THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Abstract Page

Phase II study of denosumab to define the role of bone related biomarkers in breast cancer bone metastasis
2013-0007

Core Protocol Information

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Full Title:	Phase II study of denosumab to define the role of bone related biomarkers in breast cancer bone metastasis
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Abstract

Objectives:

1.1. Primary Objective

To determine the effect of Denosumab in reducing circulating tumor cells (CTCs) among breast cancer patients with bone metastasis.

1.2. Secondary Objectives

- To determine changes in epithelial-mesenchymal transition (EMT) CTCs.
- To determine changes in Urine NTx levels.
- To determine tumor response rate by imaging tests.

1.3.Correlative Studies

- To explore changes in serum/plasma levels of cytokines/chemokines such as osteoprotegerin (OPG), osteopontin (OPN), osteocalcin (OC), parathyroid hormone (PTH), interleukin (IL)-1b, IL-6, IL-8, tumor necrosis factor (TNF)-a, tumor necrosis factor receptor (TNF-R)1/2, interleukin-1 receptor antagonist (IL-1RA).

- To explore changes in serum micro RNA (miR) levels including miR-19a, miR19b, miR-223, miR-17, miR-182, miR-144, miR-181, miR-145, miR-21, miR-146a/b, and miR-10b.

Rationale: (Be as concise as possible)

Bone is the most common metastatic site for breast cancer, and bone metastases develop in 65-75% of patients with metastatic breast cancer. These metastases can result in substantial morbidity in the form of skeletal-related events (SREs) that are defined as pathological fractures, spinal cord compression, hypercalcemia, or pain that requires radiation or surgery of the bone. Modalities used to treat breast cancer that has metastasized to the bone include chemotherapy, hormonal therapy, analgesics, radiotherapy, and orthopedic surgery.

Current management of bone metastasis is bisphosphonates, which are potent antiresorptives used in the prevention of SREs. These agents improve the structural integrity of the bone, but they are not effective in completely inhibiting the progression of bone metastases.

In normal bone, the tissue is continually renewed by remodeling, which is tightly balanced between bone resorption (osteolysis) by osteoclasts, and bone formation by osteoblasts. The formation of skeletal metastases alters the balance of bone remodeling, which favors either osteolytic or osteoblastic metastasis. Preclinical data support a model of interaction between tumor cells and the bone microenvironment, which creates a 'vicious cycle' that accelerates both bone destruction and tumor growth. The tumor cells secrete parathyroid hormone-related peptide (PtHrP), the principal stimulator of osteoclastogenesis. They also produce other osteoclast-stimulating factors, such as interleukin (IL)-11, IL-6, IL-1, prostaglandin E2, tumor necrosis factor, and macrophage colony-stimulating factor. These factors promote the expression of the receptor activator of nuclear factor kB (RANK) and RANK ligand (RANKL) on the surface of stromal cells and osteoblasts. RANKL then binds to RANK on osteoclast precursors and promotes their differentiation into active osteoclasts, leading to excessive bone loss. With reciprocal effect, the tumor growth in bone is accelerated by the production of growth factors from the stroma of the bone marrow, such as transforming growth factor (TGF)beta, insulin-like growth factors, fibroblast growth factors, and platelet-derived growth factor.

Denosumab is a fully human monoclonal antibody that specifically targets RANKL, which is one of the principal regulators of osteoclast differentiation, function, and survival. This antibody is currently the most promising potential alternative to bisphosphonates. The RANK-RANK ligand (RANKL) system has been identified as an essential mediator of osteoclast formation, function, and survival. RANKL binds RANK on osteoclasts or osteoclast precursors to stimulate or promote differentiation into osteoclasts and activate mature osteoclasts to resorb bone. Therefore, RANKL is a therapeutic target for diseases associated with increased bone resorption. Denosumab is highly specific because it binds only to RANKL and not to other members of the TNF family, including TNF-alfa, TNF-beta, TNF-related apoptosis-inducing ligand (TRAIL), or CD40 ligand. Denosumab binding to RANKL prevents the activation of RANK and inhibits the formation, activation, and survival of osteoclasts. As a consequence, bone resorption and cancer-induced bone destruction are reduced.

Denosumab has been studied in various disease settings, including metastatic bone disease, osteoporosis, cancer treatment induced bone loss, multiple myeloma, rheumatoid arthritis, and

giant cell tumor of the bone (osteoclastoma). Several studies have compared the efficacy of denosumab and bisphosphonates in patients with breast cancer, with promising results. In summary, denosumab seems to be safe and potentially more effective than bisphosphonates in normalizing bone resorptive markers and preventing SREs in breast cancer bone metastasis.

The purpose of the study is to determine the efficacy of denosumab in breast cancer patients with bone metastasis through the reduction of CTCs, and to determine the ability of denosumab to target breast cancer stem cells. We will also evaluate the tumor effect of denosumab by comprehensive imaging (PET-CT, SS and MRI as clinically indicated). At last multiple biological correlative studies will be conducted to understand the role of denosumab in breast cancer. Patients who are eligible is a newly diagnosed hormone receptor positive bone metastasis who is expected to have a very slow progression of disease.

Eligibility: (List All Criteria)

Inclusion:

1) Patients have histological confirmation of breast carcinoma.

2) Patients have progressive metastatic disease with predominantly bone metastasis with 1 or more lesions and at least 1 bone lesion has pathological confirmation, have not been treated or have been treated with any prior therapies (including bisphosphonate treatment and/or radiation therapy). Patients can have soft tissue involvement (Lymph node and skin) and/or metastatic lesions at major organ sites (i.e. lung, liver, etc).

3) Patients have positive ER expression in the primary tumor site by IHC (defined as >/=10%) (PR status is not required)

4) Adequate hematologic function: 1)Absolute neutrophil count (ANC) >/= 1.0 x 10^9/L, 2) Platelet count >/= 50 x 10^9/L, 3) Hemoglobin >/= 9.0 g/dL

5) Adequate cardiac function (LVEF >/= 45%) if patient has known cardiac dysfunction history

6) Adequate Renal function: Calculated creatinine clearance >30 ml/min

7) Adequate Hepatic function: 1) Aspartate aminotransferase (AST) </= 2.5 x ULN; 2) Alanine aminotransferase (ALT) </= 2.5 x ULN; 3) Alkaline phosphatase (Alp) </= 2.5 x ULN; 4) Total bilirubin </= 2.0 x ULN

8) Serum calcium or albumin-adjusted serum calcium >/=2.0mmol/L (8.0mg/dL) and </= 2.9 mmol/L (11.5mg/dL)

9) Patients have ability and willingness to sign written informed consent.

10) Patients are 18 years of age or older.

11) Female patients of childbearing potential (A female not free from menses > 2 years or not surgically sterilized) must be willing to use highly effective contraception to prevent pregnancy or agree to abstain from heterosexual activity throughout the study. Highly effective contraception, defined as male condom with spermicide, diaphragm with spermicide, intra-uterine device. Highly effective contraception must be used by both sexes during the study and must be continued for 5 months after the last dose of denosumab.

12) Female patients of childbearing potential must have negative serum pregnancy test </= 21 days prior to starting study treatment.

13) Patients have CTC >/=3.

Exclusion:

1) Patients have known sensitivity to any of the products to be administered during the study (e.g., mammalian derived products, calcium, or vitamin D).

2) Patients receiving concurrent anti-cancer therapy (chemotherapy, immunotherapy, radiation therapy and biological therapy) while taking study medication. However, patients receiving CDK4/6 inhibitor or mTOR inhibitor as a standard of care while on study is permitted.

3) Patients with metastatic sites that requires chemotherapy.

4) Patients with active infection and requiring IV or oral antibiotics.

5) Patients with concurrent disease or condition that would make them inappropriate for study participation, or any serious medical disorder that would interfere with patients' safety.

6) Patients have HER2-positive breast carcinoma (IHC staining more than 3+ or HER2 gene amplification by FISH)

7) Patient is pregnant or breast feeding, or planning to become pregnant within 5 months after the end of treatment.

8) Patient is of child bearing potential and is not willing to use, in combination with her partner, two highly effective methods of contraception or abstinence during treatment and for 5 months after the end of treatment.

9) Male patients.

10) Patients have prior history or current evidence of osteonecrosis/osteomyelitis of the jaw.

11) Patients have active dental or jaw condition which requires oral surgery, including tooth extraction.

12) Patients have non healed dental/oral surgery, including tooth extraction.

13) Patients planned invasive dental procedures.

14) Patients experiencing a visceral crisis including severe organ dysfunction as assessed by > Gr 2 symptomatic toxicities, laboratory studies, and/ or rapid progression of disease originating from visceral metastasis.

15) Patients that have received the study medication (Xgeva/Prolia).

Are patients <18 years of age eligible to participate in this study? ○ **Yes** ● **No**

Studies that include children must meet the criteria for inclusion.
http://www.fda.gov/ohrms/dockets/AC/04/briefing/4028B1_05_NIH-Inclusion%20of%20Children.doc
http://www.hhs.gov/ohrp/policy/populations/children.html

Studies that exclude children must have appropriate justification. Please select all that apply:

Phase I or Phase II study targeting cancer that is very unusual in pediatrics (e.g., prostate, lung, breast, chronic lymphocytic leukemia, etc.)

Are participants >65 years of age eligible to participate in this study? ● **Yes** ○ **No**

Are pregnant women eligible to participate in this study? ○ **Yes** ● **No**

Will the recruitment population at M. D. Anderson include persons who are incarcerated at time of enrollment (e.g., prisoners) or likely to become incarcerated during the study?
○ **Yes** ● **No**

Disease Group:

Breast

Treatment Agents/Devices/Interventions:

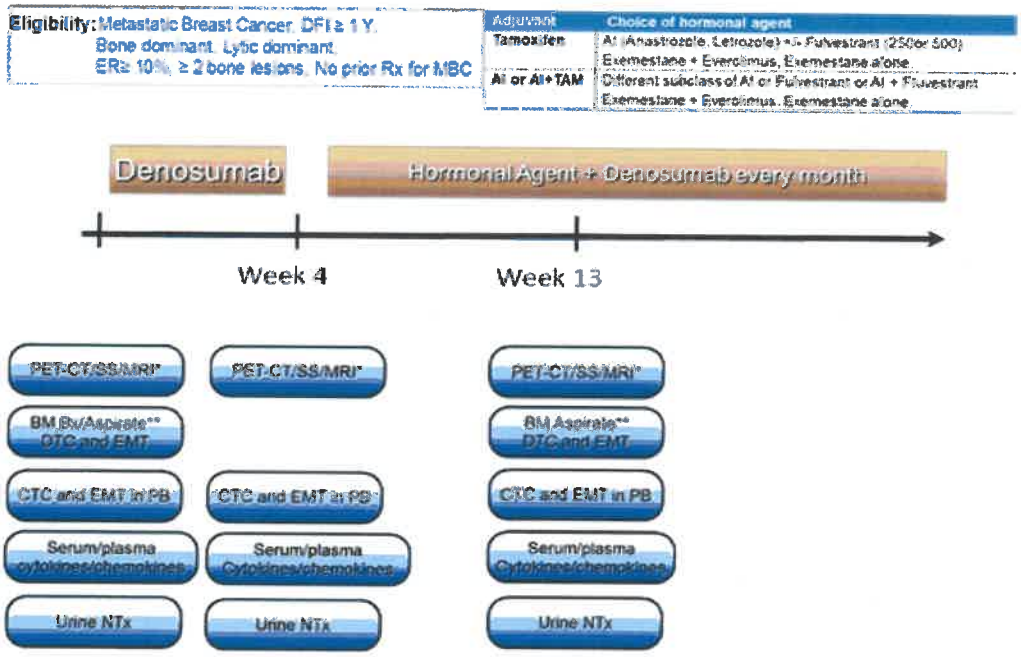
Denosumab

Proposed Treatment/Study Plan:

Is treatment assignment randomized? ○ **Yes** ● **No**

Is this a blinded or double-blinded study? ○ **Yes** ● **No**

Patients will receive a single subcutaneous (SC) administration of denosumab 120 mg every 4 weeks (+/- 5days). Starting week 4, in addition to receive denosumab every 4 weeks, patients will receive a hormonal agent. Each physician can choose hormonal agent but exclude the agent that the patients received at adjuvant therapy setting. For example, if the patient received tamoxifen at adjuvant setting, aromatase inhibitor (AI) will be used, i.e. Arimidex (anastrozole), Aromasin (exemestane) or Femara (letrozole). If the patient received AI or AI and tamoxifen, a different subclass of AI or fulvestrant will be used. Combination therapies such as AIs+ fulvestrant, Exemestane and Everolimus are also acceptable regimen. Patients may receive off study denosumab as standard of care after discontinuation of 3 months study treatment.



Study Schedule

Evaluation and Treatment	Screening/Baseline	C1 (wk1)	C1 (wk 4)	C2 (wk 5)	C3 (wk 9)	End of study (week 13)
Eligibility, Screening, Consent, Registration	X					
Medical History (prior therapies and procedures for breast cancer)	X					
Physical Examinations, Vital Signs as standard of care	X		x			x
ECOG Performance Status	X		x			x
Hematologic, and Biochemical Profiles, tumor markers*	X		X	X******	X******	x
Serum pregnancy test, if applicable	X					
PET/CT/SS/MRI*****	X		X			X
Bone Marrow Aspiration**** DCT and EMT	X					X
Blood collection: Micro RNA, CTC and EMT CTC.	X		X#			X
Serum/Plasma Cytokines/Chemokines	X		X#			X

Urine NTx	X		X#			X
EKG,ECHO/MUGA will be repeated as clinically indicated for standard of care	X					
Adverse Events	X		x	x	x	X
Denosumab injection (once every 4 weeks)		X		x	X	x**
A Hormonal agent (Administered as indicated)			X	x	x	X***

*CBC, bilirubin, Creatinine, ALT, AST, BUN, serum creatinine, calcium,phosphorus, sodium, magnesium, potassium, fasting glucose, albumin, total bilirubin, alkaline phosphatase, CA15-3 and CEA.
** After week 12, patient will be off study. It is primary physician's discretion to continue or not continue the therapy.
*** Hormonal agent: If the patient received tamoxifen at adjuvant setting, aromatase inhibitor (AL) will be used, i.e. Arimidex (anastrozole), Aromasin (exemestane) or Femara (letrozole). If the patient received AL or AL and tamoxifen, a different subclass of AL or fulvestrant will be used. After week 12, patient will be off study, it is primary physician's discretion to continue or not continue the therapy on off study basis.
****as clinically indicated/optional
*****as clinically indicated
****** Calcium and Phospharus only
# blood will be collected before hormonal therapy.

Study Enrollment:
The study population for this research will consist of participants from:

Only at MDACC

Estimated Accrual:

Total Accrual at MDACC: 35
Estimated monthly accrual at MDACC: 0-2

Accrual Comments:
None.

Is this an NCI-Cancer Therapy Evaluation Protocol (CTEP)? No

Is this an NCI-Division of Cancer Prevention Protocol (DCP)? No

Statistical Considerations:

Study Design

The primary objective of this study is to determine the effect of Denosumab in reducing circulating tumor cells (CTCs) among breast cancer patients with bone metastasis. The primary endpoint is the percentage of patients that have "low CTCs", defined as less than 5 CTCs and also including CTC 0 in 7.5 ml whole blood. We assume that 30% patients have low CTCs at

baseline. If we expect this percentage to increase to 60%, and 25% of patients maintain low CTCs at week 4, then 5% patients will become CTC positive, 35% patients will become low CTCs and 35% patients will maintain CTC positive. The proportion of discordant pairs is 40%. With a sample size of 35 evaluable patients we will have 88% power to detect a difference of 30% in percentage of patients that are low CTCs using a two-sided McNemar test with a significance level of 0.10.

On the other hand, with the same expectation of a 30% increase in percentage of patients with low CTCs, if 20% of patients maintain low CTCs at 4 weeks, then 10% patients will become CTC positive and 40% patients will become low CTCs. The proportion of discordant pairs is 50%. We will have 79% power to detect a difference of 30% in percentage of patients that are low CTCs using a two-sided McNemar test with a significance level of 0.10.

The secondary objectives include evaluating CTCs at 12 weeks after patients have been treated with denosumab alone at week 4 and 2 cycles of combination of denosumab and hormonal agents, determining EMT cellular changes, urine NTx, tumor response by PET-CT at week 4 and at week 13, exploring the changes of the cytokines/ chemokines such as OPG, OPN, OC, PTH, IL-1b, IL-6, IL-8, TNFa, TNF-R1/2, IL-1RA in plasma and serum and miRNA such as miR-19a, miR19b, miR-223, miR-17, miR-182, miR-144, miR-181, miR-145, miR-21, miR-146a/b, miR-10b at week 4 and week 13.

Summary statistics, including frequency tabulation, means, standard deviations, median, and range, will be used to describe patients' characteristics, CTC reduction, changes in epithelial mesenchymal transition (EMT) in CTCs, changes in Urine NTx levels and a series of biomarkers. The response rate will be estimated with 95% confidence interval.

For the primary endpoint, McNemar's test will be applied to test the change of percentage of patients that are low CTCs at week 4. We will also summarize CTC count, both at baseline and after 3 week treatment, as a continuous variable. The change of CTC count will be estimated and tested whether the change is significantly different from 0 using a Wilcoxon signed rank test.

For the secondary endpoint, Fisher's exact test will be used to test the association between two categorical variables, such as low CTCs, tumor response and prognostic factors. Paired t-test or Wilcoxon sign rank test will be used to test the change in epithelial mesenchymal transition (EMT) in CTCs and changes in Urine NTx levels over time, when appropriate. Wilcoxon rank sum test may be employed to test the difference of these changed between response and non-response groups.

For the correlative studies of a series of biomarkers, the association among various continuous and discrete biomarkers will be assessed first by the exploratory data analysis using scatter plot matrix, box plots, BLiP plot and trellis plot, etc. Correlation among continuous biomarkers will be examined by Pearson or Spearman rank correlation coefficients. Wilcoxon sign rank test will be used to test the change of a continuous biomarker over time. McNemar's test will be applied to test the change of a discrete biomarker over time. We will use the generalized estimating equations to model correlated discrete variables. Repeated measures analysis including mixed

effects model will be performed to analyze continuous biomarkers change over time and effect of treatment and patients' characteristics on the biomarkers changes over time.

Data Safety Monitoring Board / DSMB at MDACC:

Select the name of the data safety monitoring board (DSMB) monitoring this protocol:
Not Applicable

Please explain:
This is a single arm and not blinded phas II trial. Denosumab is FDA approved and commercially available drug for patients with breast cancer and have bone metastases, which is the same patient population in this study.

Protocol Monitoring:

Does this protocol have a schedule for interim and final analysis? No

Provide a rationale for no interim analysis.

Denosumab is FDA approved and commercially available drug for breast cancer patients with bone metastasis. For the study population, patients receive denosumab is a part of standard of care. The primary purpose of this study is to determine the effect of denosumab in reducing circulating tumor cells (CTCs) among breast cancer patients with bone metastasis. Safety profile will be monitored as standard of care during the study and is described below in protocol monitoring plan.

Protocol Monitoring Plan:

Adverse events will be assessed according to the CTCAE version 4.0. All study patients who have received any dose of denosumab will be evaluable for safety. Unexpected adverse events including laboratory adverse events deemed clinically significant by the investigator will be graded and recorded.

The ongoing review of safety data will include review of clinical AEs and SAEs. The NCI-CTC version 4.0 will be used to grade all AEs. An AE is an undesirable medical occurrence (sign, symptom, or diagnosis) or worsening of a pre-existing medical condition (diabetes, congestive heart failure, rheumatoid arthritis) that occurs after initiation of investigational product whether or not considered to be investigational product related. A worsening of an existing medical condition is one that was present at baseline (e.g., cancer, diabetes, migraine headaches, gout) and became more severe, more frequent, or increased in duration during investigational product treatment.

All AEs will be reported occurring after informed consent signing observed by the investigator or reported by the subject (whether or not attributed to investigational product), will be documented to the medical record then entered into the case report form. Abnormal laboratory values should not be reported as AEs; however, any clinical consequences of the abnormality should be reported as AEs. Hospitalization for elective surgery or routine clinical procedures that are not

the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE. The Investigator is responsible for verifying and providing source documentation for all adverse events and assigning attribution for each event for all subjects enrolled on the trial.

Intellectual Property:

1. Does this study include any agents, devices, or radioactive compound (or drug) manufactured at MD Anderson Cancer Center or by a contract manufacturer? No

Investigational New Drugs (IND):

Does this protocol require an IND? No

☒ **Please confirm that the protocol meets all criteria for exemption according to 21CFR 312.2(b) noted below:**

(b) Exemptions. (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if all the following apply:

(i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and

(v) The investigation is conducted in compliance with the requirements of 312.7.

Rationale for Exemption:
Please include a detailed rationale as to why this drug should be considered exempt from FDA IND regulations, including any available references to the prior use of the regimen or drug combination in human subjects.

Denosumab is FDA approved and commercially available drug for breast cancer patients with bone metastasis. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and to support a significant change in the advertising for the protocol.

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	Proposed in this Protocol
Disease:	Breast, prostate Cancer bone metastases	Breast cancer bone metastases

Dose:	120 mg every 4 weeks	120 mg every 4 weeks
Route of Administration:	Subcutaneous	Subcutaneous

Investigational Device (IDE):

Does this study utilize an Investigational Device? No

Sponsorship and Support Information:

Does the Study have a Sponsor, Supporter or Granting Agency? Yes

Sponsor Name: Amgen
Support Type: Industry Funding

This Sponsor/Supporter/Granting Agency will receive data.

Radioactive Material:

Does this study involve the administration of radioisotopes or a radioisotope labeled agent? No
Click here for help

Biosafety:

Does this study involve the use of Recombinant DNA Technology? No

Does this study involve the use of organisms that are infectious to humans? No

Does this study involve human/animal tissue other than blood derived hematopoietic stem cells? No

Questions should be addressed to the Transfusion Medicine Tissue Coordinator at 713-792-8630.

Laboratory Tests:

Is there any biomarker testing in this study being used to determine patient/participant eligibility, treatment assignment, or management of patient/participant care?
● Yes
○ No
○ Not Applicable For This Protocol
Please provide the name of the test(s), the purpose of the test, the performing laboratory identification and contact information, and confirm that the testing lab is CLIA certified (may attach a certificate or provide a certificate number).

Estrogen receptor CLIA-P~1.PDF

Manufacturing:

Will you manufacture in full or in part (split manufacturing) a drug or biological product at the M. D. Anderson Cancer Center for the proposed clinical study?	No

Student/Trainee Information:

Is this research being conducted as a partial fulfillment for completion of a degree?	No