

The Pace of Medicine

By Peg Ford

I was astonished at the pace at which the medical world functions when I went through my health crisis facing ovarian cancer 6 years ago. It was nothing compared to what I was to learn of the strides being made by the research and scientific world! I certainly had no idea I would be caught up in such speed when I became an advocate. I was slightly aware of how fast breakthroughs can change medicine, but I truly had no appreciation of how much, and how quickly, until my efforts and commitment to be an informed advocate took hold. Here are my reflections for the last half of 2012—a short summary of some of the activities!

In June 2012, a week before the US Supreme Court ruled on the Affordable Care Act, I was in Washington, DC, attending the 13th Annual Patient Congress of the Patient Advocate Foundation (PAF) as a member of the National Patient Advocate Foundation's (NPAF) volunteer Elite President's Council. After a full intense day of preparation, my fellow advocates and I, representing 39 states, called on Capitol Hill to visit with elected officials. We presented extremely important initiatives: Prescription Drug User Fee Act Reauthorization Drug Shortages and Breakthrough Therapies, Safeguarding the Patient Protection Provisions of Patient Protection Affordable Care Act, and Patients' Access to Treatments Act of 2012.

NPAF has been a leader in patient advocacy since 1996, focusing its activities on health policies determined to have the greatest impact on patients with chronic, debilitating, and life-threatening diseases to represent the majority of patients served by PAF, NPAF's companion organization (www.patientadvocate.org). More than 100,000 patients in all 50 states were provided case management assistance by PAF in 2011, and more than 5 million received online assistance.

Two weeks after my trip to DC, I traveled to the Dartmouth Institute for Health Policy & Clinical Practice at Dartmouth College in Hanover, New Hampshire, to participate as a patient advisor in a symposium at the Summer Institute for Informed Patient Choice entitled, "Measuring Shared Decision Making in Practice." Sessions and breakout groups discussed issues ranging from patient decision aids to identifying measurable outcomes. I also participated in a panel review on the last day to review and provide reactions to the priorities that the breakout



Peg Ford with Kay Dickersin, PhD, Professor and Director, Center for Clinical Trials, Johns Hopkins Bloomberg School of Public Health, and Director, US Cochrane Center, at the Evidence-Based Guidelines Affecting Policy, Practice and Stakeholders conference.

groups developed over the course of the 2 prior days (<http://tdi.dartmouth.edu>).

A month later, in August, I again traveled to the DC area for an FDA Training Workshop, as I received an official appointment as a member of the Office of Special Health Issues (OSHI) FDA Patient Representative Program. As stated on the OSHI website, "The Patient Representative is responsi-

On October 7, 2012, at the opening dinner of the Scripps Cancer Center's 32nd Annual Oncology Nurses Symposium, I was thrilled to be the keynote speaker, addressing 268 attendees from across the country and around the world convened at the Hilton San Diego Resort in California. I spoke on the topic, "Ovarian Cancer—the Silent Killer! NOT ANYMORE!"

It was heartwarming to hear the presentations and discussions focusing on issues vital to the patient community: communication, coordination, and shared decision making to involve and empower patients to participate in their own medical choices and care.

ble for providing the Food and Drug Administration (FDA) and the advisory committee the unique perspective of patients and family members directly affected by a serious or life-threatening disease." Further information can be found at the FDA's website www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates.

However, I also took the opportunity to share not only the success of the Survivors Teaching Students (STS): Saving Women's Lives program of the Ovarian Cancer National Alliance in San Diego, but also the value of our nurses, as perceived by patients. My opening remarks were "I am not a medical professional or healthcare provider

or researcher. I am a human being, patient, survivor, and advocate. I do not mean to imply the others mentioned are not human, but rather, I believe many are 'Angels in human form.' I hope to explain the ways in which I have arrived at this conclusion, and share about a grassroots movement happening across the country to give a voice and face to a matter of great urgency—ovarian cancer!" Cathleen Sugarman, RN, MSN, AOCNS, an oncology advanced practice nurse at Scripps Memorial Hospital in La Jolla, California, and course director, stated in her much-appreciated thank you note "You are a beacon of shining light. You inspired many nurses that evening with your enthusiasm for life and the work you have chosen as an ovarian cancer survivor."

At the end of October, I attended the American Association for Cancer Research Fifth Annual Conference in San Diego on the Science of Cancer Health Disparities in racial/ethnic minorities and the medically underserved. Much insightful information was presented, from design and strategies for clinical trials for recruitment of diverse populations, to racial-ethnic disparities in patient-provider communication, as well as overall perceptions among adult cancer survivors of the quality of follow-up care (www.aacr.org).

In November, I attended the American Society of Clinical Oncology (ASCO) Quality Care Symposium, where the 200 anticipated attendees grew to more than 600 individuals attending this, the first meeting of its kind! It was heartwarming to hear the presentations and discussions focusing on issues vital to the patient community: communication, coordination, and shared decision making to involve and empower patients to participate in their own medical choices and care. The learning objectives included reviewing the evidence base in quality research, with a focus on comparative effectiveness studies and patient-centered outcomes research, as well as evaluating opportunities for further research to improve the quality of cancer care, including disparities research, communication, and decision-making research. It was a special pleasure to see that ASCO included a presentation by Michael L. Kappel on the patient perspective (<http://quality2012.asco.org>).

I was especially delighted to attend a presentation on ASCO's innovative new program, CancerLinQ. ASCO

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is taking a leadership role with its plan “to create a searchable knowledge bank—composed of information culled from millions of medical records provided by partner physicians that will yield specific, detailed information about presenting symptoms, courses of treatment, side effects, outcomes and more.” This peer-reviewed, real-time, evidence-based healthcare technology not only will be at the fingertips of physicians and researchers, but also eventually will be a portal for patients to access! See www.conquercancerfoundation.org for information about this program.

The year 2012 included one more trip to the East Coast, this time to New York City in early December to attend the Evidence-Based Guidelines Affecting Policy, Practice and Stakeholders conference at the New York Academy of Medicine. Two full days focused on guidelines and involved all stakeholders, with breakout sessions covering such topics as how to develop pragmatic and trustworthy guidelines; how to close the gap between guidelines and clinical education; and how to incorporate consumers, including patients, in guideline development.

I sense that 2013 will provide ample opportunities for...more of this movement in which patients will play an increasingly active role, along with their providers, in their medical choices and care.

Coupling this with facilitating presentations for the STS program, it certainly has been quite a hectic year! The Ovarian Cancer Advocacy Alliance of San Diego (OCAA), with help from our volunteer ovarian cancer survivors, completed 27 STS presentations to 672 attendees, including third-year medical students at the University of California San Diego School of Medicine, physician assistants and nurse practitioners at Kaiser Permanente, and nursing students at 10 schools of nursing in San Diego County.

Oh yes, 2013 is already kicking it up a notch with our announcement of a companion program for OCAA: HEAR (H: Hope, E: Experiences, A: Awareness, R: Risks), a community

outreach program developed for civic organizations. “If Only I Knew Then, What I Know Now!” is the title of the new presentation by ovarian cancer survivors, who share their personal stories to increase individuals’ awareness of the symptoms and risk factors

of ovarian cancer to help empower women to be aware of their bodies and help spread the word about ovarian cancer awareness throughout the general public in San Diego County. In addition, I will be attending the Gynecologic Oncology Group

86th Semi-Annual Meeting and MD Anderson Cancer Center’s 15th International Symposium on Anti-Angiogenic Therapy, as well as traveling to Portland, Oregon, in late January for the Summit Regional Meeting of NPAF’s Elite President’s Council to



XTANDI® (enzalutamide) capsules for oral use
Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION
The following is a brief summary; please see the package insert for full prescribing information.

INDICATIONS AND USAGE
XTANDI is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

CONTRAINDICATIONS
Pregnancy
XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. XTANDI is not indicated for use in women. XTANDI 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
Seizure
In the randomized clinical trial, 7 of 800 (0.9%) patients treated with XTANDI 160 mg once daily experienced a seizure. No seizures occurred in patients treated with placebo. Seizures occurred from 31 to 603 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy and all seizures resolved. There is no clinical trial experience re-administering XTANDI to patients who experienced seizures. The safety of XTANDI in patients with predisposing factors for seizure is not known because these patients were excluded from the trial. These exclusion criteria included a history of seizure, underlying brain injury with loss of consciousness, transient ischemic attack within the past 12 months, cerebral vascular accident, brain metastases, brain arteriovenous malformation or the use of concomitant medications that may lower the seizure threshold. Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

ADVERSE REACTIONS
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 practice. In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer who had previously received docetaxel, patients received XTANDI 160 mg orally once daily (N = 800) or placebo (N = 399). The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. All patients continued androgen deprivation therapy. Patients were allowed, but not required, to take glucocorticoids. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids. All adverse events and laboratory abnormalities were graded using NCI CTCAE version 4. The most common adverse drug reactions (≥ 5%) reported in patients receiving XTANDI in the randomized clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in the randomized clinical trial that occurred at a ≥ 2% absolute increase in frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in the Randomized Trial

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions ^a	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal And Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0

(continued) Table 1. Adverse Reactions in the Randomized Trial

	XTANDI N = 800		Placebo N = 399	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Gastrointestinal Disorders				
Diarrhea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness ^b	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders ^c	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections And Infestations				
Upper Respiratory Tract Infection ^d	10.9	0.0	6.5	0.3
Lower Respiratory Tract And Lung Infection ^e	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal And Urinary Disorders				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning And Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin And Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

Laboratory Abnormalities
In the randomized clinical trial, Grade 1-4 neutropenia occurred in 15% of patients on XTANDI (1% Grade 3-4) and in 6% of patients on placebo (no Grade 3-4). The incidence of Grade 1-4 thrombocytopenia was similar in both arms; 0.5% of patients on XTANDI and 1% on placebo experienced Grade 3-4 thrombocytopenia. Grade 1-4 elevations in ALT occurred in 10% of patients on XTANDI (0.3% Grade 3-4) and 18% of patients on placebo (0.5% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of patients on XTANDI and 2% of patients on placebo.
Infections
In the randomized clinical trial, 1.0% of patients treated with XTANDI compared to 0.3% of patients on placebo died from infections or sepsis. Infection-related serious adverse events were reported in approximately 6% of the patients on both treatment arms.
Falls and Fall-related Injuries
In the randomized clinical trial, falls or injuries related to falls occurred in 4.6% of patients treated with XTANDI compared to 1.3% of patients on placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and hematomas.
Hallucinations
In the randomized clinical trial, 1.6% of patients treated with XTANDI were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

participate in developing our Action Plan for legislative issues for 2013.

After having attended the Salzburg Global Seminar on “The Greatest Untapped Resource in Healthcare? Informing and Involving Patients in Decisions about Their Medical Care” in Austria in December 2010—where 58 people from 18 countries fashioned

“The Salzburg Statement on Shared Decision Making,” calling on “patients and clinicians to work together to be co-producers of health”—I have a renewed sense of hope for a paradigm shift in healthcare. I sense that 2013 will provide ample opportunities for what I consider to be the great honor of witnessing more of this movement

in which patients will play an increasingly active role, along with their providers, in their medical choices and care. (“The Salzburg Statement on Shared Decision Making” was published in the September 2011 issue of *The Oncology Nurse-APN/PA*. Please go to <http://www.theoncologynurse.com/> to access the article.)

Happy New Year! ●

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-----**DRUG INTERACTIONS**-----

Drugs that Inhibit or Induce CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide in healthy volunteers. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dose of XTANDI [see *Dosage and Administration (2.2) and Clinical Pharmacology (12.3)*].

The effects of CYP2C8 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of XTANDI with strong or moderate CYP2C8 inducers (e.g., rifampin) may alter the plasma exposure of XTANDI and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP2C8 induction potential is recommended [see *Clinical Pharmacology*].

Drugs that Inhibit or Induce CYP3A4

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3 fold in healthy volunteers [see *Clinical Pharmacology (12.3)*].

The effects of CYP3A4 inducers on the pharmacokinetics of enzalutamide have not been evaluated *in vivo*. Co-administration of XTANDI with strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine) may decrease the plasma exposure of XTANDI and should be avoided if possible. Selection of a concomitant medication with no or minimal CYP3A4 induction potential is recommended. Moderate CYP3A4 inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John’s Wort may also reduce the plasma exposure of XTANDI and should be avoided if possible [see *Clinical Pharmacology*].

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady state, XTANDI reduced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozone, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring [see *Clinical Pharmacology*].

-----**USE IN SPECIFIC POPULATIONS**-----

Pregnancy. Pregnancy Category X [see *Contraindications*].

XTANDI can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of XTANDI in pregnancy and XTANDI is not indicated for use in women, it is important to know that maternal use of an androgen receptor inhibitor could affect development of the fetus. XTANDI 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 XTANDI.

Nursing Mothers

XTANDI is not indicated for use in women. It is not known if enzalutamide 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 XTANDI, 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 XTANDI in pediatric patients have not been established.

Geriatric Use

Of 800 patients who received XTANDI in the randomized clinical trial, 71 percent were 65 and over, while 25 percent were 75 and over. No overall differences in safety or effectiveness were observed between these 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 Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic castration-resistant prostate cancer and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] ≤ 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed [see *Clinical Pharmacology*].

Patients with Hepatic Impairment

A dedicated hepatic impairment trial compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild or moderate hepatic impairment (Child-Pugh Class A and B, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild or moderate baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. Baseline severe hepatic impairment (Child-Pugh Class C) has not been assessed [see *Clinical Pharmacology*].

-----**OVERDOSAGE**-----

In the event of an overdose, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizures following an overdose.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of enzalutamide.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay. Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4- and 13-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (PATIENT INFORMATION).

- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Each capsule should be swallowed whole. Do not chew, dissolve, or open the capsules.
- Inform patients receiving a GnRH analog that they need to maintain this treatment during the course of treatment with XTANDI.
- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.
- Inform patients that XTANDI may cause dizziness, mental impairment, paresthesia, hypoesthesia, and falls.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their physician. Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day.
- Apprise patients of the common side effects associated with XTANDI: asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Inform patients that XTANDI may be harmful to a developing fetus. Patients should also be informed that they should use a condom if having sex with a pregnant woman. A condom and another effective method of birth control should be used if the patient is having sex with a woman of child-bearing potential. These measures are required during and for three months after treatment with XTANDI.

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