**ELIGIBILITY CRITERIA**

**Documentation of Disease**
Progressive castration-resistant metastatic prostate cancer with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.

**Patients must have Measurable or Non-measurable Disease**

4.2.1 Measurable Disease

For **visceral or extra-nodal** lesions to be considered measurable, they must be ≥ 10 mm in one dimension, using spiral CT.

For **lymph nodes** to be considered measurable (i.e., target or evaluable lesions), they must be ≥ 20 mm in at least one dimension, using spiral CT.

4.2.2 Non-measurable Disease

All other lesions, including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions. Lesions that are considered non-measurable include bone lesions (only).

**Progressive Disease**

Patients must have progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy. For patients enrolling on the basis of soft tissue or bone progression, the baseline scan must show progression relative to a comparison scan. If the comparison scan is not available, the baseline scan report must reference the previous scan to document progression.

4.3.1 PSA progression defined by a minimum of two rising PSA levels with an interval of ≥ 1 week between each determination. Patients who received an anti-androgen must have progression documented by a minimum of two rising PSA levels with an interval of ≥ 1 week between each determination such that at least the second of these rises is ≥ 4 weeks since last flutamide or ≥ 6 weeks since last bicalutamide or nilutamide. The PSA value at the screening should be ≥ 2 μg/L (2 ng/mL).

4.3.2 Soft tissue disease progression defined by Section 13.2.3

4.3.3 Bone disease progression defined by PCWG2 with two or more new lesions on bone scan.
Prior Treatment
4.4.1 No treatment with prior taxane-based chemotherapy for metastatic disease.
   • Patients who received prior taxane-based chemotherapy as neoadjuvant or adjuvant therapy for local
disease, or who received taxane-based therapy in the PSA clinical (non-metastatic) state is allowable
provided that the total duration of exposure was six cycles or less and chemotherapy was completed more
than 6 months prior to registration.
   • Taxane-based chemotherapy that was aborted due to allergic reactions or intolerance to chemotherapy and
therefore received 1 cycle of prior therapy is allowable.
4.4.2 No prior enzalutamide, abiraterone, or other novel antiandrogen or androgen synthesis inhibitor
4.4.3 No treatment with any of the following for prostate cancer within 4 weeks prior to enrollment:
   • Hormonal therapy (e.g., AR antagonists, 5 alpha reductase inhibitors, estrogens).
     Note: Treatment with bicalutamide and nilutamide within 6 weeks prior to enrollment is not allowed.
     Treatment with flutamide within 4 weeks prior to enrollment is not allowed. Treatment with all other
     GnRH analogues or antagonists is allowed.
   • Chemotherapy
   • Biologic therapy
   • Investigational therapy
   • Immunotherapy
4.4.5 No use of herbal products that may decrease PSA levels within 4 weeks prior to enrollment
4.4.6 No use of systemic steroids greater than the equivalent of 10 mg of prednisone/prednisolone per day within 4 weeks
prior to enrollment
4.4.7 No prior use of ketoconazole for greater than 7 days.
4.4.8 No prior radiation therapy or radionuclide therapy for the treatment of metastasis within four weeks
prior to enrollment
4.4.9 Patients receiving bisphosphonate therapy or denosumab must have been on a stable dose for at least 4 weeks prior to
enrollment
4.4.10 Patients must maintain ongoing androgen deprivation therapy with a GnRH analogue, antagonist, or bilateral
orchiectomy (i.e., surgical or medical castration)

Patient History
4.5.1 No known or suspected brain metastases (NOTE: patients with treated epidural disease are allowed)
4.5.2 No planned palliative procedures for alleviation of bone pain such as radiation therapy or surgery
4.5.3 No structurally unstable bone lesions suggesting impending fracture
4.5.4 No history of seizure or any condition that may increase the patient’s seizure risk (e.g., prior cortical stroke,
significant brain trauma). No history of TIA within 12 months of enrollment.
4.5.5 No clinically significant cardiovascular disease including:
   • MI within 6 months
   • Uncontrolled angina within 3 months
   • CHF with NYHA class 3 or 4, or patients with NYHA class 3 or 4 in the past, unless a screening echo or
     MUGA performed within three months demonstrates an EF>45%
   • History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular
     fibrillation, torsades de pointes)
   • History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place
   • Hypotension (systolic BP <86 mmHg) or bradycardia (<50 bpm) at screening
   • Uncontrolled hypertension (systolic BP >170 mmHg or diastolic BP >105 mmHg at screening)
4.5.6 No GI disorder that negatively affects absorption
4.5.7 No major surgery within 4 weeks prior to enrollment

Age and performance status
4.6.1 Age ≥ 18 years of age
4.6.2 ECOG Performance Status 0-1
4.6.3 Asymptomatic or mildly symptomatic from prostate cancer. A score of 0-1 on BPI-SF Question #3 (worst pain in last
24 hours) will be considered asymptomatic, and a score of 2-3 will be considered mildly symptomatic Appendix II