

## 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.

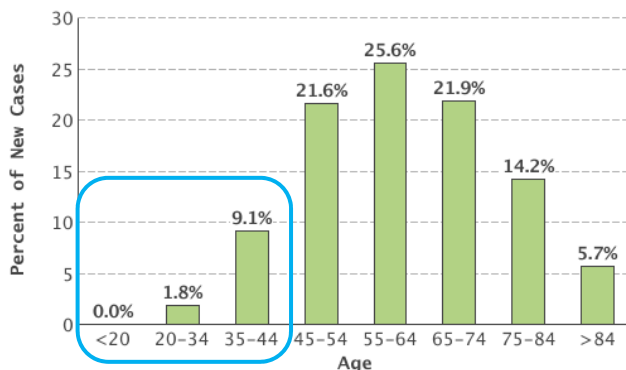
## Fertility Preservation in Breast Cancer

### 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



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

Treatment poses a risk  
of infertility

<http://seer.cancer.gov/>

# Professional guidelines highlight the need for clinicians to address fertility



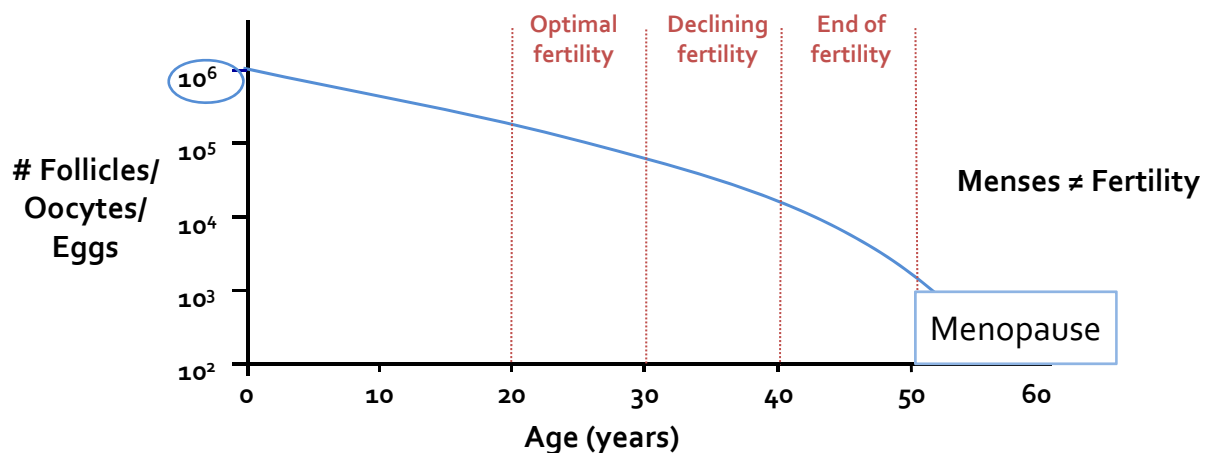
## Content Outline

- 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; Meirrow et al 2010*

## Effects of Treatment on Fertility

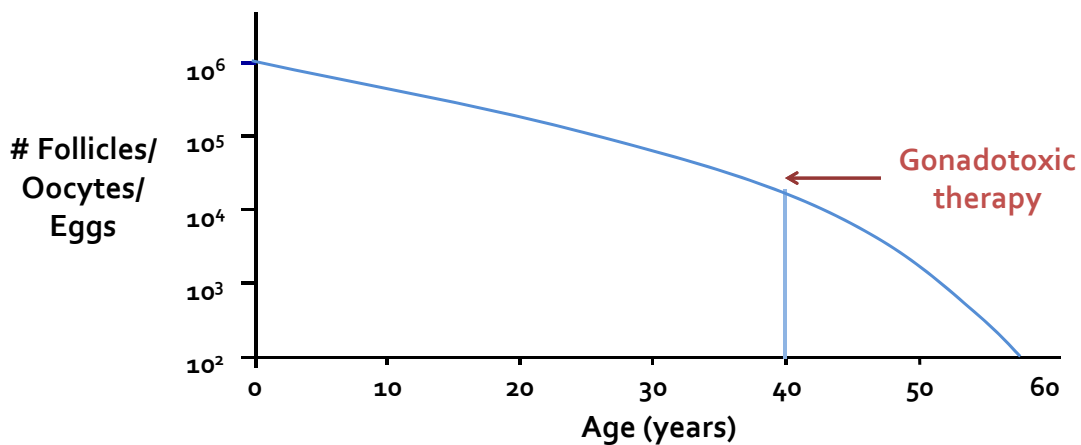
- Chemotherapy
  - Impact based on drug, cumulative dose, and age

<b>Agent</b>	<b>Risk</b>
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

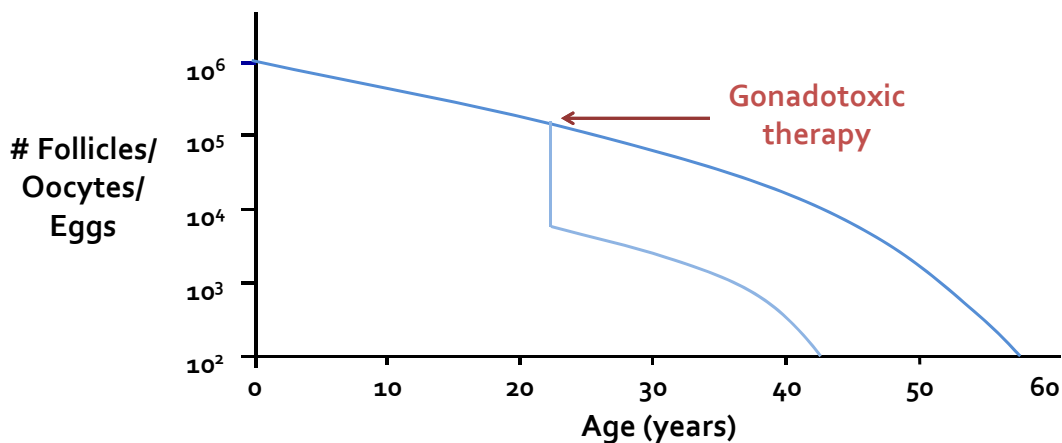
### Depletion of ovarian follicle pool



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  $\neq$  Fertility
  - Age at time of treatment is a major factor

*Kort et al 2014; Levine et al 2012; Meiorow et al 2010*

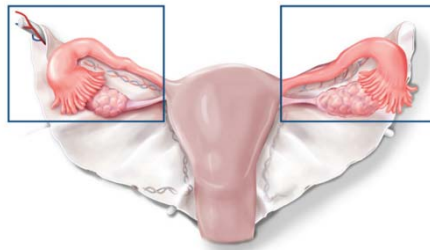
## Effects of Treatment on Fertility

- 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

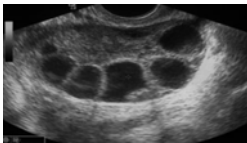
Cryopreservation

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.

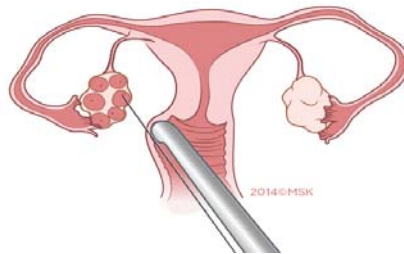
# Embryo and Oocyte Cryopreservation

Ovarian  
Stimulation



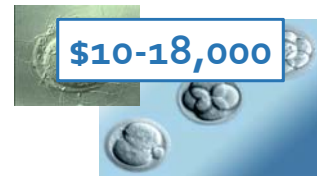
Daily hormone  
injections  
~10 days

Egg  
Retrieval



Under anesthesia

IVF  
In Vitro Fertilization



\$10-18,000

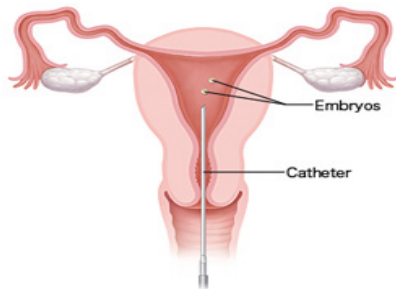
No Fertilization

\$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
  - $\geq 1$  year to ensure clearance of damaged gametes
  - 2-3 years minimum, to pass time when at greatest risk for recurrence
  - Some evidence of  $\downarrow$  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
    - $\downarrow$  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*

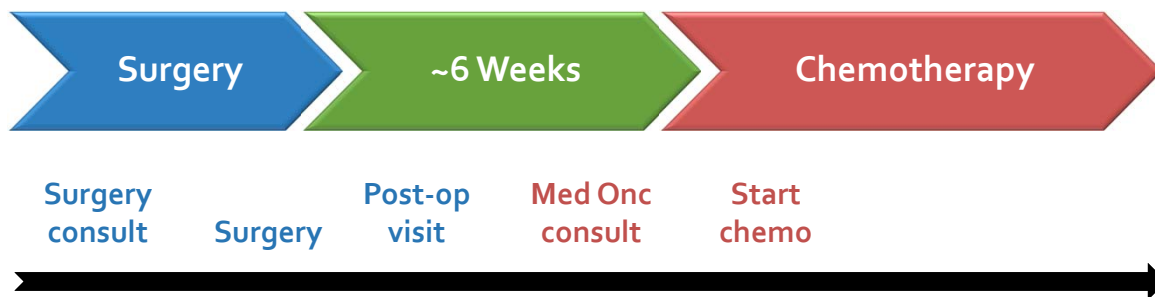


## What Does This Mean for You?

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



NCCN

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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

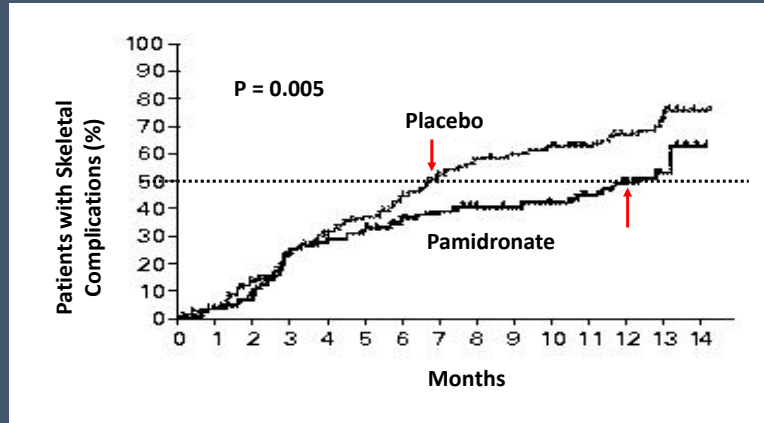
## Bone Modifying Agents in Breast Cancer

- ***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

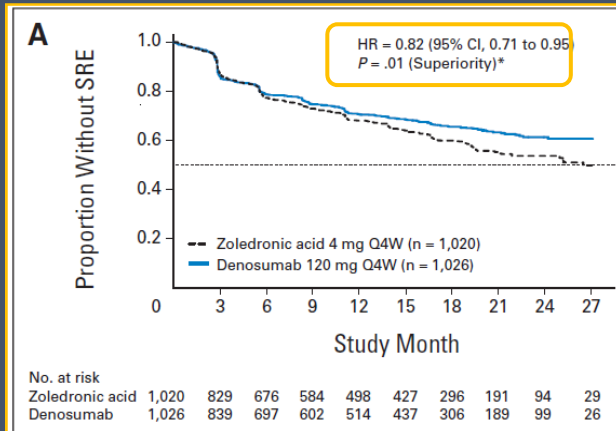


n=380

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 !!

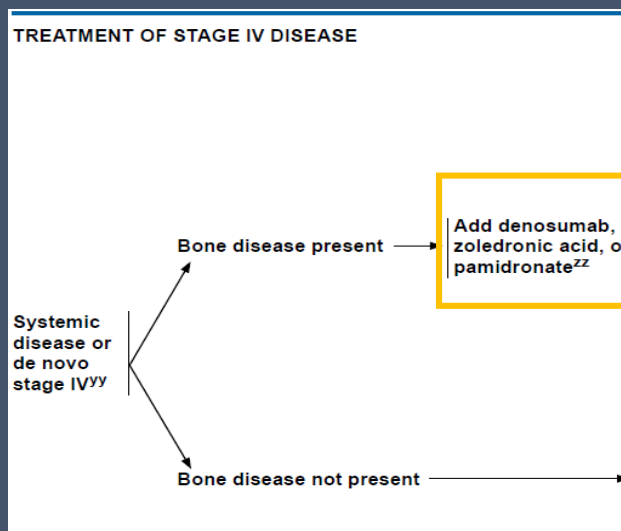
## Denosumab v Zoledronic Acid in Breast Cancer Metastatic to Bone



- 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  $\geq 3$  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

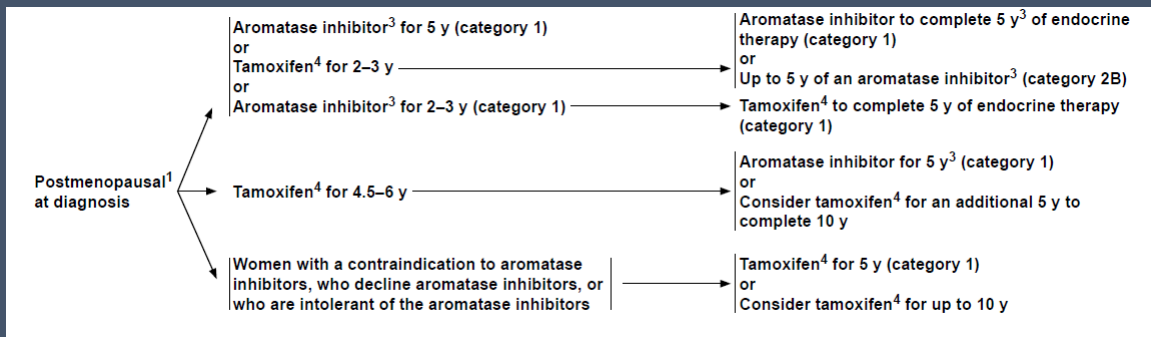
Black DM, Rosen CJ: NEJM 2016; 374:254-262

# 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

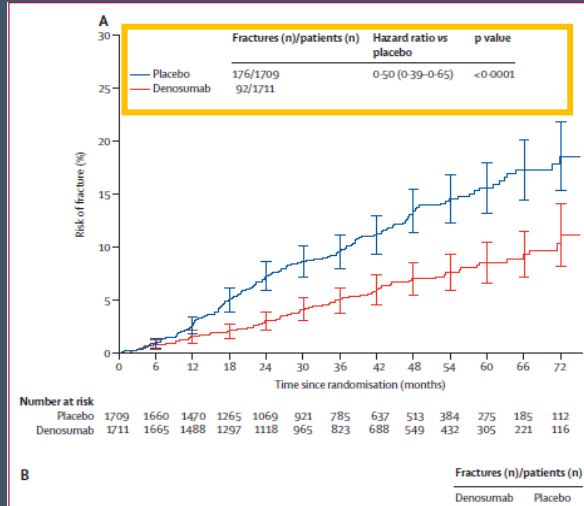
- Considerations in adjuvant endocrine therapy may include:
  - Efficacy: many regimens with category 1 NCCN support
  - Patient tolerance
  - *Bone density*
  - Endometrial cancer risk
  - Thromboembolic risk
  - Patient preference
  - Cost

## 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 (ABCSSG-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 <sup>1</sup>	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 <sup>2</sup>	3 Years vs. Standard care	299	TCs in LNs	Bone metastases were detected at the same frequency in both groups at 10 years
Powles <sup>3</sup>	2 Years vs. Placebo	1,069	Operable BC	No reduction in the incidence of bone metastasis
NSABP B-34 Paterson <sup>4</sup>	3 Years vs. Placebo	3,323	Stage 1-3 BC	No differences in DFS or OS <b>≥ 50 YO showed benefits of clodronate for RFS, bone metastasis-FI, and non-bone metastasis-FI but not OS</b>

\* Free Interval

	Ibandronate			
Von Minckwitz <sup>5</sup>	2 Years vs. Standard Care	2,994	TCs in LNs and DDC	At 38 months no difference in DFS or OS

<sup>1</sup> Diel IJ: N Engl J Med 1998; 339: 357

<sup>2</sup> Saarto T: Acta Oncol 2004; 43:650

<sup>3</sup> Powles T: J Clin Oncol 2002; 20:3219

<sup>4</sup> Paterson AH: Lancet Oncol 2012; 13: 734

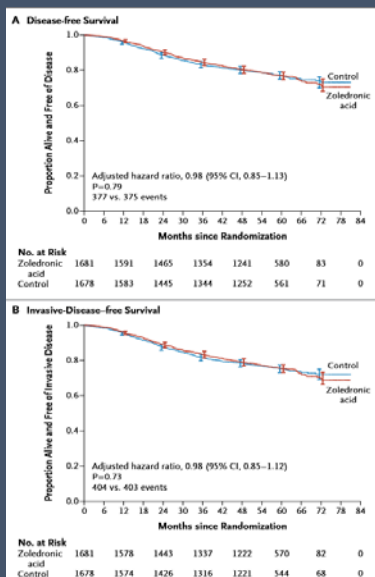
<sup>5</sup> von Minckwitz G: J Clin Oncol 2013; 31: 3531

## 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

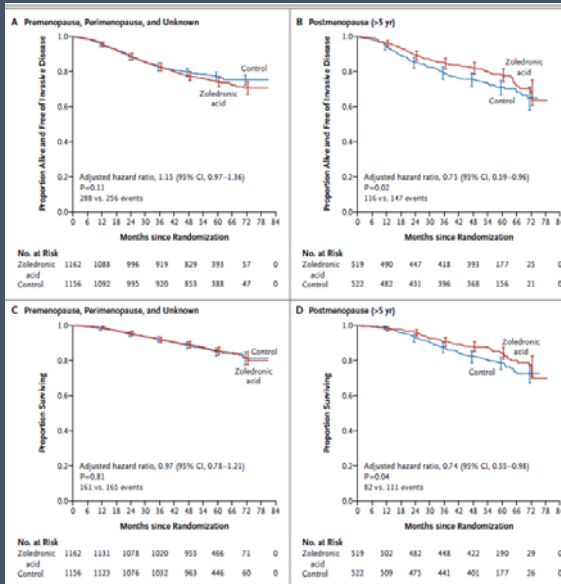
## Bisphosphonates as Adjuvant Therapy: Azure Trial



- Groups evenly balanced
- ER positive 78%
- 1-3 nodes + 62%
- $\geq 4$  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”

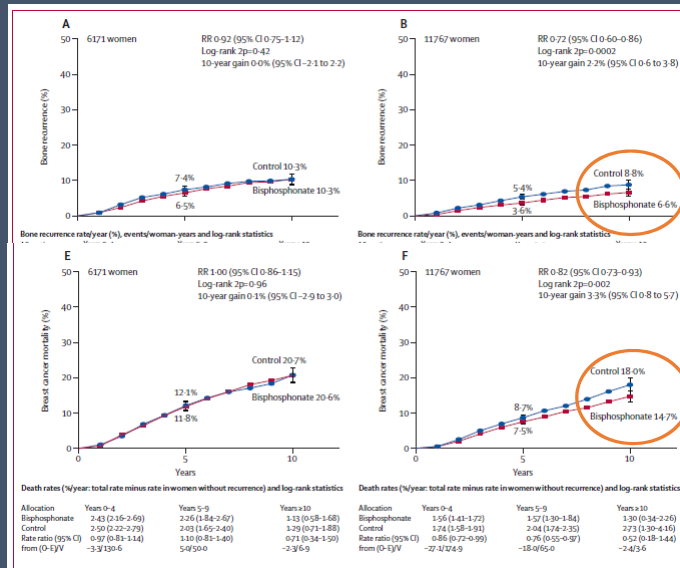
Coleman, RE: N Engl J Med 2011; 365:1396  
Coleman, RE: Lancet Oncol 2014; 15 (9):997

## 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 (ABCSCG-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