Newsletter

Prostate Cancer 101, Inc.

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The Prostate Cancer Information and Support Group of the Mid-Hudson

ZYTIGA® (abiraterone acetate) Plus Prednisone Approved for Treatment of Earlier Form of Metastatic Prostate Cancer

New indication for ZYTIGA® in combination with prednisone provides treatment option for patients with metastatic high-risk castration-sensitive prostate cancer

Findings from pivotal Phase 3 LATITUDE clinical trial data demonstrated statistically significant and clinically meaningful improvements in patients

HORSHAM, PA, February 8, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced that the U.S. Food and Drug Administration (FDA) has approved a new indication for ZYTIGA® (abiraterone acetate) in combination with prednisone for the treatment of patients with metastatic high-risk castration-sensitive prostate cancer (CSPC). The approval is based on Phase 3 data from the pivotal LATITUDE clinical trial, which found that in patients with metastatic high-risk CSPC, ZYTIGA® in combination with prednisone reduced the risk of death by 38 percent compared to placebos.

"LATITUDE was a large global trial which produced impressive and clinically significant results in overall survival," said Karim Fizazi, M.D., Ph.D., Principal Investigator and Head of the Medical Oncology Department at Institute Gustave Roussy, Villejuif, France. "With today's approval, abiraterone acetate plus prednisone could become a standard of care for patients with metastatic high-risk castration-sensitive prostate cancer."

"Today's approval marks an important step in addressing the unmet needs of patients with metastatic high-risk castration-sensitive prostate cancer by providing an option that has demonstrated improvement in overall survival," said Andree Amelsberg, M.D., Vice President of Oncology Medical Affairs at Janssen Biotech, Inc., part of the Janssen Pharmaceutical Companies of Johnson & Johnson. "This milestone is an exciting turning point for researchers and clinicians, and most importantly, for patients suffering from this disease and their families who now have an important additional therapeutic option."

LATITUDE was a multinational, multicenter, randomized, double-blind, placebo-controlled clinical trial that examined the use of ZYTIGA® 1,000 mg once daily in combination with prednisone 5 mg once daily, compared to placebos (N=1,199) in patients with newly diagnosed, metastatic high-risk CSPC, who had not received prior cytotoxic chemotherapy. All the patients received a gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The study data were presented at the plenary session of the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, and simultaneously published in The New England Journal of Medicine.[1]

The study showed ZYTIGA® in combination with prednisone reduced the risk of death by 38 percent compared to placebos (median OS not estimable vs. 34.7 months, respectively; hazard ratio (HR)=0.62; 95% confidence interval (CI): [0.51, 0.76],

p < 0.0001). Additional data demonstrated statistically significant delay in time to initiation of chemotherapy for patients in the ZYTIGA® arm compared to those in the placebo arm (median time to initiation of chemotherapy not reached vs. 38.9 months, respectively; HR=0.44; 95% CI: [0.35, 0.56], p < 0.0001).

The most common adverse reactions (≥10%) that occurred more commonly (>2%) in the ZYTIGA® arm from an analysis of pooled safety data were fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough and headache.

On November 20, 2017, the European Commission (EC) granted approval to broaden the marketing authorization for ZYTIGA® in combination with prednisone or prednisolone to include newly-diagnosed high-risk metastatic hormone-sensitive prostate cancer (HSPC). Similar submissions have been made in Japan, Canada, Mexico, Switzerland, Singapore, and the Philippines, and approved in Brazil and Taiwan. If approved, these submissions will broaden the use of ZYTIGA® in combination with prednisone or prednisolone to include an earlier stage of prostate cancer than its current indications.

Metastatic prostate cancer is cancer that has spread to another part of the body.[2] Metastatic castration-sensitive prostate cancer (CSPC), also referred to as metastatic hormone-sensitive prostate cancer (HSPC) in literature, refers to prostate cancer that still responds to testosterone suppression therapy.[2] Patients with newly-diagnosed metastatic disease and high-risk disease characteristics tend to have a poorer prognosis.[3]

About the LATITUDE Clinical Trial[4]

The Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled LATITUDE study enrolled 1,199 patients with newly diagnosed metastatic, high-risk castration-sensitive prostate cancer (CSPC), who had not received prior cytotoxic chemotherapy. The study was conducted at 235 sites in 34 countries in Europe, Asia-Pacific, Latin America, and Canada. A total number of 597 patients were randomized to receive ZYTIGA® plus prednisone, while 602 patients were randomized to receive placebo. All patients received a gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. High-risk disease was defined as having at least two of three risk factors at baseline: a total Gleason score of ≥8, presence of ≥3 lesions on bone scan, and evidence of measurable visceral metastases. Patients with significant cardiac, adrenal, or hepatic dysfunction were excluded. The median duration of treatment with ZYTIGA® and prednisone was 24 months.

About ZYTIGA®

ZYTIGA® (abiraterone acetate) in combination with prednisone is indicated for the treatment of patients

- with metastatic castration-resistant prostate cancer (CRPC)
- with metastatic high-risk castration-sensitive prostate cancer (CSPC)

Since its first approval in the U.S. in 2011, ZYTIGA® has been approved in combination with prednisone or prednisolone, in 105 countries. More than 330,000 patients worldwide, including 113,000 in the U.S., have received treatment with it, and it was the number one prescribed oral medication in the U.S. for patients with metastatic CRPC in 2016.

For more information about ZYTIGA®,visit www.ZYTIGA.com.

IMPORTANT SAFETY INFORMATION

Contraindications - ZYTIGA® (abiraterone acetate) can cause fetal harm and potential loss of pregnancy.

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)]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment.

Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, such as those with heart failure, recent myocardial infarction, cardiovascular disease, or ventricular arrhythmia. The safety of ZYTIGA® in patients with left ventricular ejection fraction <50% or New York Heart Asso-

ciation (NYHA) Class III or IV heart failure (in COU-AA-301) or NYHA Class II to IV heart failure (in COU-AA-302 and LATITUDE) has not been established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14)]*.

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. Monitor patients 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.

Hepatotoxicity - In postmarketing experience, there have been ZYTIGA®-associated severe hepatic toxicities, including fulminant hepatitis, acute liver failure and deaths. Measure serum transaminases alanine aminotransferase (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 upper limit of normal (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 (2.4)]*.

Permanently discontinue ZYTIGA® for patients who develop a concurrent elevation of ALT greater than 3X ULN and total bilirubin greater than 2X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

The safety of ZYTIGA® retreatment 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.

Adverse Reactions - The most common adverse reactions (≥10%) are fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory tract infection, cough, and headache.

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

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 enzymes CYP2D6 and CYP2C8. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, consider a dose reduction of the CYP2D6 substrate drug. In a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46% when administered with a single dose of ZYTIGA®. Patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA®.

Use in Specific Populations

- **Females and Males of Reproductive Potential: Advise males with female partners of reproductive potential to use effective**

contraception.

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

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science.

We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Research & Development, LLC and Janssen Biotech, Inc. are part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding the impact of the approval of an expanded indication for ZYTIGA® (abiraterone acetate) and potential approvals and broadened use of ZYTIGA® in combination with prednisone or prednisolone. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Biotech, Inc., any of the other Janssen Pharmaceutical Companies and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 1, 2017, including under "Item 1A. Risk Factors," its most recently filed Quarterly Report on Form 10-Q, including in the section captioned "Cautionary Note Regarding Forward-Looking Statements," and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. Neither the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

[1] Fizazi K., et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. New England Journal of Medicine. June 2017.

[2] American Society of Clinical Oncology. Prostate Cancer: Treatment Options. http://www.cancer.net/cancer-types/prostate-cancer/treatment-options. Accessed February 2018.

[3] Fizazi K., et al. LATITUDE: A phase III, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naive prostate cancer. ASCO 2017. Abstract #LBA3.

[4] Clinical trials.gov. A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Participants With High-Risk, Metastatic Hormone-Naive Prostate Cancer (mHNPC). https://clinicaltrials.gov/ct2/show/NCT01715285. Accessed February 2018.

Source: http://www.janssen.com/zytiga-abiraterone-acetate-plus-prednisone-approved-treatment-earlier-form-metastatic-prostate

ERLEADA™ (apalutamide), a Next-Generation Androgen Receptor Inhibitor, Granted U.S. FDA Approval for the Treatment of Patients with Non-Metastatic Castration-Resistant Prostate Cancer

ERLEADA™ (apalutamide), a Next-Generation Androgen Receptor Inhibitor, Granted U.S. FDA Approval for the Treatment of Patients with Non-Metastatic Castration-Resistant Prostate Cancer

- *ERLEADA™ is the first FDA-approved therapy to treat patients with non-metastatic castration-resistant prostate cancer*
- *Approval is based on Phase 3 SPARTAN clinical trial data which showed ERLEADA™ decreased the risk of distant metastasis or death by 72 percent and improved median metastasis-free survival by more than two years*

The major efficacy outcome was supported by statistically significant improvements for secondary endpoints, including time to metastasis, progression -free survival, and time to symptomatic progression

HORSHAM, PA, February 14, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today that the U.S. Food and Drug Administration (FDA) has approved ERLEADA™ (apalutamide), a next-generation androgen receptor inhibitor,[1] for the treatment of patients with non-metastatic castration-resistant prostate cancer (NM-CRPC). ERLEADA™ is the first FDA-approved treatment for these patients. Today's approval follows an FDA Priority Review designation based upon data from the Phase 3 SPARTAN study, which demonstrated a 72 percent reduction in risk of distant metastasis or death, and an increase in median metastasis-free survival (MFS) by more than two years (difference of 24.31 months) in patients with NM-CRPC.

"The need to delay metastasis is critical to the treatment of prostate cancer. Nearly 90 percent of patients with castration-resistant prostate cancer will eventually develop bone metastases, at which point the prognosis sharply worsens," said Mathai Mammen, M.D., Ph.D., Global Head, Janssen Research & Development, LLC. "We are excited about what this approval means for patients living with prostate cancer, and that physicians now have an important and much-needed treatment option that has been shown to delay the progression of castration -resistant prostate cancer."

ERLEADA™ received FDA approval based on the Phase 3 data from the SPARTAN clinical trial, which assessed the efficacy and safety of ERLEADA™ versus placebo in patients with NM-CRPC who had a rapidly rising PSA while receiving continuous androgen deprivation therapy.[2] The study was recently presented at the 2018 American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU) on Thursday, February 8, 2018 in San Francisco and published in *The New England Journal of Medicine*.[2],[3]

"The SPARTAN trial results demonstrated impressive clinical benefits in patients with non-metastatic castration-resistant prostate cancer," said Matthew Smith, M.D., Ph.D., Director of the Genitourinary Malignancies Program at the Massachusetts General Hospital Cancer Center, Professor of Medicine at Harvard Medical School, and co-principal investigator of the SPARTAN study. "As an oncologist and clinical investigator, I know how devastating it can be for patients and their families to hear that the cancer has spread. With this approval, doctors now have the chance to offer hope for delaying metastases in patients with castration-resistant prostate cancer."

"As the impact of prostate cancer continues to grow, we are reminded every day of the critical need for therapeutic options that offer patients with prostate cancer more time with their loved ones," Mark Scholz, M.D., Executive Director of the Prostate Cancer Research Institute. "Today's approval is significant, as it means that patients with non-metastatic castration-resistant prostate cancer now have a treatment option that offers renewed hope."

SPARTAN, a Phase 3, randomized, double-blind, placebo-

controlled, multi-center study, enrolled 1,207 patients with non-metastatic castration-resistant prostate cancer.[4] Patients were randomized 2:1 to receive either ERLEADA™ orally at a dose of 240 mg once daily (n=806), or placebo once daily (n=401).[4] All patients in the SPARTAN trial received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy.[4]

ERLEADA™ decreased the risk of distant metastasis or death by 72 percent compared to placebo (HR = 0.28; 95% CI, 0.23-0.35; *P*<0.0001).[4] The median MFS was 40.51 months for ERLEADA™ compared to 16.20 months for placebo, prolonging MFS by more than two years (difference of 24.31 months).[4] MFS benefit was consistently seen across patient subgroups including prostate specific antigen doubling time (PSADT) (≤6 months or >6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1).[4]

The major efficacy outcome was supported by statistically significant improvements for the following secondary endpoints: time to metastasis (TTM), progression-free survival (PFS) and time to symptomatic progression.[4] The median TTM was 40.51 months for ERLEADA™ compared to 16.59 months for placebo (HR=0.27; 95% CI, 0.22-0.34; *P*<0.0001) and the median PFS was 40.51 months compared to 14.72 months for placebo (HR=0.29; 95% CI, 0.24-0.36; *P*<0.0001).[4] Overall survival data were not mature at the time of final MFS analysis (24% of the required number of events).[4]

Warnings and Precautions include seizure, falls and fractures.[4] In the SPARTAN trial, the most common adverse reactions (≥10%) were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema.[4]

About Non-Metastatic Castration-Resistant Prostate Cancer
Non-metastatic castration-resistant prostate cancer (NM-CRPC) refers to a disease state when the cancer no longer responds to medical or surgical treatments that lower testosterone, but has not yet been discovered in other parts of the body using a total body bone scan or CT scan.[5] Features include: lack of detectable metastatic disease;[5] rapidly rising prostate-specific antigen while on androgen deprivation therapy (ADT) and serum testosterone level below 50 ng/dL.[6],[7] Ninety percent of patients with CRPC will eventually develop bone metastases, which can lead to pain, fractures and spinal cord compression.[8] The relative 5-year survival rate for patients with distant stage prostate cancer is 30 percent.[9] It is critical to delay the onset of metastasis in patients with NM-CRPC.

About ERLEADA™
ERLEADA™ (apalutamide) is an androgen receptor (AR) inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.[4]

ERLEADA™ is an AR inhibitor that binds directly to the ligand-binding domain of the AR. ERLEADA™ inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription.[4] A major metabolite, N-desmethyl apalutamide, is a less potent inhibitor of AR, and exhibited one-third the activity of ERLEADA™ in an in vitro transcriptional reporter assay.[4] ERLEADA™ administration caused decreased tumor cell proliferation and increased apoptosis leading to decreased tumor volume in mouse xenograft models of prostate cancer.[4]

Full prescribing information will be available soon at www.ERLEADA.com.

Important Safety Information[4]

CONTRAINDICATIONS
Pregnancy - ERLEADA™ can cause fetal harm and potential loss of pregnancy.

WARNINGS AND PRECAUTIONS
Falls and Fractures - In the SPARTAN study, falls and fractures occurred in 16% and 12% of patients treated with ERLEADA™ compared to 9% and 7% treated with placebo respectively. Falls were not associated with loss of consciousness or seizure. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents.

Seizure - In a randomized study (SPARTAN), two pa-

tients (0.2%) treated with ERLEADA™ experienced a seizure. Permanently discontinue ERLEADA™ in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA™. Advise patients of the risk of developing a seizure while receiving ERLEADA™ and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

ADVERSE REACTIONS
Adverse Reactions - The most common adverse reactions (≥10%) were fatigue, hypertension, rash, diarrhea, nausea, weight decreased, arthralgia, fall, hot flush, decreased appetite, fracture, and peripheral edema.

Laboratory Abnormalities

- Hematology: anemia ERLEADA™ 70% (Grade 3-4 0.4%) placebo 64% (Grade 3-4 0.5%) leukopenia ERLEADA™ 47% (Grade 3-4 0.3%) for, placebo 29% (Grades 3-4 0%), lymphopenia ERLEADA™ 41% (Grade 3-4 2%), placebo 21% (Grade 3-4 2%);
- Chemistry – hypercholesterolemia ERLEADA™ 76% (Grade3-4 0.1%), placebo 46% (Grade 3-4 0%); hypertriglycemia ERLEADA™ 70%(Grade 3-4 2%) Placebo 59% (0.8%); hypertriglyceridemia ERLEADA™ 67% (Grade 3-4 2%) placebo 49% (Grade 3-4 0.8%); Hyperkalemia ERLEADA™ 32% (Grade 3-4 2%) Placebo 22% (Grade 3-4 0.5%)

Rash - Rash was most commonly described as macular or maculopapular. Adverse reactions were 24% with ERLEADA™ versus 6% with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA™ treatment (5%) versus placebo (0.3%).

The onset of rash occurred at a median of 82 days. Rash resolved in 81% of patients within a median of 60 days (range: 2 to 709 days) from onset of rash. Four (4%) of patients treated with ERLEADA™ received systemic corticosteroids. Rash recurred in approximately half of patients who were re-challenged with ERLEADA™.

Hypothyroidism - Hypothyroidism was reported for 8% of patients treated with ERLEADA™ and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA™ and 7% of patients treated with placebo. The median onset was Day 113. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose -adjusted.

Effect of Other Drugs on ERLEADA - Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary however, reduce the ERLEADA™ dose based on tolerability *[see Dosage and Administration (2.2)]*.

DRUG INTERACTIONS

Effect of ERLEADA™ on Other Drugs – ERLEADA™ is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA™ with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA™ with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA™ and evaluate for loss of activity.

P-gp, BCRP or OATP1B1 substrates - Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. Concomitant use of ERLEADA™ with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA™ and evaluate for loss of activity if medication is continued.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science.

We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at www.twitter.com/JanssenGlobal and www.twitter.com/JanssenUS. Janssen Research & Development, LLC is part of the Janssen Pharmaceutical Companies of Johnson & Johnson.

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Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding the benefits and availability of ERLEADA™ (apalutamide) for the treatment of certain types of prostate cancer. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended January 1, 2017, including under "Item 1A. Risk Factors," its most recently filed Quarterly Report on Form 10-Q, including in the section captioned "Cautionary Note Regarding Forward-Looking Statements," and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. Neither the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

[1] Clegg. N.J., et al., Cancer Res., 2012;72:1494-1503. ARN-509: A Novel Anti-androgen for Prostate Cancer Treatment. http://cancerres.aacrjournals.org/content/72/6/1494.full-text.pdf. Accessed February 2018.

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CUA0CUOG guidelines for the management of castration-resistant prostate cancer (CRPC). Can Urol Assoc J. 2015;9(3-4):90-96. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4455631/. Accessed February 2018.

[9] American Cancer Society. Cancer Facts & Figures. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2018/cancer-facts-and-figures-2018.pdf. Accessed February 2018.

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Contributions

Our thanks to those who help us continue our outreach

Stephen Altschuler
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2018 Prostrate Cancer Patient Guide by the Prostate Cancer Foundation. URL:

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Wise Buy? Focused Ultrasound Therapies
Exciting technology, but now sold to patients on slim supporting evidence

by Paul Raeburn, Contributing Writer, MedPage Today April 28, 2017

Do a search on focused ultrasound (FUS), and you'll quickly discover that it's a kind of fairy-tale cure, helpful in the treatment of almost everything: Parkinson's disease, uterine fibroids, atrial fibrillation, congestive heart failure, Alzheimer's disease, depression, diabetes, obesity, cancers of the prostate, kidneys, pancreas, bladder, breast, and dozens more.

FUS also has its own website, run by the Focused Ultrasound Foundation, a manufacturer-supported organization dedicated to "accelerating the development and adoption of focused ultrasound." Neal Kassell, MD, the founder and chairman of the foundation and a professor emeritus of neurosurgery at the University of Virginia School of Medicine, said in a 2015 TEDx talk that FUS "could improve the health and happiness of millions of people around the world."

The technology has not, however, been greeted with universal acclaim. It has proven controversial enough in the treatment of essential tremor -- for which it has FDA approval -- that the American Academy of Neurology's 2017 meeting this week featured it in a plenary-session "controversies in neurology" debate.

At that session, Paul Fishman, a neurologist at the University of Maryland, took the "pro" side, arguing that serious adverse event rates with FUS are dramatically lower than with a more established alternative -- deep brain stimulation (DBS). Fishman also said that DBS has a significant incidence of hardware failure requiring additional surgery.

Michael S. Okun, MD, the chairman of neurology at the University of Florida -- who argued the "con" side -- did not dispute those points, but noted that the opportunity for later surgery was an advantage, because mistakes and complications can often be corrected. That's not possible with FUS, which burns away tissue. "You can't troubleshoot a focused ultrasound problem," he said.

Okun also noted that the target for FUS in Parkinson's disease is very small -- "the size of a squashed pea" -- and can't be visualized well in MRI scans. That, along with difficulties focusing the beam because of interference from the skull, means off-target ablation is likely to occur periodically. And FUS can be used on only one side of the brain, because thalamic ablation on both sides has consistently been shown to have unacceptable adverse effects. DBS, in contrast, can be safely used on both sides to achieve more complete symptom control.

Okun did acknowledge that FUS holds a great deal of promise for other neurological applications, calling the potential of using it to open the blood-brain barrier to allow larger molecules into the brain, "brilliant."

In an interview the day before the debate, Okun said that using FUS to treat essential tremor "is like trying to make an omelet without opening the egg ... You're shooting from outside the brain." And the targets are not only small but also "somatotropically organized." Particular regions of the brain are mapped to specific parts of the body, and a misplaced lesion can have harmful side effects. A wrongly mapped attempt to ease a tremor in an arm, for example, could weaken a leg, leaving a patient unable to walk, Okun said.
Further, he said, neurologists already have a powerful means of treating essential tremor. "The gold standard of making lesions in the brain is radiofrequency [ablation]. Once you've mapped a brain out and you know where the structures are, you can insert a probe and burn it."

Fishman said before the debate that the use of FUS for Parkinson's disease could be a cheaper alternative to deep-brain stimulation. And he said he is eager to see it approved by the FDA, because until then it isn't covered by insurance. "We have a waiting list of over 200 patients," he said, but he can do the procedure only on those who can pay $25,000-$35,000 out of pocket. Asked if he was excited about FUS, he said, "It's a gas!"

At the conclusion of the AAN debate, audience members were asked whether they sided with Okun or Fishman. Okun's arguments "con" won with 90% of those voting, but most audience members didn't raise their hands for either one, suggesting that they found both sides persuasive.

Kassell acknowledged the criticism, but it doesn't dampen his enthusiasm. He was able to persuade a Charlottesville, Va., neighbor, John Grisham, the best-selling author of legal thrillers, to write a short book called The Tumor, which shows how FUS could one day be used to treat glioblastoma. "This is not fiction," Grisham said. "This is the future, and it is rapidly approaching."

FUS operates by a variety of mechanisms, including ablating tissue,

delivering drugs in high concentrations to a particular point in the body, and enhancing the effectiveness of cancer immunotherapy drugs -- 18 different mechanisms in all.

Kassell said there are several areas in which the technology is nearest to routine use. One is to deliver drugs to a precise target. The drugs can be tucked inside hollow lipid spheres which are injected into the bloodstream. "You can inject millions of these into the bloodstream, and they are everywhere blood goes. But the drug is inactive except where the ultrasound is focused. At that point the microbubble bursts and delivers its pharmacological payload," Kassell said.

A second is to ablate tissue, and a third is to modulate the immune system, meaning ultrasound might have a role to play in enhancing the effectiveness of cancer chemotherapy or other drugs.

Kassell said FUS has been approved by the FDA for three things in addition to essential tremor: uterine fibroids; pain from bone metastases; and the ablation of prostate tissue to treat prostate cancer or BPH. But more are coming.

"As of today, there are almost 80 clinical indications in various stages of research and development," Kassell said. He notes that FUS can potentially be much cheaper than alternative treatments. Deep-brain stimulation for Parkinson's disease costs some $60,000 to $100,000, he said, but ultrasound can do the job for one-third of that. (Okun said in the interview that data does not yet exist to show that FUS is cheaper.) Kassell said that the foundation works with three dozen companies that make ultrasound equipment, but that the foundation is not intended to promote commercial interests -- only to spread interest in what he sees as an extremely valuable new technology. "What we're doing here at the foundation is to be engaged in a variety of activities which can move quickly to save people and save lives," he said.

Prostate cancer is one of the applications for which ultrasound looks most promising. Last year, at the annual meeting of the American Urological Association, researchers reported that almost 90% of patients with early prostate cancer remained free of radical intervention two years after treatment of a single lobe with high-intensity FUS. The report generated "cautious optimism" that the technology could play a role in the treatment of early prostate cancer.

Another application is for use with Alzheimer's disease. FUS's ability to gently open the blood-brain barrier can allow amyloid-scavenging drugs to reach and potentially destroy plaques characteristic of Alzheimer's disease.

The first human trials for Alzheimer's disease were launched in March by a neurosurgeon, Nir Lipsman, MD, PhD, at Sunnybrook Health Sciences Center in Toronto. Two of a total of six patients were treated to assess the safety of the technique before it's used more widely.

Other Alzheimer's specialists were divided over whether or not human trials are premature, but because ultrasound has been used in the brains of Parkinson's patients, some felt that it was likely to be safe for use in Alzheimer's disease. The study is also predicated on the fact that the plaques are a cause of the illness; not everyone agrees that that's the case.

Now we come to the question: Is FUS a wise buy?

"I would say definitely yes," said Fishman. "There is a product out there already, which is deep brain stimulation. For a certain fraction of those patients, they would likely opt for FUS, which is a cheaper technology, and less onerous." Asked if neurologists are excited by FUS, Fishman said, "The field is still very unaware of this technology. There may be a thousand articles in the medical literature on DBS and maybe 50 on this." He also offered "a little disclaimer ... I have the passion of a recent convert."

Asked the same question, Kassell said, "The answer is ... it depends." The economics will be hard to sort out until insurance companies begin to cover it, he said. "Some sites can fight with the insurance companies, but there is not a lot of reimbursement. People are paying cash."

At the same time, he's frustrated and unhappy at the pace of research. Asked if he was enjoying this work during what could be a relaxing retirement, he said no. Too often, he said, he sees people who could be helped, and he knows that the data is not yet there to offer them the treatment.

Kassell's vigorous promotion of FUS could backfire -- it invites skepticism. Far too many treatments that work like magic in mice or a handful of patients fail in proper clinical trials.

It's too soon to know whether FUS is one of them. It's not yet a wise buy. But when the evidence comes in, it might be. It's simply too early to dismiss it or embrace it.

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