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NCCN Guidelines Panel: Advanced Prostate Cancer
National Comprehensive Cancer Network
275 Commerce Dr., Suite 300
Fort Washington, PA 19034

Re: Request for addition of Xofigo® (radium Ra 223 dichloride) to the NCCN Guidelines for Castrate Resistant Prostate Cancer (CRPC) with bone metastasis

NCCN Guidelines Panel: Prostate Cancer

On behalf of Bayer HealthCare Pharmaceuticals and Algeta US, we respectfully request the NCCN Prostate Cancer Committees to review the enclosed data for the inclusion of radium 223 as a treatment option for patients with metastatic CRPC.

Specific Changes: We suggest adding Xofigo® (radium Ra 223 dichloride) to the treatment of Metastatic Castrate Resistant Prostate Cancer Guidelines.

FDA Clearance: The FDA approved Xofigo for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. Xofigo is an alpha particle-emitting radioactive therapeutic agent for metastatic CRPC patients.[1]

Mechanism of Action: The active moiety of Xofigo is the alpha particle-emitting isotope radium 223 (as radium Ra 223 dichloride), 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 alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium 223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.[1]

Rationale: In support of the proposed change, on May 15, 2013, the FDA has granted Xofigo (Radium 223) approval for the treatment patients with CRPC with symptomatic bone metastases and no known visceral metastatic disease. The approval was based on a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial: ALSYMPCA (ALpharadin in SYMptomatic Prostate Cancer) involving 921 men with

symptomatic metastatic castrate resistant prostate cancer (CRPC) randomized 2:1 to receive radium 223 50kBq (1.35 microcurie)/kg +best standard of care vs. matching placebo+ best standard of care.

Key data points include:

- The reduction in risk of death was 30.5% Xofigo (radium 223) group compared with the control group (HR=0.695 [95% CI: 0.581- 0.832; P=0.00007)). Median survival for patients in the radium 223 was 14.9 months compared with 11.3 months for patients in the control group in the updated analysis (prior to cross over).
    - The survival benefit favored radium 223 across all subgroups independent of the pre-specified stratification factors: docetaxel use, bisphosphonate use, and baseline alkaline phosphatase (ALP) <220 U/L or ≥220 U/L.

- A key secondary efficacy endpoint was time to first symptomatic skeletal event (SSE) defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention. There were no scheduled radiographic assessments performed on study. The survival results were supported by a delay in the time to first SSE favoring the Xofigo arm. The majority of events consisted of external beam radiotherapy to bone metastases.
- The most common adverse reactions (≥ 10%) in patients receiving radium 223 were nausea, diarrhea, vomiting, and peripheral edema.
- Grade 3 and 4 adverse events were reported among 57% of radium 223 -treated patients and 63% of placebo-treated patients
- The most common hematologic laboratory abnormalities in radium 223 -treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia.

Additionally, three Phase II studies were presented and published in peer-reviewed journals in support of the safety and efficacy of Xofigo (radium 223) in CRPC with bone metastasis assessing multiple endpoints such as safety, ALP normalization, PSA response and pain.

The following prescribing information and articles are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications.

Should you have any questions regarding the content of this letter, please do not hesitate to contact us.

Sincerely,

Mona M. Wahba

Michael Tomblyn

References:

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