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Follow-up Data Show ZYTIGA[®] Plus Prednisone Continues to Delay Progression of Metastatic Castration-Resistant Prostate Cancer in Patients without Prior Chemotherapy

Orlando, Fla., February 12, 2013 - Janssen Research & Development, LLC [Janssen] announced today that updated results showing ZYTIGA[®] (abiraterone acetate) plus prednisone continued to provide statistically significant improvements in disease progression compared to placebo plus prednisone, and longer overall survival in men with metastatic castration-resistant prostate cancer.

The Phase 3, randomized, multicenter, placebo-controlled study (COU-AA-302) also demonstrated statistically significant improvement compared to placebo in the secondary endpoints of median time to opiate use for prostate cancer pain and to initiation of chemotherapy. The data, from the latest pre-specified interim analysis of the study, will be presented at the annual American Society of Clinical Oncology Genitourinary Cancers Symposium (ASCO GU).

"These results show that the benefits of earlier use of abiraterone acetate are sustained for many patients with metastatic castration-resistant prostate cancer," said Dana Rathkopf, MD, lead investigator of the study and assistant attending physician in the Genitourinary Oncology Service at Memorial Sloan-Kettering Cancer Center in New York City. "We were particularly pleased with the long median overall survival among patients treated with abiraterone acetate plus prednisone."

Results from this most recent analysis and earlier interim analyses from COU-AA-302 were the basis of the December 2012 U.S. Food and Drug Administration (FDA) approval of an expanded indication for ZYTIGA, in combination with prednisone, for the treatment of patients with mCRPC. The European Commission has also approved an expanded indication for ZYTIGA for the treatment of patients with mCRPC.

"It's important that clinicians have proven treatments to offer patients with metastatic castration-resistant prostate cancer before chemotherapy," said Michael L. Meyers, M.D., Ph.D., vice president, compound development team leader, ZYTIGA, Janssen. "When ZYTIGA was first approved, it provided a significant option for men with metastatic castration resistant disease after chemotherapy with docetaxel; now, with its broader indication and supported by the data presented at ASCO GU, we are pleased that more mCRPC patients may benefit from this treatment option. The findings also broaden our knowledge about the therapeutic activity of ZYTIGA."

The analysis showed a statistically significant 47 percent reduction in risk of disease progression - measured as radiographic progression-free survival (rPFS) - in the ZYTIGA plus prednisone arm (ZYTIGA arm) compared to the placebo plus prednisone arm (control arm). The median rPFS was 16.5 months in the ZYTIGA arm vs. 8.3 months in the control arm [hazard ratio (HR) 0.53; 95% confidence interval (CI): 0.45 to 0.62; $P < 0.0001$].

Treatment with ZYTIGA plus prednisone also resulted in an estimated 21 percent reduction in risk of death [HR=0.79; 95% CI: 0.66, 0.96, $P = 0.0151$]. The median overall survival (OS) in the ZYTIGA arm was 35.3 months and was 30.1 months in the control arm. At the time of this interim analysis, conducted when approximately 55 percent of overall survival events (deaths) occurred, the pre-specified p-value for statistical significance was not met.

Secondary Endpoints

Treatment with ZYTIGA plus prednisone also resulted in significant improvements in all secondary study endpoints compared to the control arm, specifically:

- 39 percent decrease in the risk of initiation of cytotoxic chemotherapy for prostate cancer: a median of 26.5 months for the ZYTIGA arm vs. 16.8 months for the control arm [HR=0.61 (95% CI: 0.51, 0.72); $P < 0.0001$].
- 29 percent decrease in the risk of opiate use for cancer pain: the median time for the ZYTIGA arm was not reached and was 23.7 months for the control arm [HR=0.71; 95% CI: (0.59, 0.85); $P < 0.0002$].

Safety Findings

No new safety concerns were identified with the longer treatment with ZYTIGA compared to previously reported findings with the drug in mCRPC patients who had prior chemotherapy. In this interim analysis, fatigue, fluid retention, low blood potassium, hypertension, cardiac disorders and elevated liver transaminase enzymes were adverse events (AEs) reported more frequently in the ZYTIGA arm compared to the control arm. Patients in the ZYTIGA arm of the study experienced more grade 3 and grade 4 AEs than those in the control arm. Grade 3 or 4 AEs classified as liver toxicity, consisting primarily of reversible elevations in liver transaminase enzymes, were reported in more patients in the ZYTIGA arm than in the control arm.

Janssen previously [announced](#) that an Independent Data Monitoring Committee (IDMC) unanimously recommended unblinding this Phase 3 study after an earlier interim analysis found a statistically significant difference in rPFS and a trend in the difference in OS. Based on these results, the IDMC also recommended that patients in the control arm be offered treatment with abiraterone acetate.

Study Design

Study COU-AA-302 is a Phase 3, randomized, double-blind, multicenter, placebo-controlled international clinical study, which evaluated ZYTIGA plus prednisone compared to placebo plus prednisone in 1,088 men with mCRPC who had failed androgen deprivation therapy and had not received cytotoxic chemotherapy.

Patients were randomized either to receive ZYTIGA 1,000 milligrams (mg) administered orally once daily plus prednisone 5 mg administered orally twice daily, or placebo orally daily plus prednisone 5 mg administered twice daily. The co-primary endpoints of the study are rPFS and OS.

About ZYTIGA

Since its first approval in the U.S. in 2011, ZYTIGA has been approved in more than 65 countries. More than 50,000 men worldwide have received treatment with ZYTIGA, and it is quickly becoming one of the cornerstones of treatments with mCRPC.

More information about ZYTIGA can be found at www.zytiga.com.

Indication

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

IMPORTANT SAFETY INFORMATION

Contraindications - ZYTIGA[®] (abiraterone acetate) 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.

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.

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.

Hepatotoxicity - Monitor liver function and modify, withhold, or discontinue ZYTIGA[®] dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (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.

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-∞} (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.

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.

Drug Interactions - ZYTIGA[®] is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate. *In vitro*, ZYTIGA[®] inhibits CYP2C8. There are no clinical data on its use 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.

Based on *in vitro* data, ZYTIGA[®] is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution during treatment with ZYTIGA[®].

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

About Janssen Research & Development

Janssen Research & Development is headquartered in Raritan, N.J. and has affiliated facilities in Europe, the United States and Asia. Janssen Research & Development is leveraging a combination of internal and external innovation to discover and develop novel medicines and solutions in five distinct therapeutic areas: Neuroscience, Oncology, Immunology, Infectious Diseases and Vaccines, and Cardiovascular and Metabolism. For more information about Janssen Research & Development visit www.janssenrnd.com.

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