New Developments in Oncology Bone Health

Presented as a Live Webinar

Thursday, June 12, 2014
1:00 p.m. – 2:00 p.m. EDT

Wednesday, July 16, 2014
12:00 p.m. – 1:00 p.m.

Tuesday, July 29, 2014
2:00 p.m. – 3:00 p.m.

www.ashpadvantage.com/bonehealth

Planned and conducted by ASHP Advantage and supported by an educational donation provided by Amgen.

Activity Overview

This activity will provide an overview of the types of bone loss and bone-related events that affect cancer patients. The risk factors, incidence, and prevalence of these events, as well as their impact on morbidity, mortality, and quality of life will be discussed. Currently available agents targeting bone health will be described, as well as the approach to using these agents in both the preventative and treatment settings for patients with cancer. Finally, the role of the pharmacist in assessing patients' risk factors and recommending therapies for bone-directed treatment will be presented. Clinical patient vignettes will be used to illustrate the decision-making process throughout the presentation.

Learning Objectives

At the conclusion of this knowledge-based educational activity, participants should be able to

- Describe the types of bone loss and bone-related events that affect cancer patients and the influence of these events on morbidity, mortality, and quality of life.
- Compare and contrast the mechanism of action, efficacy, and safety of available therapies for use to prevent skeletal complications in cancer patients.
- Explain the mechanism of action, data, and potential role of available bone-targeted therapies in the treatment of cancer.
- Describe the approach to decision making when selecting an appropriate bone-targeted therapy for particular cancer patients.

Continuing Education Accreditation

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-14-477-L01-P for the live activity and ACPE activity #0204-0000-14-477-H01-P for the on-demand activity).

Participants will process CPE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home study activity.

Webinar Information

Visit www.ashpadvantage.com/bonehealth to find:

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information

Additional Educational Activities in this Initiative

This live activity will be archived and offered as web-based on-demand learning at www.ashpadvantage.com/bonehealth.

Activity Faculty

Chad M. Barnett, Pharm.D., BCOP
Clinical Pharmacy Specialist – Breast Oncology
Division of Pharmacy
University of Texas MD Anderson Cancer Center
Houston, Texas

Chad M. Barnett, Pharm.D., BCOP, is Clinical Pharmacy Specialist in the Division of Pharmacy at The University of Texas MD Anderson Cancer Center in Houston, Texas. In addition to his patient care responsibilities, Dr. Barnett is involved in precepting oncology pharmacy practice residents on the Breast Medical Oncology rotation. Dr. Barnett also serves as clinical faculty for the ASHP Oncology Pharmacy Preparatory Review Course. He has authored numerous book chapters and articles and has presented nationally on topics related to breast cancer and bone health in patients with cancer. Dr. Barnett is also actively involved in breast cancer research.

Dr. Barnett received his Doctor of Pharmacy degree from the University of Kansas in Lawrence, Kansas. He completed a pharmacy practice residency at The Methodist Hospital in Houston, Texas and an oncology pharmacy practice residency at the University of Texas M.D. Anderson Cancer Center in Houston, Texas. Dr. Barnett became a Board-Certified Oncology Pharmacist (BCOP) in 2006.

Kamakshi V. Rao, Pharm.D., BCOP, CPP, FASHP
Clinical Manager, Pharmacy Residency Programs
Oncology and Bone Marrow Transplant Clinical Pharmacist
University of North Carolina Hospitals and Clinics
Chapel Hill, North Carolina

Kamakshi V. Rao, Pharm.D., BCOP, CPP, FASHP, is a clinical manager over pharmacy residency programs and an oncology and bone marrow transplant clinical pharmacist practitioner at the University of North Carolina Medical Center in Chapel Hill, North Carolina. She also serves as Associate Professor of Clinical Education at the UNC Eshelman School of Pharmacy.

Dr. Rao earned her Doctor of Pharmacy degree from Rutgers University Ernest Mario School of Pharmacy. She completed a pharmacy practice residency at the Medical College of Virginia and an oncology fellowship at The Cancer Institute of New Jersey.

Dr. Rao is an active member of the American Society of Health-System Pharmacists (ASHP), Hematology/Oncology Pharmacy Association, and American Society for Blood and Marrow Transplantation. She is currently a board-certified oncology pharmacist and a Fellow of the ASHP.

Disclosure Statement

In accordance with the Accreditation Council for Continuing Medical Education's Standards for Commercial Support and the Accreditation Council for Pharmacy Education's Guidelines for Standards for Commercial Support, ASHP Advantage requires that all individuals involved in the development of activity content disclose their relevant financial relationships. A commercial interest is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients. A person has a relevant financial relationship if the individual or his or her spouse/partner has a financial relationship (e.g., employee, consultant, research grant recipient, speakers bureau, or stockholder) in any amount occurring in the last 12 months with a commercial interest whose products or services may be discussed in the educational activity content over which the individual has control. The existence of these relationships is provided for the information of participants and should not be assumed to have an adverse impact on presentations.

All faculty and planners for ASHP Advantage education activities are qualified and selected by ASHP Advantage and required to disclose any relevant financial relationships with commercial interests. ASHP Advantage identifies and resolves conflicts of interest prior to an individual's participation in development of content for an educational activity.

The following faculty and planners report no relationships pertinent to this activity:

- Chad M. Barnett, Pharm.D., BCOP
- Kamakshi V. Rao, Pharm.D., BCOP, CPP, FASHP
- Jill A. Sellers, Pharm.D.

ASHP staff has no relevant financial relationships to disclose.

New Developments in Oncology Bone Health

Chad M. Barnett, Pharm.D., BCOP
Clinical Pharmacy Specialist - Breast Oncology
Division of Pharmacy
The University of Texas M.D. Anderson Cancer Center
Houston, Texas

Kamakshi V. Rao, Pharm.D., BCOP, CPP, FASHP
Clinical Manager, Pharmacy Residency Programs
Oncology/Bone Marrow Transplant Clinical Pharmacist Practitioner
Director, PGY-1 Pharmacy Residency Program
UNC Hospitals and Clinics
Associate Professor of Clinical Education
UNC Eshelman School of Pharmacy
Chapel Hill, North Carolina

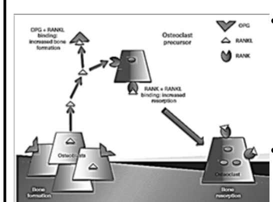
Learning Objectives

- Describe the types of bone loss and bone-related events that affect cancer patients and the influence of these events on morbidity, mortality, and quality of life.
- Compare and contrast the mechanism of action, efficacy, and safety of available therapies for use to prevent skeletal complications in cancer patients.
- Explain the mechanism of action, data, and potential role of available bone-targeted therapies in the treatment of cancer.
- Describe the approach to decision making when selecting an appropriate bone-targeted therapy for particular cancer patients.

Bone Health in Cancer Patients

- **Background and risk factors**
- Screening and diagnosis
- Prevention and treatment strategies
  - Cancer treatment induced bone loss
  - Metastatic disease induced bone loss/ skeletal related events (SRE)
- Novel agents and emerging science

Normal Bone Physiology



- Normal bone homeostasis is a balance between
  - Osteoblasts: new bone formation
  - Osteoclasts: bone resorption
- Process is regulated by the RANKL pathway
  - Receptor activator factor-kappa B ligand (RANKL)
  - Osteoprotegerin (OPG)

Lustberg M et al. *J Clin Oncol.* 2012; 30:3665-74.

See enlargement, p. 15

Balance between RANKL and OPG

- RANKL and OPG are both produced by osteoblasts
  - RANKL binds to RANK receptor on osteoclasts, to stimulate bone resorption
  - OPG is a "decoy receptor" for RANKL. Binding of RANKL to OPG therefore inhibits osteoclast induced bone resorption, allowing bone formation to predominate
- The ratio/balance between RANKL and OPG is the foundation of normal bone remodeling

Incidence of Bone Disorders in the General Population

- ***Osteoporosis*** - bone mineral density >2.5 standard deviations below the mean for normal young white women
  - Affects 10 million individuals over age 50 in the US
- ***Osteopenia*** - bone mineral density 1-2.5 standard deviations below the mean for normal young white women
  - Affects 33.6 million people over age 50 in the US
- Fracture
  - Occurs in 1.5 million individuals annually due to bone disease

Lifetime Risk of Fracture at Age 50

Type of Fracture	White Women	White Men
Hip (%)	17.5	6.0
Vertebra (%)	15.6	5.0
Forearm (%)	16.0	2.5
Any of the 3 above	39.7	13.1

Cummings SR et al. *Lancet.* 2002; 359:1761-7.

Question #1

Which of the following diseases is NOT associated with an increased risk of bone disease?

a. Prostate cancer
b. Breast cancer
c. Non-Hodgkins lymphoma
d. Multiple myeloma

Risk Factors for Bone Disease in Cancer Patients – Treatment Related Factors

Endocrine	Genetic	Lifestyle	Nutritional	Diseases
Menopause	Family history	Smoking	Low calcium	**Breast cancer**
Oopherectomy	Race	Alcohol	**Low vitamin D**	**Prostate cancer**
GnRH agonists	Sex	**Sedentary lifestyle**		**Lung cancer**
Hypoestrogenic states	**Low body weight**	**Chronic corticosteroid use**		**Multiple myeloma**
Androgen deprivation		**Prolonged immobilization**		**Stem cell transplant**
Early menopause				**Pediatric ALL**
Hypogonadism				

Lustberg M et al. *J Clin Oncol.* 2012; 30:3665-74.

Bone Health in Cancer Patients

- Background and risk factors
- **Screening and diagnosis**
- Prevention and treatment strategies
  - Cancer treatment induced bone loss
  - Metastatic disease induced bone loss/SRE
- Novel agents and emerging science

Screening and Diagnosis – DEXA scan

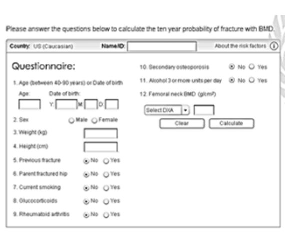
- The gold standard of bone mineral density (BMD) measurement is dual-energy x-ray absorptiometry (DEXA) scanning
  - T-Score - bone density compared with what is normally expected in a healthy young adult of your sex

Diagnosis	Criterion - BMD
Normal	T score better than -1
Osteopenia	T score between -1 and -2.5
Osteoporosis	T score < -2.5
Severe Osteoporosis	T score < -2.5 + osteoporotic fracture

  - Z-Score - number of standard deviations above or below what's normally expected for someone of a particular age, sex, weight, and ethnic or racial origin

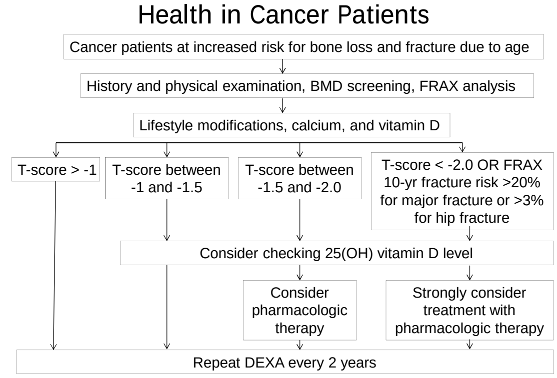
Screening and Diagnosis – Tool

- FRAX® - World Health Organization Fracture Risk Assessment Tool
  - Computer based tool which integrates clinical information, with or without measured BMD, to calculate the 10-year probability of major osteoporotic fracture and hip fracture
  - Takes into account modifiable and nonmodifiable risk factors



See enlargement, p. 15

Algorithm for Management of Bone Health in Cancer Patients



Gralow JR et al. *J Natl Compr Canc Netw*. 2013; 11(Suppl 3):S1-50.

Bone Health in Cancer Patients

- Background and risk factors
- Screening and diagnosis
- **Prevention and treatment strategies**
  - **Cancer treatment induced bone loss**
  - Metastatic disease induced bone loss/SRE
- Novel agents and emerging science

Chemotherapy Induced Bone Loss

- Hormonal therapy
  - Aromatase inhibitors in breast cancer
  - Androgen deprivation therapy in prostate cancer
- Chemotherapy induced ovarian failure (CIOF)
- Hematopoietic stem cell transplant

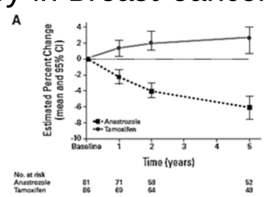
Question #2

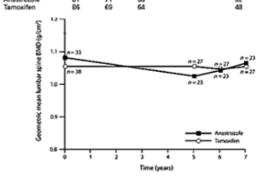
Which of the following agents is associated with the highest rate of bone loss in women with breast cancer?

a. Aromatase inhibitors
b. Tamoxifen
c. Corticosteroids
d. Fulvestrant

Hormonal Therapy in Breast Cancer

- ATAC Trial: randomized 6,241 ER+ postmenopausal women to 5 years of anastrazole or tamoxifen
  - Fractures occurred in 11% of anastrazole patients compared to 7.7% of tamoxifen patients ($p<0.001$)at 68 months of follow up
    - After treatment ceased, fracture rates equalized between arms





Eastell R et al. *J Clin Oncol.* 2008; 26:1051-8; Eastell R et al. *Ann Oncol.* 2011; 22:857-62.

See enlargement, p. 16

Hormonal Therapy in Prostate Cancer

- Numerous trials have evaluated the effect of ADT on bone mineral density and fracture risk:
  - Prospective study compared patients receiving >1yr of ADT to matched controls
  - Analysis of 15,716 men with fractures and 47,149 controls showed prostate cancer to be a significant factor associated with increased risk of fracture

Years of ADT	None	2	4	6	8	10
N	N=124	N=112	N=61	N=37	N=35	N=21
% Normal	19.4	17.8	16.4	10.8	5.7	0
% Osteopenia	45.2	39.3	34.4	29.7	28.5	19.4
%Osteoporosis	35.4	42.9	49.2	59.5	65.7	80.6

Morote J et al. *Urology.* 2007; 69:500-4.

Chemotherapy Induced Ovarian Failure

- Effect of chemotherapy on ovarian function depends on age, class of chemotherapy, and cumulative exposure
  - Risk of CIOF increases with age due to decreased ovarian reserve
    - In pediatric patients, treatment before puberty reduces likelihood of CIOF (Hodgkins, pediatric ALL)
- In women who retain menstrual function after chemotherapy, natural menopause may occur at an earlier age than matched controls

Lustberg M et al. *J Clin Oncol.* 2012; 30:3665-74.

Hematopoietic Stem Cell Transplant (HCT)

- Numerous factors increase the risk of bone loss in patients undergoing HCT:
  - High dose chemotherapy/radiation
  - Calcineurin inhibitors (tacrolimus, cyclosporine)
  - Gonadal failure
  - Prolonged corticosteroid use
- Bone loss occurs within 6-12 months after HCT. Recovery occurs first in the lumbar spine, then in the femoral neck
- For patients requiring longer-term therapy with steroids and calcineurin inhibitors, bone marrow transplant may remain low and not return to normal

Treatment Options

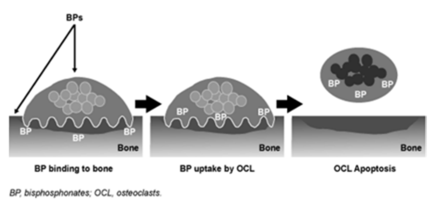
- Options for treatment have grown over the past 10 years
  - Bisphosphonates
  - Denosumab
  - Selective estrogen receptor modulators
  - Teriparatide

But never forget the basics….

- Calcium
  - Calcium carbonate
  - Calcium gluconate
  - Calcium citrate
- Vitamin D
  - Monitoring for deficiency
  - Supplementation
- Weight bearing exercises

Bisphosphonates
Mechanism of Action

- Decrease bone resorption and increase bone mineralization by inhibiting osteoclast activity



Roodman GD. Clinical Care Options: treatment of myeloma bone disease. August 9, 2010 (URL in ref list).

See enlargement, p. 16

Bisphosphonates
Available Agents

Agent	FDA approved doses
Alendronate (Fosamax®) PO	Prevention: 5 mg Qday/35 mg Qweek Treatment: 10 mg Qday/70 mg Qweek
Risedronate (Actonel®) PO	5 mg Qday/35 mg Qweek/150 mg Qmonth
Ibandronate (Boniva®) PO/IV	150 mg PO Qmonth/3 mg IV Q3months
Pamidronate (Aredia®) IV (malignancy only)	60-90 mg IV Q3-4 weeks
Zoledronic Acid (Zometa®, Reclast®) IV	Nonmalignant: 5 mg Q2years Malignant: 5 mg Qyr, 4 mg Q3-6months

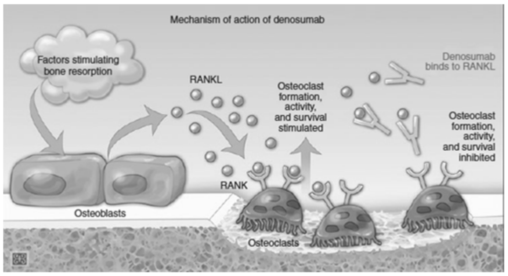
- Majority of cancer trials have used IV bisphosphonates

Bisphosphonates
Toxicities

- Hypocalcemia
  - Increased risk in patients with vitamin D deficiency and when not used in the setting of hypercalcemia
- Renal toxicity
  - Acute tubular necrosis with zoledronic acid: Increased incidence with faster infusions
- Osteonecrosis of the jaw
  - Pain, numbness, exposed bone
  - Incidence reported at 1-10 %
  - Increased risk in those with previous jaw trauma or dental surgery/extraction
  - Cumulative dose relation
  - IV bisphosphonates > PO bisphosphonates

Denosumab (Prolia®)

- Monoclonal antibody directed towards RANKL



Lewiecki EM, Bilezikian JP. *Clin Pharmacol Ther.* 2012; 91:123-33.

See enlargement, p. 17

Denosumab
Dosing and Toxicities

Dosing

- 60 mg SC Q6 months (Prolia®)
  - Treatment of osteoporosis in patients at risk for fracture
  - Bone loss induced by AI's or ADT
- 120 mg SC Q4 weeks (Xgeva®)
  - Treatment of metastatic disease to prevent skeletal related events

Toxicities

- Hypocalcemia
- Infusion reactions
- Osteonecrosis of the jaw
- Hypophosphatemia

Denosumab versus ZA (All Phase III Trials)
Selected Adverse Events of Any Severity

Body System	Denosumab (n=2841) %	Zoledronic acid (ZA)(n=2836) %
Gastrointestinal		
Nausea	31	32
Diarrhea	20	19
General		
Fatigue/Asthenia	45	46
Laboratory		
Hypocalcemia	18	9
Hypophosphatemia	32	20
Neurological		
Headache	13	14
Respiratory		
Dyspnea	21	18
Cough	15	15

Xgeva™ product information. Amgen, Inc, Thousand Oaks, CA; August 2013.

AI Induced Bone Loss
Z-FAST/ZO-FAST trials

Postmenopausal breast cancer patients receiving letrozole 2.5mg PO Qday x 5 years

- Immediate treatment ZA starts immediately
- Delayed treatment: ZA starts when patients experience:
  1. T score < -2.0
  2. Non-traumatic fracture
  3. Asymptomatic fracture at 36 months

- Primary endpoint: % change in spine BMD at 12 months
- Secondary endpoint: % change in total hip BMD

Brufsky AM et al. *Cancer.* 2012; 118:1192-201; Coleman R et al. *Ann Oncol.* 2013; 24:398-405.

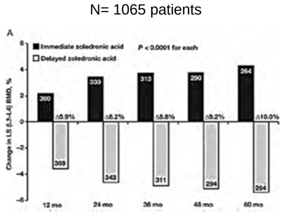
AI Induced Bone Loss
Z-FAST/ZO-FAST trials

Z-FAST results

- N=602
- Upfront ZA progressively increased lumbar spine (LS) and total hip (TH) BMD
- Delayed ZA had significant decreases in LS and TH BMD
- ZA produced substantial increase in BMD regardless of baseline T score, osteoporosis risk factors, or chemotherapy status.

ZO-FAST results

N= 1065 patients



Brufsky AM et al. *Cancer.* 2012; 118:1192-201; Coleman R et al. *Ann Oncol.* 2013; 24:398-405.

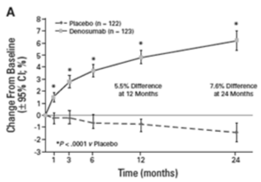
See enlargement, p. 17

AI Induced Bone Loss
Denosumab's role

- Hormone Ablation Bone Loss Trial in Breast Cancer (HALT-BC)
- Phase III trial in 252 women with early stage ER+ Breast cancer, on AI therapy, with evidence of low bone mass (T score of -1 to -2.5)
  - Denosumab 60 mg SC Q6 months x4 vs. placebo
- Primary endpoint: % change in lumbar spine BMD at 12 months

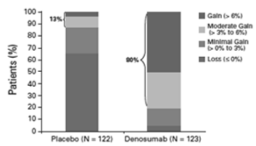
Ellis GK et al. *J Clin Oncol.* 2008; 26:4875-82.

AI Induced Bone Loss
Denosumab's role



% Change in LS BMD from baseline for all patients at 24 months

Proportion of patients preserving LS BMD at 24 months



Ellis GK et al. *J Clin Oncol.* 2008; 26:4875-82.

See enlargement, p. 18

ADT Induced Bone Loss

222 patients with M0 prostate CA either:
Within 1 year of starting ADT
Within 2 weeks of orchiectomy

- Zoledronic acid 4 mg IV Q3 months x 48 weeks (n= 112)
- Placebo (n= 110)

- Primary Endpoint: % change in lumbar spine BMD
- Secondary Endpoint: % change in total hip BMD

Israeli RS et al. *Clin Genitourin Cancer.* 2007; 5:271-7.

ADT Induced Bone Loss

- Results demonstrate significantly increased BMD in patients treated with ZA vs. placebo

% change from baseline BMD		
	Lumbar Spine	Total Hip
Zoledronic acid	+4.7	+1.6
Placebo	-2	-2.1
P-value	<0.0001	<0.0001

Israeli RS et al. *Clin Genitourin Cancer.* 2007; 5:271-7.

ADT Induced Bone Loss
Denosumab (HALT-PC)

- Randomized, double blind study in patients with prostate cancer on ADT, without metastatic disease
  - Denosumab 60mg SC Q6 months vs. placebo
  - 1468 men (734 denosumab, 734 placebo)
- Primary endpoint: % change from baseline in LS BMD

Smith MR et al. *N Engl J Med.* 2009; 361:745-55.

ADT Induced Bone Loss
Denosumab (HALT-PC)

Time point	Cumulative incidence of new vertebral fractures		P-value
	Placebo	Denosumab	
12 months	1.9 N=13	0.3 N=2	0.004
24 months	3.3 N=22	1.0 N=7	0.004
36 months	3.9 N=26	1.5 N=10	0.006

- At 24 months, 6.7% difference in bone mineral density between denosumab and placebo, favoring denosumab

Smith MR et al. *N Engl J Med.* 2009; 361:745-55.

Chemotherapy Induced Ovarian Failure

- CALGB 79809

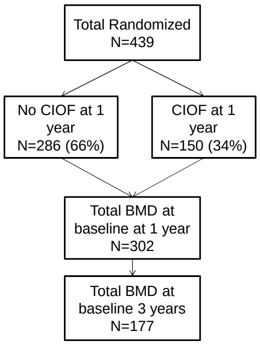
Premenopausal women with breast cancer receiving adjuvant therapy

- ZA 4 mg Q3 months x 8 starting at 1-3 months
- ZA 4 mg Q3months x8 starting at 12-14 months

- Primary Endpoint: % change in LS BMD at 1 year
- Secondary Endpoint: % change in LS BMD at 3 years

Shapiro CL et al. *Eur J Cancer.* 2011; 47:683-9.

Chemotherapy Induced Ovarian Failure – CALGB 79809



Median percentage difference in BMD

	ZA early	ZA late	P
CIOF @1y	1.2	-6.7	<0.001
All @ 1y	1.4	-5.5	<0.001
All @ 3y	1.0	-0.5	0.019

Shapiro CL et al. *Eur J Cancer.* 2011; 47:683-9.

CTIBL Summary

- Cancer patients may be at increased risk for bone loss and fracture due to cancer treatments
- Patients at risk for CTIBL should be assessed for bone loss risk
- Bisphosphonates and denosumab are appropriate options for prevention and treatment of CTIBL

Bone Health in Cancer Patients

- Background and risk factors
- Screening and diagnosis
- **Prevention and treatment strategies**
  - Cancer treatment induced bone loss
  - **Metastatic disease induced bone loss/SRE**
- Novel agents and emerging science

Question #3

RJ is a 66 year old man with newly diagnosed multiple myeloma. Which of the following options would be appropriate for reduction of skeletal-related events (SRE)?

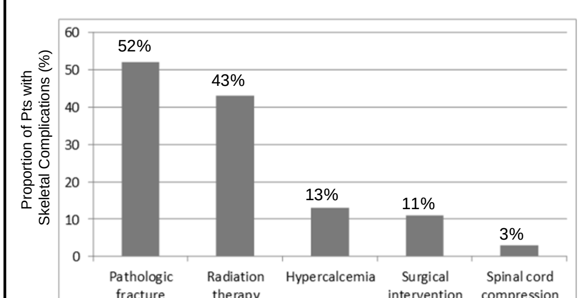
1. Zoledronic acid or pamidronate
2. Denosumab
3. Pamidronate
4. Zoledronic acid or denosumab

SRE Associated with Bone Metastases

- Pathological fractures
  - Nonvertebral
  - Vertebral compression
- Spinal cord compression/collapse
- Radiation therapy
- Surgery to bone
- Hypercalcemia
  - Not included in some studies

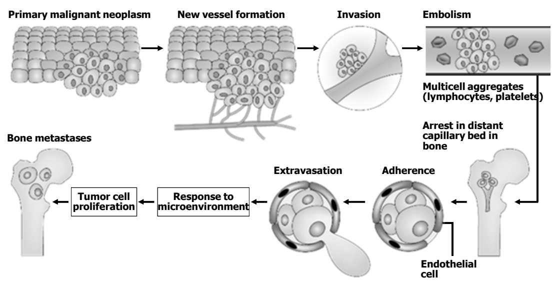
Van Poznak CH et al. *J Clin Oncol.* 2011; 29:1221-7.

Prevalence of SRE in Patients with Metastatic Breast Cancer



Lipton A et al. *Cancer*. 2000; 88:1082-90.

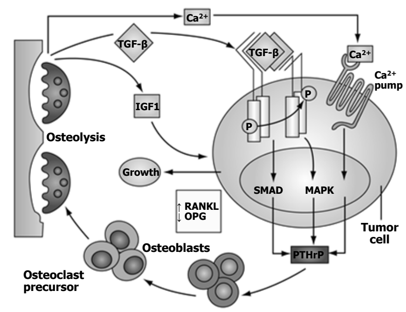
Development of Bone Metastases



Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer* (Mundy GR. *Nat Rev Cancer.* 2002; 2:584-93) copyright 2002.

See enlargement, p. 18

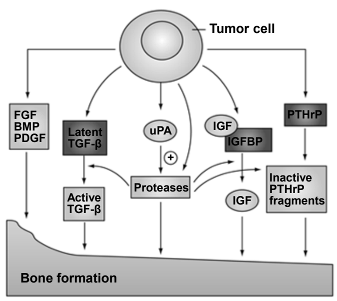
Osteolytic Bone Metastases



Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer* (Mundy GR. *Nat Rev Cancer.* 2002; 2:584-93) copyright 2002.

See enlargement, p. 19

Osteoblastic Bone Metastases



Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer* (Mundy GR. *Nat Rev Cancer.* 2002; 2:584-93) copyright 2002.

See enlargement p. 19

Treatment of Bone Metastases

- Antineoplastic therapy
- **Bone modifying agents (BMA)**
  - **Bisphosphonates**
  - **RANK-L inhibitors**
- Localized radiation
- Radiopharmaceuticals
- Surgery

Bisphosphonates for Breast Cancer to Bone

Study treatments	Number of patients	Pts with an SRE (%)	Median time to first SRE (mo)
Pamidronate 90 mg IV q3-4 weeks	380	43	13.1
Placebo		56	7.0
Pamidronate 90 mg IV q4weeks	371	56	10.4
Placebo		67	6.9
ZA 4 mg IV q4weeks	227	30	NR*
Placebo		50	12.1
Pamidronate 90 mg IV q3-4 weeks	524 (chemotherapy)	46 vs 49 (combined analysis)	11.6
ZA 4 mg IV q3-4weeks			12.2
Pamidronate 90 mg IV q3-4 weeks	606 (endocrine therapy)		13.8
ZA 4 mg IV q3-4weeks			12.3

*NR, not reached

Hortobagyi GN et al. *N Engl J Med*. 1996; 335:1785-91; Theriault RL et al. *J Clin Oncol.* 1999; 17:846-54; Kohno N et al. *J Clin Oncol.* 2005; 23:3314-21; Rosen LS et al. *Cancer*. 2003; 98:1735-44.

Bisphosphonates for Castration-Resistant Prostate Cancer to Bone

Study treatments	Number of patients	Pts with an SRE (%)	Median time to first SRE (mo)
Pamidronate 90 mg IV q3weeks	350	25	N/A*
Placebo		25	N/A
ZA 4 mg IV q3weeks	122	38	16.3
Placebo		49	10.7

*N/A, not available

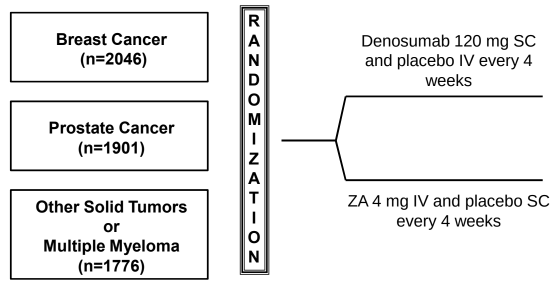
Small EJ et al. *J Clin Oncol*. 2003; 21:4277-84; Saad F et al. *J Natl Cancer Inst*. 2004; 96:879-82.

Bisphosphonates in Cancer to Bone (w/o breast and prostate cancers)

Study treatments	Number of patients	Pts with an SRE (%)	Median time to first SRE (mo)
Zoledronic acid 4 mg IV q3weeks	507	39	7.9
Placebo		46	5.2

Rosen LS et al. *Cancer*. 2004; 100:2613-21.

Denosumab versus ZA Study Schema



Xgeva™ product information. Amgen, Inc., Thousand Oaks, CA; August 2013.

Denosumab vs. Zoledronate in Patients with Bone Metastases

	Denosumab	Zoledronic acid	HR (95% CI)	P-value (noninferiority)
Breast cancer (n=2046)				
Median time to first SRE	Not reached	26.4 mo	0.82 (0.71-0.95)	<0.001[1]
Castrate-resistant prostate cancer (n=1901)				
Median time to first SRE	20.7 mo	17.1 mo	0.82 (0.71- 0.95)	<0.001[2]
Solid tumors (other than breast and prostate) and multiple myeloma (n=1776)				
Median time to first SRE	20.5 mo	16.3 mo	0.84 (0.71- 0.98)	<0.001[3]

[1]p=0.01 (superiority), [2]p=0.008 (superiority), [3]p=0.06 (superiority)

Xgeva™ product information. Amgen, Inc., Thousand Oaks, CA; August 2013.

Denosumab versus ZA in Patients with Cancer to Bone (w/o breast and prostate cancers)

	HR (95% CI)	P-value
Risk of disease progression	1.00 (0.89 to 1.12)	1.0
Risk of death	0.95 (0.83 to 1.08)	0.43

- Risk of death stratification (HR < 1.0 favors denosumab):
  - HR 0.79 for NSCLC (95%CI 0.65-0.95)
  - HR 2.26 for multiple myeloma (MM) (95%CI 1.13-4.50)
  - HR 1.08 for other solid tumors (95%CI 0.90-1.30)

Henry DH et al. *J Clin Oncol*. 2011; 29:1125-32.

ASCO Guidelines for the Use of BMA in MM

- Bisphosphonates should be considered in all patients with MM receiving first-line antimyeloma therapy
- Appropriate options include:
  - Pamidronate 90 mg IV over no less than 2 hours every 3-4 weeks
  - Zoledronic acid 4 mg IV over no less than 15 minutes every 3-4 weeks

Terpos E et al. *J Clin Oncol*. 2013; 31:2347-57.

ASCO Guidelines for the Use of BMA in Breast Cancer to Bone

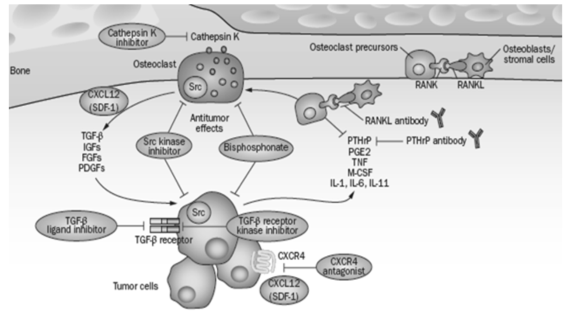
- Appropriate options for breast cancer to bone:
  - Pamidronate 90 mg IV over no less than 2 hours every 3-4 weeks
  - Zoledronic acid 4 mg IV over no less than 15 minutes every 3-4 weeks
  - Denosumab 120 mg SC every 4 weeks
- Insufficient evidence to demonstrate greater efficacy of one agent over another

Van Poznak CH et al. *J Clin Oncol*. 2011; 29:1221-7.

Bone Health in Cancer Patients

- Background and risk factors
- Screening and diagnosis
- Prevention and treatment strategies
  - Cancer treatment induced bone loss
  - Metastatic disease induced bone loss/SRE
- **Novel agents and emerging science**

Interaction Between Tumor Cells and the Bone Microenvironment



Onishi T et al. *Nat Rev Clin Oncol*. 2010; 7:641-51.

See enlargement, p. 20

SRC inhibitors

- Proto-oncogene non-receptor tyrosine kinase
- Has been shown to be involved in bone remodeling, cancer metastasis, and tumor growth
- Dasatinib is currently being evaluated in clinical trials for patients with metastatic bone disease from solid tumors
  - Ongoing phase II study in patients with stage IV breast cancer that has spread to bone (NCT00410813)

Mackiewicz-Wysocka M et al. *Expert Opin Investig Drugs*. 2012; 21:785-95.

Endothelin A Receptor Antagonists

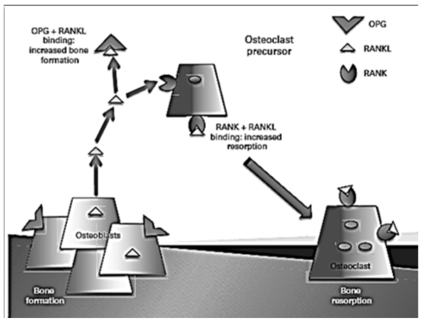
- Endothelin-1 (ET-1) can stimulate osteoblast activity and promote metastasis of prostate cancer via stimulation of the endothelin A (ETA) receptor
- Atrasentan and zibotentan are ETA receptor antagonists being evaluated in clinical trials
  - Zibotentan no longer being evaluated in patients with prostate cancer to bone due to lack of efficacy
  - Awaiting results with atrasentan and zoledronic acid in patients with prostate cancer to bone (NCT00181558)

Mackiewicz-Wysocka M et al. *Expert Opin Investig Drugs*. 2012; 21:785-95.

Summary

- Malignancy associated bone loss and bone involvement are associated with significant morbidity
- Appropriate screening can help identify patients at high risk, to minimize or avoid consequences
- Pharmacists can play an important role in medication selection and dosing

Normal Bone Physiology

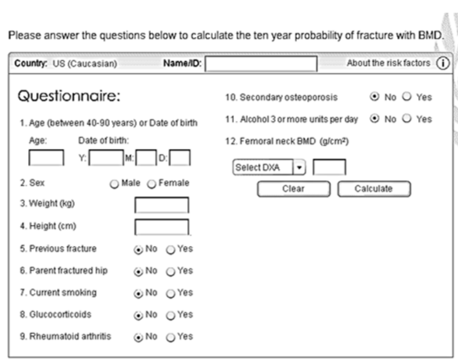


- Normal bone homeostasis is a balance between
  - Osteoblasts: new bone formation
  - Osteoclasts: bone resorption
- Process is regulated by the RANKL pathway
  - Receptor activator factor-kappa B ligand (RANKL)
  - Osteoprotegerin (OPG)

Lustberg M et al. *J Clin Oncol.* 2012; 30:3665-74.

Screening and Diagnosis – Tool

- FRAX® - World Health Organization Fracture Risk Assessment Tool
  - Computer based tool which integrates clinical information, with or without measured BMD, to calculate the 10-year probability of major osteoporotic fracture and hip fracture
  - Takes into account modifiable and nonmodifiable risk factors

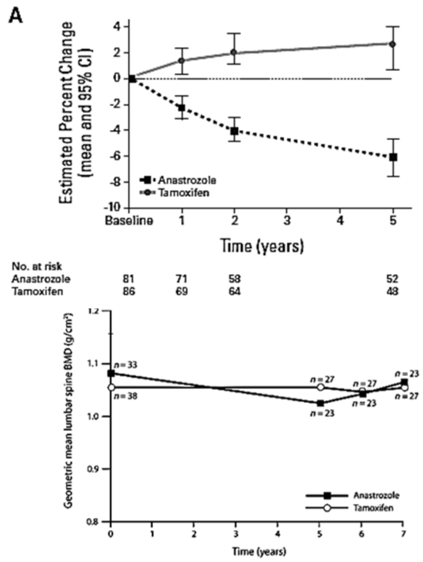

Please answer the questions below to calculate the ten year probability of fracture with BMD.

Country: US (Caucasian) Name/ID: About the risk factors

Questionnaire:

1. Age (between 40-90 years) or Date of birth
   Age: Date of birth: Y: M: D:
2. Sex Male Female
3. Weight (kg)
4. Height (cm)
5. Previous fracture No Yes
6. Parent fractured hip No Yes
7. Current smoking No Yes
8. Glucocorticoids No Yes
9. Rheumatoid arthritis No Yes
10. Secondary osteoporosis No Yes
11. Alcohol 3 or more units per day No Yes
12. Femoral neck BMD (g/cm²)
    Select DXA
    Clear Calculate

Hormonal Therapy in Breast Cancer

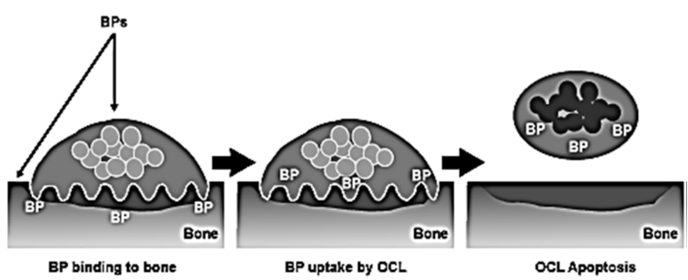


- ATAC Trial: randomized 6,241 ER+ postmenopausal women to 5 years of anastrazole or tamoxifen
  - Fractures occurred in 11% of anastrazole patients compared to 7.7% of tamoxifen patients (p<0.001)at 68 months of follow up
    - After treatment ceased, fracture rates equalized between arms

Eastell R et al. *J Clin Oncol.* 2008; 26:1051-8; Eastell R et al. *Ann Oncol.* 2011; 22:857-62.

Bisphosphonates
Mechanism of Action

- Decrease bone resorption and increase bone mineralization by inhibiting osteoclast activity

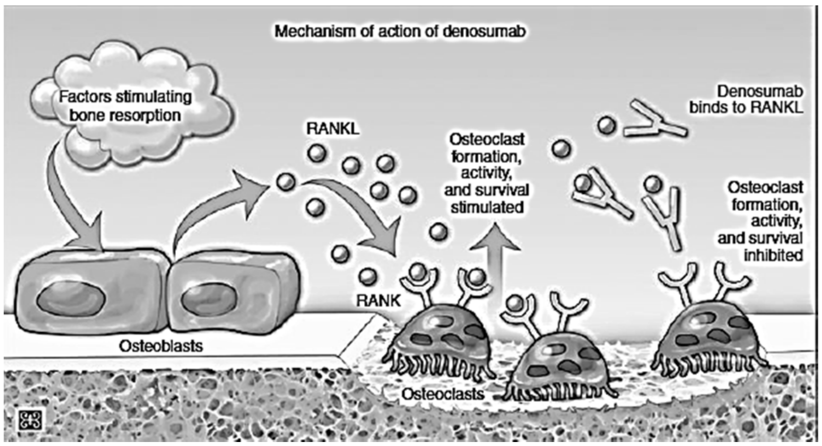


BP, bisphosphonates; OCL, osteoclasts.

Roodman GD. Clinical Care Options: treatment of myeloma bone disease. August 9, 2010 (URL in ref list).

Denosumab (Prolia®)

- Monoclonal antibody directed towards RANKL



Lewiecki EM, Bilezikian JP. *Clin Pharmacol Ther.* 2012; 91:123-33.

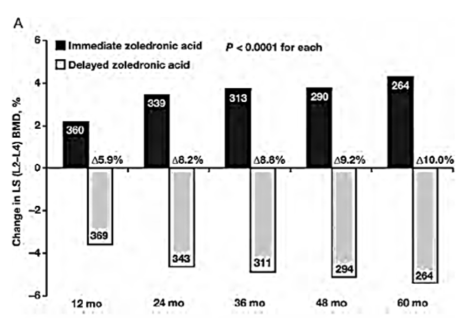
AI Induced Bone Loss
Z-FAST/ZO-FAST trials

Z-FAST results

- N=602
- Upfront ZA progressively increased lumbar spine (LS) and total hip (TH) BMD
- Delayed ZA had significant decreases in LS and TH BMD
- ZA produced substantial increase in BMD regardless of baseline T score, osteoporosis risk factors, or chemotherapy status.

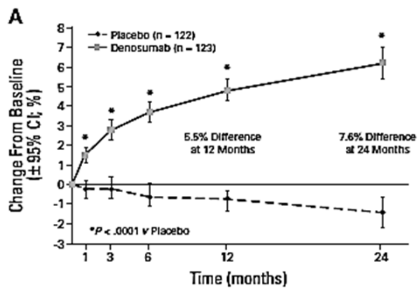
ZO-FAST results

N= 1065 patients



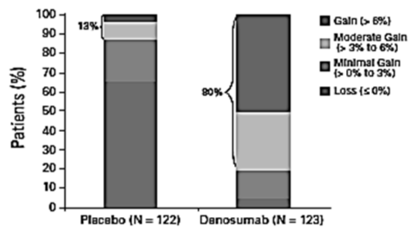
Brufsky AM et al. *Cancer.* 2012; 118:1192-201; Coleman R et al. *Ann Oncol.* 2013; 24:398-405.

AI Induced Bone Loss
Denosumab's role



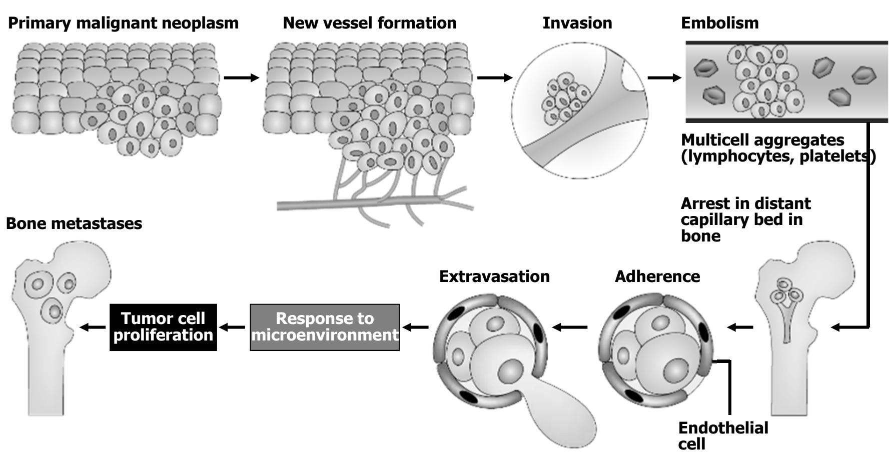
% Change in LS BMD from baseline for all patients at 24 months

Proportion of patients preserving LS BMD at 24 months



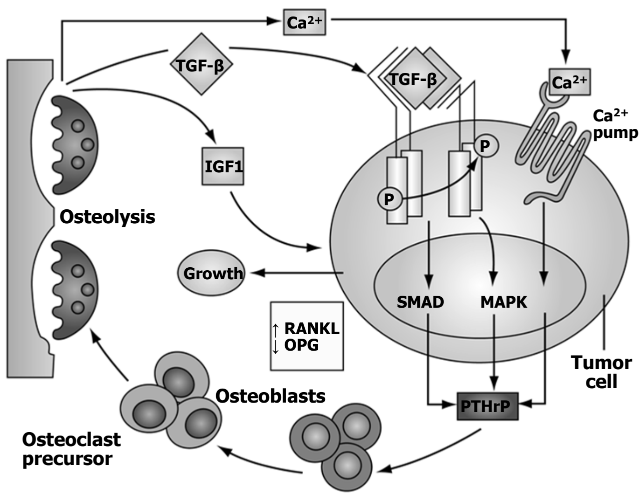
Ellis GK et al. *J Clin Oncol.* 2008; 26:4875-82.

Development of Bone Metastases



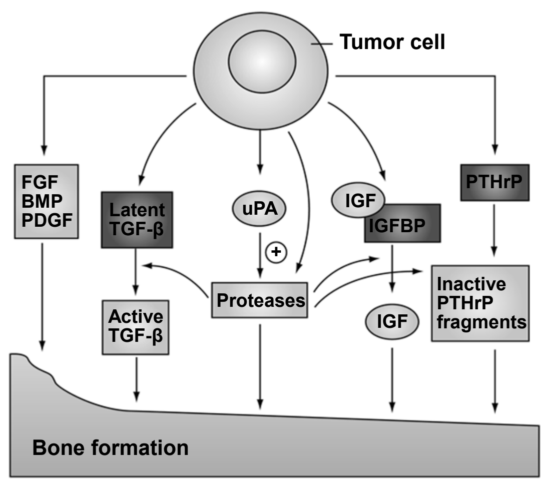
Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer* (Mundy GR. *Nat Rev Cancer.* 2002; 2:584-93) copyright 2002.

Osteolytic Bone Metastases



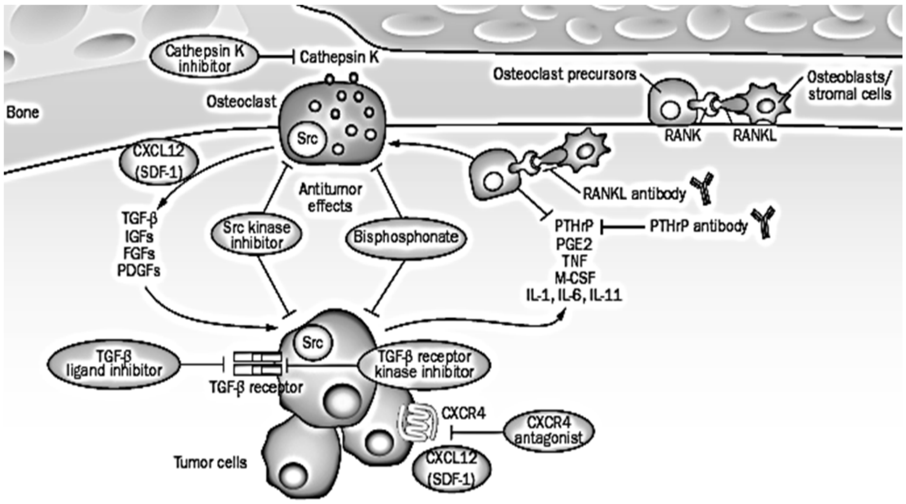
Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer* (Mundy GR. *Nat Rev Cancer.* 2002; 2:584-93) copyright 2002.

Osteoblastic Bone Metastases



Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Cancer* (Mundy GR. *Nat Rev Cancer.* 2002; 2:584-93) copyright 2002.

Interaction Between Tumor Cells and the Bone Microenvironment



Onishi T et al. *Nat Rev Clin Oncol*. 2010; 7:641-51.

Selected References

1. Brufsky AM, Harker WG, Beck JT et al. Final 5-year results of Z-FAST trial: adjuvant zoledronic acid maintains bone mass in postmenopausal breast cancer patients receiving letrozole. *Cancer*. 2012; 118:1192-201.

2. Coleman R, de Boer R, Eidtmann H et al. Zoledronic acid (zoledronate) for postmenopausal women with early breast cancer receiving adjuvant letrozole (ZO-FAST study): final 60-month results. *Ann Oncol.* 2013; 24:398-405.

3. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet.* 2002; 359:1761-7.

4. Eastell R, Adams JE, Coleman RE et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol.* 2008; 26:1051-7.

5. Eastell R, Adams J, Clack G et al. Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial. *Ann Oncol.* 2011; 22:857-62.

6. Ellis GK, Bone HG, Chlebowski R et al. Randomized trial of denosumab in patients receiving adjuvant aromatase inhibitors for nonmetastatic breast cancer. *J Clin Oncol.* 2008; 26:4875-82.

7. Gralow JR, Biermann JS, Farooki A et al. NCCN task force report: bone health in cancer care. *J Natl Compr Canc Netw*. 2013; 11(Suppl 3):S1-50.

8. Henry DH, Costa L, Goldwasser F et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. *J Clin Oncol*. 2011; 29:1125-32.

9. Hortobagyi GN, Theriault RL, Porter L et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med*. 1996; 335:1785-91.

10. Israeli RS, Rosenberg SJ, Saltzstein DR et al. The effect of zoledronic acid on bone mineral density in patients undergoing androgen deprivation therapy. *Clin Genitourin Cancer.* 2007; 5:271-7.

11. Kohno N, Aogi K, Minami H et al. Zoledronic acid significantly reduces skeletal complications compared with placebo in Japanese women with bone metastases from breast cancer: a randomized, placebo-controlled trial. *J Clin Oncol*. 2005; 23:3314-21.

12. Lewiecki EM, Bilezikian JP. Denosumab for the treatment of osteoporosis and cancer-related conditions. *Clin Pharmacol Ther.* 2012; 91:123-33.

13. Lipton A, Theriault RL, Hortobagyi GN et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer*. 2000; 88:1082-90.

14. Lustberg M, Reinbolt RE, Shapiro CL. Bone health in adult cancer survivorship. *J Clin Oncol.* 2012; 30:3665-74.

15. Mackiewicz-Wysocka M, Pankowska M, Wysocki PJ. Progress in the treatment of bone metastases in cancer patients. *Expert Opin Investig Drugs*. 2012; 21:785-95.

16. Morote J, Morin JP, Orsola A et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. *Urology.* 2007; 69:500-4.

17. Mundy GR. Metastasis to bone: causes, consequences and therapeutic opportunities. *Nat Rev Cancer.* 2002; 2:584-93.

18. Onishi T, Hayashi N, Theriault RL et al. Future directions of bone-targeted therapy for metastatic breast cancer. *Nat Rev Clin Oncol*. 2010; 7:641-51.

19. Roodman GD. Treatment of myeloma bone disease. Clinical Applications for Managing Skeletal Integrity in the Cancer Patient: Current and Novel Treatment Strategies. *Clinical Care Options: Oncology*. http://www.clinicaloptions.com/Oncology/Treatment%20Updates/Bone%20Health%20Oncology/Modules/MM_Bone_Health/Pages/Page%202.aspx (accessed 2014 Apr 5).

20. Rosen LS, Gordon D, Kaminski M et al. Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma: a randomized, double-blind, multicenter, comparative trial. *Cancer*. 2003; 98:1735-44.

21. Rosen LS, Gordon D, Tchekmedyian NS et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. *Cancer*. 2004; 100:2613-21.

22. Saad F, Gleason DM, Murray R et al. Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *J Natl Cancer Inst*. 2004; 96:879-82.

23. Shapiro CL, Halabi S, Hars V et al. Zoledronic acid preserves bone density in premenopausal women who develop ovarian failure due to adjuvant chemotherapy: final results from CALGB trial 79809. *Eur J Cancer.* 2011; 47:683-9.

24. Small EJ, Smith MR, Seaman JJ et al. Combined analysis of two multicenter, randomized, placebo-controlled studies of pamidronate disodium for the palliation of bone pain in men with mestastatic prostate cancer. *J Clin Oncol*. 2003; 21:4277-84.

25. Smith MR, Egerdie B, Hernandez Toriz N et al. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med.* 2009; 361:745-55.

26. Terpos E, Morgan G, Dimopoulos MA et al. International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. *J Clin Oncol*. 2013; 31:2347-57.

27. Theriault RL, Lipton A, Hortobagyi GN et al. Pamidronate reduces skeletal morbidity in women with advanced breast cancer and lytic bone lesions: a randomized, placebo-controlled trial. Protocol 18 Aredia Breast Cancer Study Groups. *J Clin Oncol*. 1999; 17:846-54.

28. Van Poznak CH, Temin S, Yee GC et al. American Society of Clinical Oncology executive summary of the clinical practice guideline update on the role of bone-modifying agents in metastatic breast cancer. *J Clin Oncol*. 2011; 29:1221-7.

29. Xgeva™ (demosumab) product information. Amgen, Inc, Thousand Oaks, CA; August 2013.

Abbreviations

ADT	androgen deprivation therapy
AI	androgen inhibitor
ASCO	American Society of Clinical Oncology
ATAC	anastrazole, tamoxifen, alone or in combination
BMA	bone modifying agents
BMD	bone mineral density
BMP	bone morphogenic proteins
CA	cancer
CIOF	chemotherapy induced ovarian failure
DEXA	dual energy x-ray absorptiometry
ER	estrogen receptor
ET-1	endothelin-1
ETA	endothelin A
FGF	fibroblast growth factors
GnRH	gonadotropin-releasing hormone
HCT	hematopoietic stem cell transplant
HR	hazard ratio
IGF	insulin-like growth factor
IGFBP	insulin-like growth factor-binding protein
LS	lumbar spine
MAPK	mitogen-activated protein kinase
MM	multiple myeloma
NSCLC	non-small cell lung cancer
OPG	osteoprotegerin
PDGF	platelet-derived growth factor
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related peptide
RANK	receptor activator factor-kappa B
RANKL	receptor activator factor-kappa B ligand
SRE	skeletal related events
TGF	transforming growth factor
TH	total hip
uPA	urokinase
ZA	zoledronic acid

Self-assessment Questions

1. Which of the following adverse events was more common with denosumab compared to zoledronic acid for treatment of metastatic cancer to bone?

    a. Osteonecrosis of the jaw.
    b. Cough.
    c. Nausea.
    d. Hypophosphatemia.

2. The bisphosphonates reduce skeletal related events in patients with metastatic cancer to bone by:

    a. Promoting osteoclast apoptosis and decreasing osteoclast bone resorption.
    b. Binding to RANK-ligand and inhibiting the stimulatory effects on osteoclast activity.
    c. Pharmacologically mimicking the effects of osteoprotegerin and stimulating osteoclastic activity.
    d. Simulating osteoblasts and increasing bone formation.

3. AJ is a 56 year-old male with castration-resistant prostate cancer to the bone receiving docetaxel. Which of the following medication(s) would be appropriate to reduce the risk of skeletal-related events?

    a. Denosumab.
    b. Pamidronate or zoledronic acid.
    c. Zoledronic acid or denosumab.
    d. Pamidronate, zoledronic acid, or denosumab.

Answers

1. d
2. a
3. c