Sponsor

Novartis

Generic Drug Name

MCS110

Therapeutic Area of Trial

Prostrate cancer with bone metastasis

Approved Indication

Investigational

Study Number

CMCS110A2101

Title

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.

Phase of Development

Phase I/II. This study was terminated during phase I (prior to Phase II)

Study Start/End Dates

30 Dec 2008 to 27 Aug 2009

Study Design/Methodology

This was an open label study, multicenter study, Phase I/II pharmacokinetics and pharmacodynamics study with asymptomatic castrate-resistant prostate cancer with bone metastasis, who have not received any bisphosphonates in the 12 months prior to enrollment. The study included a dose escalation and a dose expansion phase. The dose escalation phase (Phase I) that was guided by a two parameter Bayesian logistic regression model (BLRM) using the escalation with overdose control (EWOC) principle. The study was terminated prior to the dose expansion phase (Phase II). In the Phase I cohort patients received MCS110 at 0.01 mg/kg, administered IV, once every 2 weeks for three 28-day cycles. The starting dose of 0.01 mg/kg was based on the MABEL principle since a No Observed Adverse Effect Level (NOAEL) was not identified in the 13-week GLP toxicity study. The provisional dose levels in this study were: 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 10.0, and 20.0 mg/kg, but the study was terminated after completing the 0.01 mg/kg co-

hort.

Centres

2 centers in the United states

Publication

No publication available

Objectives

Primary objective(s)

Dose escalation phase

- To determine the maximum maximum-tolerated dose (MTD) or optimal biological dose (OBD) of MCS110.
- To characterize dose limiting toxicity (DLT) of escalating doses MCS110.

Dose expansion phase

- To assess the effect of MCS110 on bone resorption marker uNTx.

Secondary objective(s)

Dose escalation phase and Dose expansion phase

- To determine the safety and tolerability of escalating doses of MCS110, including acute and chronic toxicities.
- To characterize the PK of single and repeated doses of MCS110
- To characterize the binding kinetics of the M-CSF/MCS110 complex
- To assess the potential immunogenicity of intravenously infused MCS110
- To assess the effect of MCS110 on markers of bone resorption (urine NTx, serum CTx, and Trap5b) and on markers of bone formation (serum osteocalcin, bone specific alkaline phos-phatase, PINP)

Test Product (s), Dose(s), and Mode(s) of Administration

IV of MCS110 0.01 mg/kg was administered once every 2 weeks for three 28-day cycles.

Reference Product(s), Dose(s), and Mode(s) of Administration

Not applicable

Criteria for Evaluation

Efficacy

- Changes in markers of bone resorption and formation (pre- vs. post-treatment)
  - Markers for bone resorption (uNTx, sCTx, and Trap5b).
  - Markers for bone formation [serum osteocalcin, bone-specific alkaline phosphatase, amino terminal propeptide of type I procollagen (PINP)].
- Frequency of new skeletal related event (SRE) defined as pathological fractures, requirement for radiation therapy or surgery to the bone, or spinal cord compression. Onset date of newsreel was defined as the date of objective diagnosis (e.g. date of x-ray for pathological fractures) or intervention.
- Changes in PSA levels in patients not receiving secondary hormonal therapy to assess the anti-tumor effect of MCS110.

Safety

- Evaluation of adverse events and serious adverse events assessed and graded for severity
- Regular monitoring of hematology, coagulation panel, serum chemistries, urinalysis and serum immunoglobulins
- Physical examinations included measuring vital signs and weight.
- Cardiology monitoring included cardiac enzyme assessments, cardiac imaging, and 12-lead electrocardiograms (ECGs).

Bioanalytics

Pharmacokinetic and drug immunogenicity:

- MCS110 levels and antibody analyses were performed throughout the study
- Binding kinetics of M-CSF/MCS110 complex

Biomarker

- The effect of MCS110 on calcium and phosphate metabolism (PTH, Ca++, PO4---, Vitamin, D3, calcitonin, and PTHrP) were assessed.
- Immunophenotyping of lymphocytes by FACS analysis and measurement of soluble CSF-1R from blood were performed throughout the study.
- Effect of MCS110 on humoral and cellular immune response parameters.

Statistical Methods

Data was planned to be summarized with respect to demographic and baseline characteristics, efficacy measurements (including selected biomarker measurements for bone resorption, and bone formation), safety measurements, and all relevant pharmacokinetic and pharmacodynamic

measurements using descriptive statistics (quantitative data) and contingency tables (qualitative data). Since the study was terminated before dose expansion phase, data was analyzed and/or presented for the dose escalation phase only.

The safety analysis was to consist of AE listings, laboratory flagging of notable values in listings, and listing of other tests (e.g., electrocardiogram, vital signs) was to be listed by dose group. Trial data was to be analyzed when all patients continuing treatment had been followed for 3 cycles.

Efficacy analysis was not performed due to early termination of the study. All adverse events recorded during the study were listed. The safety population was used.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Men ≥18 years with asymptomatic castrate-resistant prostate cancer with bone metastases who have not received any bisphosphonates in the 12 months prior to enrollment.
- 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).
- History of disease progression following surgical or chemical castration.
- 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).
- ECOG performance status ≤ 2 and life expectancy of at least 6 months.

Exclusion criteria

- Prior cytotoxic chemotherapy for metastatic prostate cancer (prior cytotoxic chemotherapy is allowed only if it was administered in the neoadjuvant or adjuvant setting).
- Patients with > grade 1 CTCAE edema at screening.
- Concomitant disease(s) known to influence calcium metabolism including hyperparathyroidism, hyperthyroidism and/or Paget's disease of bone.
- Patients with a history of primary central nervous system tumors, brain metastases, clinically significant drug allergy, atopic allergy, immuno-compromise and interstitial lung disease.
- Active or chronic infection (bacterial, viral, fungal), autoimmune disease, active or latent tuberculosis.
- Patients for whom orthopedic surgery or radiation therapy is currently scheduled or planned to correct or treat defects related to metastatic bone lesions.

Number of Subjects

Phase I:

- Planned: 24 to 36 patients.
- Enrolled: 3 patients.
- Analyzed: 3 patients.

Demographic and Background Characteristics

A total of 3 male patients were enrolled with histologically confirmed prostate cancer with ≥ 1 bone metastatic lesion. The median age was 59 years. Of the 3 patients enrolled, 2 were Caucasians and 1 was Black.

Primary Objective Result(s)

The study was terminated after treatment of 3 patients and completion of 0.01 mg/kg dose cohort. The MTD was not defined. No DLT were reported among the 3 patients treated with MCS110.

Secondary Objective Result(s)

Efficacy results

Skeletal related event (SRE) and markers of bone absorption were assessed to evaluate the biologic activity of MCS110:

- Of the 3 patients treated, none of the patients experienced new SRE during the study period.
- Due to the small number of patients enrolled (n=3), no conclusion could be drawn regarding the biologic activity. No consistent direction of change was seen in any of the bone markers. However, one patient showed a pronounced cyclical pattern of changes in some biomarkers, especially PINP and Bone-specific alkaline phosphatase (BSAP). While this patient achieved a higher drug concentration than the other 2 patients, the changes in monocyte subset (from the immunophenotype of lymphocyte analysis) could not be evaluated since the patient's baseline sample was not collected. Therefore, it is unclear whether higher drug exposures may be correlated with the pronounced biomarker pattern.

Anti-tumor effect of MCS110:

- Effect of MCS110 on PSA levels in patients not receiving secondary hormonal therapy were not assessed as all patients treated also received secondary hormonal therapy during the study.

Safety Results

All reported adverse events occurring in patients at 0.01 mg/kg dose level

Adverse Events	Cohort 1 (0.01 mg/kg dose level) N = 3 n (%)	Worst CTCAE Grade Reported
Anemia	2 (67)	3
Chest pain (intermittent sternal pain)	1 (33)	2
Chills	1 (33)	1
Constipation	1 (33)	1
Decubitus ulcer	1 (33)	1
Diarrhea	1 (33)	1
Dizziness	1 (33)	2
Fatigue	1 (33)	1
Gait disturbance	1 (33)	2
Gastroesophageal reflux disease	1 (33)	1
Hot flush	1 (33)	1
Hypotension	1 (33)	2
Leukocytosis	1 (33)	1
Nausea	1 (33)	1
Oedema peripheral	1 (33)	1
Pneumonia	1 (33)	1
Pyrexia	1 (33)	1
Urinary tract infection	1 (33)	1
Weight decreased	1 (33)	1

Study drug-related adverse event:

- Adverse events suspected to be related to MCS110 were chills (grade 1), dizziness (grade 2), and hypotension (grade 2). These adverse events occurred in 1 patient, and were symptoms of an infusion reaction.

Serious Adverse Events and Deaths:

No SAEs, deaths, or discontinuation due to adverse event were reported in the 3 patients treated with MCS110.

Date of Clinical Trial Report 04-Mar-2010
Date Inclusion on Novartis Clinical Trial Results Database 22-Sep-2010
Date of Latest Update