### Critères d'éligibilité

- Histologiquement confirmé diagnostic de prostate adenocarcinoma:
- Asymptomatic or mildly symptomatic (defined as no opioids and Brief Pain Inventory score)
- Metastatic to bone with ≥ 2 bone metastases (area of increase uptake on 99mTC BS (Technetium-99m bone scintigraphy) confirmed by standard X-Ray, Computed tomography (CT), or Magnetic resonance imaging (MRI)) with or without additional lymph node metastases. Visceral metastases are not allowed
- Progressive Castration-resistant prostate cancer (CRPC) according to Prostate Cancer Working Group 2 (PCWG2) i.e. either of:
  - For patients who manifest disease progression solely as a rising Prostate-specific antigen (PSA) level. PCWG2 criteria require documentation of a sequence of rising PSA values at a minimum of 1-week intervals with the last value ≥ 2 ng/ml.
  - For patients with disease progression manifest in the bone, irrespective of progression by rising PSA, PCWG2 guidelines require appearance of 2 or more new lesions. Ambiguous results should be confirmed by other imaging modalities than bone scan and x-ray (e.g.: CT-scan or MRI).
  - For patients with disease progression manifest at nodal sites, irrespective of progression by rising PSA, PCWG2 requires progression according to RECIST 1.1.
- Ongoing androgen deprivation therapy with LHRH (Human luteinizing hormone-releasing hormone) agonist or antagonist or bilateral orchiectomy
- Patients must be at least 18 years old
- WHO Performance status 0-1
- Charlson score ≤ 3
- Castrate serum levels of testosterone (< 50 ng/dL)
- Biochemistry and hematology:
  - Adequate bone marrow function (absolute neutrophil count 1.5109/L; platelets 100 109/L, and hemoglobin > or = 10.0 g/dL).
  - Total bilirubin level ≤ 1.5 x institutional upper limit of normal (ULN), except for patient with
Gilbert's disease 5.0 ULN
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x ULN
- Creatinine ≤ 1.5 x ULN
- Albumin > 25 g/L
- Normal cardiac function according to local standard by 12-lead Electrocardiogram (ECG) (complete, standardized 12-lead recording)
- Able to swallow the study drug and comply with study requirements
- Prior or concomitant therapy
  - Prior docetaxel is permitted under the following conditions: start within 2 months of Androgen deprivation therapy (ADT) initiation, given for a maximum of 6 cycles and progression within 6 months of the last dose of docetaxel.
  - Previous treatment with bicalutamide, flutamide, prednisone, or dexamethasone is allowed if it was stopped at least 4 weeks prior to entry in the study
  - Patients taking bisphosphonates or denosumab are eligible if they have received a stable dose for 4 weeks or more prior to randomization. (These treatments may then be continued on study)
  - use of adequate birth control measures during the study treatment period and for at least 3 months after last dose of enzalutamide and 6 months after the last dose of Ra223.
- Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
- Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations

Critères d'exclusion
- No known history of central nervous system metastases or leptomeningeal tumor spread.
- No significant cardiovascular disease including:
  - Myocardial infarction within 6 months prior to screening
  - Uncontrolled angina within 3 months prior to screening
  - Congestive heart failure New York Heart Association (NYHA) class III or IV, or patients with history of congestive heart failure NYHA class III or IV in the past, unless a screening echocardiogram or multi-gated acquisition scan (MUGA) performed within 3 months results in a left ventricular ejection fraction that is ≥ 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
  - Uncontrolled hypertension as indicated by a resting systolic blood pressure > 170 mm Hg or diastolic blood pressure > 105 mm Hg at screening
  - Hypotension as indicated by systolic blood pressure < 86 millimeters of mercury (mm Hg) at screening
  - Bradycardia as indicated by a heart rate of < 45 beats per minute on the screening ECG and on physical examination
  - patients having received docetaxel for CRPC are excluded.
- No prior treatment with enzalutamide or Ra223
- No prior and concomitant treatment with Cyp17 inhibitors (abiraterone, orteronel) and ketoconazole
- No prior hemibody external radiotherapy. Patients who received other types of prior external radiotherapy are allowed provided that the bone marrow function is assessed and meets the protocol requirements for hemoglobin, absolute neutrophil count and platelets
- No prior therapy with other radionuclides (e.g., strontium-89, samarium-153, rhenium-186, or rhenium-188)
- No involvement in another therapeutic trial involving an experimental drug
- No anticancer therapy or treatment with another investigational agent within the last 4 weeks prior to randomization
- No known hypersensitivity to compounds related to enzalutamide or Ra223
- No prior history of malignancies other than prostate adenocarcinoma (except patients with basal cell, squamous cell carcinoma of the skin, in-situ carcinoma or low-grade superficial bladder cancer), or the patient has been free of malignancy for a period of 3 years prior to randomization date
- No history of seizure, including any febrile seizure, loss of consciousness, or transient ischemic attack within 12 months of enrollment (registration date), or any condition that may pre-dispose to seizure (e.g., prior stroke, brain arterio-venous malformation, head trauma with loss of consciousness requiring hospitalization)
- No major surgery within 4 weeks prior to treatment
- No intake of narcotic analgesia for bone pain
- No drug or alcohol abuse
- No other serious illness or medical condition, such as but not limited to:
  - Any infection ≥ Grade 2 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4
  - No gastrointestinal disorder affecting absorption (e.g., gastrectomy or active peptic ulcer disease)
  - Crohn's disease or ulcerative colitis
  - Bone marrow dysplasia
  - Fecal incontinence
  - Life-threatening illness unrelated to cancer
- No condition which, in the investigator's opinion, makes the patient unsuitable for trial participation