Insights for Urologists, Administrators and Case Managers

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Updates in UROLOGY Practice Management

Prepping Your Practice for a Prostate Cancer Clinic

Urologists have seen more advances in the treatment of metastatic castration-resistant prostate cancer (CRPC) in the last few years than they did in the previous few decades. Although this new era of innovation and advancement is exciting for physicians and important for patients, the onslaught of advances has left some urologists and urology practices rushing to adapt and stay up-to-date.

Once docetaxel was approved for the treatment of metastatic CRPC in 2004, patients with symptomatic advanced CRPC were frequently referred to a medical oncologist for treatment.

Now, patients with metastatic CRPC have multiple treatment options. The approval of Provenge, an immunotherapy, Zytiga, a CYP17 inhibitor, and Xtandi, an oral androgen receptor inhibitor, all of which extend survival in this disease setting, changed the landscape of treatment for CRPC, and allowed many urologists to keep patients with metastatic disease within their practice for a longer portion of their treatment. However, it has also meant that urology practices have to adapt their in-house capabilities, in many cases, by gaining more knowledge, more staff, and more space.

More Knowledge

One of the initial barriers to incorporating these new treatments into urology practices is often knowledge. The approval of these new therapeutics have come rapidly in the last five years, leaving little time for urologists to adjust to one drug before another is approved. Each of these newly approved drugs is unique, administered differently, and has certain challenges associated with it.

When Provenge was approved in 2010 it was the first cancer immunotherapy ever approved by the FDA.[1] Because Provenge is best suited in patients with asymptomatic or minimally symptomatic metastatic CRPC, the first challenge for urologists was to begin to more closely monitor their patients in order to catch metastatic disease as early as possible. Prostate specific antigen (PSA) is not always the best marker for tracking disease progression in these patients, and, unfortunately, there is currently little consensus on the optimal timing of imaging and bone scans (see sidebar on page 2). Therefore, it is important for any practice that decides to treat these patients to develop treatment protocols and pathways to help guide its physicians in the early identification of these patients.

Once a patient is identified as being a suitable candidate for Provenge, urologists are confronted by a series of challenges associated with the drug's administration. Patients receiving Provenge undergo three leukapheresis procedures at baseline, week two and week four.[2] Three days after leukapheresis is completed the patient presents to the physician's office for an IV infusion of Provenge. In addition, patients must premedicate with acetaminophen and an antihistamine.

Although Zytiga is an orally administered drug, it is also associated with a set of challenges for urologists who are not experienced with the drug. Patients must be educated to take Zytiga on an empty stomach and to take the pills at the same time each day. Additionally, in clinical trials Zytiga was associated with elevated levels of liver enzymes in up to 5% of patients treated with the drug. Therefore, physicians must monitor liver enzymes closely including a test at baseline, every two weeks for first 12 weeks of treatment, and monthly thereafter.[3]

Xtandi is also orally administered, but requires no laboratory monitoring or use of prednisone. However, some patients can experience fatigue, dizziness, or other side effects associated with the central nervous system.[4]

In-Office Drugs for Advanced Prostate Cancer Administered by Urologists

- Zytiga (abiraterone acetate)
- Xtandi (enzalutamide)
- Ketoconazole (Nizoral, Sebizole)
- Bicalutamide (Casodex)
- Zoledronic Acid (Zometa)
- Denosumab (Xgeva)
- LHRH agonists and antagonists
- Provenge (sipuleucel-T)

Despite these challenges, if a practice makes the decision to treat and monitor these patients, and develops a culture where that is a priority, the knowledge should follow in time, especially with the help of one or more physician champions.

More Staff

The administration of IV infusions as well as the increased need for monitoring of patients are just two examples of processes that may require more staff as urology practices incorporate these new treatment options.

A practice that anticipates treating patients with Provenge should hire a nurse or nurse practitioner that is trained in administering infusions. Depending on the volume of patients, this position could be per diem or may need to be full-time.

Provenge is not the only drug that requires a staff member familiar with infusions. Zometa is currently FDA approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors.[5] Administration of Zometa will require about an hour of nurse time for infusion and recovery period; however, there may be fewer people using Zometa since the approval of Xgeva, which has been shown to be superior to Zometa in clinical trials.[6]

Any increase in the number of patients treated in a practice would logically increase the expected number of prior authorizations. Prior authorization requirements may vary for each of these new drugs and may also vary by payer (see sidebar for example). Prior authorizations are nothing new to urologists, who have likely been required to submit them for many years in certain cases where patients need surgery or radiotherapy for their prostate cancer. The American Medical Association published results of a survey in 2010 that showed that physicians spend about 20 hours per week dealing with preauthorizations.[7] Another study published in 2011 estimated that U.S. nursing staff spent about 20.6 hours per physician in the practice per week interacting with payers, and that the total cost of time spent on these interactions amounted to about $83,000 per year per physician.[8]

Practices must be prepared to address how they will handle the completion of prior authorizations. For smaller practices, this could mean additional responsibilities for the person within the group who already processes prior authorizations, likely becoming a full-time role. However, larger practices dealing with a high volume of patients may see a significant increase in the time needed to complete these prior authorizations forms, and may have to hire additional staff to meet that need.

Additionally, for patients who are uninsured or underinsured, practices will have to have a staff member familiar with pharmaceutical companies' variety of rebates, discounts or payment assistant programs.

Prior Authorization Requirements

Preauthorization requirements may vary by the treatment type and the payer. For example, a payer may require one or more of the following for each patient requesting prior authorization for Zytiga:

- Diagnosis of metastatic castration-resistant prostate cancer (given in combination with prednisone)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Serum prostate-specific antigen (PSA) greater than or equal to 5 ng/mL
- Two sequential rising PSA levels obtained two or three weeks apart, or other evidence of disease progression
- Must not have severe hepatic impairment, New York Heart Association (NYHA) Class III or IV heart failure, or history of adrenal or pituitary gland disorders
- Serum potassium level between 3.5-5mEq/L

Source: Fallon Community Health Plan. Prior Authorization Approval Criteria. Zytiga (abiraterone). http://www.fchp.org/providers/pharmacy/~/media/Files/FCHP/Imported/Zytiga_abiraterone.pdf.ashx. Accessed September 26, 2014.

Priority Health. Priority Health Medicare prior authorization form. Zytiga (abiraterone). https://www.priorityhealth.com/~/~/media/documents/drug-auth-forms/t-z/zytiga-pa-medicare.pdf. Accessed September 26, 2014.

More Space

Finally, urology practices looking to expand their treatment of patients with metastatic CRPC may also need additional office space. As mentioned, both Zometa and Provenge are given as infusions. Patients coming in for these therapies will need somewhere comfortable to rest during their treatment. Although it is possible to use existing practice space for the administration of these infusions, that will decrease the amount of space available to see other patients.

In addition, some urology practices may be considering adapting their practice to administer chemotherapy in the future, especially as research continues on the optimal timing of chemotherapy (see article on page 4). If that is a possibility, investing in more space may be a necessity.

1. American Cancer Society. Cancer Vaccines. http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/immunotherapy-cancer-vaccines. Accessed September 26, 2014.
2. Provenge. Short therapy duration and sustained immune response. http://www.provengehcp.com/TheProvengeDifference/ShortTherapyDuration.aspx. Accessed September 26, 2014.
3. ZYTIGA [package insert]. Janssen Biotech Inc; May 2014.
4. XTANDI [package insert]. Astellas Pharma US Inc; September 2014.
5. ZOMETA [package insert]. Novartis; April 2014.
6. XGEVA [package insert]. Amgen; 2010-2014.
7. American Medical Association. New AMA survey finds insurer preauthorization policies impact patient care. http://www.ama-assn.org/ama/pub/news/news/survey-insurer-preauthorization.page. Accessed September 12, 2014.
8. Morra D, Nicholson S, Levinson W, et al. US Physician practices versus Canadians: spending nearly four times as much money interacting with payers. *Health Aff.* 2011;30:1443-1450.

Group Issues Recommendations for Early Detection of Metastases

In March 2014, a group of physicians from the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) Group published a set of recommendations for the optimal early identification of metastases in patients with prostate cancer, the presence or absence of which "is one of the most important factors influencing the selection of therapy in prostate cancer."[1]

The group was convened to study the current literature, but found no consensus of eligibility criteria, type of imaging modality or the frequency with which scans should be conducted. The recommendations set forth by the RADAR group require further validation and should be updated to include new and emerging information and technology.

1. Crawford ED, Stone NN, Yu EY, et al. Challenges and recommendations for early identification of metastatic disease in prostate cancer. *Urology.* 2014;83:664-669.

RADAR Group Recommendations for Early Detection of Metastases in Prostate Cancer

NEWLY DIAGNOSED PATIENTS	BIOCHEMICAL RECURRENT PATIENTS	M0 CASTRATE-RESISTANT PATIENTS
Scan high-risk patients and intermediate-risk patients with at least two of the following criteria positive: • PSA level greater than 10 ng/mL • Gleason score of 7 • Palpable disease (≥ T2b)	• First scan when PSA level between 5 and 10 ng/mL • Imaging frequency if negative for previous scan: Second scanning when PSA is 20 ng/mL and every doubling of PSA level thereafter (based on PSA testing every three months)	• First scan when PSA level of 2 ng/mL or greater • Imaging frequency if negative for previous scan: Second scanning when PSA is 5 ng/mL and every doubling of PSA level thereafter (based on PSA testing every three months)

Make the Transition to Prostate Cancer Clinic

As each practice begins to treat more patients with advanced prostate cancer, it must adapt and grow in a way that makes financial and practical sense. Below Ronald F. Tutrone, Jr., MD, FACS, CPI, of Chesapeake Urology Research Associates, Gordon A. Brown, DO, FACS, of Delaware Valley Urology, and Bryan A. Mehlhaff, MD, of Oregon Urology Institute, share details about their practices transitions.

Ronald F. Tutrone, Jr., MD, FACS, CPI: Our transition at Chesapeake Urology Research Associates was a very planned decision. We initially considered hiring a urologic oncologist until we realized that I am better geared toward treating these patients. These patients had been my patients for a long time and they were more comfortable staying with a urologist. When there is a change in specialist, the patient may view it as the physician throwing in the towel and saying, "I have nothing else to offer you." When it is a small group practice, two to three doctors, you have a limited number of advanced prostate cancer patients; when you have more than 50 urologists there tends to be a whole lot of these patients that fit the bill of metastatic vs. non-metastatic castrate-resistant prostate cancer (CRPC). Having this wealth of patients with this disease, we at Chesapeake Urology said, "We really need to address this oncoming storm."

The first thing we did was adopt Provenge into our practice, and made it an integral part of treating our metastatic minimally symptomatic patients with CRPC. We made the conscious effort of not just implementing a program but building a physical facility to treat patients. At first we were sort of "shooting from hip" and administering Provenge in exam rooms. However, we then realized they are getting an infusion and tying up that exam room for two hours was not practical.

Instead, we decided to lease space across from my office and build an infusion center. At the center, we have six cubicles with private televisions, curtains, windows, and lounge chairs and spaces to accommodate up to six patients getting Provenge infusions. We did a pro forma on how many patients we anticipated to treat and what the cost would be. The goals are to not lose money, provide a valuable treatment, and treat patients and improve their overall survival.

We also had to hire an administrator to simply manage advanced prostate cancer patients and facilitate the preapproval process of getting them coverage for Provenge. They also handled educating these patients about Provenge.

We are now at the end of our third year doing this. Initially, some doctors were slow to adapt it. It was a challenge capturing all of these patients, but overall, it has been a huge success in our office.

Gordon A. Brown, DO, FACS: When my practice began to incorporate more of these treatments into our practice capabilities, the decision was mostly a clinical one. In 2010, after the publication of the Provenge paper in *The New England Journal of Medicine*, I was one of the first urologists in the state of New Jersey to utilize Provenge. I wanted to try to give a survival advantage to patients with CRPC in my practice. Up to this point there existed limited treatment options for this patient population other than chemotherapy. With the advent of new therapies for management of the patient with advanced prostate cancer, we saw an opportunity to expand our care of this patient throughout their continuum of disease. This prompted the development of an advanced prostate cancer care model at Delaware Valley Urology.

Based on the hypothesis that prompt delivery of therapies proven to extend overall survival in this patient population was preferential, we developed an androgen deprivation clinic to identify early transition to CRPC. To do this successfully, we had to ensure we had the dedicated office space (infusion room), mid-level support, as well as administrative support to adequately identify, enroll, and monitor treatment of this patient population. We developed our androgen deprivation clinic by interrogating our EMR system to more efficiently identify patients and follow them prospectively.

Bryan Mehlhaff, MD: When we initially adopted each new therapy in our office, we focused on one treatment area to establish the confidence and consistency of the treatment. Once we felt that the process was standardized, it was then expanded to other interested physicians in our group in their treatment areas in our office. Some physicians prefer to internally refer to physicians that have an interest in advanced prostate cancer. We have the luxury of all of our physicians practicing out of the same office, which facilitates communication and establishes the best practices for the care of these patients.

The continuing challenge is identifying patients who are appropriate for the various therapies efficiently. We now review every patient on LHRH therapy monthly to be sure we are monitoring these patients for bone health, metastatic disease, and development of CRPC. This also allows us to review patients who might benefit from inclusion in a clinical trial.

Developing a Referral Pathway at Your Practice

Once a urology practice has made the decision to begin to treat more patients with metastatic castration-resistant prostate cancer (CRPC), and identified a physician champion to lead the effort, a process must be put in place to identify those patients who could benefit from these new therapies. Below Bryan A. Mehlhaff, MD, of Oregon Urology Institute, Ronald F. Tutrone, Jr., MD, FACS, CPI, of Chesapeake Urology Research Associates, and Gordon A. Brown, DO, FACS, of Delaware Valley Urology, share details about their practices methods for capturing these patients.

Bryan A. Mehlhaff, MD: Within my group, I have developed a pathway for treating patients with prostate cancer. Within this pathway are detailed descriptions of how a typical patient progresses, and where new treatment options fit in. We have this pathway, which also includes information on relevant clinical trials, posted throughout our clinical areas. This pathway allows us to approach these patients with a degree of standardization. If any of my partners have questions, or there is confusion about a treatment, they know we can review and discuss options. There has to be a comfort level among the doctors and staff to do that. Both staff and providers feel that we can make a difference in improving the survival and quality of the lives of our advanced prostate cancer patients.

Gordon A. Brown, DO, FACS: Within our practice, we identified one or two other physicians, in addition to me, who felt comfortable learning about these new therapies and had a desire to treat these patients. We developed our practice with the understanding that patients within the practice who met certain criteria would be referred on to us for treatment.

Initially, we screened for these patients by looking at CPT or J codes. We looked at patients who had diagnoses of 185 (prostate cancer) who were also receiving androgen deprivation therapy or patients who were on Xgeva. All of those patients were potential candidates for advanced prostate cancer clinic enrollment. Those patients were all screened for their symptomatology and their performance status, etc., essentially for the appropriateness of therapy and proper therapeutic selection.

Later, we began to try to do this on a more sophisticated level, and started to look at a quarterly basis for patients who were just on androgen deprivation therapy but did not yet have bone metastases and had a 185 diagnosis for their rising PSA. We were looking for these patients before they were metastatic to pull them from our records and enroll them in the clinic.

Ronald F. Tutrone, Jr., MD, FACS, CPI: We have an EHR and it really is a challenge to data mine to try to capture which patients have CRPC and metastatic disease. We assigned an administrator to use our records to capture all patients on hormonal therapy, and there were several thousand, then we made an Excel spreadsheet and tracked PSA levels to find patients who were castrate resistant. From there, we identified patients who were metastatic or non-metastatic and tracked when they were last scanned. Based on those results, we had the administrator contact that practicing physician to ask if they had considered using Provenge in that patient. That is how we do it to this day.

Future Directions: Combination Treatment with Hormonal, Chemotherapy

Research about the proper sequencing of the newer therapies for castration resistant prostate cancer is ongoing, but new studies are also being done to examine whether or not patients with hormone-naive metastatic prostate cancer should be given chemotherapy early in their treatment.

According to data from the CHAARTED study, the combination of standard androgen deprivation therapy (ADT) with six cycles of docetaxel conferred a significant overall survival benefit in men with hormone-sensitive prostate cancer compared to treatment with ADT alone. Data from the phase III ECOG-led trial were presented by Christopher J. Sweeney, MBBS, associate professor at Harvard Medical School, at the 2014 ASCO Annual Meeting.

According to Dr. Sweeney, the data attempt to provide answers to an ongoing debate about when chemotherapy should be introduced to patients with hormone-sensitive disease. Early chemotherapy could be beneficial to these patients because the therapy could attack de-novo testosterone independent clones early in the process, allowing ADT to keep prostate cancer in remission longer. In addition, if chemotherapy is delayed, by the time of disease progression some patients are too frail to undergo the treatment. On the other hand, by delaying chemotherapy, ADT will take

Continued on page 11

In mCRPC therapy...

Is there more to the story?

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

INDICATION

ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

IMPORTANT SAFETY INFORMATION

Contraindications—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.

Adverse Reactions—The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion.

The most common laboratory abnormalities (≥20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia.

Increased ZYTIGA® Exposures With Food—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Adrenocortical Insufficiency (AI)—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

mCRPC=metastatic castration-resistant prostate cancer; AST=aspartate aminotransferase; ALT=alanine aminotransferase.

Please see additional Important Safety Information on the next page.
Please see brief summary of full Prescribing Information on subsequent pages.

For men with mCRPC who progressed on ADT

In a clinical trial, patients had a median overall survival on ZYTIGA® (abiraterone acetate) of...*

More than 1,000 days. And every day tells a story.

35.3 MONTHS MEDIAN OVERALL SURVIVAL FOR ZYTIGA® plus prednisone† vs **30.1 MONTHS** with placebo plus prednisone (active compound).‡

5.2 MONTHS IMPROVEMENT IN MEDIAN OVERALL SURVIVAL compared with placebo plus prednisone.

Co-primary end point—overall survival: hazard ratio (HR)=0.792; 95% CI: 0.655, 0.956; *P*=0.0151; prespecified value for statistical significance not reached.

Co-primary end point—radiographic progression-free survival: median not reached for ZYTIGA® plus prednisone vs a median of 8.28 months for placebo plus prednisone. HR=0.425; 95% CI: 0.347, 0.522; *P*<0.0001.

IMPORTANT SAFETY INFORMATION (cont)

Increased ZYTIGA® Exposures With Food—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

Hepatotoxicity—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

*__Study Design:__ ZYTIGA®, in combination with prednisone, was evaluated in a phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients with mCRPC who had not received prior chemotherapy (N=1,088). Patients were using a luteinizing hormone-releasing hormone (LHRH) agonist or were previously treated with orchiectomy. In the ZYTIGA® arm, patients received ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily. In the placebo arm, patients received placebo orally once daily + prednisone 5 mg orally twice daily. In this study, the co-primary efficacy end points were overall survival (OS) and radiographic progression-free survival.

ADT=androgen-deprivation therapy.

Janssen Biotech, Inc.

Janssen
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Please see brief summary of full Prescribing Information on subsequent pages.

Drug Interactions—Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see Dosage and Administration (2.3)]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate drug. *In vitro*, ZYTIGA® inhibits CYP2C8. There are no clinical data on the use of ZYTIGA® with drugs that are substrates of CYP2C8. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

Use in Specific Populations—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

†At a prespecified interim analysis for OS, 37% (200/546) of patients treated with ZYTIGA® plus prednisone compared with 43% (234/542) of patients treated with placebo plus prednisone had died.

‡Prednisone, as a single agent, is not approved for the treatment of prostate cancer.

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Every day tells a story.

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ZYTIGA® (abiraterone acetate) Tablets
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE
ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS
Pregnancy: ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations]*.

WARNINGS AND PRECAUTIONS
Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1) in full Prescribing Information]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA *[see Adverse Reactions]*.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14) in full Prescribing Information]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions]*.

Hepatotoxicity: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2) in full Prescribing Information]*.

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Increased ZYTIGA Exposures with Food: ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions]*.
- Hepatotoxicity *[see Warnings and Precautions]*.
- Increased ZYTIGA Exposures with Food *[see Warnings and Precautions]*.

Clinical Trial Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Study 1: Metastatic CRPC Following Chemotherapy: Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥2.5X ULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT >5X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a ≥2% absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

	ZYTIGA with Prednisone (N=791)		Placebo with Prednisone (N=394)	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[2]	29.5	4.2	23.4	4.1
Muscle discomfort[3]	26.2	3.0	23.1	2.3
General disorders				
Edema[4]	26.7	1.9	18.3	0.8
Vascular disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6	0	7.6	0
Renal and urinary disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in Study 1

	Abiraterone (N=791)		Placebo (N=394)	
Laboratory Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hypertriglyceridemia	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Hypokalemia	28.3	5.3	19.8	1.0
Hypophosphatemia	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

Study 2: Metastatic CRPC Prior to Chemotherapy: Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0

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Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2 (continued)

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Edema peripheral, Pitting edema, and Generalized edema
[3] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of Study 2

	Abiraterone (N=542)		Placebo (N=540)	
Laboratory Abnormality	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia[1]	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

[1]Based on non-fasting blood draws

Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: non-infectious pneumonitis.

DRUG INTERACTIONS

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency *[see Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when

dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

In vitro, ZYTIGA inhibits CYP2C8. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category X *[see Contraindications].:* ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

Nursing Mothers: ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

Geriatric Use: Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with Hepatic Impairment: The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n=8) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (n=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2) in full Prescribing Information, Warnings and Precautions,* and *Clinical Pharmacology (12.3)] in full Prescribing Information.*

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Patients with Renal Impairment: In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3) in full Prescribing Information]*.

OVERDOSAGE

Human experience of overdose with ZYTIGA is limited.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

Storage and Handling: Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations]*.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

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cells out of cycle and be less responsive to cytotoxics. Some patients will respond to ADT for a long time, eliminating the need for chemotherapy.

The CHAARTED study was designed to test if administering docetaxel at the start of ADT for hormone-naive metastatic prostate cancer would prolong overall survival compared with ADT alone. The study included 790 men who were randomly assigned to ADT with or without six cycles of docetaxel 75 mg/m^2 every 21 days.

Data analysis showed that the median overall survival was increased from 44 months with ADT alone to 57.6 months with combined ADT and docetaxel (HR = 0.61; 95% CI, 0.47-0.80). The survival effect found with combined treatment was particularly strong among patients with high volume metastatic disease, where a 17-month improvement in median overall survival was seen (32.2 months for ADT vs. 49.2 months for ADT plus docetaxel; HR = 0.60; 95% CI, 0.45-0.81). No significant difference was seen in patients with low volume disease.

Additionally, combined therapy benefitted all subgroups analyzed in the study regardless of age, volume of disease, race, Gleason score, prior local therapy, or skeletal-related events.

As a secondary endpoint, the researchers looked at the number of patients able to achieve a PSA of less than 0.2 ng/mL at six and 12 months. Twice as many patients assigned to the combined therapy arm achieved this goal at six months (27.5% vs. 14.0%; $P < 0.0001$) and 12 months (22.7% vs. 11.7%; $P < 0.0001$). Patients assigned to ADT and docetaxel also had significantly improved median time to castration-resistant prostate cancer and clinical progression compared to patients assigned to ADT alone ($P < 0.0001$ for both).

Sweeney CJ. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): An ECOG-led phase III randomized trial. Abstract #LBA2. Presented at: 2014 ASCO Annual Meeting, Chicago.

What are the the potential implications of the CHAARTED trial results for urologists?

Gordon A. Brown, DO, FACS: From my perspective what that trial demonstrated is that those patients with high volume disease and bone metastases at the time of diagnosis have a survival advantage in the context of administering chemotherapy upfront. Generally speaking, prostate cancer patients progress slowly over time as opposed to showing up with high volume, bone metastases, being symptomatic, and with a PSA of 2,000. In that patient population it is compelling data and begs the question: Should we move chemotherapy earlier on? I think that the incidence of neuropathy and the toxicity of Taxotere in minimally symptomatic hormone-naive patients still precludes its use early on in the disease because we have other good options, both initially, as well as at the time of disease progression, some of which are orally available and are demonstrated to have a survival benefit. I don't think in the low burden patient with a good performance status that [chemotherapy] is the right choice up front, but in a high volume symptomatic patient it makes a lot of sense.

We are working towards being able to administer chemotherapy in our office, either by hiring a medical oncologist or training one of our physicians.

Ronald F. Tutrone, Jr., MD, FACS, CPI: The CHAARTED data provides strong data supporting the combined use of hormonal therapy with docetaxel in patients with high volume hormone-naive metastatic prostate cancer. It behooves any urologist starting their patient on ADT to discuss this important data in the select group that may benefit from this.

Bryan A. Mehlhaff, MD: The CHAARTED trial showed a very significant survival increase of 13 months in those patients treated with LHRH therapy combined with docetaxel chemotherapy, and 17 months in patients with more aggressive disease. The significance of these findings cannot be ignored. This trial began in 2006, which was before the other advanced treatments became available. It is unknown how the results of this trial would differ if patients were enrolled now with the other newer therapies available as the standard of care. Also, this category of patients, those who have metastatic disease at the time of initial diagnosis of prostate cancer, is fortunately a less common initial presentation. The challenge now will be to consider how chemotherapy fits into the management of advanced prostate cancer patients. More studies are needed to evaluate the appropriate sequencing of the bounty of new prostate cancer treatments.

James A. Sylora, MD: The long history of PSA screening has significantly reduced the number of patients presenting with widely metastatic disease. For the small number of patients who will present with widely metastatic disease, this option seems reasonable. The morbidity of early chemotherapy will likely preclude its use for early metastatic disease. I would still prefer Provenge, Zytiga, or Xtandi for hormone-refractory prostate cancer.

Q What was the key to your practice building a successful prostate cancer clinic?

Ronald F. Tutrone, Jr., MD, FACS, CPI: The key at our practice is that we have physician champions in prostate cancer. There used to just be a few of us, but we opened this up to all urologists in our group who would like to treat these patients and learn more. We have an education dinner every quarter where speakers come in and give talks about certain drugs and how the drugs are administered. We have formed groups that we call "pods," and there is an advanced prostate cancer champion within each pod who will attend these meetings to become educated about how to treat these patients. There is no longer a geographic barrier and patients have access to a champion without having to drive 20 or 30 miles to see me.

Bryan A. Mehlhaff, MD: The number one key to having a successful prostate cancer clinic was having a physician champion. I had to go to advisory boards and come back with an understanding of those new therapies. I had to talk with partners and staff and get things organized. Another key step was buy-in. One by one each partner had one of their patients that they were closest with reach a point in their disease where these treatments could really make a difference. Once that happened they were on board.

Gordon A. Brown, DO, FACS: The key in my practice was me, or having a physician champion. I had a desire to take care of these patients because I felt it was within my realm. We are a large group and had a lot of infrastructure in place, in terms of physician assistants and nurse practitioners and people to help give us administration support for pre-certification. We had the resources that made it easier to develop. Where it becomes challenging is in a smaller practice that has a very high patient volume, and where it is, in many cases, easier for the provider to send the patient to someone else as opposed to dealing with the patient internally. We never viewed this as a revenue stream per say, but as a continuum of care and a quality of care issue. We wanted to maintain relationships, and we felt that with the advent of newer therapies we could deliver that treatment as effectively and help to ensure patient outcomes were appropriate until they needed chemotherapy.

James A. Sylora, MD: My practice is only partially on the way to having built a prostate cancer clinic. The key, so far, has been a physician champion who is eager to treat these patients with these new therapies. One of the hardest parts has been getting urologists, someone trained to think surgically to switch their mindset and become more medical.

> *"The number one key to having a successful prostate cancer clinic was having a physician champion."*

Patient Description:

A 63-year-old man presents to your office for follow-up. The patient has a history of intermediate-risk disease for which he underwent RALP and adjuvant radiotherapy. Three years post-op his PSA begins to increase to 9.1.

The patient underwent a bone scan, which was negative. The patient has a history of hypertension, for which he is currently taking antihypertensive agents. His liver function tests are within normal limits. The patient was assigned an LHRH antagonist, which he continued for 2.5 years.

His PSA subsequently increased again to 1.5 with a testosterone level of 18 ng/dL. Bicalutamide was added to his therapy and six months later his PSA had increased again to 3.5 ng/mL. Although the patient is symptomatic, evaluation showed three to six metastases in the spine and one in the hip.

What are treatment options for this patient, and how would you monitor their disease progression?

Ronald F. Tutrone, Jr., MD, FACS, CPI: This patient has symptomatic metastatic castration-resistant prostate cancer (CRPC). I would stop bicalutamide and start him on either Zytiga/prednisone or Xtandi, and consider the addition of Xofigo if his symptoms do not improve after two to three months.

Bryan A. Mehlhaff, MD: Treatment with Provenge, Zytiga, and now Xtandi prior to chemotherapy are options for this patient. If a patient is a candidate for Provenge, we will consider this first. In fact, we avoid the use of bicalutamide as a secondary hormonal maneuver in favor of offering these other treatments with known survival advantage. Following Provenge, we transition patients to Zytiga, the timing of initiating this second therapy depends on the patient's course. Now Xtandi is also an option for these patients. Monitoring continues with periodic imaging and attention to any new patient complaints that might indicate clinical progression. Laboratory monitoring with a comprehensive metabolic panel, and PSA level is done monthly if the patient is on Zytiga. Periodic check of total testosterone and complete blood count is also warranted.

Gordon A. Brown, DO, FACS: Now that Provenge and Zytiga are both options in the prechemotherapy setting, either would be a good option for this patient. I tend to give Provenge first and then use Zytiga after. The idea here is to delay chemotherapy because of its toxicity.

With that being, said we will often transition patients onto Zytiga after Provenge.

Zytiga monitoring currently requires that you look at baseline metabolic panels, liver function tests including bilirubin, as well as looking at blood pressure and for signs or symptoms of peripheral edema prior to initiation of therapy. It is also recommended that you follow the patient with liver function tests and bilirubin every two weeks for the first three months and every month thereafter. I also get a metabolic panel once a month to look at potassium. As far as monitoring PSA, I would look at their PSA starting at two months after they start Zyitga and then on a monthly basis. I do not transition patients off of Zytiga because of PSA progression alone. I like to document that they have had radiographic or clinical progression of their disease.

James A. Sylora, MD: The options of treatment would include Provenge, Zytiga and Xtandi. I would prefer to use Provenge initially and follow with one of the oral agents later.

Patient Description:

A 62-year-old man underwent a simple prostatectomy for T3a Gleason 4+3=7 in 2007. His postoperative PSA nadired at 0.5 ng/mL, but at three months past his operation it increased to 0.7. The patient underwent salvage external beam radiotherapy. His PSA went to 0.1 ng/mL, but at two years past his operation it increased to 3.6 ng/mL. A bone scan showed to metastases at L5 and left sacrum. A CT showed no nodes.

The patient was started on hormonal therapy and his PSA went to <0.1 ng/mL. A baseline DEXA scan showed osteopenia and the patient was started on denosumab 120 mg subcutaneously monthly for prevention of skeletal-related events.

In 2013, his PSA began to increase from 0.1 ng/mL to 0.5 ng/mL then 1.1 ng/mL. Testosterone was less than 15. The patient received three infusions of Provenge, which he tolerated well. His PSA one-month post-Provenge increased further to 5.7 ng/mL. A follow-up bone scan showed increasing bone metastases and the patient began to have some back pain that was relieved with occasional Lortab.

What are the next steps for this patient?

Ronald F. Tutrone, Jr., MD, FACS, CPI: Following Provenge it is not unusual for the patient's PSA to continue to increase. In a patient like this we would typically recommend a bone scan every six months to a year. If there is a large increase in the PSA, we might increase that to a bone scan every three months.

I would consider this patient a good candidate for Zytiga. He already received Provenge and does not have visceral metastases, so this is where Zytiga is indicated for castration-resistant prostate cancer (CRPC) prior to chemotherapy. Using Zytiga, this patient could see as much as a 4.5-month survival advantage. The other option for this patient would have been ketoconazole, but the patient does not get the same long-term benefit with that treatment. If the patient continues to have back pain, he could also be started on Xofigo, which would not only alleviate the back pain but provides a 2.6-month survival advantage as well.

Bryan A. Mehlhaff, MD: There are three treatments that the patient could receive. He can go on Zytiga oral medication, or he is also a candidate for Xofigo the radiopharmaceutical. In my office this patient would probably be enrolled in a clinical trial that we have going on where he would get both. Zytiga is an androgen synthesis inhibitor. The idea is that the tumor cell itself is making androgen and stimulating itself. Zytiga can be very effective at not only lowering PSA but, most importantly, the patient feels better as the progression of his disease is slowed or halted. Now Xtandi is also an option. I would see this patient month to month. Finally, this patient should be maintained on monthly Xgeva to prevent skeletal-related events, and there is additional evidence that Xgeva can decrease the development of new bony metastatic disease.

Gordon A. Brown, DO, FACS: It is interesting because from a prostate cancer perspective I think this patient should go right onto Zytiga and prednisone combination. This combination may give him some symptomatic relief, will significantly extend his survival, and delay his time to chemotherapy and his time to requiring continuous narcotics for his bone-related pain. With respect to his skeletal-related event, Xofigo is available now, which was not in the last six to 12 months. Xofigo is a radionuclide that is FDA-approved for treatment of patients with bone metastases, and will actually extend survival in patients with metastatic CRPC and bone metastases. It is the first bone-directed agent that has been demonstrated to improve survival.

Xofigo and Zytiga are usually administered sequentially, but patients can have overlapping Zytiga and Xofigo. One does not necessarily take the place of the other. Radiation oncologists are administering the radium; urologists are not, but a lot of urologists now have access to radiation oncologists in their practice.

The other thing that should be mentioned is the ongoing use of Xgeva. Xgeva needs to be administered on a monthly basis, and the physician has to monitor calcium levels and follow the patient appropriately with scans.

James A. Sylora, MD: To treat this patient a physician should consider something like Zytiga as a pre-chemotherapy treatment. Because the patient also had symptomatic bone metastases, you could also consider Xofigo.

Physician Participants

The following physicians have contributed their knowledge and experience to the preparation of the content of this newsletter.

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Ronald F. Tutrone, Jr., MD, FACS, CPI, is chief of urology at the Greater Baltimore Medical Center, and medical director at Chesapeake Urology Research Associates. Dr. Tutrone has experience in the treatment of urologic malignancies, including kidney, bladder and prostate, lapropscopic treatment of renal and adrenal tumors, kidney stone treatment, urinary incontinence, and prostate disorders. Dr. Tutrone earned his medical degree from Rutgers University Medical School. He is certified by the American Board of Urology and is a fellow of the American College of Surgeons.

Bryan A. Mehlhaff, MD

Bryan A. Mehlhaff, MD, is a urologic oncologist and medical director of research at the Oregon Urology Institute. He gained experienced in adult and pediatric urology, endourology, and minimally invasive surgery as an assistant urology professor at Albany Medical College before entering private practice. Dr. Mehlhaff earned his medical degree from Oregon Health Sciences University. He is certified as a medical physician and surgeon by the Oregon Board of Medical Examiners and by the American Board of Urology.

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James A. Sylora, MD, is the president of Associated Urological Specialists, LLC in Palos Heights, Ill. Dr. Sylora earned his medical degree from Loyola University Stritch School of Medicine. His residency was at the University of Minnesota. He is board certified by the American Board of Urology. He has special interest in robotic surgery for the treatment of prostate, kidney and bladder cancer.

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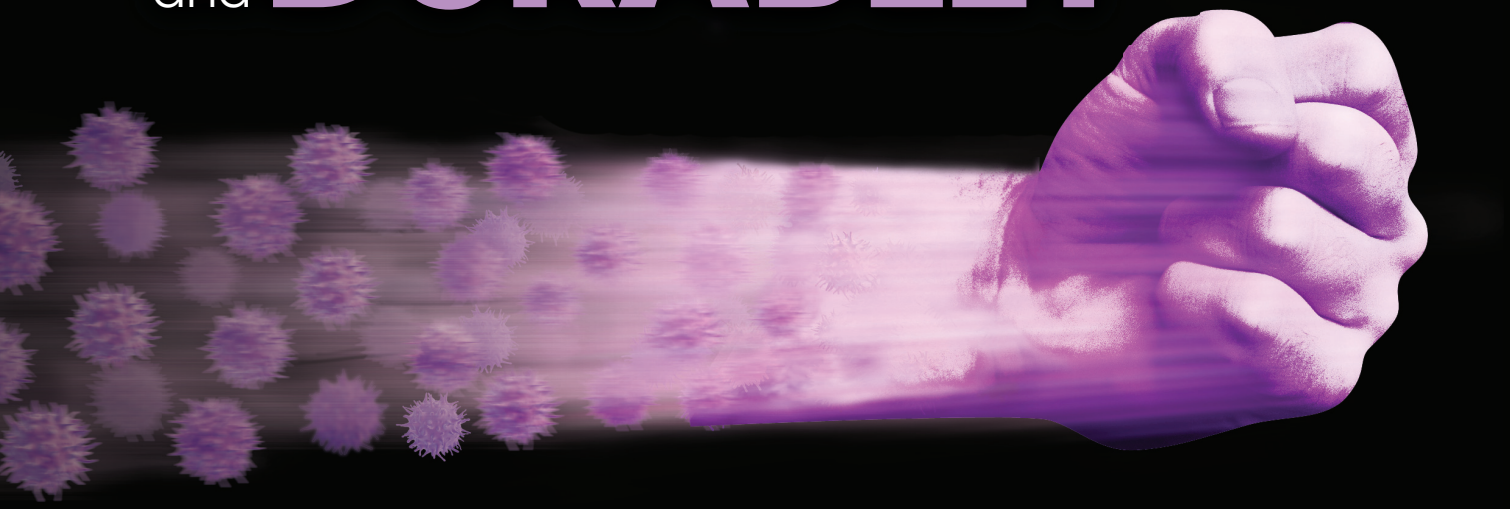

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