze and validate this as an imaging biomarker for metastatic disease. The purpose of this initial study was to assess safety, biodistribution, normal organ dosimetry, and optimal imaging time post-injection for lesion detection.

Methods: Ten patients with metastatic prostate cancer received 5 mCi of ^{89}Zr-huJ591. Four whole-body scans with multiple whole-body count rate measurements and serum activity concentration measurements were obtained in all patients. Biodistribution, clearance, and lesion uptake by ^{89}Zr-huJ591 immuno-PET imaging was analyzed and dosimetry was estimated using MIRD techniques. Initial assessment of lesion targeting of ^{89}Zr-huJ591 was done. Optimal time for imaging post-injection was determined.

Results: The dose was well tolerated with mild chills and rigors seen in two patients. The clearance of ^{89}Zr-huJ591 from serum was bi-exponential with biological half-lives of 7 ± 4.5 h (range 1.1-14 h) and 62 ± 13 h (range 51-89 h) for initial rapid and later slow phase. Whole-body biological clearance was 219 ± 48 h (range 153-317 h). The mean whole-body and liver residence time was 78.7 and 25.6 h, respectively. Dosimetric estimates to critical organs included liver 7.7 ± 1.5 cGy/mCi, renal cortex 3.5 ± 0.4 cGy/mCi, and bone marrow 1.2 ± 0.2 cGy/mCi. Optimal time for patient imaging after injection was 7 ± 1 days. Lesion targeting of bone or soft tissue was seen in all patients. Biopsies were performed in eight patients for a total 12 lesions, all of which were histologically confirmed as metastatic prostate cancer. One biopsy-proven lesion was not positive on ^{89}Zr-huJ591, while the remaining 11 lesions were ^{89}Zr-huJ591 positive. Two biopsy-positive nodal lesions were noted only

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GENETIC STRATIFICATION OF GLEASON 7 PROSTATE CANCER

A prostate cancer susceptibility variant demonstrated potential for identifying heterogeneous Gleason 7 prostate cancers that have a more aggressive phenotype, a study of 1,800 men with prostate cancer showed.

Carriers of the variant allele A on a single nucleotide polymorphism (SNP) associated with prostate specific antigen (PSA) levels almost doubled the likelihood that a patient had the more aggressive 4+3 Gleason score versus the less aggressive 3+4 score.

The SNP known as rs2735839 "has been shown to modulate PSA level, providing strong biologic plausibility for its association with prostate cancer aggressiveness," reported Xifeng Wu, MD, PhD, of the MD Anderson Cancer Center in Houston, in an article published in *Clinical Cancer Research*.

Prostate cancer that has a Gleason pathology score of 7 has long been a source of uncertainty among clinicians and patients. A Gleason score ≤6 signifies a less aggressive cancer and a score ≥8 correlates with high-risk, aggressive disease. In contrast, some Gleason 7 prostate cancers exhibit low-risk behavior, whereas others have an aggressive phenotype. Identifying a marker for high-risk Gleason 7 prostate cancer could prove useful for clinician decision making.

Wu and colleagues performed genome-wide association studies involving 1,827 white men with prostate cancer and genotyped 72 SNPs associated with prostate cancer susceptibility. SNPs associated with low-risk disease (Gleason ≤6) were compared with those related to high-risk disease (Gleason ≥8). Statistically significant SNPs were further evaluated for their potential to stratify Gleason 7 into high- and low-risk subgroups.

Three SNPs (including rs2735839) had significant associations with high-risk prostate cancer ($P<0.05$). Additionally, patients with Gleason pattern 4+3 prostate cancer were significantly more likely to be carriers of the variant A allele of rs2735839. Neither of the remaining two high-risk SNPs had significant associations with Gleason pattern 4+3.

We reported for the first time that rs2735839 can stratify Gleason score 7 patients, which would be clinically important for more accurately assessing

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

"What is the difference between willow bark extract or 'salicin' and aspirin (acetylsalicylic acid)? About 50 dollars a month!"

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

Editor's 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:

There is a lot of talk about low-dose aspirin (acetylsalicylic acid) to reduce the risk of prostate cancer or the recurrence of prostate cancer, but before considering this option make sure you do not pay $50 a month for aspirin in disguise (also known as willow bark extract or salicin)!

Recent research from the American Association of Cancer Research (AACR) annual meeting suggests men taking aspirin might reduce their risk of aggressive prostate cancer.[1] However, if you have been following my column in the Us TOO newsletter (How could you miss it? It is so popular and your friends will love you for reading it!) then you will remember that you should only take aspirin if the benefits outweigh the risk.

In other words, men and women at a moderate to high risk for heart disease should take low-dose aspirin. But those with a low risk should not. Secondly, in those that need aspirin to prevent heart disease, there may now be the benefit of anti-cancer effects. It is well known that aspirin has plenty of research in the area of colon cancer prevention followed by many other cancers including prostate cancer and even now pancreatic cancer.

Anyhow, my point here is that if you and the doctor you trust most with your health have decided that aspirin is right for you, please only purchase inexpensive children's or low-dose (81 mg) aspirin by itself! Many companies are now selling osteoarthritis pain relievers with willow bark extract or the compound "salicin" in the pill. What you are not being told is that "salicin" and willow bark are just modified natural sources of **ASPIRIN**. In my opinion, it is just a way of making you pay up to $50 a month for aspirin!

Some of the better selling osteoarthritis products on the market contain "salicin" and people feel better on these products in clinical trials. Gee, I wonder why (sarcasm alert)?! Could it be because they are simply told to stop all pain relievers before the clinical study; then they end up taking a modified form of aspirin (double sarcasm alert)?! In my opinion, YES!!

So, remember if you end up needing aspirin or any product for pain or prevention of any condition and it has willow bark or "salicin" in there please do not buy it. Just go out and get yourself some cheap low-dose (pennies per day) ASPIRIN and send me all the money you saved so I can spend it on the all-important MOYAD BEER FUND; especially because our football team is forcing me to drown my sorrows lately in more beer than usual!

Reference

1. AACR news release, 29 September 2014.
http://www.aacr.org/Newsroom/Pages/News-Release-Detail.aspx?ItemID=604#.VDxllWAtCM9

Q&A Interview on Cancer Immunotherapy in Prostate Cancer with Dr. Neal Shore, Medical Director of the Carolina Urologic Center (CURC)

1. *Recent studies, including a report published earlier this month in JAMA Internal Medicine, suggest urologists may have the greatest impact on the treatment decisions of newly diagnosed patients. Since the majority of prostate cancer patients are diagnosed and first treated by their urologist (as opposed to an oncologist), how does this affect your recommendations to patients?*

   Prostate cancer treatment is changing dramatically for both patients and physicians. Because prostate cancer is so heterogeneous, some patients with very aggressive forms of the disease may need interventional therapy while other patients may not require any immediate treatment. Since urologists are often the first to treat prostate cancer patients, we must learn how to better stratify patients based on disease stage, which will inform our recommendations to treat versus just actively monitor a patient. This means staying up to date on new screening and diagnostics technologies as well as the many new treatment options now available to patients with advanced and aggressive forms of the disease. The role of the urologist has changed in that we are now better able to treat patients with more advanced disease, as many of these innovative therapies can be administered in a urology clinic, meaning patients can stay with their urology team as their disease progresses to more advanced stages. As such, some of the larger urology clinics have developed truly comprehensive centers of excellence for all aspects of prostate cancer.

2. *Until only a few years ago, there were only a few treatment options available to patients with prostate cancer, particularly those with later stages of the disease. Can you describe how the treatment landscape for patients has changed over the last few years with the arrival of new therapies?*

   Prior to 2010, there was really only one treatment for prostate cancer patients who had become unresponsive to androgen deprivation therapy. We now have six treatment options available, with more in development. This growth in options has certainly changed the patient treatment experience, particularly for advanced-stage patients who may have already progressed through some of the first-line treatment options.

3. *Could you give a brief overview of treatment options that are now available to prostate cancer patients? What about upcoming therapies that are in clinical development?*

   In 2010, the first therapeutic cancer vaccine for any advanced solid tumor, Provenge® (sipuleucel-T), was approved for the treatment of advanced prostate cancer. Following that, two oral therapies were approved, Zytiga® (abiraterone acetate) and Xtandi® (enzalutamide), which both work on the androgen-axis and are well tolerated by patients.

   We then had the introduction of a second chemotherapy, Jevtana® (cabazitaxel), which is also relatively well tolerated though it is associated with a higher risk of adverse events than some of these other treatments. Most recently, the first radiopharmaceutical for a solid tumor, Xofigo® (radium-223 dichloride), was approved for the treatment of symptomatic bone-metastases in patients with advanced prostate cancer. What is very appealing is that all of these treatment options offer distinct mechanisms of action, are well tolerated, and all have been shown to extend survival. With this wide array of therapies, patients have a number of options to pursue if their initial treatment is unsuccessful.

   In terms of new therapies in development, there is significant interest in the cancer immunotherapy approach, which aims to harness the native immune system to better combat cancer cells. There are multiple approaches and programs in development, but I will focus on two in late stage development. One late-stage clinical product in development is PROSTVAC®, which in a Phase 2 study for the treatment of advanced prostate cancer showed an 8.5 month increase in overall survival, the largest shown in a clinical study for the disease. However, this still needs to be confirmed in the Phase 3 clinical study, which is currently underway. PROSTVAC®, like Provenge®, is considered an active immunotherapy, focusing on what we refer to as T-cell activation in order to train the immune system to recognize cancer cells and stimulate an anti-tumor immune response. Another treatment in Phase 3 clinical development is ipilimumab, which is currently being investigated for the treatment of melanoma and prostate cancer. Ipilimumab represents another class of immunotherapies known as checkpoint inhibitors, which are designed to block cancer cells' ability to escape the immune system, allowing white blood cells to fight the cancer. Checkpoint inhibitors focus on removing the blockade on the immune system; however the treatment itself does not necessarily mount an anti-tumor response.

4. *What are the main concerns of patients when evaluating treatment options? How do you address their concerns? What about those considering clinical trials?*

   Frequent concerns of my patients when evaluating treatment options are generally: what is the potential impact on my quality of life? Can I tolerate this therapy? Is it covered by my insurance?

   My response is that all these treatments are, by and large, reasonably well tolerated by most patients. While chemotherapy may be the most toxic and immunotherapy is oftentimes the least toxic, as long as treatment is being administered under the supervision and care of a qualified physician, the likelihood of adverse events can be minimized. Additionally, all of the FDA approved therapies for prostate cancer are covered by Medicare and most insurance providers. Furthermore, all the companies offering these therapies provide patient assistance programs to support patients who may be uninsured or have significant co-pays.

   For patients considering clinical trials, my response is that none of these approved options would exist if it were not for the heroes of prior clinical trials. Sites are well vetted by an array of groups (including study sponsors, clinical research organizations, and ethics boards) which hold them to the highest of standards. As such, patients should receive exceptional care and monitoring under an intense magnifying glass due to the regulatory process.

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CANCER IMMUNOTHERAPY IN PROSTATE CANCER *(Continued from page 4)*

5. *Since the launch of Provenge®, have patients been more open to trying an immune-based therapy?*

   When Provenge® was first approved, both patients and physicians required additional education on the approach, such as information on how it worked and what the safety profile looks like.

   Now that we have this larger body of research and experience, there is certainly optimism for immunotherapeutic approaches and there are even some that now believe that immunotherapy should be the front line foundational treatment for all patients with prostate cancer. There is a strong case being made for this thinking.

6. *What about combining immunotherapies with other treatment approaches, such as hormone therapy, radiation therapy or even chemotherapy? What are the potential benefits of using an active immunotherapy as front-line treatment?*

   It is a very exciting time for research of these potential combinations and treatment sequences. Given the different methods of action, we certainly expect to combine immunotherapies with other therapy types, and there is a growing body of evidence that the use of an immunotherapy as the front-line treatment is ideal. By coming in early with an immunotherapy agent, this allows for greater time for the immune system to mount a targeted anti-cancer response while not precluding the use of other subsequent treatment options. There is already some preliminary data that suggests there may be some synergistic effect with subsequent therapies though more clinical evidence is still needed to confirm these expectations.

7. *Given the excitement around cancer immunotherapy, specifically around the development of checkpoint inhibitors, how do you see the future of prostate cancer treatment progressing (i.e. combinations, sequencing, etc.)? What role do active immunotherapies, or therapeutic vaccines, play in the evolving treatment landscape?*

   Researchers and physicians are optimistic about the combination of immunotherapies with other treatment types. While emphasis on the field has recently focused on checkpoint-inhibitors, T-cell activators (such as Provenge® and PROSTVAC®) will also play a major role in treatment of the disease and it is becoming clear that these active immunotherapies will be an important foundational step in treatment against prostate cancer.

8. *It is believed that by combining immunotherapeutic approaches, such as pairing a checkpoint inhibitor with an active immunotherapy, there could be a potential therapeutic synergy. It is also anticipated by many that the pairing of these two treatment approaches could result in a gas/brake dynamic targeting cancerous cells. Could you explain what the expectation is for these kinds of combinations?*

   The concept of combining immunotherapeutic approaches is perhaps one of the most exciting aspects of the evolving cancer treatment landscape. Everyone is born with an immune system designed to fight foreign particles, antigens and other potential hazards. But as we age, our body may no longer fight off these invaders effectively. Cancers in particular have been able to side-step this innate immune ability of ours.

   However, by combining these different immunotherapeutic approaches, using active immunotherapies to activate white blood cells ("accelerate" the immune system), and using checkpoint inhibitors to disable cancer cells' ability to inhibit these white blood cells ("remove the brakes"), there may be an opportunity to achieve an adaptive and lasting anti-cancer effect that could remain even after therapy is no longer being administered. This type of approach could help to slow down the production of cancer cells with limited adverse events, while prolonging survival. With appropriate sequencing, these combinations are expected to have an amplified treatment benefit in both androgen-sensitive and castration-resistant populations. These are certainly high expectations. But given early data so far, there is definitely reason for optimism.

Disclosure: Dr. Shore is an investigator for Bavarian Nordic's Phase 3 PROSPECT clinical study.

References

1. Hoffman KE, Niu J, Shen Y, et al. Physician Variation in Management of Low-Risk Prostate Cancer: A Population-Based Cohort Study. *JAMA Intern Med.* 2014;174(9):1450-1459. doi:10.1001/jamainternmed.2014.3021.

ZYTIGA®

(Continued from page 1)

professor of clinical medicine and urology at the University of California, San Francisco, and lead investigator of the COU-AA-302 study. "The use of subsequent therapies did not impact the statistical significance between the ZYTIGA and control arms – and makes these results all the more compelling after adjusting for the crossover effect."

The US Food and Drug Administration based its approval of ZYTIGA plus prednisone for treating men with mCRPC prior to chemotherapy on a planned second interim analysis of COU-AA-302, which met the co-primary endpoint of radiographic progression-free survival (rPFS). Based on results from the final analysis, Janssen has initiated regulatory submissions to relevant health authorities for a revision to the ZYTIGA label.

"Since the first report of interim data, ZYTIGA has become a key part of the treatment arsenal that doctors use to treat mCRPC, because it significantly delayed the progression of the disease and prolonged overall survival," Dr. Ryan added. "This final analysis also demonstrates a consistent safety profile with long-term co-administration of prednisone."

In addition, the final analysis demonstrated a significant improvement in median time to opiate use for cancer-related pain compared to placebo plus prednisone (median 33.4 vs. 23.4 months, respectively; HR 0.72 [95% CI, 0.61–0.85]; p=0.0001). With two additional years (a total of four years) of follow-up since the last clinical cutoff (median 49.2 months), the safety profile of ZYTIGA remained unchanged compared to previous reports.

COU-AA-302 is an international, randomized, double-blind, placebo controlled Phase 3 study that included 1,088 men with mCRPC who had not received prior chemotherapy, and were randomized to receive ZYTIGA (abiraterone acetate) 1,000 milligrams (mg) administered orally once daily plus prednisone 5 mg administered twice daily or placebo plus prednisone 5 mg administered twice daily.

Please go to www.ZYTIGA.com for more information about ZYTIGA®.

ESMO 2014 Congress, abstract 753O

PRNewswire, 28 September 2014

PSA BOUNCE AFTER RADIOTHERAPY AND OUTCOMES *(Continued from page 1)*

at very low-risk, low-risk, intermediate-risk, high-risk, or very high-risk of prostate cancer recurrence based on disease pathology. Men with very low-risk disease and an expected survival of ≥20 years, with low-risk disease and an expected survival of ≥10 years, or with "favorable" intermediate-risk disease were treated with either external-beam RT or brachytherapy. The choice of which treatment to use was based upon patient preference.

Patients were followed every three to six months with a PSA test for the first five years. After that time, they had an annual PSA test. Biochemical failure was defined as a ≥2.0 ng/mL rise in PSA above the nadir value, with no subsequent fall in response to antibiotics. The investigators analyzed the association between a PSA bounce and age, Gleason score, type of RT, androgen deprivation therapy (ADT), Sexual Health Inventory for Men score, National Comprehensive Cancer Network recurrence risk group, pretreatment PSA level, and clinical stage.

The first PSA bounce after RT was identified at 17 months (95% confidence interval [CI] 15–18 months). This finding was in contrast to men who experienced biochemical failure; for them, the median time to a first PSA bounce was 41 months (95% CI 28–53 months). In total, 33% of men experienced at least one PSA bounce. The median magnitude was 1.0 ng/mL (range, 0.4–17.0 ng/mL). Patients 70 years and older were more likely to have a bounce. On multivariate analysis, the sole identifiable predictor of a likely PSA bounce was a Gleason score of 6.

Closing Thoughts

Experiencing a PSA bounce was associated with improved bDFS. A PSA bounce occurred sooner after RT than a PSA recurrence of prostate cancer. The investigators noted that caution should be used when interpreting a rising PSA after neoadjuvant and adjuvant ADT. Gradual recovery of testosterone levels after the completion of ADT may cause the PSA level to rise and is not necessarily indicative of a biochemical recurrence. They also indicated that prostate biopsies should not be completed until 24 to 30 months after the cessation of radiotherapy.

Because a PSA bounce occurs in a sizeable number of prostate cancer patients treated with RT, clinicians should make their patients aware of this phenomenon, concluded the investigators.

Richard B. Wilder, MD, of the Department of Radiation Oncology, Moffitt Cancer Center, Tampa, Florida, is the corresponding author of this article in the International Journal of Clinical Oncology. The authors reported no potential conflicts of interest.

The content in this post has not been reviewed by the American Society of Clinical Oncology, Inc. (ASCO®) and does not necessarily reflect the ideas and opinions of ASCO®.

ASCO Post, 1 October 2014

BAYER AND ORION INITIATE PHASE III TRIAL OF NOVEL PROSTATE CANCER AGENT ODM-201 IN MEN WITH HIGH-RISK NON-METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Bayer HealthCare and Orion Corporation, a pharmaceutical company based in Espoo, Finland, have begun to enroll patients in a Phase III trial with ODM-201, an investigational novel oral androgen receptor (AR) inhibitor in clinical development for the treatment of men with prostate cancer. The study, called ARAMIS, evaluates ODM-201 in men with castration-resistant prostate cancer (CRPC) who have rising PSA levels and no detectable metastases. The trial is designed to determine the effects of the treatment on metastasis-free survival.

"The field of treatment options for prostate cancer patients is evolving rapidly. However, once prostate cancer becomes resistant to conventional anti-hormonal therapy, many patients will eventually develop metastatic disease," said Dr. Joerg Moeller, member of the Bayer HealthCare Executive Committee and head of global development. "The initiation of a Phase III clinical trial for ODM-201 marks the starting point for a potential new treatment option for patients whose cancer has not yet spread and is an important milestone for Bayer in our ongoing effort to meet the unmet needs of people affected by cancer."

Earlier this year, Bayer and Orion had entered into a global agreement under which they will jointly develop ODM-201, with Bayer contributing a major share of the costs of future development. Bayer will commercialize ODM-201 globally and Orion has the option to co-promote ODM-201 in Europe. Orion will be responsible for the manufacturing of the product.

The ARAMIS trial is a randomized, Phase III, multicenter, double-blind, placebo-controlled trial evaluating the safety and efficacy of oral ODM-201 in patients with non-metastatic CRPC who are at high risk for developing metastatic disease. About 1,500 patients are planned to be randomized in a 2:1 ratio to receive 600mg of ODM-201 twice a day or matching placebo. Randomization will be stratified by PSA doubling time (PSADT ≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no).

The primary endpoint of this study is metastasis-free survival (MFS), defined as time between randomization and evidence of metastasis or death from any cause. The secondary objectives of this study are overall survival (OS), time to first symptomatic skeletal event (SSE), time to initiation of first cytotoxic chemotherapy, time to pain progression, and characterization of the safety and tolerability of ODM-201.

ODM-201 is an investigational novel androgen receptor (AR) inhibitor with unique chemistry that is designed to block the growth of prostate cancer cells. ODM-201 binds to the AR with high affinity and inhibits receptor function by blocking its cellular function. In nonclinical models, ODM-201 has shown to only minimally penetrate the blood-brain barrier.

A Phase II clinical trial conducted in patients with progressive metastatic CRPC assessed the efficacy and safety of three dose levels of ODM-201 (100mg, 200mg and 700mg given twice a day) in 124 patients. The study included patients who were treated previously with abiraterone and/or chemotherapy as well as patients who were chemotherapy-naïve. The results showed that ODM-201 provided disease suppression and had a favorable safety profile. The results were presented at the international ECCO oncology congress at the end of September 2013 and published in June 2014 in *The Lancet Oncology*.

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16 September 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/

Editor's 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* starts with an important update to the randomized study of ZYTIGA® plus prednisone in men with metastatic castrate resistant prostate cancer (mCRPC) who had not yet received chemotherapy. Its initial approval was based on showing it significantly delayed time to radiographic evidence of progression of metastatic disease. Many people were critical that the approval was not based on showing an improvement in overall survival, perhaps a more important endpoint for these types of studies. Also, since men on prednisone alone could crossover to the combination, many people thought that any follow-up would have trouble showing an improvement in survival.

Fortunately, their concerns were not realized; in fact, a significant 4.4 month improvement in overall survival was still detected. Is this a home run in terms of progress in therapy for mCRPC? No, but it is yet another significant advance in managing these individuals compared with the 1980's and 1990's when half of men lived less than three years. Although not a cure, ZYTIGA is helping a large proportion of men live longer with a good quality of life. Remember, when a study says one-half of men lived longer than roughly six years, some proportion of them will live much longer than that. Now we need to find out the optimum sequence for using PROVENGE®, ZYTIGA, and XTANDI®.

The Bottom Line: Men with (mCRPC) derive a significant improvement in overall survival from receiving the combination of Zytiga and prednisone before chemotherapy.

a2p1c2 To many men, any rise in their PSA after local therapy has been a cause for concern. However, it is well known that a PSA "bounce" occurs often after external beam radiation therapy (EBRT) or brachytherapy (BT). The question is whether this bounce has any long-term implications for the patient? Naghavi et al performed a retrospective analysis looking at this question and found that a bounce occurred in about one-third of men undergoing these treatments after 15–18 months. Importantly, the likelihood of a true biochemical recurrence was significantly lower in those men who had a bounce compared to those who did not. Given the timing of these increases, they now recommend waiting at least 24-30 months before performing a biopsy for the PSA increase to avoid unnecessary testing. One of the possible causes of some of the PSA changes is the ending of ADT therapy, which lowers PSA. As the testosterone level returns back to normal, a small increase in PSA may occur that is not a reflection of recurrent disease. The curious question now needing an answer is what is happening following a PSA bounce that appears to benefit patients?

The Bottom Line: A PSA bounce after EBRT or BT is very common and may offer some benefit for unclear reasons.

a3p1c3 An interesting study by Gray et al looked at changes in the rates of active surveillance (AS), radical prostatectomy (RP) and RT from 2004-2011. They found that surgery was increasing in men with low- and intermediate-risk disease and EBRT and BT were declining. The proportion of men assigned to AS also rose during this same period. This finding is somewhat surprising given concerns that the increased ownership of IMRT machines by urologists might lead to a shift toward this treatment. We cannot tell from the study whether rates of EBRT differ significantly between urologists owning an interest in the equipment compared to those that do not have ownership. We also do now know if the increase in RPs results from a small percentage of urologists performing a larger volumes of RPs by attracting more men or whether across the board, the median number of RPs done by urologists is increasing.

The rate of RPs among African American (AA) men were lower than for Caucasians. This result is curious but it is unclear if this is due to physician and patient biases and/or economic issues. Lastly, the increase in AS is a little encouraging but many would still consider a rate of about 18 percent to be much lower than it should be. The authors suggest that the reason for any increase is because of a decline in the use of RT rather than an increase in RPs.

The Bottom Line: RP is on the rise and RT is on the decline for men with localized prostate cancer and we do not know why that is occurring.

a4p2c2 Is AS safe in men with Gleason 3+4 on biopsy? Currently, most doctors offering AS have avoided doing so out of concern that more aggressive disease will go untreated leading to a poor outcome. Ploussard et al have addressed this question by performing a retrospective analysis looking at the final pathology after RP in men with Gleason 3+4 on their biopsy. They found a decline in Gleason score in only 8 percent and an increase in 25 percent. Importantly, a PSA >10 ng/mL, having more than two cores positive or having a PSA density >0.15 were all associated with more unfavorable pathology. Although the study was retrospective, the data do support some of those concerns about selecting these men for AS. The authors discuss future tools that may help in the selection process including MRI, early re-biopsy and the use of serum markers. However, they omitted what may be the most important opportunity, which is to use genetic tests. For example, the Genomic Prostate Score can provide more accurate estimates of the likelihood of having organ confined disease or not having Gleason 4+4 or higher. One fact must be true; many of the men with Gleason 3+4 cannot be in danger otherwise the failure rates for men currently on AS for Gleason 3+3 would be much worse. The reason is we know that about 30 percent of them are under-graded when the biopsy is compared to the RP specimen.

The Bottom Line: Although this retrospective study raises concerns about selecting AS in men with a Gleason 3+4 on biopsy, a significant proportion of these men still are good candidates. But the real challenge is how to individually discriminate them from non-candidates.

a6p3c1 Another opportunity for assessing men with Gleason 3+4 could involve the measurement of single nucleotide polymorphisms. Wu et al performed such an analysis by measuring SNP rs2735839 and two other SNP's in men with Gleason less than 7 and those with Gleason 8 or higher. This one SNP was significantly more likely to be present in men with Gleason 4+3 or higher compared to the less aggressive cancers. Further studies are needed to validate and quantify the predictability of using these markers but clearly progress is being made in further identifying factors distinguishing low- and high-risk cancers.

The Bottom Line: Measuring specific SNP's may offer another way to differentiate low- and high-risk cancers.

RADICAL PROSTATECTOMY RATES RISING *(Continued from page 1)*

ble over the study period (about 8% and 10%, respectively), whereas RP rates rose from 30.6% to 41.3%, the researchers reported. The rates of combined EBRT plus ADT declined from 30.4% to 28.0% and BT rates fell from 8.7% to 4.1%. Rates of primary ADT dropped from 7.2% to 5.8%.

On multivariable analysis, the researchers found that black men were 48% less likely than whites to undergo RP versus RT. Individuals without insurance and those covered by Medicaid were 34% and 50% less likely, respectively, than those with private insurance to have RP rather than RT. Patients living in low-income areas also were less likely to undergo RP versus RT.

"I think one of the most surprising trends that we didn't expect to find was that, over the study period, the use of RP for patients went up by double digits across all risk groups," Dr. Gray told Renal & Urology News. "This was particularly striking for low-risk patients. While AS increased slightly for patients with low-risk disease, the absolute number of patients on AS was low, and, during this time, rates of surgery were increasing. This suggests that it is primarily the patients that would typically be treated with RT who are being placed on AS, not the patients who are primarily discussing AS versus RP with their urologist.

"The trend for increased use of surgery in high-risk disease is concerning," Dr. Gray added. "Many patients with high-risk disease who are undergoing surgery have indications for post-operative RT and perhaps hormonal therapy, and are therefore potentially being subjected to multiple treatments that can additively affect quality of life."

As for why black men are less likely than whites to undergo RP, the reasons are unclear. "One hypothesis is that the majority of RPs are occurring at large academic centers," Dr. Gray said. "There are ample data to suggest that racial minorities lack access to high quality medical care. Additionally, minorities who live in rural areas may not have the resources that would allow them to travel to a center which could offer RP. Other socioeconomic factors may also be at play given the correlation between higher income and the receipt of RP.

Renal and Urology News, October 2014

^{89}ZR-HUJ591 PET IMAGING

(Continued from page 2)

on ^{89}Zr-huJ591 study, while the conventional imaging modality was negative.

Conclusion: ^{89}Zr-huJ591 PET imaging of prostate-specific membrane antigen expression is safe and shows good localization of disease in prostate cancer patients. Liver is the critical organ for dosimetry, and 7 ± 1 days is the optimal imaging time. A larger study is underway to determine lesion detection in an expanded cohort of patients with metastatic prostate cancer.

GLEASON 7 PROSTATE CANCER

(Continued from page 3)

the clinical behavior of the intermediate-grade prostate cancer and for tailoring personalized treatment and post-treatment management, the authors concluded.

Medpage OncoBriefs, 4 October 2014

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