

TYPE OF CANCER: Prostate Cancer with Bone Metastases
TYPE OF TRIAL: Phase I/II
TRIAL SPONSOR: Novartis

PRINCIPAL INVESTIGATOR: Nicholas Vogelzang, M.D.
CONTACT PERSON: JoAnn Abia RN, CCRP
(702) 822-5149

STUDY SUMMARY

A Phase I/II open-label study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of MCS110 in patients with prostate cancer and bone metastases

TREATMENT OVERVIEW

- During the Escalation Phase, patients will receive MCS110 on days 1 and 15 of every 28-day cycle for up to 3 cycles
- During the Expansion Phase, patients will be randomized to receive either MCS110 on days 1 and 15 of every 28-day cycle for up to 3 cycles or Zometa on day 1 of every 28-day cycle for up to 3 cycles

PRE-TREATMENT ASSESSMENTS

- Demographics
- Medical History
- Hepatitis B and C screening
- TB skin test
- Serum Testosterone
- Physical exam
- Vital signs
- Cardiac enzymes
- EKG
- Chest X-ray
- Cardiac Echo/MUGA
- Radiological bone survey
- Hematology
- Coagulation
- Biochemistry
- Urinalysis
- Other study specific labs

ENTRANCE CRITERIA FOR PARTICIPATION IN TRIAL

INCLUSION CRITERIA

1. Histologically confirmed prostate cancer with ≥ 1 bone metastatic lesion demonstrated by X-ray and/or computed tomography (CT) and/or radionuclide scan and/or MRI (bone metastatic lesions demonstrated on radionuclide scans should be confirmed by X-ray, CT, or MRI)
2. History of disease progression following surgical or chemical castration
3. Current gonadal androgen ablation with a luteinizing hormone-releasing hormone analog or history of orchiectomy (secondary hormonal therapy with agents such as bicalutamide, nilutamide, flutamide, or ketoconazole are permitted but not required)
4. Men 18 years or older
5. ECOG performance status ≤ 2
6. Patients must have the following laboratory values:
 - Absolute Neutrophil Count (ANC) $\geq 1.5 \times 10^9/L$
 - Hemoglobin (Hgb) ≥ 10 g/dL (transfusion may be administered for eligibility)
 - Platelets $\geq 100 \times 10^9/L$
 - Serum total bilirubin $\leq 1.5 \times$ ULN (upper limit of normal)
 - AST and ALT $\leq 2.5 \times$ ULN
 - Calculated creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault equation:
 - $CrCl = [140 - \text{age (years)}] \times \text{weight (kg)} / [72 \times \text{serum Cr (mg/dL)}]$
 - Corrected serum calcium > 8.0 mg/dL (2.0 mmol/L) and < 12.0 mg/dL (3.0 mmol/L) at the screening visit (calcium may be supplemented for eligibility)
 - PSA > 2.0 ng/mL
 - Serum testosterone < 50 ng/mL (1.7 nmol/L)
7. Time since the last dose of prior therapy to treat underlying malignancy:
 - Cytotoxic chemotherapy administered in neo-adjuvant or adjuvant setting - > 6 months.
 - Biologic therapy (e.g. antibodies) - ≥ 8 weeks
 - ≥ 5 t_{1/2} of a small molecule therapeutic
 - ≥ 5 t_{1/2} of any other investigational agents

Patients must have recovered from all reversible toxicities related to their previous treatment.

8. Life expectancy of at least 6 months
9. Patients must give written informed consent to participate in this study

EXCLUSION CRITERIA

1. Planned concurrent treatment with cytotoxic or biological therapy for the duration of the study

2. Prior cytotoxic chemotherapy for metastatic prostate cancer (prior cytotoxic chemotherapy is allowed only if it was administered in the neoadjuvant or adjuvant setting)
3. Bisphosphonate within previous 12 months prior to enrollment
4. Patients with > grade 1 CTCAE edema at screening
5. Structurally unstable bone lesions suggesting impending fracture
6. Concomitant disease(s) known to influence calcium metabolism including hyperparathyroidism, hyperthyroidism and/or Paget's disease of bone.
7. Current active dental problems including
 - Infection of the teeth or jawbone
 - Dental or fixture trauma
 - Current or previous osteonecrosis of the jaw
 - Exposed bone in the mouth
 - Slow healing after dental procedures
 - Recent (within 6 weeks) or planned dental or jaw surgery during the study (extraction, implants)
 - Prior radiation therapy to treat diseases of the mouth
8. Patients with a history of primary central nervous system tumors or brain metastases or who have signs/symptoms attributable to brain metastases and have not been assessed with radiologic imaging to rule out the presence of brain metastases
9. Previous or concurrent malignancy except adequately treated basal cell carcinoma or squamous cell skin cancer; or other solid tumor treated curatively and without evidence of recurrence for at least 3 years prior to study entry.
10. History of clinically significant drug allergy; history of atopic allergy (asthma, urticaria, eczematous dermatitis). A known hypersensitivity to the study drug or drugs similar to the study drug.
11. Active or latent tuberculosis (positive tuberculin skin test, evidence of pulmonary involvement on chest x-ray)
12. History of interstitial lung disease
13. Autoimmune disease
14. Any active or chronic infection (bacterial, fungal, viral)
15. History of immuno-compromise
16. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
17. Farm workers
18. Men who drink un-pasteurized milk
19. Other concurrent severe and/or uncontrolled concomitant medical conditions (e.g. uncontrolled diabetes, uncontrolled diarrhea)
20. Peripheral vascular disease requiring active therapy or having had surgery < 12 months prior to starting study drug
21. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
 - Angina pectoris \leq 3 months prior to starting study drug
 - Acute myocardial infarction \leq 6 months prior to starting study drug

- LVEF < lower limit of normal at treating institution as determined by MUGA scan or echocardiogram
 - Other clinically significant heart disease (e.g. symptomatic congestive heart failure, uncontrolled arrhythmia, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
 - History of coronary angioplasty or stent placement \leq 3 months prior to starting study drug
 - History of carotid endarterectomy or stent placement \leq 3 months prior to starting study drug
 - A past medical history of clinically significant ECG abnormalities or a family history of a prolonged QT-interval syndrome
22. Patients who have received wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) \leq 4 weeks or limited field radiation for palliation \leq 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
23. Patients for whom orthopedic surgery or radiation therapy is currently scheduled or planned to correct or treat defects related to metastatic bone lesions
24. Patients who are currently receiving immunosuppressive treatment and the treatment cannot be discontinued prior to starting study drug
25. Patients who have undergone major surgery \leq 2 weeks prior to starting study drug or who have not recovered from side effects of such therapy
26. All sexually active patients must agree to use adequate contraceptive methods (partner use of oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or if patient is vasectomized) throughout the study.
27. Patients unwilling or unable to comply with the protocol