2016

NCCN CONGRESS SERIES™
National Comprehensive Cancer Network

BREAST CANCER

with Updates from the 2015 San Antonio Breast Cancer Symposium

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2016

NCCN CONGRESS SERIES™
National Comprehensive Cancer Network

Supportive Care: Fertility Preservation & Use of Bone Modifying Agents in Patients with Breast Cancer

Presented by:

Joanne Frankel Kelvin, MSN, RN, CNS, AOCN
Memorial Sloan Kettering Cancer Center

John H. Ward, MD
Huntsman Cancer Institute at the University of Utah

March 17, 2016

Moderated by Rose K. Joyce
NCCN, Conferences and Meetings Department

This activity is supported by educational grants from AstraZeneca, Celgene Corporation, Genomic Health, Inc., Lilly, Novartis Oncology, and Pfizer.

Q&A and Technical Support

- Please use the Q&A feature on the right-hand portion of your screen for any clinical questions and logistical concerns you have regarding the session. This is the only online method of communicating questions or concerns. Should you need additional assistance please e-mail **education@nccn.org** or call 215-690-0300 and ask to be connected with someone in the NCCN Conferences and Meetings Department.
- While NCCN is pleased to respond to as many questions as possible during this webinar, NCCN will not be able to respond to your individual questions of a clinical nature after the webinar has concluded. We are also not able to offer recommendations on patient care regarding specific cases.
- This webinar includes audience polling. When you see a polling slide appear, get ready to vote. Please note that it can take a few moments to collect the results.

Attendance Lists & Registration

- If you are participating with a group of peers, a list of everyone who attended in your group must be submitted within two weeks of the activity in order for the participants to be eligible to receive credit. This list is in addition to individual registration. Attendee lists will not be accepted after two weeks post-activity.
- Lists can be sent to **education@nccn.org** and should contain full contact information for each participant, including first and last name, credentials, mailing address, phone number, and e-mail address.
- If you have not individually registered, please register at: **http://www.cvent.com/d/9fqzgs.**

Accreditation Information

Intended Audience

This educational program is designed to meet the educational needs of oncologists, nurses, pharmacists, and other health care professionals who manage patients with breast cancer.

Learning Objectives

Following this program, participants should be able to:

- Discuss fertility preservation options with patients to inform treatment decision making.
- Counsel patients about the supportive and therapeutic role of antiresorptive agents for the management of bone health.

Accreditation Information

Physicians

National Comprehensive Cancer Network (NCCN) is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

National Comprehensive Cancer Network designates this web-based activity for a maximum of 1.25 *AMA PRA Category 1 Credits*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses

National Comprehensive Cancer Network (NCCN) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's (ANCC) Commission on Accreditation. NCCN designates this educational activity for a maximum of 1.25 contact hours. Accreditation as a provider refers to the recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity.

Kristina M. Gregory, RN, MSN, OCN, is our lead nurse planner for this educational activity.

Accreditation Information

Pharmacists

Pharmacy Educational Objective: *After completing this activity, the participant should be able to:*
- Provide accurate and appropriate counsel as part of the treatment team.

Accreditation Statement

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Type of Activity: Knowledge

UAN: 0836-0000-16-020-L01-P

Credit Designation: National Comprehensive Cancer Network designates this continuing education activity for 1.25 contact hours (0.125 CEUs) of continuing education credit in states that recognize ACPE accredited providers.

Attention Pharmacists: ACPE and NABP have implemented CPE Monitor as a way to electronically track all ACPE-accredited CPE Units. In order to receive credit for this activity, please enter your six-digit NABP e-profile ID and birth date in the format of MMDD as part of the Overall Evaluation. If you have not already done so, please complete your e-profile at http://www.nabp.net to obtain your NABP e-Profile ID.

To comply with ACPE standards, pharmacists must complete all activity requirements within **30 days** of the live event date.

Accreditation Information

How to Claim Credit:

Within 5 business days after this educational program, you will receive an e-mail with information on how to claim credit for this activity. A statement of credit will be issued only upon completion of the activity evaluation form & immediate post-test within **30 days** of the activity date. A certificate will be electronically generated immediately upon completion of the evaluation.

All credit claiming must be done online through NCCN's continuing education portal at **http://education.nccn.org/node/78132.**

Should you not receive an e-mail within 5 days, please contact us at **education@nccn.org.**

Accreditation Information

- It is required by the ACCME that all educational activities are designed to change participant ***competence, performance, or patient outcomes.***
- To meet this requirement, NCCN asks that all participants complete the outcomes measures described below:
  - The post-test and evaluation as indicated in e-mail you will receive within 3-5 business days of the conclusion of this activity. This is required to receive credits or your certificate of completion. You must be registered in advance to receive credits or certificate. Certificates will be generated automatically upon successful completion of this step.
    - There will be a separate WebEx evaluation at the conclusion of this program, which is optional and does not go to NCCN.
  - The follow-up post test (to be sent 30 days after the activity has ended to demonstrate an increase in participant competence)
- NCCN greatly appreciates your compliance with completing the aforementioned post-test and surveys. All of these measures will be available by logging into your account at **http://education.nccn.org**. Reminder e-mails will be sent to the participants via e-mail. If you have any questions or concerns, please e-mail **education@nccn.org.**

Disclosures

The ACCME/ANCC/ACPE defines “conflict of interest” as when an individual has an opportunity to affect CE content about products or services of a commercial interest with which he/she has a financial relationship.

ACCME, ACPE, and ANCC focuses on financial relationships with commercial interests in the 12-month period preceding the time that the individual is being asked to assume a role controlling content of the CE activity. ACCME, ACPE, and ANCC have not set a minimal dollar amount for relationships to be significant. Inherent in any amount is the incentive to maintain or increase the value of the relationship. The ACCME, ACPE, and ANCC defines “’relevant financial relationships” as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.

All faculty for this continuing education activity are competent in the subject matter and qualified by experience, training, and/or preparation to the tasks and methods of delivery.

Faculty Disclosures

Disclosure of Relevant Financial Relationships

All faculty and activity planners participating in NCCN continuing education activities are expected to disclose any relevant financial relationships with a commercial interest as defined by the ACCME's, ANCC's, and ACPE's Standards for Commercial Support. All faculty presentations have been reviewed for adherence to the ACCME's Criterion 7: The provider develops activities/educational interventions independent of commercial interests (SCS 1, 2, and 6) by experts on the topics. Full disclosure of faculty relationships will be made prior to the activity.

Faculty Disclosures

The faculty listed below have no relevant financial relationships to disclose:

Joanne Frankel Kelvin, MSN, RN, CNS, AOCN

The faculty listed below have disclosed the following relevant financial relationships:

John H. Ward, MD
Galena Biopharma, Inc: Scientific Advisor

NCCN Staff Disclosures

NCCN Staff Disclosures
The activity planning staff listed below has no relevant financial relationships to disclose:

Ann Gianola, MA; Mark Geisler; Kristina M. Gregory, RN, MSN, OCN; Kristin Kline Hasson; Rose Joyce; Joan S. McClure, MS; Diane McPherson; Deborah Moonan, RN, BSN; Liz Rieder; Shannon K. Ryan; Kathy Smith, CMP, CHCP; Jennifer McCann Weckesser

The NCCN clinical information team listed below, who have reviewed content, has no relevant financial relationships to disclose:

Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Dorothy Shead, MS

Faculty Biography

Joanne Frankel Kelvin, MSN, RN, CNS, AOCN, is a Clinical Nurse Specialist in the Cancer and Fertility Program at Memorial Sloan Kettering Cancer Center.

Ms. Kelvin received her Bachelor and Master of Science in Nursing degrees from the State University of New York at Stony Brook. She is a credentialed Advanced Oncology Certified Nurse.

Ms. Kelvin's work focuses on improving education for patients with cancer about the risks to fertility from treatment, the options for fertility preservation before treatment, and the options for building a family after treatment. In addition to patient education, Ms. Kelvin develops resources for patients and clinicians, educates the clinical staff, and assists with the facilitation of clinical research related to reproductive health of cancer survivors within Memorial Sloan Kettering**.**

Ms. Kelvin has lectured nationally on fertility preservation and has shared her expertise in this area in well-known publications such as *Cancer* and the *Clinical Journal of Oncology Nursing*. She has been recognized with several awards and grants for nursing excellence, leadership, and research, including the Oncology Nursing Society Clinical Lectureship Award.

Ms. Kelvin is on the Board of Directors for the Alliance for Fertility Preservation and is a co-investigator on Moffitt Cancer Center's R-25 training grant. Through this NCI-funded Grant, Ms. Kelvin has helped establish *Educating Nurses about Reproductive Issues in Cancer Healthcare* (ENRICH), an innovative online training program for oncology nurses. She currently serves as a member of the ENRICH Curriculum Advisory Committee expert panel.

Faculty Biography

John H. Ward, MD, is the Margaret A. Amundsen Endowed Professor of Medicine and a member of the Oncology Division in the Department of Internal Medicine at the University of Utah School of Medicine. He previously served as the Chief of the Oncology Division at the University of Utah School of Medicine and as President of the Medical Staff of the University of Utah Hospital and Clinics.

A graduate of the University of Utah School of Medicine, Dr. Ward completed an internal medicine residency at Duke University and a fellowship in hematology/oncology at the University of Utah School of Medicine. He is board-certified in internal medicine, with subspecialties in medical oncology and hematology.

Dr. Ward treats patients affected by a variety of malignant diseases, with an emphasis on breast cancer. He is principal investigator for SWOG cooperative group studies at the University of Utah.

Dr. Ward has received numerous accolades for his work, including the Haskel Schiff Award for excellence in the practice of clinical medicine from Duke University, the James L. Parkin, MD Award for outstanding clinical teaching from the University of Utah School of Medicine, and the inaugural Huntsman Cancer Foundation Humanitarian Award.

Dr. Ward is a fellow of the American College of Physicians and a member of several medical societies, including the American Society of Clinical Oncology (ASCO) and the Southwest Oncology Group. He has authored or coauthored numerous articles, book chapters, and abstracts that have appeared in publications such as the *Journal of Biological Chemistry*, *Science*, the *Journal of Clinical Oncology*, and *Blood*.

Dr. Ward is a member of the NCCN Breast Cancer Panel and NCCN Breast Cancer Risk Reduction Panel. He also serves on the NCCN Oncology Research Program Afatinib Scientific Review Committee and the NCCN Foundation Young Investigator Award Review Committee. He previously participated in the NCCN Task Forces for Breast Cancer in the Older Woman, Adjuvant Breast Cancer, and HER2 Testing in Breast Cancer.

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National Comprehensive Cancer Network

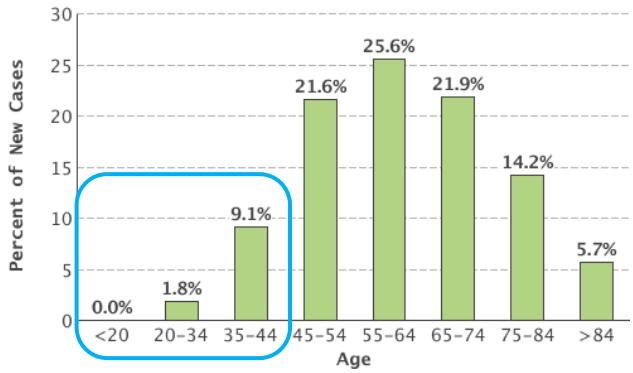
Fertility Preservation in Breast Cancer

Cancer and Fertility: Issues for Women with Breast Cancer

Joanne Frankel Kelvin, MSN, RN, CNS, AOCN
Fertility Nurse Specialist
Memorial Sloan Kettering Cancer Center

Many young women are diagnosed each year with breast cancer in the US

Percent of new cases by age



http://seer.cancer.gov/

>25,000 women
< 45 years of age
diagnosed each year

Treatment poses a risk of infertility

Professional guidelines highlight the need for clinicians to address fertility

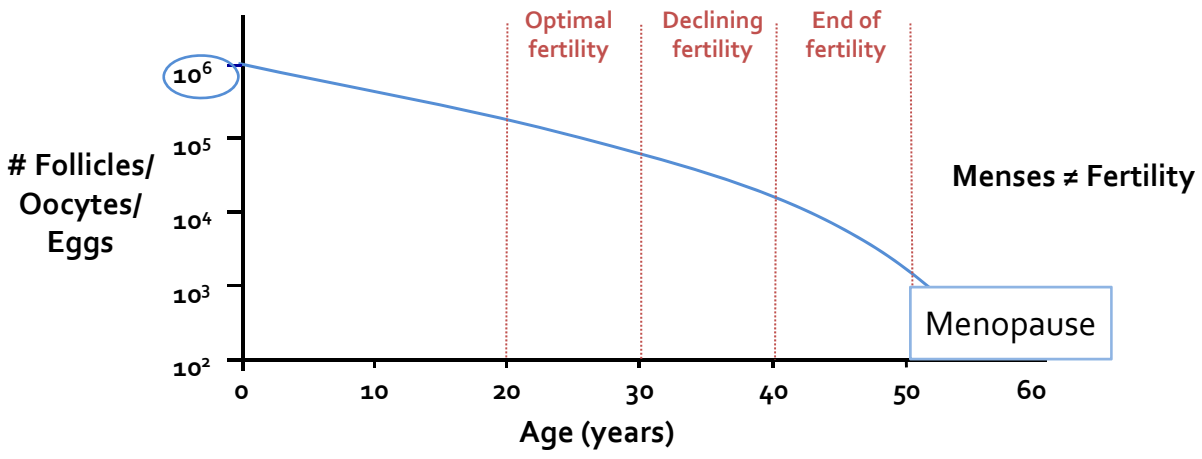
Content Outline

- Effects of breast cancer treatment on fertility
- Options to preserve fertility before treatment
- Clinical considerations

Content Outline

- **Effects of breast cancer treatment on fertility**
- Options to preserve fertility before treatment
- Clinical considerations

Effect of Age on Ovarian Reserve



Adapted from Faddy et al 1992

Effects of Treatment on Fertility

- Chemotherapy
  - Causes depletion of ovarian follicle pool
    - Diminished ovarian reserve
    - Premature ovarian failure
    - Infertility and menopause at a young age

Kort et al 2014; Levine et al 2012; Meirow et al 2010

Effects of Treatment on Fertility

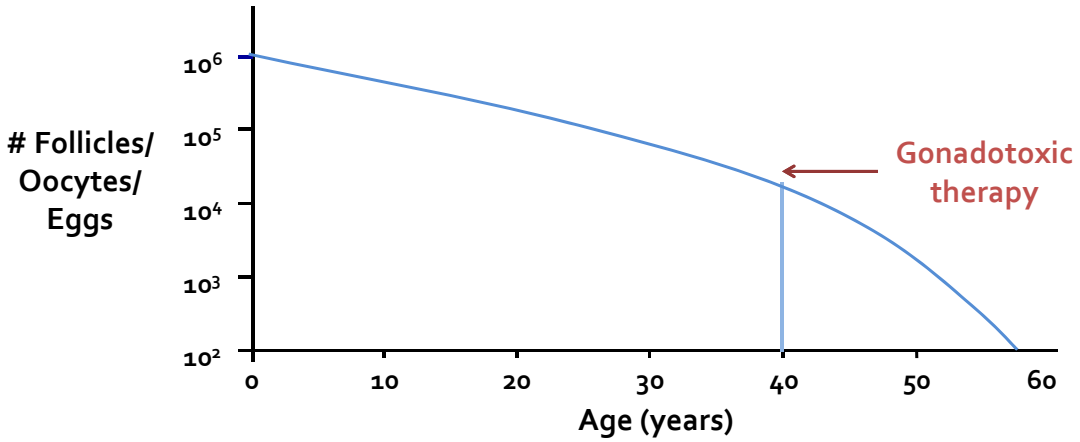
- Chemotherapy
  - Impact based on drug, cumulative dose, and age

Agent	Risk
Alkylating agents (cyclophosphamide)	High
Anthracyclines (doxorubicin, epirubicin)	Intermediate
Antimetabolites (fluorouracil, methotrexate)	Low
Taxanes (paclitaxel, docetaxel)	Conflicting data

Ronn & Holzer 2015

Effects of Treatment on Fertility

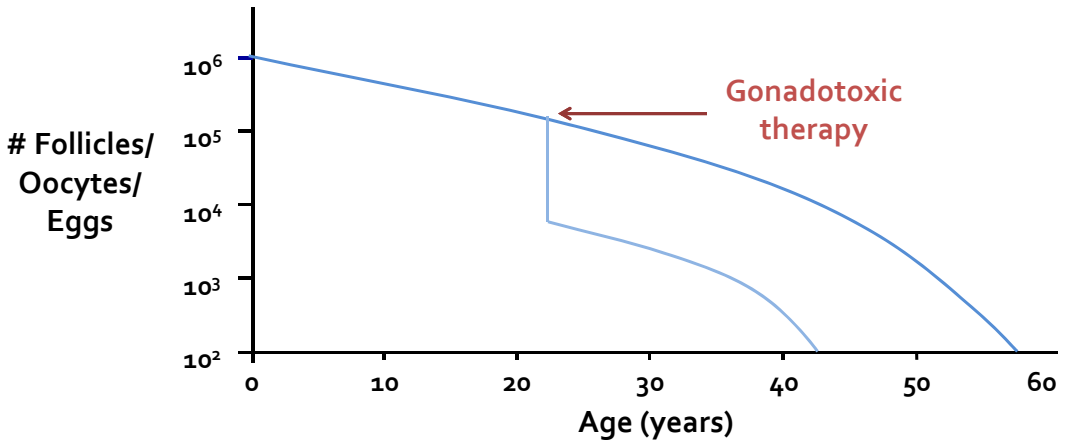
Depletion of ovarian follicle pool



Adapted from Faddy et al 1992

Effects of Treatment on Fertility

Depletion of ovarian follicle pool



Adapted from Faddy et al 1992

Effects of Treatment on Fertility

- Chemotherapy
  - It is impossible to predict with certainty who will be affected permanently
  - Menses ≠ Fertility
  - Age at time of treatment is a major factor

Kort et al 2014; Levine et al 2012; Meirow et al 2010

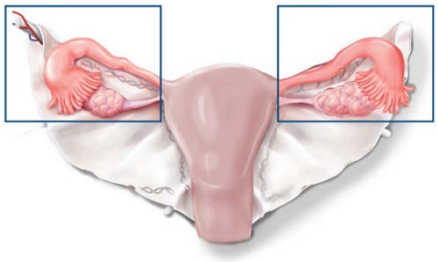
Effects of Treatment on Fertility

- Biologics (trastuzumab, pertuzumab)
  - No evidence of risk
- Endocrine therapy (tamoxifen; ovarian suppression with aromatase inhibitor)
  - Effect on ovarian reserve is unclear
  - Need to postpone pregnancy creates a risk because of ovarian aging with the passage of time

Ronn & Holzer 2015

Effects of Treatment on Fertility

- Risk-reducing bilateral oophorectomy (BRCA+)
  - Infertility
  - Menopause



Content Outline

- Effects of breast cancer treatment on fertility
- **Options to preserve fertility before treatment**
- Clinical considerations

Fertility Preservation Options

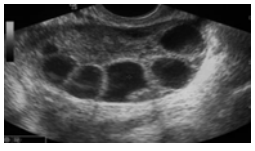
Cryopreservation

Reduction of Toxicity

Even a single treatment with gonadotoxic therapy can affect gamete quality and DNA integrity, so fertility preservation must be completed before treatment begins.

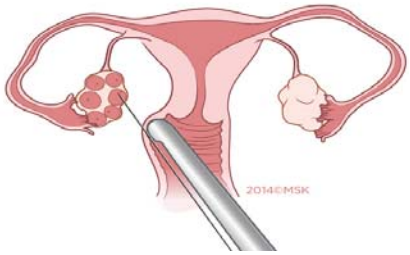
Embryo and Oocyte Cryopreservation

Ovarian Stimulation



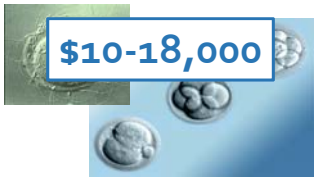
Daily hormone injections ~10 days

Egg Retrieval



Under anesthesia

IVF In Vitro Fertilization



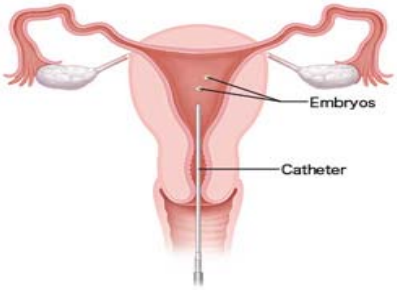
No Fertilization

$7-15,000

ASRM 2013; Kort 2014; Rodriguez-Wallberg & Oktay 2015

Embryo and Oocyte Cryopreservation

Embryo Transfer



Hormonal supplementation if needed to prime the endometrial lining

Thawed Embryos

Live Birth Rate / Transfer (*by Age*)

<35	35-37	38-40	41-42	>42
44%	**41%**	**36%**	**32%**	**21%**

Thawed Oocytes

Live Birth Rate / Transfer

29%-43%

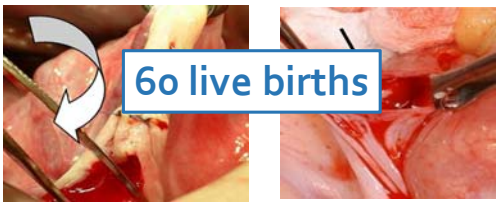
Live Birth Rate / Vitrified Oocyte (*by Age*)

<33	35	40	42
10%	**8%**	**2%**	**0.5%**

Cobo et al 2015; Potdar et al 2014; Rienzi et al 2012; SART 2013

Ovarian Tissue Cryopreservation

- Experimental option for women who can't delay treatment
- Oophorectomy or ovarian cortical biopsies
- Future reimplantation
  - Orthotopic –remaining ovary or peritoneum
  - Heterotopic – forearm or abdominal wall
- Potential risk of re-introducing cancer cells



ASRM 2014; Chung et al 2013; Demeestere et al 2015 ; Dolman 2013; Donnez & Dolmans 2015; Jensen et al 2015

Ovarian Suppression

- GnRH agonists: leuprolide, goserelin, triptorelin
- Mechanism of action is unclear
  - Suppression of FSH → ↓ follicle recruitment and maturation → protection from chemo destruction?
- Administered as a monthly injection
  - Start 1-2 weeks before first chemotherapy
- Will cause menopausal symptoms

Blumenfeld et al 2015; Del Mastro et al 2011; Lambertini et al 2015; Moore et al 2015

Ovarian Suppression

- Results have been conflicting – investigational

PROMISE (ER+)

↓ POF (8% vs 22%) ↑ pregnancies (5.4% vs 3%)

POEMS (ER-)

↓ POF (8.9% vs 25.9%) ↑ pregnancies (21% vs 11%)

Blumenfeld et al 2015; Del Mastro et al 2011; Lambertini et al 2015; Moore et al 2015

Fertility Preservation Decision-Making

- Importance of having a biologic child
- Risk of infertility from treatment
- Likelihood of success with egg or embryo freezing
- Comfort with using assisted reproductive technology
- Concerns about safety
- Religious, cultural, ethical beliefs
- Emotional distress related to diagnosis
- Family support
- Financial resources

Content Outline

- Effects of breast cancer treatment on fertility
- Options to preserve fertility before treatment
- **Clinical considerations**

Safety of Embryo and Oocyte Cryopreservation

- Safety of stimulation
  - Natural cycle unlikely to be successful
  - Aromatase inhibitor to ↓ estrogen with hormone sensitive tumors or history of DVT/PE
    - No evidence of ↑ recurrence thus far

ASRM 2013; Azim et al 2008; Cakmak & Rosen 2013; Chung et al 2013; Corbett et al 2014; Noyes et al 2013; Reddy & Oktay 2012; Ronn & Holzer 2015

Safety of Embryo and Oocyte Cryopreservation

- Safety of treatment delay
  - Random start protocols to begin stimulation anytime in follicular or luteal phase of cycle
  - A defined process for referring to reproductive endocrinologists with expedited scheduling minimizes delays
  - Some patients will have time for 2 cycles

ASRM 2013; Cakmak & Rosen 2013; Chung et al 2013; Corbett et al 2014; Noyes et al 2013; Reddy & Oktay 2012

Safety of Pregnancy After Breast Cancer

- Maternal health
  - <10% pregnancy (1/2 rate of other ca survivors)
  - No adverse effect on survival – ↓ risk recurrence and death
    - Observed regardless of ER status
    - Healthy mother effect or protective effect?

Azim et al 2011; Azim et al 2013; Calhoun and Hansen 2006; De Bree et al 2010; Lawrenz et al 2012; Pagani et al 2011; Pagani et al 2015; Peccatori et al 2013; Ronn & Holzer 2015

Safety of Pregnancy After Breast Cancer

- Child's health
  - No evidence of ↑ congenital abnormalities in offspring of parents who received prior chemotherapy
  - Lactation has no detrimental effect
    - Many women can adequately breast feed with one breast

Lawrenz et al 2012; Meirow 2010; Meneses & Holland 2014; Pagani et al 2011

Safety of Pregnancy After Breast Cancer

- Optimal time to wait from diagnosis
  - ≥ 1 year to ensure clearance of damaged gametes
  - 2-3 years minimum, to pass time when at greatest risk for recurrence
  - Some evidence of ↓ survival if < 6 months

Azim et al 2011; Calhoun and Hansen 2006; De Bree et al 2010; Lawrenz et al 2012; Peccatori et al 2013; Ronn & Holzer 2015

Safety of Pregnancy After Breast Cancer

- Considerations for patients on endocrine therapy
  - Unclear if interruption of therapy will ↓ effectiveness in preventing recurrence
  - Unclear optimal timing for interruption of therapy
  - POSITIVE trial – to evaluate safety of interruption
  - Must be off tamoxifen at least 2 months

Azim et al 2011; Azim et al 2013; Calhoun and Hansen 2006; De Bree et al 2010; Lawrenz et al 2012; Pagani et al 2011; Pagani et al 2015; Peccatori et al 2013; Ronn & Holzer 2015

Considerations for BRCA+ Patients

- Preimplantation genetic diagnosis (PGD)
  - Detects a mutation associated with a specific medical disorder known to be present in a parent
  - Allows for embryo selection
  - Religious and ethical considerations

Trophoblast Biopsy

Brezina & Kutteh 2014

Contraception for Women with Breast Cancer

- Even though there is a risk of infertility from treatment, many patients will not develop infertility
- Discuss the need for effective contraception at initial visit
- Non-hormonal contraceptive options
  - Copper T IUD
  - Condom

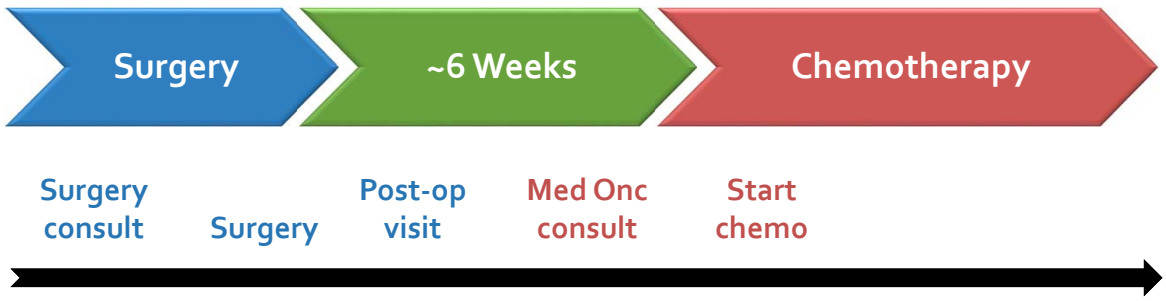
ACOG Committee Opinion 2011

What Does This Mean for You?

The goal is to ensure patients have the opportunity to participate in decision-making – to avoid regret in the future

Timing is key!
Initiate the discussion as early as possible!

What Does This Mean for You?



Oocyte/embryo cryopreservation takes 2-3 weeks
Must be completed before starting chemotherapy

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Use of Bone Modifying Agents in Patients with Breast Cancer

John H. Ward, MD

Margaret A. Amundsen Professor of Medicine
Oncology Division, Department of Medicine
University of Utah School of Medicine
Huntsman Cancer Institute at the University of Utah

Bone Modifying Agents in Breast Cancer

- Prevention of cancer-related morbidity
- Management of side effects of therapy
- Control tumor growth - Adjuvant therapy

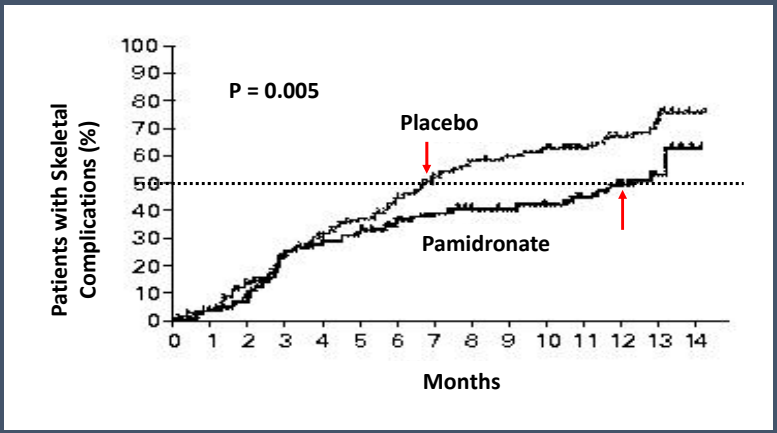
Bone Modifying Agents in Breast Cancer

- ***Prevention of cancer-related morbidity***
- Management of side effects of therapy
- Control tumor growth - Adjuvant therapy

Consequences of bone metastases

- Skeletal related events
  - Pathologic fractures
  - Radiation to bone
  - Surgery on bone
  - Hypercalcemia
  - Spinal cord compression
- Pain
- Limitations in mobility
- Reduction in quality of life

20 years ago: Time to the First Skeletal Event in women with Lytic Bone metastases: Pamidronate v. Placebo

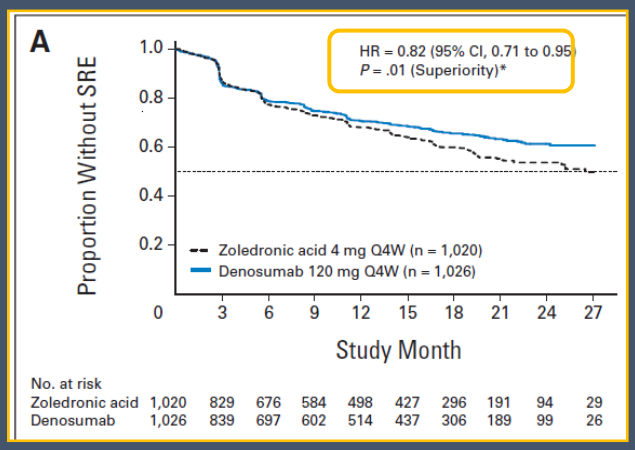


n=380

Hortobagyi G.N., et al. *NEJM* 335 (24):1785, 1996

This study, now 20 years old, led to dramatic improvements in the care of patients with lytic bone metastases due to cancer, and was immediately practice changing – and with just 380 patients !!

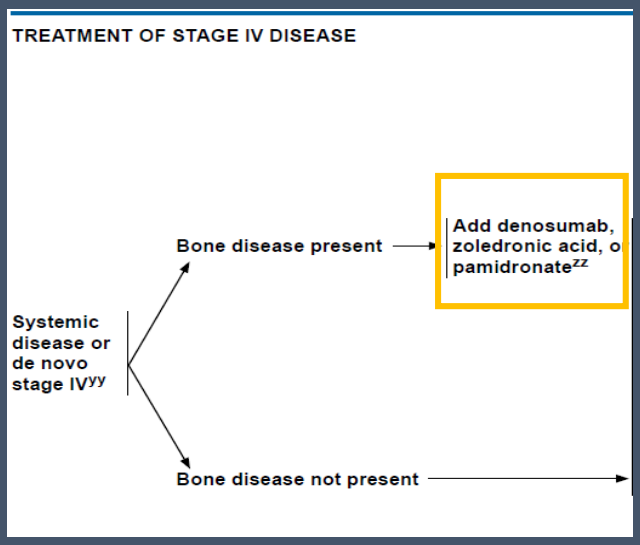
Denosumab v Zoledronic Acid in Breast Cancer Metastatic to Bone



- N= 2046
- 120 mg of denosumab v 4 mg zoledronic acid q 4 wk
- Primary endpoint: time to first SRE
- Proportion with SRE improved with denosumab
- ONJ: 2.0% with denosumab, 1.4% with zoledronic acid

Stopek et al: J Clin Oncol 2010 28:5132-39

NCCN Guidelines - 2016



The NCCN Guidelines for Breast Cancer (Version 1.2016). Page BINV-19 © 2016 National Comprehensive Cancer Network, Inc.

NCCN Guidelines (footnote zz)

- Denosumab, zoledronic acid, or pamidronate should be given in addition to antineoplastic therapy if bone metastases are present and expected survival is ≥ 3 months
- Patients should receive vitamin D and calcium supplements
- Patients should have a baseline dental examination

Other considerations

- Convenience for the patient
- Convenience for the staff
- Cost
  - Wide geographic variability
  - We *always* require pre-authorization (unquantified cost)
- Tolerance

Bone Modifying Agents in Breast Cancer

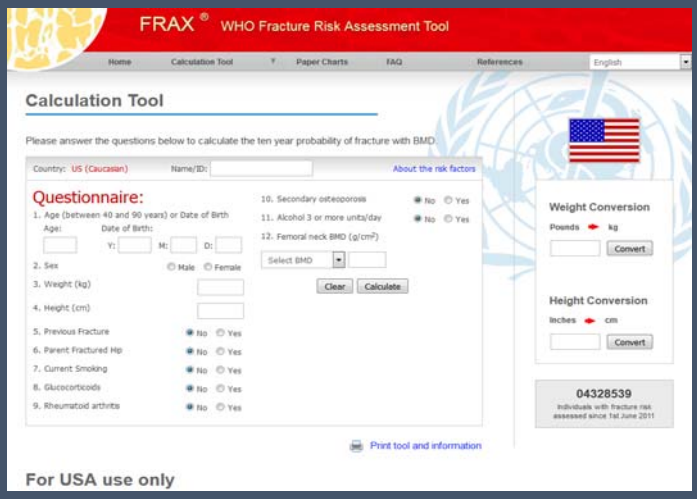
- Prevention of cancer-related morbidity
- ***Management of side effects of therapy***
- Control tumor growth - Adjuvant therapy

Management of Side Effects of Therapy

- Osteoporosis results in 1.5 million fractures/year in the United States
- Treatment generally recommended for postmenopausal women with a BMD T-score of -2.5, or less or a FRAX score indicating increased fracture risk
- Bisphosphonates and denosumab both reduce the risk of fractures
- Osteonecrosis of the jaw and atypical femur fractures: reported but rare
- Non-pharmacologic recommendations include total calcium intake of 1000-1500 mg/ day and total vitamin D intake of 600-800 mg/d

Black DM, Rosen CJ: NEJM 2016: 374:254-262

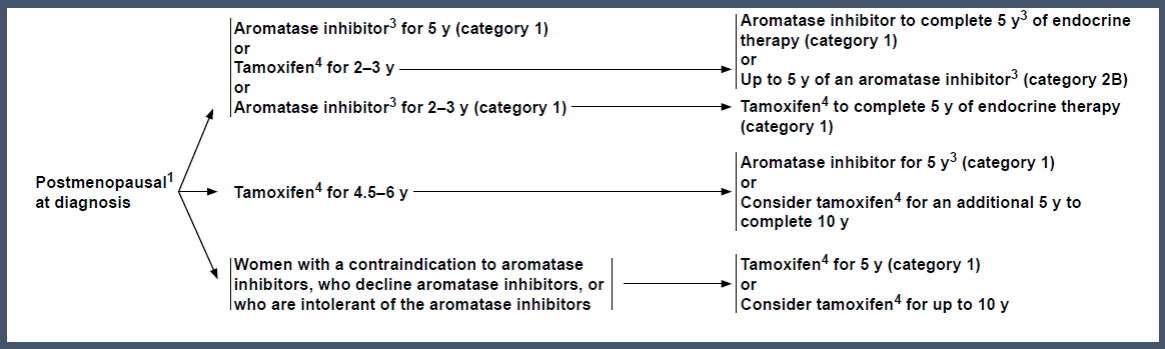
FRAX WHO Fracture Assessment Tool



http://www.shef.ac.uk/FRAX/tool.aspx?country=9

Management of Side Effects of Therapy

- Considerations in adjuvant endocrine therapy may include:
  - Efficacy: many regimens with category 1 NCCN support



The NCCN Guidelines for Breast Cancer (Version 1.2016). Page BINV-J. © 2016 National Comprehensive Cancer Network, Inc.

Management of Side Effects of Therapy

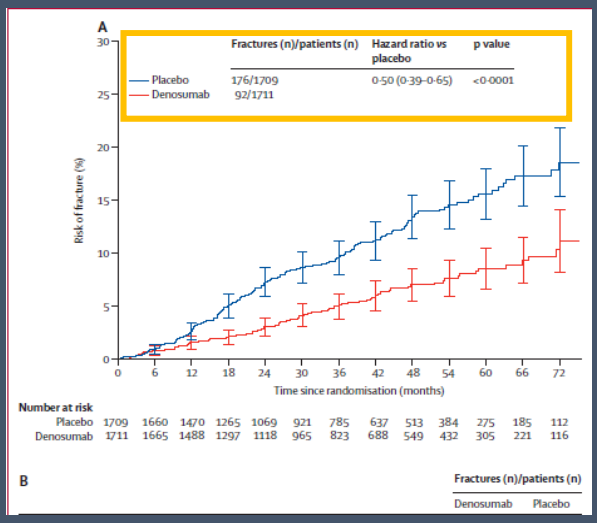
- Considerations in adjuvant endocrine therapy may include:
  - Efficacy: many regimens with category 1 NCCN support
  - Patient tolerance
  - *Bone density*
  - Endometrial cancer risk
  - Thromboembolic risk
  - Patient preference
  - Cost

Adjuvant Denosumab in Breast Cancer (ABCSG-18)

- Prospective, randomized, double blind, placebo-controlled trial in post-menopausal early stage ER+ breast cancer patients receiving aromatase inhibitors
- Denosumab 60 mg versus placebo, given SC every 6 months
- Daily supplements of calcium 500 mg, and vitamin D (at least 400 iu) “highly recommended”
- Primary endpoint: first clinical fracture

Gnant et al: Lancet 2015; 386: 433-43

Adjuvant Denosumab in Breast Cancer (ABCSG-18)



- N= 3425
- 50% reduction in risk of fracture
- Adverse events – no difference
- 35 potential dental problems proactively identified, no case judged to meet criteria for ONJ

- Conclusion: Denosumab q 6 months reduces fracture risk in this population

Gnant et al: Lancet 2015; 386: 433-43

NCCN Stance (full text in footnote pp)

- Bisphosphonates or denosumab acceptable to treat osteoporosis or osteopenia in women with breast cancer
- Optimal duration of either therapy – not established
- Factors to consider in duration: BMD, response, and risk factors
- Should have baseline dental examination
- Should take supplemental calcium and vitamin D

Bone Modifying Agents in Breast Cancer

- Prevention of cancer-related morbidity
- Management of side effects of therapy
- ***Control tumor growth - Adjuvant therapy***

Bisphosphonates as Adjuvant Therapy

Author	Clodronate	N	Population	Results
Diel[1]	2 Years vs. Standard care	302	TCs in BM	Distant metastasis at 3 Years 13% vs. 29% Deaths at 3 Years 4% vs. 15%
Saarto[2]	3 Years vs. Standard care	299	TCs in LNs	Bone metastases were detected at the same frequency in both groups at 10 years
Powles[3]	2 Years vs. Placebo	1,069	Operable BC	No reduction in the incidence of bone metastasis
NSABP B-34 Paterson[4]	3 Years vs. Placebo	3,323	Stage 1-3 BC	No differences in DFS or OS ≥ 50 YO showed benefits of clodronate for RFS, bone metastasis-FI, and non-bone metastasis-FI but not OS
* Free Interval				
	Ibandronate			
Von Minckwitz[5]	2 Years vs. Standard Care	2,994	TCs in LNs and DDC	At 38 months no difference in DFS or OS

[1] Diel IJ: N Engl J Med 1998; 339: 357

[2] Saarto T: Acta Oncol 2004; 43:650

[3] Powles T: J Clin Oncol 2002; 20:3219

[4] Paterson AH: Lancet Oncol 2012; 13: 734

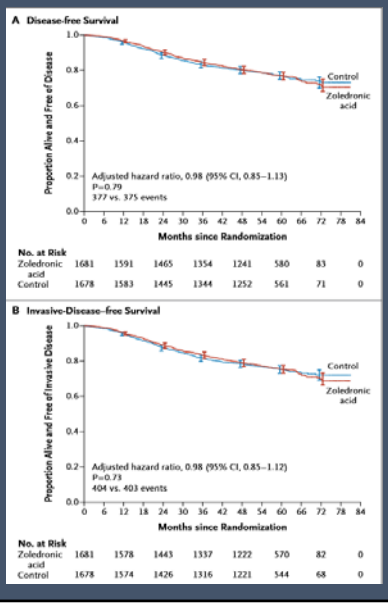
[5] von Minckwitz G: J Clin Oncol 2013; 31: 3531

Bisphosphonates as Adjuvant Therapy: Azure Trial

- Zoledronic Acid in Pre- and Postmenopausal Breast Cancer
- N1 or a T3–T4 Primary Tumors; 19 Doses over 5 years; No Ovarian Suppression
- N= 3,360; follow-up 83 months

Coleman, RE: N Engl J Med 2011; 365:1396
Coleman, RE: Lancet Oncol 2014; 15 (9):997

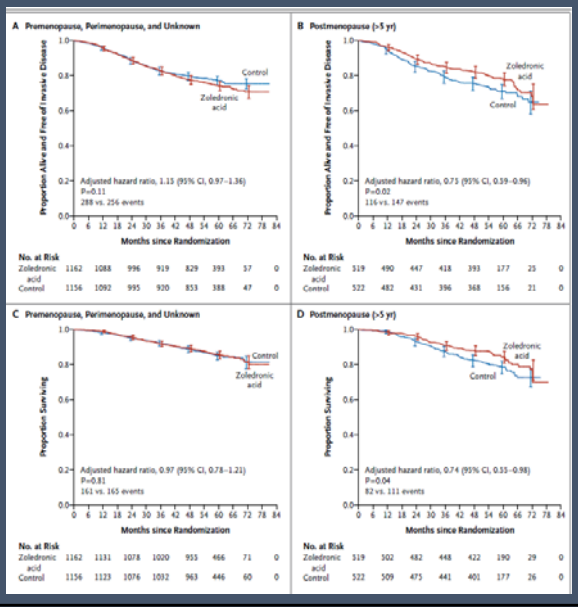
Bisphosphonates as Adjuvant Therapy: Azure Trial



- Groups evenly balanced
- ER positive 78%
- 1-3 nodes + 62%
- ≥ 4 nodes + 36%
- Centrally confirmed jaw osteonecrosis:
  17 cases – 1.1% (all receiving Z)
- ***No difference in overall survival***

Coleman, RE: N Engl J Med 2011; 365:1396
Coleman, RE: Lancet Oncol 2014; 15 (9):997

Bisphosphonates as Adjuvant Therapy: Azure Trial



- Pre-planned subgroup analysis
- Trend toward better freedom from invasive disease in post menopausal women

BUT

"In conclusion, our findings do not support the routine use of zoledronic acid in unselected patient with early stage breast cancer"

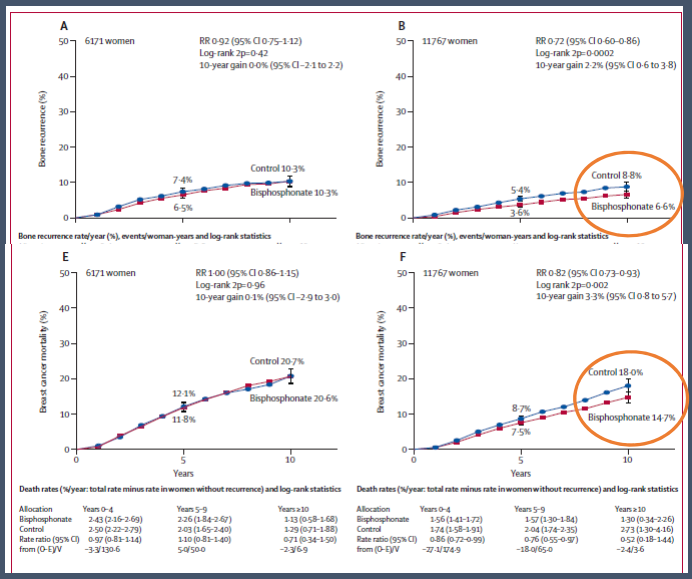
Coleman, RE: N Engl J Med 2011; 365:1396
Coleman, RE: Lancet Oncol 2014; 15 (9):997

Bisphosphonates as Adjuvant Therapy: EBCTCG meta-analysis

- Data from 18,766 women with trials of bisphosphonate of 2-5 years duration, median follow-up – 5.6 years
- *Overall* reductions in recurrence, distant recurrence, and breast cancer mortality of "only borderline significance"
- Among 11,767 postmenopausal women, there was a reduction in bone recurrence (RR – 0.72) and breast cancer mortality (RR – 0.82)
- Absolute difference – small; no ONJ data

EBCTCG: Lancet 2015; 386: 1353-61

Bisphosphonates as Adjuvant Therapy: EBCTCG meta-analysis



Bone recurrence:
Absolute difference – 2.4%

Death rates:
Absolute difference – 3.3%

EBCTCG: Lancet 2015; 386: 1353-61

Adjuvant Denosumab in Breast Cancer (ABCSG-18)

- Secondary endpoint: disease free survival (DFS)
- Of the 3,425 patients, 72% had tumors < 2 cm in size
- At 84 months, DFS in the denosumab group was 83.5% compared to 80.4% - borderline significance (p=0.515)
- Advantage greater in those with tumors > 2 cm
- No overall survival currently available

San Antonio Breast Cancer Symposium, 2015 (Gnant et al)

Bisphosphonates as Adjuvant Therapy

- NCCN – not currently on guideline
- St. Gallen's – 2015 (Breast Care 2015; 10:124-130)
  - Adjuvant bisphosphonates indicated during adjuvant endocrine therapy for postmenopausal women with estrogen-responsive disease
  - Vote: Yes -58% , No -42%
  - No consensus on agent or duration

Bisphosphonates as Adjuvant Therapy Audience Response Question

You have a 68 year old patient with a stage IIB (T1, N2, M0), strongly ER/PR+, HER2 negative breast cancer who has normal bone density. She has completed chemotherapy and radiation therapy. You are ready to start adjuvant hormonal therapy.

Would you offer this patient adjuvant bisphosphonates?

A. YES

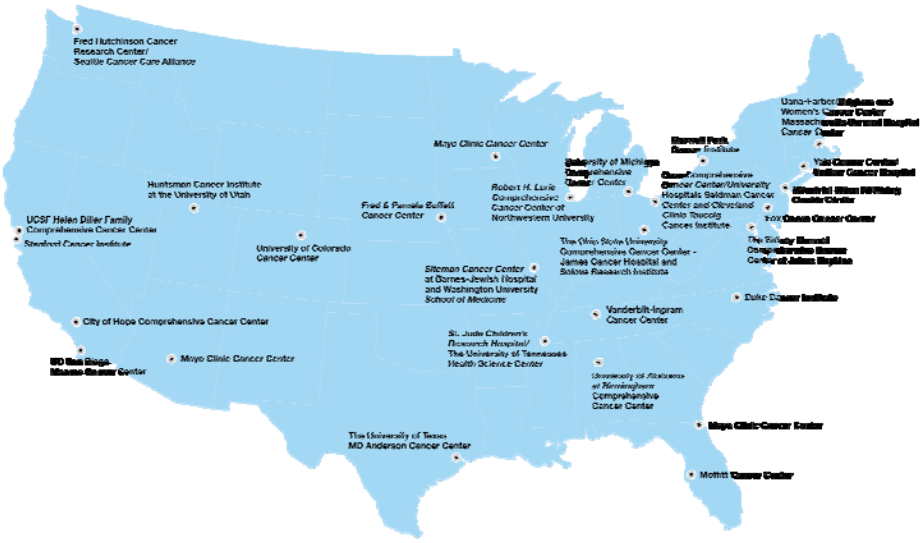
B. NO

Summary

- Bone modifying agents have many roles in the care of breast cancer patients
- For 20 years, they have been known to reduce the rate of skeletal-related events -- a major advance in the care of patients with bone metastases. Bisphosphonates and denosumab are both effective, with a slight edge to denosumab
- Breast cancer patients receiving aromatase inhibitors should have their bone health monitored, and treatment for reduced bone density considered
- Adjuvant bisphosphonate therapy to reduce metastatic disease remains controversial

Thank you!

NCCN Member Institutions



Upcoming Webinars – Register at NCCN.org/events

- **Early Stage Breast Cancer: Role of Multigene Assays & SABCS Updates on Adjuvant & Neoadjuvant Therapies**
  Friday, April 8 at 2:30 PM [EDT]
  Matthew Goetz, MD, *Mayo Clinic Cancer Center*
  Sarika Jain, MD, MSCI, *Robert H. Lurie Comprehensive Cancer Center of Northwestern University*
  Cesar A. Santa-Maria, MD, *Robert H. Lurie Comprehensive Cancer Center of Northwestern University*
- **Early Stage Breast Cancer: Adjuvant Radiation, Surgical Management, & SABCS Updates on Local Therapy**
  Friday, April 22 at 8:45 AM [EDT]
  Benjamin O. Anderson, MD, *Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance*
  Seema A. Khan, MD, *Robert H. Lurie Comprehensive Cancer Center of Northwestern University*
  Kilian E. Salerno, MD, *Roswell Park Cancer Institute*

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