Bayer HealthCare

News Release

Intended for U.S. Media Only

Bayer Initiates Phase 3 Trial of Xofigo® (radium Ra 223 dichloride) Injection in Combination with Abiraterone Acetate for Asymptomatic or Mildly Symptomatic Chemotherapy-Naïve Patients with Bone Predominant Metastatic Castration-Resistant Prostate Cancer

WHIPPANY, N.J., April 2, 2014 – Bayer HealthCare Pharmaceuticals Inc. today announced that the company has begun to enroll patients in a trial studying Xofigo® (radium Ra 223 dichloride) injection in combination with abiraterone acetate and prednisone/prednisolone for the treatment of asymptomatic or mildly symptomatic chemotherapy-naïve patients with bone predominant metastatic castration-resistant prostate cancer (mCRPC). The randomized, double-blind, placebo-controlled Phase 3 trial is designed to determine the effects of this combination treatment on symptomatic skeletal event-free survival.

“Studies such as this one are important, as they help us understand the safety and efficacy of combining FDA-approved treatments for metastatic castration-resistant prostate cancer,” said Pamela A. Cyrus, MD, Vice President and Head of U.S. Medical Affairs, Bayer HealthCare Pharmaceuticals.

Xofigo is approved by the U.S. Food and Drug Administration for the treatment of patients with CRPC, symptomatic bone metastases and no known visceral metastatic disease and is available in the United States at licensed facilities.[1]

Abiraterone acetate is a product of the Janssen Pharmaceutical Companies and is available in more than 80 countries. In the U.S., it is marketed under the brand name Zytiga® and indicated with prednisone or prednisolone for use in men with metastatic prostate cancer in whom the disease has progressed while receiving treatment with androgen deprivation therapy.[2, 3]

Phase 3 Trial Design

The randomized double-blind, placebo-controlled Phase 3 trial will investigate whether providing radium Ra 223 dichloride (radium-223) in combination with abiraterone acetate and prednisone/prednisolone will increase symptomatic skeletal event free survival (SSE-FS). The trial

will enroll approximately 800 patients who will be randomized in a 1:1 ratio to receive study treatment (either radium-223 or placebo in addition to abiraterone acetate plus prednisone/prednisolone and best supportive care for the first six cycles followed by abiraterone acetate plus prednisone/prednisolone thereafter) until an on-study symptomatic skeletal event (SSE) occurs (or other withdrawal criteria are met).

The international study is sponsored by Bayer and will be conducted in collaboration with Janssen Research and Development in various regions, including sites in Europe, the U.S., Australia, Brazil and Japan.

For further information about the study, please visit www.clinicaltrials.gov and search NCT02043678.

About Xofigo® (radium Ra 223 dichloride) Injection

Xofigo is an alpha particle-emitting radioactive therapeutic agent with an anti-tumor effect on bone metastases. The active ingredient in Xofigo is the alpha particle-emitting isotope radium-223, which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. The high linear energy transfer of Xofigo may cause double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium Ra 223 dichloride is less than 100 micrometers which may limit the damage to the surrounding normal tissue.[1]

Important Safety Information for Xofigo® (radium Ra 223 dichloride) Injection

- **Contraindications:** Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman.
- **Bone Marrow Suppression:** In the randomized trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was

similar for patients treated with Xofigo and placebo. Myelosuppression – notably thrombocytopenia, neutropenia, pancytopenia, and leucopenia – has been reported in patients treated with Xofigo.

Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 × 10^9/L and the platelet count ≥50 × 10^9/L. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care.
- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.
- **Administration and Radiation Protection:** Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.
- **Adverse Reactions:** The most common adverse reactions (≥10%) in the Xofigo arm vs the placebo arm, respectively, were nausea (36% vs 35%), diarrhea (25% vs 15%), vomiting (19% vs 14%), and peripheral edema (13% vs 10%). Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in the Xofigo arm (≥10%) vs the placebo arm, respectively, were anemia (93% vs 88%), lymphocytopenia (72% vs 53%), leukopenia (35% vs 10%), thrombocytopenia (31% vs 22%), and neutropenia (18% vs 5%).

For full prescribing information visit
http://labeling.bayerhealthcare.com/html/products/pi/Xofigo_PI.pdf.

About Castration-Resistant Prostate Cancer (CRPC) and Bone Metastases

Prostate cancer is the most common cancer among men in the United States (other than skin cancer).[4] Approximately four percent of prostate cancer cases are considered distant, which means that the cancer has spread beyond the prostate to distant areas of the body (metastasized).[5]

Bone is the most common site in the body to be affected by metastatic cancer, and bone metastases are particularly prevalent in patients with prostate cancer. [6, 7] Approximately 90 percent of patients with metastatic prostate cancer show evidence of bone metastases.[8] Bone metastases can lead to an increase in frequency of skeletal events and are shown to be one of the main causes of death in patients with CRPC. [6, 8]

About Oncology at Bayer

Bayer is committed to delivering *science for a better life* by advancing a portfolio of innovative treatments. The oncology franchise at Bayer now includes three oncology products and several other compounds in various stages of clinical development. Together, these products reflect the company's approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated.

About Bayer HealthCare Pharmaceuticals Inc.

Bayer HealthCare Pharmaceuticals Inc. is the U.S.-based pharmaceuticals business of Bayer HealthCare LLC, a subsidiary of Bayer AG. Bayer HealthCare is one of the world's leading, innovative companies in the healthcare and medical products industry, and combines the activities of the Animal Health, Consumer Care, Medical Care, and Pharmaceuticals divisions. As a specialty pharmaceutical company, Bayer HealthCare Pharmaceuticals Inc. provides products for General Medicine, Hematology, Neurology, Oncology and Women's Healthcare. The company's aim is to discover and manufacture products that will improve human health worldwide by diagnosing, preventing and treating diseases.

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Forward-Looking Statement
This news release may contain forward-looking statements based on current assumptions and forecasts made by Bayer Group or subgroup management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the Bayer website at www.bayer.com. The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

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1. XOFIGO® (radium Ra 223 dichloride) [Prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, May 2013.
2. ZYTIGA® (Abiraterone acetate) [Prescribing Information]. Janssen Biotech, Inc. February 2014.
3. ZYTIGA® (Abiraterone acetate) [Summary of Product Characteristics]. Janssen Biotech, Inc. February 2014.
4. American Cancer Society. Prostate Cancer: Detailed Guide. Available at: http://www.cancer.org/acs/groups/cid/documents/webcontent/003134-pdf.pdf
5. National Cancer Institute, Surveillance Epidemiology and End Results (SEER). SEER Stat Facts: Prostate; Survival & Stage, 2002-2008.
6. Lange PH, Vasella RL. "Mechanisms, hypotheses and questions regarding prostate cancer metastatic to bone." Cancer & Metastasis Reviews.1999;17:331-336
7. Coleman R. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev. 2001;27:165-176.
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