LEARNING OBJECTIVES

At the end of the presentation and after reviewing the accompanying reading materials, the participant should be able to:

1. Outline the most appropriate screening and prevention strategy for breast cancer.
2. Describe the most appropriate patient-specific therapy and monitoring for a stage of disease.
3. Apply the clinical data underlying therapeutic treatment recommendations.
4. Explain expected outcomes to a given therapeutic modality in terms of response and toxicity or other endpoints (e.g., survival, clinical benefit, etc.).
5. Devise and communicate appropriate plans for preventing, monitoring and treating adverse reactions associated with treatment of breast cancer.
6. Compare the available bone modifying agents for the management of skeletal-related events in patients with metastatic breast cancer to the bone.
7. Design an antiemetic regimen for the management of chemotherapy-induced nausea and vomiting in a patient receiving chemotherapy for breast cancer.
8. Identify anticancer agents that increase the risk of cardiotoxicity in patients with breast cancer.
9. Create a monitoring plan for patients who have completed adjuvant or neoadjuvant therapy for early stage or locally advanced breast cancer.
OVERVIEW OF DISEASE AND MANAGEMENT

**Patient case #1:** AC is a 64 y/o postmenopausal white woman with lobular carcinoma in situ (LCIS). She is in relatively good health with a significant family history for breast cancer (mother diagnosed at age 55, sister diagnosed at age 45, maternal aunt diagnosed at age 60, and a maternal aunt with ovarian cancer diagnosed at age 59). Her age of menarche was 13, and she has no children. She took birth control pills for approximately 10 years and has had normal annual mammograms since the age of 40, with the exception of her recent diagnosis of LCIS. She comes in today to discuss options for risk reduction given the recent diagnosis of LCIS. What are her options for breast cancer risk reduction?

I. **EPIDEMIOLOGY**

A. Most common cancer in women in the U.S (29%). An estimated 235,030 cases will be diagnosed in 2014 (232,670 women, 2360 men).

B. Second most common cause of cancer related death in women (15%). An estimated 40,430 people in the U.S. will die of breast cancer in 2014.

C. An estimated 62,570 new cases of in situ breast cancers are expected in U.S. women in 2014.

D. The estimated incidence has remained relatively flat since 2003, however mortality has proportionally decreased. Death rates have steadily decreased since the 1990s. The decreased incidence since 2001 is thought to be due to reduction in the prevalence of HRT since the WHI results were released and possibly a decrease in mammography utilization. The reduction in mortality is thought to be due to improved treatments both in the adjuvant and metastatic setting, as well as effects of early diagnosis through screening efforts.

<table>
<thead>
<tr>
<th>5-year survival</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>99%</td>
</tr>
<tr>
<td>Regional</td>
<td>85%</td>
</tr>
<tr>
<td>Distant</td>
<td>25%</td>
</tr>
<tr>
<td>Unstaged</td>
<td>50%</td>
</tr>
</tbody>
</table>

E. Lifetime risk (birth to death) of developing breast cancer in American women is approximately 1 in 8 (12.3%).

II. **ETIOLOGY AND RISK FACTORS**

A. Etiology is unknown

1. Genetics

   a. Hereditary breast cancer represents 5-10% of all breast cancer cases.

      1) *BRCA1* and *BRCA2* (tumor suppressor genes)

         a) Increased incidence of breast and ovarian cancers (*BRCA1*) and woman and male breast cancers and ovarian cancers (*BRCA2*).  

         b) Relatively rare in general population (1:500); estimated carrier frequency is 1:40 for Ashkenazi Jewish women.

         c) The probability of developing breast or ovarian cancer by 70 years of age in women with a *BRCA1* mutation is estimated to be 57% for breast cancer and 40% for ovarian cancer. For
patients with BRCA2 mutations, the probability of developing breast or ovarian cancer by 70 years of age is estimated to be 49% for breast cancer and 18% for ovarian cancer.  

d) More than 700 (BRCA1) and 300 (BRCA2) mutations identified; variable penetrance (proportion of patients with the mutation who exhibit clinical symptoms).

e) Individuals likely to benefit most from genetic counseling and testing are listed in TABLE 2.

f) Prognostic significance of carrier status is disputed (mixed results from clinical trials).
   i. Mechanism of proteins not fully elucidated.
   ii. Play a key role in response to DNA damage and interact with other proteins involved in DNA repair and apoptosis.

g) Non-carriers (those who are tested and are found not to carry the family-specific mutation) have cancer risks similar to the average women in the population and are recommended to follow general population cancer screening guidelines.

### TABLE 2: Characteristics Associated with an Increased Likelihood of BRCA1 or BRCA2 Mutations

<table>
<thead>
<tr>
<th>Personal Characteristics</th>
<th>Family History Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer at an early age (40 years or less)</td>
<td>Two first-degree relatives with breast cancer, one diagnosed &lt; 50 years</td>
</tr>
<tr>
<td>Bilateral breast cancer</td>
<td>Three or more first- or second-degree relatives with breast cancer, any age</td>
</tr>
<tr>
<td>Malignancy associated with the BRCA1 phenotype</td>
<td>Both breast and ovarian cancer in first- or second-degree relatives</td>
</tr>
<tr>
<td></td>
<td>First-degree relative with bilateral breast cancer</td>
</tr>
<tr>
<td></td>
<td>Male breast cancer</td>
</tr>
<tr>
<td></td>
<td>Two or more first- or second-degree relatives with ovarian cancer</td>
</tr>
<tr>
<td></td>
<td>First or second-degree relatives with breast or ovarian cancer and Ashkenazi Jewish ancestry</td>
</tr>
</tbody>
</table>

2) p53
   a) Tumor suppressor gene (“guardian of the genome”)
   b) Associated with Li-Fraumeni syndrome of multiple hereditary cancers; less than 1% of breast cancers are associated with this syndrome.
   c) Approximately 30% of breast cancers have mutation, inactivation, loss or down-regulated expression of p53.

3) Mutations in moderate penetrance genes such as ATM, CHEK2, or PALB2 may also be evaluated in the future

4) NCCN guidelines are available for Genetic/Familial High-Risk Assessment of Breast and Ovarian Cancer
5) The USPSTF also has recommendations for risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women.

b. Progression genes

1) HER2 (Human Epidermal Growth Factor Receptor-2, erbB-2) proto-oncogene

   a) Encodes for human epidermal growth factor receptor-2 (protein, p185).

   b) Amplification/overexpression generally imparts a poorer prognosis; chemotherapy sensitivity (such as with anthracyclines, this is controversial); endocrine therapy resistance (also controversial).

   c) Amplified/overexpressed in approximately 20-25% of all breast cancers.

   d) Controversial as an independent prognostic factor.

   e) Used primarily to select patients who will benefit from HER2-directed therapy.

   f) Guidelines for HER2 testing are available from the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP)

      i. HER2 status should be determined on every primary invasive breast cancer, recurrence, and at presentation of metastatic disease (if stage IV and specimen is available)

      ii. Immunohistochemistry (IHC)

         a) Measures protein expression on cell surface.

         b) Scale: 0 = no staining or incomplete, faint staining in ≤ 10% of cells; 1+ = faint incomplete staining > 10% of cells; 2+ = weak complete staining of membrane > 10% of cells or intense staining in ≤ 10% of cells; 3+ = complete, intense staining of membrane > 10% of cells.

         c) Testing by ISH indicated if IHC is 2+ (equivocal)

         d) Subjective interpretation; image analysis being investigated to make this process more objective.

         e) Other limitations include preanalytic (e.g., sample processing), analytic (e.g., type of antigen) and postanalytic (e.g., interpretation criteria) variables.

      iii. In-situ hybridization (ISH)

         a) Identifies the presence of gene amplification.
ISH reported as copy number with single probe test or as a ratio of HER2 gene copy number: Chromosome 17 copy number with dual probe test.

With a single probe test:
(i) Positive ≥ 6 HER2 signals/cell
(ii) Equivocal  = 4-6 HER2 signals/cell
(iii) Negative < 4 HER2 signals/cell

With a dual probe test, a ratio is reported:
(i)  ≥ 2.0 = ISH positive
(ii) < 2.0  
  ▪  ≥ 6 HER2 signals/cell = ISH positive
  ▪  4-6 HER2 signals/cell = ISH equivocal
  ▪  < 4 HER2 signals/cell = ISH negative

Testing by IHC indicated if ISH is equivocal

ISH maybe more predictive of benefit with trastuzumab than IHC.

Optimal method for determining HER2 status is unknown.

Algorithms for testing outlined in ASCO/CAP guidelines.

Other in situ hybridization methods are available, must be validated by comparison to a FDA-approved FISH assay

Chromogenic in situ hybridization (CISH) differs from FISH in that it utilizes a different probe methodology allowing for a conventional microscope for evaluation. CISH was utilized in some clinical trials with trastuzumab.

Dual in situ hybridization (ISH) detects HER2 and chromosome 17 on a single slide using a standard light microscope.

Silver enhanced in situ hybridization (SISH) is another test for gene amplification, but is not available in the US.
Eligibility for clinical trials differs; careful examination of these criteria is essential for adequate interpretation of trial results.

Other testing methods are under investigation (e.g. reverse transcription polymerase chain reaction (RT-PCR), DNA expression by microarray, etc.)

2. Tumorigenesis
   a. Malignant progression involves early changes in proliferation by systemic hormones (such as estrogen and progesterone) and local growth factors (such as TGF-α).
   b. Continuum from atypical hyperplasia ⇒ ductal carcinoma in situ (DCIS) ⇒ invasive ductal carcinoma (IDC).
   c. Involves many steps, some of which may be bypassed in familial forms or inflammatory breast cancers.

B. Risk Factors (>60% of breast cancer patients have no identifiable risk factors beyond female gender and aging)

1. Age – incidence of breast cancer increases with age; but more than half that risk occurs after the age of 60 years.

2. Family history of breast cancer - first and second-degree relatives impart an increased risk; early-onset breast cancer in a family member is suggestive of a hereditary predisposition (see TABLE 2). The overall risk is 1.5- to 3- fold greater if a woman has a mother or sister with breast cancer.

3. Endogenous estrogen exposure
   a. Early age of menarche (typically defined as ≤ 12 y/o) increases risk (increased by a factor of 1.050 for each year younger at menarche).
   b. Late age of natural menopause (typically defined as ≥ 55 y/o) increases risk (increased by a factor of 1.029 for each year older at menopause).
   c. Early induced menopause (bilateral salpingo-oophorectomy or BSO) before 50 y/o decreases risk, with further risk reduction as the age of BSO decreases.
   d. Age at birth of first child ≥ 30 y/o or nulliparity increases risk.
   e. Distinct subtypes of breast cancer, particularly estrogen-independent subtypes, may differ in this risk factor.
   1) In one study, women with breast cancer who delivered > 3 children were 1.5-fold more likely to be diagnosed with triple-negative (estrogen receptor (ER) negative, progesterone receptor (PR) negative, HER2 normal) breast cancer (odds ratio (OR), 1.53; 95% CI: 1.1-2.1) than nulliparous women with breast cancer.
4. **Benign breast disease** – increased risk for both proliferative breast disease without atypia (Relative risk (RR) = 1.5-2.0) and atypical hyperplasia (RR = 4.5-5.0).

5. **Radiation exposure** - atomic bomb, radiotherapy for lymphoma or other cancer, historical uses of radiation.

6. **Obesity and body mass index (BMI)**\(^{11}\)
   a. Complex association between BMI, obesity, and breast cancer incidence; differs by age and menopausal status.
   b. In premenopausal women – slight decrease in risk with increasing weight (RR 0.92; 95% CI 0.88–0.97; \(P < 0.001\)).
   c. In postmenopausal women – increased incidence of breast cancer with increasing weight (RR 1.12; 95% CI 1.08–1.16; \(P < 0.0001\)).
   d. May also be related to distribution of fat and/or body composition.

7. **Physical activity**\(^{12}\)
   a. Lower risks associated with greater physical activity; observed in both pre- and postmenopausal women (stronger association for postmenopausal vs. premenopausal women).
   b. Not clear whether adolescent activity, adult activity or lifetime activity provides the most benefit.

8. **Diet**
   a. Epidemiological data show a positive correlation between higher dietary fat intake and breast cancer risk. This correlation is stronger in postmenopausal women than in premenopausal women.
   b. A meta-analysis of 31 case control and 14 cohort studies on dietary fat reported a small but significant RR (1.13 95% CI 1.03-1.25) when the highest and lowest fat intake categories were compared.\(^{13}\)
   c. Prospective clinical trials have not shown a significant reduction in breast cancer risk with modification of dietary fat.\(^ {14,15}\)
   d. No association with other macro- or micronutrients.

9. **Exogenous estrogen exposure**
   a. Risks of postmenopausal estrogen replacement therapy (ERT) and oral contraceptives (OC) are controversial. For OC, most clinicians feel that the benefits far outweigh the risks of developing breast cancer for most women. For ERT, changing views based on current evidence.
   b. A meta-analysis of 13 prospective cohort studies reported a non-significant increase in breast cancer incidence for patients who used OC compared to those who had never used OC.\(^ {16}\)
1) Authors of this meta-analysis were not able to differentiate breast cancer risk based on the formulations of oral contraceptives, which vary from product to product.

c. Women’s Health Initiative (WHI) - Estrogen vs. Estrogen + progesterone

1) WHI trial Prempro® arm discontinued early; HR=1.3 (1.0-1.6) with 290 breast cancer cases.  

2) WHI trial Premarin® arm stopped after nearly 7 years mean follow-up due to an increased incidence of stroke. Breast cancer incidence not increased at the time of stopping.

d. Prospective studies (WHI) appear to indicate little benefit related to cardiac events and questionable benefits for the bones (in terms of fracture rates and mortality), as well.

e. Epidemiologic studies indicate an association between the release of WHI results, a decline in use of HRT and a decline in the incidence of breast cancer diagnoses.

f. The increased risk of breast cancer in patients who received HRT in the WHI trial declined after discontinuation of estrogen and progesterone.

g. Premarin alone in the WHI trial significantly decreased the incidence of breast cancer compared to patients who received placebo after 11.8 years of follow-up (HR 0.77, 95% CI 0.62–0.95; p=0.02), but additional trials are needed before this can be recommended for breast cancer risk reduction.

h. The impact of HRT use on breast cancer risk varies according to race, BMI and breast density.

10. Alcohol

a. Epidemiological data has shown that risk increases with consumption (relative risk of breast cancer increased by 7% for each additional 10 g of alcohol per day).

b. Increased risk of breast cancer has been shown with even low-moderate alcohol intake (equivalent to 3-6 drinks/week=RR 1.2; 95% CI 1.1-1.2).

c. A causal relationship has not been proven; moderation is a sensible approach.

11. Breast density and mammographic patterns

a. A mammographic measure of the amount of glandular tissue relative to fatty tissue in the breast.

b. Risk associated with certain mammographic patterns and appears to be genetically determined.

c. Women with more radiodense breast tissue are at a higher risk compared to women with more radiolucent breast tissue (between 2 and 6 times that of women of the same age with little density).
12. **Gail Model risk assessment tool**\(^{27}\)
   a. Useful for white women with a **limited** family history to assist with decisions regarding cancer prevention.
   b. Mathematical model to determine RR of developing breast cancer compared to an age-matched control at 5 years and during your lifetime.
   1) Age
   2) Number of first-degree relatives with invasive breast cancer
   3) Nulliparity or age at first birth
   4) Number of breast biopsies
   5) Atypical hyperplasia Many assumptions; not validated with other races. A more accurate model for risk assessment in African American women is available.\(^{28}\)

13. **Breast cancer risk assessment tool used in prevention studies**\(^{29}\)
   a. Incorporates components of the Gail Model with data from the Breast Cancer Detection and Demonstration Project (a mammography screening project conducted in the 1970s).
   b. Available on the web, tool used in the NSABP prevention trials P1 and STAR.
   c. Most frequently used to determine eligibility for chemoprevention with tamoxifen, raloxifene, exemestane, or clinical trial.

14. Many other tools also available
   a. **Claus model**\(^{30}\)
      1) Includes current age, family history of breast cancer (mother, sisters, grandmothers, maternal and paternal aunts), and the age of onset in affected relatives.
      2) Estimates risk of breast cancer based on these characteristics.
      3) Does not take into account ethnicity, male breast cancers, ovarian cancers, personal medical history or reproductive history.
      4) Slightly better predictor than Gail for people with a more extensive family history of breast or ovarian cancer.
   b. **BRCAPRO**\(^{31}\)
      1) Includes breast cancer in the proband (first family member identified with breast cancer) and all affected first-degree (FDRs) and second-degree relatives (SDRs) (unilateral and bilateral breast cancers), ovarian cancer in the proband (first family member identified with ovarian cancer) and all affected FDRs and SDRs, age of onset of all cancers, age of unaffected relatives, age of oophorectomy (if applicable), Ashkenazi Jewish status, mutation carrier status (if known).
      2) Computer program for calculating an individual’s probability of carrying a deleterious mutation of **BRCA1, BRCA2**, neither, or both.
      3) Limitations include:
a) Assumes all affects due to BRCA1 or BRCA2.

b) Tends to overestimate importance of bilateral breast cancer and underestimate importance of ovarian cancer.

c) Cannot account for DCIS, prophylactic breast surgery, or other cancers.

**Patient case #1 (continued):** AC is at an increased risk for developing invasive breast cancer due to her LCIS. In addition, her 5-year Gail risk of developing breast cancer is calculated at 3.7%, based on her previously listed risk factors. The Gail model may potentially underestimate her risk of invasive breast cancer due to her significant family history. She is not interested in genetic testing at this time. She is postmenopausal. What are her breast cancer risk reduction options at this time? What other patient counseling points should be emphasized (e.g., screening recommendations, other cancer risk assessment/screening)?

### III. **ANATOMY & PATHOPHYSIOLOGY**

A. The breast is comprised of ducts, lobules, fatty tissue, other connective tissues, and intramammary lymph nodes.

B. Regional lymph nodes include axillary and internal mammary lymph node chains. Level III axillary lymph nodes also referred to as infracavicular. Supraclavicular also considered regional lymph nodes in the current AJCC staging system.

C. Pathologic types of breast cancer

1. Ductal carcinoma in situ (DCIS) - premalignant lesion; hallmark clustered microcalcifications on mammogram; usually curable with resection alone; role of radiation and tamoxifen being studied (see treatment section for details).

2. Lobular carcinoma in situ (LCIS) - not a premalignant lesion; risk factor for breast cancer; both breasts are at equal risk; included in prevention studies with tamoxifen, raloxifene, exemestane, and anastrozole (see treatment section for details).

3. Invasive lobular carcinoma (ILC) - second most common type of breast cancer (15%); more likely to metastasize to serosal surfaces.

4. Invasive ductal carcinoma (IDC) - most common type of breast cancer (70%); worst prognosis of all types of breast cancer.

5. Others: tubular, mucinous, papillary, medullary; generally have better prognosis compared to IDC (favorable histologies). National Comprehensive Cancer Network (NCCN) guidelines address management.

6. Also sarcomas, carcinosarcomas, sarcomatous carcinomas, squamous cell and others - rare variants with generally poor prognosis.

7. Phyllodes tumor (cystosarcoma phyllodes) – rare tumors comprised of both stromal and epithelial elements; stratified as benign, borderline and malignant subtypes. NCCN guidelines address management as a separate entity.
IV. SCREENING & PREVENTION

A. Screening

1. Breast self-examination (BSE)
   a. Not generally recommended; little data supporting reduction in mortality when used alone. Meta-analysis of randomized trials of BSE has shown no effect on breast cancer mortality.\textsuperscript{33} May lead to high rates of unnecessary biopsies.
   b. Many organizations endorse some type of screening guidelines with or without BSE. American Cancer Society (ACS) does still mention that women 20 years and older should be presented the benefits, limitations and harms of BSE.\textsuperscript{34} NCCN states that women 25 years and older should have breast awareness.\textsuperscript{35} USPSTF recommends against teaching BSE\textsuperscript{36} (See TABLE 3).
   c. Difficult to separate impact of different screening tools (BSE, clinical breast exam, and mammogram); all three should be viewed as complimentary modalities.
   d. If performed, perform monthly; week after menses.
   e. Education is required to ensure careful examination and prompt reporting to a health care professional if any abnormalities are noted.

2. Clinical breast examination (CBE)
   a. Not uniformly recommended. May be most beneficial with mammograms (at the same time). No clinical trial has compared CBE + screening mammograms to screening mammograms alone.
   b. Difficult to separate impact of different screening tools (BSE, CBE, and mammogram); all three should be viewed as complimentary modalities.
   c. ACS still recommends, at least every 3 years for women aged 20-39 years and annually for women \( \geq 40 \) years (See TABLE 3).\textsuperscript{34}
   d. Training of qualified personnel is necessary to ensure quality of examination.

3. Mammography
   a. Agency for Health Care Policy and Research (AHCPR) guidelines dictate the technical procedures for high-quality mammograms; ACR (American College of Radiology) MAP (Mammography Accreditation Program) established voluntary quality standards; BI-RADS\textsuperscript{®} categories (0 - 6) are used to standardize the reading or analysis of the mammograms under these standards.
   b. Definite evidence that annual screening mammography reduces the mortality from breast cancer in women 50 y/o or older.
   c. Data is lacking in women 75 y/o or older. The decision to stop screening should be individualized based on the potential benefits and risk of screening and in the context of overall health. An excellent review regarding mammographic screening in this population is available.\textsuperscript{37}
   d. Women ages 40-49 years:
      1) Controversial; many randomized, controlled clinical trials assessing this question.
2) Studies had differing eligibility criteria; problems with control groups including some women with a known breast mass were included in the screening population.

3) A systematic review conducted by the USPSTF estimated that the “number needed to invite for screening to extend one woman’s life” (NNI) for women aged 40 to 49 years was 1,904 compared to an estimated NNI of 1,339 for women aged 50 to 59 years and 377 in women aged 60 to 69 years.\(^{38}\)

4) A study from Sweden evaluated breast cancer mortality in areas of the country where women aged 40-49 were invited to screening with mammography (study group) compared to areas where women were not invited to screening (control group).\(^{39}\)

   a) The estimated number needed to invite to screening to save one life was estimated to be 1,252.

   b) This and other studies provide additional support for mammographic screening in this age group.

5) Still under debate, but should take into account the potential benefits and harms of screening mammography and an individualized assessment of risk for breast cancer to help guide decisions (see TABLE 3).

4. Breast MRI

   a. American Cancer Society guidelines\(^{40}\) indicate that breast MRI screening is appropriate as an adjunct to mammography in women with the following (based on evidence):

      1) \textit{BRCA} mutation carrier.

      2) FDR of a \textit{BRCA} mutation carrier, but untested.

      3) Lifetime risk ~ 20-25% or greater, as defined by BRCAPRO or other models largely dependent on family history.

   b. Other recommendations based on expert consensus opinion include the following:

      1) Radiation to chest between age 10 and 30 years.

      2) Li-Fraumeni syndrome and FDRs.

      3) Cowden and Bannayan-Riley-Ruvalcaba syndromes and FDRs.

   c. Still controversial in other high-risk groups and for women with a personal history of breast cancer (see TABLE 3).
<table>
<thead>
<tr>
<th>Average risk</th>
<th>ACS (^{35,40})</th>
<th>NCCN (^{35})</th>
<th>USPSTF (^{36})</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSE</td>
<td>Age ≥ 20 y: discussion of benefits, limitations, and harms; prompt reporting of any changes; periodic exam acceptable</td>
<td>Age ≥ 25 y: breast awareness</td>
<td>Recommends against teaching</td>
</tr>
<tr>
<td>CBE</td>
<td>Age 20-39 y: every 3 years Age ≥ 40 y: every year (as long as in good health) (prior to mammogram)</td>
<td>Age 25 to 39 y: every 1-3 years Age ≥ 40 y: annually</td>
<td>Insufficient evidence</td>
</tr>
<tr>
<td>Mammogram</td>
<td>Age ≥ 40 y: annually (as long as in good health) (after CBE)</td>
<td>Age ≥ 40 y: annually</td>
<td>Age 40-50 y: decision to start biennial mammography is individualized Age 50-74 y: biennial Age &gt;75 y: Insufficient evidence</td>
</tr>
</tbody>
</table>

**High risk\(^{a,b}\)**

<table>
<thead>
<tr>
<th>BSE</th>
<th>NA</th>
<th>All ages: breast awareness</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBE</td>
<td>NA</td>
<td>All ages: every 6-12 months (if prior RT, begin 8 to 10 y after RT or age 40, whichever comes first) Annual for women with prior RT (age &lt;25) beginning 8 to 10 y after RT</td>
<td>NA</td>
</tr>
<tr>
<td>Mammogram</td>
<td>Annually w/ MRI</td>
<td>Annual for all categories (+ CBE) (if prior RT, begin 8 to 10 y after RT or age 40, whichever comes first) except women with prior RT (age &lt; 25 y)</td>
<td>NA</td>
</tr>
<tr>
<td>Breast MRI</td>
<td>Annually w/ mammogram</td>
<td>Recommended annually w/ mammogram + CBE for patients with prior RT (age ≥ 25y) or for patients with a lifetime risk &gt; 20%</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Abbreviations:** ACS = American Cancer Society; BSE = breast self-exam; CBE = clinical breast exam; MRI = magnetic resonance imaging; NA = not applicable; NCCN = National Comprehensive Cancer Network; USPSTF = United States Preventive Services Task Force.

\(^a\) High risk is defined by the ACS as women with 1) a known BRCA1/2 gene mutation; 2) untested women with first-degree relative with a known BRCA1/2 gene mutation; 3) lifetime risk of breast cancer of 20-25% or greater using a risk assessment tool based largely on family history; 4) radiation therapy to the chest between the ages of 10 and 30 years; 5) Li-Fraumeni syndrome, Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome or first-degree relatives with one of these syndromes.

\(^b\) High risk is defined by the NCCN as women with 1) prior thoracic radiation therapy < 30 years; 2) 5-year risk of ≥ 1.7% of invasive breast cancer in women ≥ 35 years old (per Gail Model); 3) lifetime risk of > 20% as defined by models that are largely based on family history; 4) pedigree suggestive of or known genetic predisposition; 5) LCIS, ADH, or ALH; 6) prior history of breast cancer.
B. Prevention (“risk reduction”)

1. Prophylactic mastectomies - decreases risk by at least 90%.

2. Bilateral oophorectomy - decreases estrogen exposure; decreases risk of breast cancer by about 50%.

3. Primary prevention trials
   a. Tamoxifen vs. placebo
      1) NSABP Breast Cancer Prevention Trial (BCPT, P1)\textsuperscript{41}
      2) 13,388 women at high-risk of developing breast cancer.
         a) Age 60 years or older.
         b) Age 35-59 years with modified Gail model (5-year RR ≥ 1.66%).
         c) Diagnosis of LCIS.
      3) Risk assessment in women < 60 y/o based on modified Gail model (5-year RR ≥ 1.66%).
      4) Benefits: reduction in incidence of invasive (49%) and noninvasive breast cancers (50%); reduction in invasive breast cancers in women with LCIS (56%) and with atypical hyperplasia (86%); reduced incidence of ER positive tumors, but not ER negative tumors. Reduction in incidence of invasive and noninvasive breast cancers persisted with 7 years of follow up.\textsuperscript{42} Risks: increase in incidence of endometrial cancer (significantly increased in women ≥ 50 y/o), thromboembolic events (pulmonary embolism (PE) and deep vein thrombosis (DVT)), significantly increased in women ≥ 50 y/o), cataracts, hot flashes, and vaginal discharge.
      5) Interim analysis after about 4 years (median 54.6 months) of follow-up; study stopped early; crossover allowed.
      6) No reliable data regarding survival differences (potentially due to crossover).
      7) Subset analyses: Women with \textit{BRCA1} mutations did not have a reduction in breast cancer incidence with tamoxifen. Women with \textit{BRCA2} mutations have a similar reduction in breast cancer incidence compared with the entire study population.\textsuperscript{43}
   b. Other trials with tamoxifen have not demonstrated a significant reduction in incidence of breast cancer (Royal Marsden and Italian trials), while others have shown a significant reduction (IBIS-1). These trials were much smaller and included an inherently different study population relative to the P1 trial (e.g., women were allowed to continue hormone replacement therapy during the clinical trial).
   c. Overview analysis of all 4 prevention trials with tamoxifen has been published.\textsuperscript{44} Included the effects of adjuvant tamoxifen on contralateral breast cancer incidence.
      1) Data from this analysis indicate an overall reduction in breast cancer incidence of 34%-38% with tamoxifen, but no effect on all-cause mortality.
2) Isolated to reduction in incidence of ER-positive tumors only; no reduction in ER-negative tumors.

3) Rates of endometrial cancer (RR=2.4), venous thromboembolic events (RR=1.9) were significantly increased; incidences of cardiovascular events (myocardial infarction (MI), stroke, transient ischemic attack (TIA)) were variable among the studies.

d. STAR trial (NSABP P2)\textsuperscript{45}

1) 19,747 postmenopausal women; similar eligibility to P1, but all women were postmenopausal.
   a) Gail model risk $\geq 1.66\%$.
   b) At least 35 years of age.
   c) Diagnosis of LCIS.

2) Randomized to 5 years of tamoxifen 20 mg daily or raloxifene 60 mg daily.

3) Benefits: similar reduction in incidence of invasive breast cancers (RR 1.02, 95% CI 0.82-1.28); numerically fewer cases of noninvasive breast cancer with tamoxifen (RR 1.40, 95% CI 0.98-2.00); no difference in fractures or total deaths.

4) Risks: Statistically greater number of patients with endometrial hyperplasia (RR 0.16, 95% CI 0.09-0.29), VTE (PE + DVT) (RR 0.70, 95% CI 0.54-0.91), and cataracts (RR 0.79, 95% CI 0.68-0.92) with tamoxifen than raloxifene; numerically more endometrial cancers and MIs, but these did not reach statistical significance, probably due to the small number of events.

5) Outcome: women enrolled in the study were allowed to cross over if they wished; still following women and tracking outcomes; FDA-approved raloxifene for reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer.

6) Update with 81 months of follow-up\textsuperscript{46}
   a) Significant increase in risk of invasive breast cancer in patients who received raloxifene compared to tamoxifen (RR 1.24, 95% CI: 1.05–1.47).
   b) Numerical increase in risk of non-invasive breast cancers with raloxifene vs. tamoxifen (RR 1.22, 95% CI: 0.95–1.59).
   c) Toxicity greater with tamoxifen vs. raloxifene
      i. Uterine cancers (RR 0.55; 95% CI: 0.36–0.83).
      ii. VTE (RR 0.75; 95% CI: 0.60–0.93).
      iii. Cataracts (RR 0.80; 95% CI: 0.72–0.89) and cataract surgeries (RR 0.79; 95% CI: 0.70–0.90).

e. SERM meta-analysis\textsuperscript{47}

1) Analyzed data from 9 clinical trials with 83,399 women who received a SERM (tamoxifen, raloxifene, arzoxifene, and lasofoxifene) vs. placebo
2) SERM use resulted in a significant reduction in breast cancer incidence compared to placebo (RR 0.62; 95% CI: 0.56–0.69).

3) Patients who received a SERM also had significantly increased risk of VTE (RR 1.73; 95% CI: 1.47–2.05) and a significant reduction in vertebral fractures (RR 0.66; 95% CI: 0.59–0.73) compared to those who received placebo.

f. A benefit/risk index has been created to quantify benefits from chemoprevention with tamoxifen or raloxifene for women 50 years old or older based on results from the WHI, NSABP P1 and STAR trials.48

1) Based on a woman’s risk factors: age, ethnicity, breast cancer risk, and hysterectomy.

2) Projected 5-year risk of invasive breast cancer was calculated from the NCI.29

3) The provided tables can help identify appropriate candidates for chemoprevention with tamoxifen or raloxifene.

g. Other SERMs

1) Toremifene
   a) No data available for chemoprevention
   b) No advantage over tamoxifen in treatment of breast cancer.
   c) Not likely to be more advantageous in prevention either.

h. Aromatase inhibitors (AIs)

1) Reductions in contralateral breast cancer risk were seen in adjuvant trials with AIs (ATAC, MA-17, IES, and BIG 1-98); 42% reduction in contralateral breast cancers with anastrozole vs. tamoxifen (ATAC).

2) NCIC CTG MAP 3 trial49
   a) 4,560 postmenopausal women 35 y/o or older with one of the following risk factors:
      i. Greater than or equal to 60 y/o.
      ii. Gail model risk ≥ 1.66%.
      iii. Diagnosis of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), LCIS, or DCIS treated with mastectomy.
   b) Randomized to 5 years of exemestane 25 mg PO daily or placebo daily (or exemestane + celecoxib; this arm was discontinued after 31 patients due to concerns about cardiovascular safety).
   c) Benefits: significant reduction in incidence of invasive breast cancers (annual incidence, 0.19% vs. 0.55%, HR 0.35 with exemestane, 95% CI 0.18-0.70); ADH, ALH, and LCIS occurred in 0.2% in the exemestane group and 0.5% in the placebo group, HR 0.36, 95% CI 0.11-1.12.
   d) Risks: Arthritis, hot flashes, fatigue, sweating, insomnia, diarrhea, nausea, joint pain, and muscle pain were more common in the exemestane group; fractures, osteoporosis,
cardiovascular events and deaths were not statistically different.

e) Limitations: short median follow-up (35 months), small total number of breast events (66), only a small number of patients had DCIS (2.5%).

3) IBIS II\textsuperscript{50}

a) 3,864 postmenopausal women aged 40 to 70 y/o with:

i. At least 4 times greater risk than general population (aged 40-44 years).

ii. At least 2 times greater risk than general population (aged 45-60 years).

iii. At least 1.5 times greater risk than general population (aged 60-70 years).

iv. 10 year breast cancer risk of >5% by the Tyrer-Cuzick model

v. Diagnosis of ADH, ALH, LCIS, or DCIS treated with mastectomy.

b) Randomized to 5 years of anastrozole 1 mg PO daily or placebo daily

c) Median follow-up of 5 years

d) Benefits: significant reduction in incidence of invasive and non-invasive breast cancers favoring anastrozole (2.8% vs. 5.6%, HR 0.47, 95% CI 0.32-0.68); ADH, ALH, and LCIS occurred in 0.2% in the anastrozole group and 0.5% in the placebo group, HR 0.36, 95% CI 0.11-1.12.

e) Risks: musculoskeletal events, arthralgias, carpal tunnel syndrome, joint stiffness, vasomotor symptoms, dry eyes, vaginal or uterine prolapse, vaginal dryness, vaginal pruritus, and hypertension were more common in the anastrozole group; fractures, cardiovascular events and deaths were not statistically different.

4) Aromatase inhibitors are not currently FDA-approved for this use, insurance may not cover.

5) NCCN currently lists AIs as a category 1 option for postmenopausal women desiring breast cancer risk reduction therapy but there are no data comparing the benefits and the risks of exemestane or anastrozole to those of tamoxifen and raloxifene.\textsuperscript{51}

i. Targeting ER-negative tumors (e.g., bisphosphonates, statins, metformin) currently being investigated.

j. NCCN Breast Cancer Risk Reduction Guidelines\textsuperscript{51}

1) Risk reduction therapy for women with history of LCIS, 5-year Gail risk ≥ 1.7%, >20% lifetime risk, pedigree suggestive of genetic predisposition, known genetic predisposition, prior thoracic radiotherapy < 30 years of age; life expectancy ≥ 10 years; and the woman desires risk reduction therapy.
2) Options for risk reduction include:
   a) Bilateral total mastectomy ± reconstruction
   b) Bilateral salpingo-oophorectomy (BSO) with peritoneal washings (pathologic assessment should include fine sectioning of ovaries and fallopian tubes).
   c) Risk reduction agent:
      i. Baseline gynecologic assessment (for women with intact uterus).
      ii. Baseline bone density evaluation (for postmenopausal women).
      iii. Premenopausal – clinical trial or tamoxifen.
   iv. Postmenopausal – clinical trial, tamoxifen, raloxifene, or AI.

3) NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian.\textsuperscript{6}
   a) Specifies more detailed criteria for consideration of risk reduction therapy and the type of therapy recommended based on the risk category (see guideline for details).
   k. Guidelines from ASCO\textsuperscript{52} and the USPSTF\textsuperscript{7} regarding the use of pharmacologic agents for breast cancer risk reduction are also available.

\begin{boxed-caption} Patient case #1 (continued): AC was counseled on the risks vs. benefits of a SERM or an AI therapy x 5 years. Since she is postmenopausal, tamoxifen, raloxifene, exemestane, and anastrozole are potential options for this patient. Based on the long-term data from the STAR trial showing superiority of tamoxifen compared to raloxifene in risk reduction of invasive breast cancer, she elected to take tamoxifen 20 mg daily x 5 years. Due to the risk of ovarian cancer (maternal aunt with ovarian cancer, multiple relatives with breast cancer), AC was also counseled about risk reduction options for ovarian cancer (oophorectomy). She was reluctant to pursue a surgical approach, but was offered genetic counseling with possible testing in order to further assess her risk of both breast and ovarian cancers. Her BRCAPRO risk was calculated at 35%, which lead to a recommendation for annual breast MRI to accompany her mammograms, clinical breast exams, and breast self-exams. \end{boxed-caption}

V. SIGNS & SYMPTOMS\textsuperscript{53}

A. Usually presents as a painless mass (solitary, unilateral, solid, hard, irregular, and nonmobile) – 90%. 
B. Stabbing or aching pain may be the first symptom – 10%.
C. Less commonly nipple discharge, retraction, or dimpling may be the first sign.
D. 80% of women first detect some abnormality themselves; detection via screening mammogram is becoming increasingly common due to increased acceptance and compliance with routine screening mammography. CBE is not often the primary source of detection, but is routine for verification when a suspicious area is felt by the patient or detected on screening mammography.
E. For lesions localized to the breast, referred to as early stage breast cancer (usually includes stage I and II).
F. For lesions that are larger, involve local lymph node basins or involve the skin or chest wall, referred to as locally advanced breast cancer (LABC).

G. Inflammatory breast cancer is a unique type of LABC (discussed later).

H. Approximately 10% of patients will present with signs and symptoms of distant metastatic disease; these patients generally have neglected a breast mass for months to years (result of delayed diagnosis).

I. Approximately 50% of patients initially diagnosed with non-metastatic breast cancer will later develop metastases despite multimodality therapy, usually within 3-5 years following potentially curative therapy.

VI. DIAGNOSIS & STAGING

A. Diagnosis

1. History and physical exam (including a thorough CBE), diagnostic mammogram (more detailed than screening), and possibly ultrasound (US) of breast and lymph node basins.

2. Biopsy required of an abnormality on mammogram that is suspicious or of a palpable breast mass.

   a. Biopsy of a palpable mass

      1) FNA – not able to distinguish invasive vs. noninvasive cancer; false negatives and insufficient specimens occur (4%-10% false negative rate); requires an experienced cytopathologist.

      2) Core-needle biopsy – can distinguish invasion and other important biologic markers can be determined from this tissue; false negatives and incomplete characterization of the tumor can occur (approximately 3% false negative rate).

      3) Excisional biopsy – more painful and not cosmetically acceptable in many cases; may require additional surgery if margins are positive.

   b. Biopsy of a mass detected only on mammogram – stereotactic, mammographically guided, core-needle biopsy should be performed.

   c. Biopsy of a mass detected by mammogram, but not felt might be detectable by ultrasound and biopsy can be performed under ultrasound guidance; ultrasound also allows for examination of lymph node basins.

3. All patients should have a CBC, liver function tests, diagnostic mammogram (US if needed), pathologic review, ER/PR/HER2 status, fertility counseling (if premenopausal), and genetic counseling if at high risk for hereditary breast cancer. Breast MRI is optional.  

4. For stage I-IIB: Other staging studies are based on signs or symptoms, and may include a bone scan, computed tomography (CT)/US/magnetic resonance imaging (MRI) of the abdomen, or chest CT. Positron emission tomography (PET)/CT scanning is not recommended for clinical stage I, II, or operable III breast cancer.

5. For stage IIA-C: Consider a chest CT, CT or MRI of the abdomen (with or without the pelvis), and bone scan or sodium fluoride PET/CT. PET/CT may be considered as an optional additional study for patient with stage III disease (category 2B recommendation).
Patient case #2: LG is a 45 y/o premenopausal African-American woman who presents to the clinic with a newly diagnosed left breast cancer found on screening mammogram, confirmed by ultrasound and core biopsy. The breast mass measured 2.1 x 1.5 cm and her axillary lymph nodes were negative by ultrasound examination. Core biopsy of the left breast mass indicates an invasive ductal carcinoma, nuclear grade 2 (moderately differentiated), ER = 85%, PR = 80%, HER2 IHC = 0, HER2 FISH = normal; Ki-67 = 20% (see Prognostic Factors section below for details on Ki-67). All other staging studies were negative for metastases. Based upon this information, list the treatment options for this woman.

B. Staging updated on January 1, 2010^{4th}

1. Most of the changes occurred in the classification of lymph nodes.
   a. Isolated tumor cells are defined as 0.2 mm or nonconfluent or nearly confluent clusters of < 200 cells in a single histological lymph node cross section.
   b. New classification system for patients after neoadjuvant therapy.
   c. New sub-stages have been designated for stage I (IA and IB); stage IB includes patients with T0 and T1 tumors and micrometastatic disease in the lymph nodes (N1mi).
   d. A new category has been created to define the presence of either disseminated tumor cells identified in bone marrow or circulating tumor cells or other tissues if not exceeding 0.2 mm (M0i+).
   e. All invasive breast cancers should be assigned a combined histological tumor grade using the Elston-Ellis modification of the Scarf-Bloom-Richardson grading system.
# TABLE 4: Breast Cancer Staging as of January 2010

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor (T)</strong></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>DCIS, LCIS or Paget’s disease of nipple</td>
</tr>
<tr>
<td>T1</td>
<td>≤ 2cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>&gt; 2cm but not &gt; 5cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 5cm in greatest dimension</td>
</tr>
<tr>
<td>T4</td>
<td>Any size with direct extension to chest wall or skin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical (N)</strong></td>
<td><strong>Pathologic (pN)</strong></td>
</tr>
<tr>
<td>N0</td>
<td>No metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in movable ipsilateral axillary LN(s)</td>
</tr>
<tr>
<td>N2</td>
<td>pN0 (i -) No mets H&amp;E, negative IHC</td>
</tr>
<tr>
<td>N2a</td>
<td>Mets in ipsilateral LN(s) fixed or matted</td>
</tr>
<tr>
<td>N2b</td>
<td>Mets in clinically detected&quot; ipsilateral IMC in the absence of axillary LN mets</td>
</tr>
<tr>
<td>N3</td>
<td>pN0 (i+) No mets H&amp;E, positive IHC, not &gt; 0.2mm</td>
</tr>
<tr>
<td>N3a</td>
<td>pN0 (mol-) No mets H&amp;E, negative molecular findings (RT-PCR)</td>
</tr>
<tr>
<td>N3b</td>
<td>pN0 (mol+) No mets H&amp;E, positive molecular findings (RT-PCR)</td>
</tr>
<tr>
<td>N3c</td>
<td>pN1mi Micromets ( &gt; 0.2 mm and/or more than 200 cells, none &gt; 2.0 mm)</td>
</tr>
<tr>
<td>N3a</td>
<td>pN1i Metasts in ipsilateral infraclavicular LN(s)</td>
</tr>
<tr>
<td>N3b</td>
<td>pN1a Metasts in 1-3 axillary LN(s)</td>
</tr>
<tr>
<td>N3c</td>
<td>pN1b IMC nodes with microscopic disease detected by SLND but not clinically detected¹</td>
</tr>
<tr>
<td></td>
<td>pN1c Metasts in 1-3 axillary LN(s) and IMC nodes with microscopic disease detected by SLND but not clinically detected¹</td>
</tr>
<tr>
<td>N3</td>
<td>pN2 Metasts in 4-9 LNs (at least one tumor deposit &gt; 2mm)</td>
</tr>
<tr>
<td></td>
<td>pN2a Metasts clinically detected IMC in the absence of axillary LN mets</td>
</tr>
<tr>
<td>N3</td>
<td>pN3 Metasts 10 or more LNs (at least one tumor deposit &gt; 2mm), or metastasis to the infraclavicular LN(s)</td>
</tr>
<tr>
<td></td>
<td>pN3a Metasts in clinically detected&quot; ipsilateral IMC in the presence of one of more positive axillary lymph nodes, or in more than 3 axillary lymph nodes and in IMC with microscopic disease detected by SLND, but not clinically detected¹</td>
</tr>
<tr>
<td></td>
<td>pN3b Metasts in clinically detected&quot; ipsilateral IMC in the presence of one of more positive axillary lymph nodes, or in more than 3 axillary lymph nodes and in IMC with microscopic disease detected by SLND, but not clinically detected¹</td>
</tr>
<tr>
<td></td>
<td>pN3c Metasts in ipsilateral SCLN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metastases (M)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No clinical or radiological evidence of distant metastases</td>
</tr>
<tr>
<td>cM0(1+)</td>
<td>No clinical or radiological evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells identified in blood, bone marrow, or other nonregional nodal tissues that are no larger than 0.2mm in a patient without symptoms or signs of metastases</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases as determined by classic clinical and radiological means and/or histologically proven larger than 0.2mm</td>
</tr>
</tbody>
</table>

¹"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle biopsy with cytologic examination. "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination. **Abbreviations:** M0 = metastases; LN(s) = lymph node(s); IMC = internal mammary chain lymph nodes; SCLN = supraclavicular lymph node(s); H&E = hematoxylin & eosin staining.
<table>
<thead>
<tr>
<th>Stage Grouping</th>
<th>TNM Classification</th>
<th>Stage Grouping</th>
<th>TNM Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
<td>IIB</td>
<td>T2, N1, M0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>T3, N0, M0</td>
</tr>
<tr>
<td>IA</td>
<td>T1*, N0, M0</td>
<td>IIA</td>
<td>T0-3, N2, M0</td>
</tr>
<tr>
<td>IB</td>
<td>T0, N1mi, M0</td>
<td>IIIB</td>
<td>T3, N1-2, M0</td>
</tr>
<tr>
<td></td>
<td>T1*, N1mi, M0</td>
<td></td>
<td>T4, N0-2, M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T0-1, N1**, M0</td>
<td>IIIC</td>
<td>Any T, N3, M0</td>
</tr>
<tr>
<td></td>
<td>T2, N0, M0</td>
<td>IV</td>
<td>Any T, Any N, M1</td>
</tr>
</tbody>
</table>

*Includes T1mi.
**T0 and T1 tumors with nodal micrometastasis only are excluded from Stage IIA and are classified as Stage IB.


C. Prognostic factors other than staging

1. Response to primary therapy and stage of disease after primary therapy
   a. Primary resistance to systemic chemotherapy is a very poor prognostic indicator.
   b. Pathologic complete response (pCR, defined as absence of tumor in pathologic specimen of breast tissue and/or lymph node tissue) after primary chemotherapy is associated with a better relapse-free survival compared to patients with less than a pCR.55

2. Chemotherapy-induced amenorrhea (premenopausal women)
   a. May be an indicator of drug toxicity and therefore enhanced clinical benefit.
   b. Similar benefit (including improved survival in one study) regardless of ER/PR status.56

3. Estrogen and/or progesterone receptor status
   a. ER positive tumors are generally less aggressive than ER negative tumors.
   b. Also true for progesterone receptors.
   c. Not an independent prognostic factor in the absence of endocrine therapy.
   d. Predicts response to endocrine therapy.

4. Histologic/nuclear grade - grade 1 (well differentiated); grade 2 (moderately differentiated); grade 3 (poorly differentiated). Poorly differentiated tumors generally have a worse prognosis.

5. Proliferative markers - faster growing, more aggressive, but might be more responsive to chemotherapy (e.g., Ki-67, mitotic index).

6. Lymphatic/vascular invasion - indicative of spread to other structures within the breast; generally an unfavorable prognostic factor.

7. Ploidy - aneuploid tumors are a poor prognostic factor.

8. Diabetes - has been associated with reduced survival in some studies.

9. Obesity and BMI - poorer outcomes in obese women regardless of menopausal status, although not all studies support this correlation.57

10. HER2 amplification/overexpression
a. More aggressive tumors (in both node positive and negative patients).

b. Thought to be poor prognostic factor, however, patients with HER2-overexpressed metastatic breast cancer (MBC) treated with first-line trastuzumab had improved one-year survival rates compared to patients with HER2-normal MBC as well as patients with HER2-overexpressed MBC who did not receive trastuzumab.58

c. Predicts response to HER2-directed therapy (trastuzumab and lapatinib, pertuzumab, ado-trastuzumab emtansine).

Patient case #2: LG is staged as a T2, N0, M0, ER/PR positive and HER2 normal, with a moderate growth fraction (Ki-67) and a moderate histologic grade. No other pathologic features were mentioned. She has Stage II disease and has several good prognostic features (ER/PR+, HER2 normal). She would like to avoid chemotherapy if possible. Are there any other tests you would like to have in order to make decisions regarding her systemic adjuvant therapy?

11. Other prognostic tools

a. **Adjuvant!**59

   1) Decision tool for adjuvant chemotherapy; independently validated.60
   2) Estimates 10-year risk of cancer-related mortality or relapse without systemic adjuvant therapy.
   3) Estimates the risk reduction with adjuvant therapy.
   4) Estimates the risk from therapy.
   5) Limitations: prognostic factors are not all-inclusive (HER2 status not included); limitations of the databases as references; small tumors not well characterized to make general decisions (e.g., T1 not separated into ≤ 0.5cm, 0.6-1cm and 1-2 cm).
   6) Good graphics to explain to patients risks and benefits; continually updated with new information from clinical trials.

b. **Oncotype DX**

   1) Commercially available multigene test – screens for expression of 21 genes, resulting in a recurrence score.
   2) Has been validated with tamoxifen and anastrozole.
   3) Can be used to determine risk of recurrence or death from breast cancer in women with HR-positive, HER2 normal, node-negative, invasive breast cancer (Recurrence Score).

   a) A low recurrence score (< 18) indicates a low risk of recurrence with endocrine therapy alone (tamoxifen was the treatment in the validation study), indicating that perhaps adjuvant chemotherapy could be avoided.
   b) A high recurrence score (≥ 31) would indicate a high risk of recurrence despite endocrine therapy, indicating a need for adjuvant chemotherapy followed by endocrine therapy.
   c) When an intermediate score (18-30) is obtained, it is difficult to determine the value of additional therapy. This intermediate group is the focus of an ongoing clinical trial.
(TAILORx) where patients with RS of 11-25 are randomized to endocrine therapy alone vs. chemotherapy followed by endocrine therapy. The trial has completed accrual but results are not yet available.

4) Recurrence score by Oncotype DX has also been shown to correlate with risk of locoregional recurrence.  

5) The Oncotype DX assay has been validated in multiple clinical trials.

   a) The validation set for the NSABP B14 study included 668 women with ER+, lymph node-negative early stage breast cancer treated with adjuvant tamoxifen for 5 years.  
      i. Results showed a significant difference in distant recurrence at 10 years in the 3 groups (see TABLE 6).

   b) The validation set for the NSABP B20 study included 227 women with ER+, lymph node-negative early stage breast cancer treated with adjuvant tamoxifen for 5 years versus 424 patients treated with tamoxifen and chemotherapy (CMF or MF).  
      i. Results showed:
         1. A significant benefit with chemotherapy in the high-risk group (TABLE 6).
         2. Unclear benefit of chemotherapy in the intermediate risk group (TABLE 6).
         3. No benefit of chemotherapy in the low risk group (TABLE 6).

6) Use of Oncotype DX can identify a group of patients with lymph node positive breast cancer who may derive little benefit from anthracycline-based chemotherapy.

   a) Oncotype DX is controversial in patients with lymph node positive breast cancer; this patient population is the focus of an ongoing clinical trial (RxPONDER) where patients with one to three positive lymph nodes and an RS of 25 or less are randomized to endocrine therapy alone vs. chemotherapy followed by endocrine therapy.

<table>
<thead>
<tr>
<th></th>
<th>NSABP B14&lt;sup&gt;62&lt;/sup&gt;</th>
<th>NSABP B20&lt;sup&gt;63&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low risk (RS &lt;18)</strong></td>
<td>93.2%</td>
<td>96.8%</td>
</tr>
<tr>
<td><strong>Int risk (RS 18-30)</strong></td>
<td>85.7%</td>
<td>90.9%</td>
</tr>
<tr>
<td><strong>High risk (RS ≥31)</strong></td>
<td>69.5%</td>
<td>60.5%</td>
</tr>
</tbody>
</table>
c. **Mammaprint**
   1) Commercially available multigene test – screens for expression of 70 genes, resulting in either a good prognosis or a poor prognosis classification.
   2) More reliable than other standard systems with clinical and histological markers.
   3) Consecutive patients were enrolled (pT1-2, both node-negative and node-positive, and 52 years of age or younger) and were not selected based on treatment.\(^{65}\)
   4) Might be useful in determining risk of recurrence when deciding on adjuvant systemic therapy.
   5) Initially required the use of fresh frozen tissue, but use on paraffin-embedded tissue was made available in 2012.
   6) Currently being prospectively compared with Adjuvant! (MINDACT trial).

d. **PAM50 (Prosigna\textsuperscript{TM})**
   1) Commercially available multigene test – screens for expression of 50 genes (+ 5 control genes).
   2) Identifies intrinsic breast cancer subtypes (luminal A/B, HER2 enriched, basal-like).
   3) Predicts distant relapse-free survival and likelihood of recurrence at 10 years in ER+ postmenopausal patients with node-negative or node-positive breast cancer treated with endocrine therapy.
   4) Will be evaluated against Oncotype DX in the RxPONDER trial.

12. An excellent review of multigene tests is available.\(^{66}\)

13. Others (most not currently recommended by ASCO for use as prognostic markers) - circulating tumor cells (CTCs), p53, urokinase plasminogen activator (uPA), plasminogen activator inhibitor (PAI-1), cathepsin D, cyclin E, proteomic analysis, multiparameter gene expression analysis.\(^{67}\)

D. Sites of metastases

1. Most common sites are bone, liver, lung, brain, and distant lymph nodes and/or skin.

2. Tumor markers – used in conjunction with diagnostic imaging, history and physical examination for monitoring patients with metastatic disease during active therapy.
   a. **CEA** - commercially available; positive predictive value 66%; negative predictive value 84%; sensitivity 45%; specificity 81%-96%; normal: < 3 ng/ml (nonsmokers) or < 6 ng/ml (smokers).
   b. **CA 27-29** - Truquant BR\textsuperscript{®}; commercially available; positive predictive value 67-83%; negative predictive value 88-93%; sensitivity 58-62%; specificity 90-98%; normal < 32-47 U/ml.
   c. **CA 15-3** - commercially available; positive predictive value 85%; negative predictive value 88%; sensitivity 57-64%; specificity 87-97%; normal < 32-38 U/ml.
   d. Both CA 27.29 and CA 15-3 measure similar mucinous proteins (MUC1 antigen).
e. Not recommended for routine surveillance with early stage breast cancer in an otherwise asymptomatic patient with no specific findings on physical exam (see Survivorship section). 68

**Patient case #2:** Her Oncotype DX Recurrence Score was 12. What locoregional and systemic adjuvant therapy, if any, would be appropriate to recommend for this woman?

### VII. TREATMENT

#### A. Pure Noninvasive Breast Cancers 32

1. **LCIS**
   
   a. Surgical resection (either initially or after core needle biopsy) to rule out DCIS or invasive cancer (although still somewhat controversial).
   
   b. After surgery, options include:
      
      1) Observation - risk of developing invasive cancer is low – 21% over 15 years.
      
      2) Consider risk reduction with:
         
         a) Tamoxifen for premenopausal women.
         
         b) Tamoxifen, raloxifene, or AI for postmenopausal women.
      
      3) Consider bilateral mastectomies ± reconstruction (risk is equal in both breasts) for risk reduction in special circumstances.
         
         a) If patient has bilateral mastectomies, then there is no reason to use tamoxifen/raloxifene/exemestane for risk reduction (no breast tissue remaining to protect).

2. **DCIS**
   
   a. Local management
      
      1) Lumpectomy + radiation therapy **OR**
      
      2) Total mastectomy ± reconstruction **OR**
      
      3) Lumpectomy without radiation
         
         a) After lumpectomy, radiation reduces recurrence rates of DCIS by about 50%69; half of recurrences are invasive and half are DCIS; no survival difference between the 3 approaches.

   b. Axillary lymph node dissection is **NOT** recommended for patients with pure DCIS. Strongly consider a sentinel lymph node biopsy (SNB) in patients treated with mastectomy or excision in an anatomic location compromising the completion of a future SNB procedure.

   c. Tamoxifen
      
      1) For patients with DCIS (especially ER+) following breast conserving surgery, consider tamoxifen for 5 years to decrease risk of ipsilateral recurrence for:
         
         a) Patients treated with breast conserving surgery + XRT.
         
         b) Patients treated with breast conserving surgery alone.
i. **NSABP B24**

(a) Tamoxifen x 5 years after breast conserving surgery + XRT demonstrated an absolute risk reduction of 5% and a relative risk reduction of 37%.\(^{70}\)

(b) Retrospective analysis of this trial found that the benefit of tamoxifen is limited to ER-positive DCIS (decrease in any breast cancer event compared to placebo HR 0.58, \(p = 0.001\))\(^{71}\)

(c) Further follow-up showed a 15-year cumulative risk of invasive ipsilateral breast cancer was 10% for XRT + placebo and 8.5% for XRT + tamoxifen (HR 0.68; 95%CI 0.49-0.95, \(p=0.025\))\(^{72}\)

ii. Results from the United Kingdom/ANZ DCIS trial also support the use of adjuvant tamoxifen in this population\(^{73}\)

2) Consider for risk reduction in women treated with total mastectomy (decrease development of contralateral second primary breast cancers).

   d. AIs being compared to tamoxifen for DCIS in postmenopausal women (anastrozole vs. tamoxifen for 5 years in NSABP B35).

B. Stage IA, IB, IIA, IIB Invasive Breast Cancers (Early Stage) or T3 N1 M0\(^{32}\)

1. **Goals of therapy:** CURE

   a. In clinical trials, rates of cure determined by comparisons of DFS and OS.

   b. In individual patients, determined by long-term survival without recurrence; patient lives a normal life span and dies of unrelated cause. No way to prospectively predict who will recur and who will not.
2. **Summary** - Most patients are eligible for primary surgery ± radiation therapy. However, some patients who otherwise are candidates for breast conserving surgery except for the size of the tumor (in relationship to the size of the breast) may be better served with neoadjuvant/preoperative chemotherapy to attempt to shrink the tumor and possibly allow for breast conserving surgery.

3. **Locoregional therapy (surgery ± radiation therapy)**
   a. Total mastectomy + surgical axillary staging (if w/ axillary lymph node dissection, then called modified radical mastectomy) ± reconstruction OR
   b. Breast conserving surgery (segmental mastectomy, lumpectomy, etc.) + surgical axillary staging + XRT
   1) Meta-analysis of 10,801 patients in 17 RCT of radiotherapy vs. no radiotherapy after breast conserving surgery showed a reduction in the 10-year risk of first recurrence by 15.7% (95%CI 13.7-17.7, 2p<0.00001) and the 15-year risk of breast cancer death by 3.8% (95%CI 1.6-6.0, 2p<0.00005) favoring radiation.74
2) Contraindications include:
   a) Absolute
      i. Radiation prohibited during pregnancy.
      ii. Diffuse suspicious or malignant appearing microcalcifications on mammography.
      iii. Widespread disease that cannot be incorporated by local excision through a single incision that achieves negative margins with a satisfactory cosmetic result.
      iv. Positive pathologic margin.
   b) Relative
      i. Prior radiation therapy to chest wall or breast.
      ii. Active connective tissue disease involving the skin (especially scleroderma and lupus).
      iii. Tumors > 5 cm.
      iv. Focally positive margin.
      v. Women with a known or suspected genetic predisposition to breast cancer.

3) Candidates for this procedure include:
   a) Willingness to undergo radiation therapy.
   b) Appropriate breast-to-tumor ratio (in terms of size) allowing for a good cosmetic result.

4) Plans for reconstruction need to be considered and taken into account when planning the initial surgical approach to therapy.

c. Breast conserving surgery has a slightly higher rate of locoregional recurrences, but does not appear to effect survival (see TABLE 7).

### TABLE 7: Modified Radical Mastectomy Compared with Conservative Surgery plus Radiation Therapy

<table>
<thead>
<tr>
<th></th>
<th>Mastectomy (n=1994)</th>
<th>BCS + XRT (n=2067)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional recurrence</td>
<td>193</td>
<td>298</td>
<td>1.561 (1.289-1.890)</td>
</tr>
<tr>
<td>(number of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>730</td>
<td>793</td>
<td>1.070 (0.935-1.224)</td>
</tr>
<tr>
<td>(number of deaths)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BCS = breast conservative surgery (segmental mastectomy); XRT = radiotherapy.

Data from Jatoi I and Proschan MA. Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: a pooled analysis of updated results.75

32 Surgical Axillary Staging

1) Axillary lymph node dissection (ALND) – level I & II pathologic examination
   a) Required if:
      i. Clinically node positive at diagnosis (pathologically confirmed w/ FNA) OR
i. Sentinel node positive or not identified.

b) In the absence of definitive data demonstrating superior survival from ALND, patients with favorable tumors, those for whom adjuvant systemic therapy is unlikely to be affected, for the elderly, or those with serious comorbid conditions, ALND may be considered optional.

2) Lymphatic mapping with sentinel lymph node biopsy (SLNB) preferred

a) Can be performed prior to or after neoadjuvant chemotherapy

b) Candidates for this procedure meet all of the following criteria:
   i. Experienced sentinel lymph node team available
   ii. Clinically negative lymph nodes OR negative FNA/core biopsy of clinically suspicious lymph nodes.

c) Data from a single randomized trial (n=891) suggests that completing an ALND following SLNB in women with clinically node negative T1-T2 tumors, fewer than 3 involved SLN, and undergoing BCS with XRT who did not receive neoadjuvant chemotherapy results in higher morbidity, no improvement in local recurrence, and no difference in DFS or OS with SLNB alone.76

   i. Therefore, patients who meet all of these criteria are recommended to consider no further axillary surgery even if 2 sentinel lymph nodes are found to be positive.32

d) Guidelines for SNB are also available from ASCO77

d. Reconstruction

1) Implants (immediate reconstruction preferred if radiation indicated)
   a) Saline – utilized with an expander system; complications of encapsulation.
   b) Silicone – approved by FDA in November 2006; two companies (Allergan and Mentor).
   c) Cohesive gel implants – conform to chest wall contour.
   d) Dual chamber saline/silicone gel-filled implants – allow for expansion without need for two-step procedure.

2) Autologous tissue flaps (delayed until after radiation preferred)
   a) Latissimus dorsi myocutaneous flaps - often used for wound closure; can be used with an implant.
   b) Transrectus abdominus myocutaneous (TRAM) flap - uses stomach muscle to form breast mound; “tummy tuck” with breast reconstruction.
   c) Gluteal flaps - obvious deformity of the buttocks; not as desirable cosmetic effect.
3) Decision is based on patient preference, body habitus, smoking history, comorbidities, plans for radiation, and expertise of reconstruction team.

e. Radiation therapy after mastectomy

1) Required in patients with:
   a) 4 or more positive axillary lymph nodes.

2) Strongly consider in patients with:
   a) 1-3 positive axillary lymph nodes.
   b) Conflicting category 1 evidence; controversial inclusion in NCCN.32

3) Consider for patients with:
   a) Primary tumors > 5 cm and negative axillary LN.
   b) Positive surgical margins and negative axillary LN.
   c) Tumors 5 cm or smaller, close surgical margins, and negative axillary LN.

4) Not recommended for patients with:
   a) Negative axillary lymph nodes AND
   b) Tumors 5cm or smaller AND
   c) Negative margins.

Patient case #2 (continued): LG would be a candidate for primary surgery. Depending on the size of the breast compared to the size of the tumor and the patient’s wishes, she may be a candidate for breast conserving surgery with radiation therapy. If she were to have a lumpectomy, lymphatic mapping with sentinel lymph node biopsy would be the most appropriate option. Radiation therapy would be required with a lumpectomy. If this patient underwent a mastectomy, post-mastectomy radiation would only be considered if she were to have positive lymph nodes or close or positive surgical margins. What about systemic therapies?

4. Neoadjuvant (preoperative) chemotherapy for large stage IIA & IIB tumors
   a. Patients otherwise fulfill requirements for breast conserving surgery except for tumor size.
   b. Primary systemic therapy may allow for breast conserving surgery.
      1) Chemotherapy is the gold standard; hormone therapy can be considered in HR-positive, postmenopausal women; trastuzumab-containing regimen should be considered for HER2-positive patients.
      2) NSABP B18 – breast conservation rates higher after neoadjuvant chemo (AC x 4); but survival no different versus adjuvant chemotherapy (AC x 4).35
      3) If respond to neoadjuvant chemotherapy, then go on to breast conserving surgery followed by XRT.
      4) See Stage III section for further information.

5. Systemic adjuvant therapy for early stage breast cancer (Stage IA, IB, IIA, IIB)
   a. Goal of therapy is to CURE the patient, prevent recurrences and eradicate micrometastatic disease.
b. Appropriate therapies: endocrine therapy, chemotherapy, and biologic therapy (trastuzumab/pertuzumab).

FIGURE 2: Systemic Adjuvant Therapy for Node-Negative, HR-Positive Breast Cancer

Abbreviations: T = tumor; diff = differentiated; HER2 = human epidermal growth factor receptor-2.

- Treatment should be individualized for patients > 70 years based on the presence or absence of comorbid conditions.
- Adjuvant chemotherapy and endocrine therapy should be given sequentially with chemotherapy preceding endocrine therapy.
- This is a population of breast cancer patients that was not studied in the available randomized trials. The decision to use trastuzumab must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain absolute benefits that may exist with trastuzumab therapy.
FIGURE 3: Systemic Adjuvant Therapy for Node-Negative, HR-Negative Breast Cancer

Abbreviations:  
T = tumor; diff = differentiated; HER2 = human epidermal growth factor receptor-2.

a Treatment should be individualized for patients > 70 years based on the presence or absence of comorbid conditions.
b This is a population of breast cancer patients that was not studied in the available randomized trials. The decision to use trastuzumab must balance the known toxicities of trastuzumab, such as cardiac toxicity, and the uncertain absolute benefits that may exist with trastuzumab therapy.

FIGURE 4: Systemic Adjuvant Therapy for Node-Positive Breast Cancer

Abbreviations:  
T = tumor; diff = differentiated; HR = hormone receptors; HER2 = human epidermal growth factor receptor-2.

a Treatment should be individualized for patients > 70 years based on the presence or absence of comorbid conditions.
b Adjuvant chemotherapy and endocrine therapy should be given sequentially with chemotherapy preceding endocrine therapy.
Patient case #2 (continued): LG underwent a segmental mastectomy with sentinel lymph node mapping with biopsy (T = 2.0 cm with clear margins, 3 sentinel lymph nodes identified and all were negative). What systemic therapy, if any, would be recommended (according to the NCCN guidelines v3.2014)?

c. Endocrine therapy

1) Determination of ER and PR positivity- ASCO/CAP Recommendations for Testing of Estrogen and Progesterone Receptors in Breast Cancer\textsuperscript{78}
   a) ER and PR status should be determined on all newly diagnosed invasive breast cancers and breast cancer recurrences.
   b) ER and PR status should be determined by IHC (equivalent or superior to ligand binding assays).
   c) The Panel recommended considering endocrine therapy in patients whose breast tumors show at least 1% ER+ and/or PR+ cells and withholding endocrine therapy if less than 1%.
   d) Data suggests that patients with higher hormone receptor levels will have a higher probability of positive outcomes with endocrine therapies (overall survival, disease-free survival, etc.).
   e) Reasonable considering the mild toxicity profile of endocrine agents, should consider the risks and benefits of endocrine therapy for each patient.

2) Definition of menopause:
   a) Prior bilateral oophorectomy.
   b) Age ≥ 60 years.
   c) Age < 60 years and amenorrheic for ≥ 12 months in the absence of chemotherapy, tamoxifen, toremifene, or LHRH agonist and FSH and plasma estradiol levels in postmenopausal range.
   d) If taking tamoxifen or toremifene and age < 60 years, then FSH and plasma estradiol levels should be in postmenopausal range.
   e) It is not possible to assign menopausal status to women receiving an LHRH agonist.
   f) In women premenopausal at the time of neo/adjuvant chemotherapy, amenorrhea is not a reliable indicator of menopausal status.

3) Endocrine therapy given concurrently during chemotherapy has been shown to decrease DFS\textsuperscript{79}

4) The most recent meta-analysis of adjuvant tamoxifen found that the proportional risk reduction of tamoxifen was independent of the timing of chemotherapy (concurrent vs. sequential), but these trials were not randomized to investigate the timing of chemotherapy and tamoxifen administration\textsuperscript{80}
5) Chemotherapy is typically given first and then endocrine therapy, sequentially.32

6) Premenopausal women
   a) Tamoxifen for 5 years with or without ovarian ablation/suppression (OAS)
      i. EBCTCG overview analysis 2011 indicates a substantial benefit in ER positive disease (all patients regardless of age or menopausal status).80 See TABLE 8.
      ii. Ongoing clinical trials investigating the addition of OAS to tamoxifen or an AI. Preliminary data is available from ABCSG-12 and a combined analysis of the SOFT and TEXT trials (see ovarian ablation or suppression section). May consider OAS if patient not amenorrheic after chemotherapy.
   b) After 5 years
      i. If patient remains premenopausal, consider an additional 5 years of tamoxifen or no further therapy.32 ASCO guidelines state that women who remain premenopausal or perimenopausal should be offered an additional 5 years of tamoxifen.81
         (a) Conflicting data exists regarding the benefit of tamoxifen therapy for greater than 5 years. Three trials have evaluated 10 years of tamoxifen compared to five years
         (b) NSABP B14 showed no benefit of tamoxifen beyond 5 years82
         (c) Patients in the ATLAS trial (n=6846 ER+ breast cancer patients) had a decreased risk of recurrence (RR 0.84; CI 0.76-0.94) and improved survival (639 vs 722 deaths, p=0.01) with 10 years of tamoxifen, but had an increased risk of endometrial cancer (HR 1.74; CI 1.30-2.34) and pulmonary embolism (HR 1.87; CI 1.13-3.07) compared to patients who took tamoxifen for 5 years (12,894 patients evaluated for toxicity)83
         (d) Patients in the aTTom trial had a decreased risk of recurrence (580 vs 672, p=0.003), but not breast cancer mortality (404 vs 456, p=0.06) with 10 years of tamoxifen, and had an increased risk of endometrial cancer (RR 2.20; CI 1.31-2.34) and death from endometrial cancer (RR 1.1% vs. 0.6%; p=0.0284
      ii. If patient becomes postmenopausal, then an AI or tamoxifen for an additional 5 years can be considered.
7) Postmenopausal women
   a) AI for 5 years
   b) Tamoxifen for 2-3 years followed by AI to complete 5 years or up to 5 years of an AI
      i. Although included in the NCCN guidelines as an option, use of an AI for longer than a total of 5 yrs after tamoxifen for 2-3 years is not supported by data from randomized clinical trials.
   c) AI for 2-3 years followed by tamoxifen to complete 5 years
   d) Tamoxifen for 4.5-6 years followed by an AI for an additional 5 years.
   e) Tamoxifen for 4.5-6 years followed by tamoxifen for an additional 5 years.
   f) Women with contraindication to AIs, who decline AIs or who are intolerant of the AIs, tamoxifen for 5 or 10 years.

8) Tamoxifen (pre- and postmenopausal women)
   a) Historically very effective in reducing the odds of recurrence and death.
      i. Meta-analysis of 21,457 patients from 20 RCT of 5 years of tamoxifen vs. none (See TABLE 8.)
      ii. Reduction in odds of recurrence ≈ 40%
      iii. Reduction in odds of death ≈ 25%.
      iv. Reduction in incidence of contralateral breast cancer ≈ 40%.
      v. There was substantial benefit with tamoxifen even in patients with weakly ER positive tumors (10-19 fmol/mg).
      vi. In patients with ER positive tumors, the effect of tamoxifen was independent of PR status or level, age, nodal status, or use of chemotherapy.
   b) Combination data indicate:
      i. Premenopausal: LHRH agonists + tamoxifen not significantly better than either treatment modality alone
      ii. Postmenopausal: Anastrozole + tamoxifen no better than tamoxifen alone.
      iii. Pre- or postmenopausal: Chemotherapy then tamoxifen appears to be better than chemotherapy alone.
   c) Serious complications: endometrial cancer [38% increase; primarily in ≥ 50 y/o (per P1 trial); prognosis may be good, but controversial], thromboembolic events (2-3 fold increase; primarily in ≥ 50 y/o; treatable problem), uterine sarcomas
(rare events, but increased incidence; more aggressive form of endometrial cancer; poor prognosis).

d) Other complications: hot flashes, vaginal discharge, irregular menses (premenopausal), increased risk of cataracts.

e) Beneficial effects: may prevent bone loss (postmenopausal); lowers total cholesterol (may decrease overall cardiovascular mortality?).

f) CYP2D6 testing: tamoxifen is metabolized through multiple enzymes including CYP3A4, CYP2C19, CYP2D6, and others to metabolites which appear to be more active than the parent compound (endoxifen and 4-hydroxytamoxifen).

i. It has been hypothesized that polymorphisms in the CYP2D6 enzyme can lead to increased or decreased formation of endoxifen and may be related to improved or diminished clinical outcomes, respectively.

ii. Retrospective data in regards to worsened outcomes with specific CYP2D6 polymorphisms are contradictory86, and current NCCN breast cancer guidelines recommend against routine CYP2D6 testing for patient receiving tamoxifen.32

iii. See Treatment of Hot Flashes section for details on potential drug interactions with CYP2D6 inhibitors.

TABLE 8: Historical Impact of Adjuvant Tamoxifen for Breast Cancer (about 5 years of tamoxifen)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient Group</th>
<th>No. of Randomized Trials</th>
<th>No. of Patients Randomized</th>
<th>Reduction in Annual Odds of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence (%)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>All</td>
<td>20</td>
<td>21,457</td>
<td>28±2</td>
</tr>
<tr>
<td></td>
<td>ER positive</td>
<td></td>
<td></td>
<td>38±3</td>
</tr>
<tr>
<td></td>
<td>ER negative</td>
<td></td>
<td></td>
<td>3±5</td>
</tr>
<tr>
<td></td>
<td>ER unknown</td>
<td></td>
<td></td>
<td>30±6</td>
</tr>
</tbody>
</table>

Abbreviations: No. = number.

Data from: Early Breast Cancer Trialists’ Collaborative Group (EBCTCG)80

9) Ovarian ablation or suppression (premenopausal women)

a) Meta-analysis demonstrated benefit with ovarian ablation or suppression compared to control patients (See TABLE 9).87

i. Included women less than 50 y/o (2% postmenopausal, 98% premenopausal) (ER positive or unknown).

ii. Ovarian ablation by surgical or radiotherapeutic means.

iii. Ovarian suppression with LHRH agonists; included primarily goserelin (one trial with triptorelin).

iv. Reduction in odds of recurrence ≈ 17%.

v. Reduction in odds of death ≈ 13%.
b) Updated information from EBCTCG with LHRH agonists included 16 trials with 11906 women with HR-positive tumors only; goserelin (n=13), triptorelin (n=2), leuprolide (n=1); chemotherapy mostly CMF, no taxanes; most LHRH agonists given for 2 years, but some 18 months, 3 years or 5 years.

c) Broadly support results of previous analyses, but also demonstrate:

i. Benefit of LHRH agonists after chemotherapy in women < 40 y/o, but not in older premenopausal women.

ii. Equivalence of LHRH agonist with chemotherapy in HR-positive cancers, but not in HR-negative cancers.

iii. Brings to light importance of side effect profiles in choosing which type of treatment to offer; still concerned with long-term toxicities (e.g., osteoporosis, cardiovascular disease, etc.).

iv. Chemotherapy regimens typically not those used in contemporary medicine in the US.

v. Also, does not address the use of complete estrogen blockade (LHRH agonist + AI).

d) Ovarian suppression in combination with tamoxifen

i. Tamoxifen alone or combined with ovarian suppression (included use of goserelin, leuprolide, oophorectomy, or ovarian irradiation)

ii. Enrolled patients had negative lymph nodes after surgery and did not receive chemotherapy.

iii. The trial was stopped early due to slow accrual

iv. DFS and OS were similar between the two groups

v. Rates of grade 3 or higher toxicities were higher in patients who received tamoxifen and ovarian suppression compared to patients who received tamoxifen alone (22.4% vs 12.3%, p=0.004).

vi. Tamoxifen alone is recommended in premenopausal women by ASCO

e) Ovarian suppression in combination with AIs

i. ABCSG 12- Ovarian suppression with goserelin and anastrozole or tamoxifen +/- zoledronic acid for 3 years.

ii. At a median of 62 months of follow-up, DFS was not significantly changed between endocrine therapies (HR = 1.08, p=0.591).

iii. However, in a retrospective analysis of patients with disease recurrence, the relative risk of death was significantly higher in the anastrozole group than the tamoxifen group (HR 2.0, 95% CI 1.23-3.24, p=0.005).
iv. Ovarian suppression with triptorelin, oophorectomy, or ovarian radiation and tamoxifen or exemestane for 5 years was evaluated in a combined analysis of the SOFT and TEXT trials.\textsuperscript{90}

v. At 68 mo of median follow-up, 5 year DFS was 91.1% with exemestane/OS and 87.3% with tamoxifen/OS (HR 0.72, 95% CI 0.6-0.85, p<0.001); OS was not significantly different.

vi. Fractures, musculoskeletal symptoms, vaginal dryness, decreased libido, and dyspareunia were more frequent with exemestane/OS and thromboembolic events, hot flushes, sweating, and urinary incontinence were more common with tamoxifen/OS.

f) Ovarian suppression in combination with an AI is not currently included as an option for premenopausal women in the NCCN\textsuperscript{32} or ASCO\textsuperscript{81} guidelines.

g) See Bisphosphonate section for further details regarding zoledronic acid results.

h) Ongoing trials addressing many questions (SOFT, TEXT, PERCHE, PROMISE).

### TABLE 9: Historical Impact of Adjuvant Ovarian Ablation/Suppression for Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient Group**</th>
<th>No. of Randomized Trials</th>
<th>No. of Patients Randomized</th>
<th>Reduction in Annual Odds of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Recurrence (%)</td>
</tr>
<tr>
<td>Ovarian ablation</td>
<td>&lt; 50 y/o</td>
<td>21</td>
<td>11,313</td>
<td>17±4</td>
</tr>
</tbody>
</table>

**Abbreviations:**

- y/o = years old; No. = number.
- * Ovarian ablation by surgery or irradiation; ovarian suppression with LHRHI (goserelin or triptorelin).
- ** Patients included in these clinical trials were not selected based on hormone-receptor status.
- Data from: Early Breast Cancer Trialists' Collaborative Group (EBCTCG).\textsuperscript{85}

### 10) Aromatase Inhibitors (postmenopausal women)

a) First-line adjuvant therapy compared with tamoxifen

i. Anastrozole – approved for adjuvant therapy for early stage breast cancer (1 mg daily for 5 years); superior to tamoxifen (ATAC trial).

ii. Letrozole – approved for adjuvant therapy for early stage breast cancer (2.5 mg daily for 5 years); superior to tamoxifen (BIG 1-98 trial).

iii. Exemestane – The TEAM trial evaluated tamoxifen (5 years) vs. exemestane (5 years). DFS not significantly different between the two arms, although results numerically favor exemestane (HR 0.89; 2.75 years of follow-up).

iv. Meta-analysis of AI x 5 years vs. tamoxifen x 5 years.\textsuperscript{91}
(a) Included data from ATAC and BIG 1-98 studies (n=9,856).

(b) Absolute decrease in breast cancer recurrence at 5 yrs (9.6% vs. 12.6%) and 8 yrs (15.3% vs. 19.2%) favoring the AI group.

v. Randomized phase III trial comparing anastrozole x 5 years vs. exemestane x 5 years for postmenopausal patients with ER+ ESBC (n=7576).92

(a) After a median follow-up of 4.1 years, estimated event-free survival (primary endpoint, 91.2% vs. 91%, HR 1.02; 95% CI 0.87-1.18) and overall survival not significantly different (HR 0.93; 95% CI 0.77-1.13).

(b) Exemestane is a reasonable option for initial AI therapy.

b) Second-line adjuvant therapy after 2-3 years of tamoxifen (switching strategy)

i. Anastrozole (three trials to date) – 1 mg daily to complete 5 years of adjuvant endocrine therapy; superior to tamoxifen alone for 5 years.

ii. Exemestane (IES trial) – 25 mg daily to complete 5 years of adjuvant endocrine therapy; superior to tamoxifen alone for 5 years.93

iii. In BIG 1-98, sequential treatment with letrozole and tamoxifen (Tam → Let and Let → Tam) were compared with letrozole for 5 years. With 8.1 years of median follow-up, the sequential arms did not significantly decrease the risk of a DFS event compared to letrozole alone in either comparison.94

iv. In an evaluation of TEAM trial after results of the IES study were made available, there was no difference in 5 year DFS with sequential tamoxifen x 2.5-3 yrs → exemestane to complete 5 yrs of treatment compared to exemestane x 5 years (HR 0.97, 5.1 years of follow-up).95

v. Meta-analysis of Tam→AI for total of 5 years vs. Tam x 5 years.91

(a) Included data from ARNO 95, IES, ITA, and ABCSG VIII studies (n=9,015).

(b) Absolute decrease in breast cancer recurrence at 3 years (5.0% vs. 8.1%) and 6 years (12.6% vs. 16.0%) after switching favoring the AI group.
c) **Second adjuvant therapy after 5 years of tamoxifen (extended strategy)**

i. Letrozole (MA-17 trial) – 2.5 mg daily for another 5 years superior to placebo; duration of therapy unclear at this time, but patients on the trial stopped after 5 years of therapy; original randomization occurred within 3 months of completion of 5 years of tamoxifen; after adjustment for treatment crossover, DFS (HR 0.52; 95% CI 0.45-0.61) and OS (HR 0.61; 95% CI 0.52-0.71) was superior with letrozole compared to placebo.96

   (a) Delayed treatment with letrozole also improved DFS compared to patients who received placebo (median 2.8 years from stopping Tam; range 1.1-7.1 years).97

ii. Exemestane (NSABP B-33) – 25 mg daily for another 5 years vs. placebo; stopped when MA-17 results available; recent report of available data (about half of initial accrual goal) indicate non-significant benefit in 4-year DFS (91% vs. 89%; RR = 0.68; p=0.07) with 30 months median follow-up.98

d) **NCCN guidelines**32

i. Panel believes that all three selective aromatase inhibitors (anastrozole, letrozole, exemestane) have similar antitumor efficacy and similar toxicity profiles.

ii. Optimal duration of aromatase inhibitors in adjuvant therapy is uncertain.

e) **Excellent review:** ASCO Update on Adjuvant Endocrine Therapy for Women with HR Positive Breast Cancer.81

f) **Side effects:** hot flashes, arthralgias/myalgias, mild headache and diarrhea, bone loss (osteoporosis, fractures), vaginal dryness, cardiovascular events.

g) More in depth information regarding toxicities with adjuvant endocrine therapy in postmenopausal women is available99

h) Consider concurrent use of bisphosphonate (trials ongoing for bone loss and breast cancer outcomes).

i. Oral agents for prevention of osteoporosis and fractures (in osteopenic patients).

   (a) See Survivorship section for further details on management of bone health.

ii. Bisphosphonates may affect cancer outcomes

   (a) ABCSG 12- premenopausal patients received ovarian suppression with goserelin and anastrozole or tamoxifen +/- zoledronic acid.89
(i) Zol 4 mg q6mo x 3 years improved DFS compared to patients that did not receive Zol at a median follow-up of 62 months (92% vs. 88%, HR = 0.68 95%CI 0.51-0.91, p=0.009).

(b) ZO-FAST evaluated up-front or delayed Zol for prevention of bone loss during endocrine treatment of postmenopausal women with early stage breast cancer found that DFS was significantly improved in the group that received up-front Zol (HR = 0.588, p=0.0314).100

(c) AZURE trial - adjuvant Zol in patients with stage II/III breast cancer.101

(i) Randomized 3360 women to standard adjuvant therapy +/- Zol q3-4 wks x 6 doses, then q3mo x 8 doses, then q6mo x 5 doses.

(ii) After a median follow-up of 84 months, DFS (primary endpoint) and overall survival were not significantly different.

(iii) The rates of invasive DFS were higher with Zol among women who were over 5 years since menopause at trial entry (HR 0.77; 95% CI, 0.63 to 0.96)

(iv) Significantly higher rates of confirmed ONJ in Zol group (26 confirmed cases vs none in control group, cumulative incidence 2.1%).102

(d) Data is conflicting regarding the use of bisphosphonates for reducing breast cancer recurrence in premenopausal and postmenopausal women; adjuvant bisphosphonates are not currently recommended by major breast cancer guidelines in this setting.32
Patient case #2 (continued): According to the NCCN guidelines, LG would be a candidate for adjuvant endocrine therapy alone, based on the tumor size, nodal status, hormone-receptor status, and the results of the Oncotype DX test. She is premenopausal and underwent a segmental mastectomy with sentinel lymph node mapping with biopsy (with negative lymph nodes), which will require adjuvant radiation therapy. For premenopausal patients, the endocrine therapy of choice would be tamoxifen 20 mg daily for 5 years. If at that time LG becomes postmenopausal, then she could consider an additional 5 years of therapy with an aromatase inhibitor or continue on tamoxifen for an additional 5 years. If after 5 years of therapy with tamoxifen, she remains premenopausal, then she could either discontinue adjuvant therapy or continue on tamoxifen for an additional 5 years.

What if LG was postmenopausal before starting treatment? For postmenopausal patients, NCCN guidelines recommend the incorporation of an aromatase inhibitor. Options include use of an aromatase inhibitor for 5 years, tamoxifen for 2-3 years followed by an aromatase inhibitor to complete 5 years of endocrine therapy, or tamoxifen for 5 years followed by an additional 5 years of therapy with an aromatase inhibitor or tamoxifen. All of these are appropriate options. If she could not tolerate an aromatase inhibitor, tamoxifen for 5 or 10 years would be an acceptable option.

Patient case #3: HA is a 34 y/o premenopausal white woman who presents to the clinic with a newly diagnosed right breast cancer found by the patient, confirmed with mammogram, ultrasound and core biopsy. By ultrasound she was found to have an abnormal appearing mass which was documented by core biopsy to represent cancer, measuring 2.6 x 2.5 x 2.1 cm. Pathology of the right breast mass indicate an invasive ductal carcinoma, nuclear grade 3 (poorly differentiated), ER = 0%, PR = 0%, HER2 FISH = normal; Ki-67 = 80%. Her oncologist also palpated a lymph node in her axilla, which was verified by US and positive for ductal carcinoma by fine needle aspiration. All other staging studies were negative for metastases. The patient underwent modified radical mastectomy which revealed a 2.7 cm tumor and 2 of 18 lymph nodes positive for cancer.

Based upon this information, list the systemic treatment options for this woman.

d. Adjuvant Chemotherapy

1) Summary
   a) The optimal regimen in any clinical situation has not been determined; no standard regimen; many acceptable, evidence-based regimens demonstrate improvement in reducing the risk of recurrent breast cancer.
   b) Node-negative vs. node-positive: controversial whether or not to include a taxane in node-negative disease (NCCN does not differentiate regimen based on nodal status, although there are some RCTs that support taxane use in high-risk node negative patients).\textsuperscript{103,104}
   c) NCCN now identifies “preferred” chemotherapy regimens.
      i. The NCCN panel states that the preferred designation takes efficacy, toxicity, and treatment schedules into consideration.
      ii. No detailed reasoning is provided.

2) Historically, overview analysis of polychemotherapy indicates a benefit with combination chemotherapy regimens versus nothing (See TABLE 10)\textsuperscript{87}
   a) Reduction in odds of recurrence \( \approx 25\% \).
b) Reduction in odds of death ≈ 15%.

c) All ages benefit; magnitude of benefit may vary depending on age; not enough data at time of this analysis to indicate a benefit or lack of benefit with women older than 70 years.

d) Absolute reduction in risk of recurrence or death is greater for patients with ER- tumors when compared with ER+ tumors.

e) Node-positive patients derive a greater absolute benefit from polychemotherapy.

f) Duration of therapy longer than 3-6 months does not appear to improve survival.

g) Most recent update is the first to include taxanes (See TABLE 11).

TABLE 10: Historical Impact of Adjuvant Polychemotherapy for Breast Cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patient Group</th>
<th>No. of Randomized Trials</th>
<th>No. of Patients Randomized</th>
<th>Reduction in Annual Odds of Recurrence (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>All</td>
<td>60</td>
<td>28,764</td>
<td>23 ± 2</td>
<td>17 ± 2</td>
</tr>
<tr>
<td></td>
<td>&lt; 40 y/o</td>
<td></td>
<td></td>
<td>40 ± 6</td>
<td>29 ± 7</td>
</tr>
<tr>
<td></td>
<td>40-49 y/o</td>
<td></td>
<td></td>
<td>36 ± 4</td>
<td>30 ± 5</td>
</tr>
<tr>
<td></td>
<td>50-59 y/o</td>
<td></td>
<td></td>
<td>23 ± 3</td>
<td>15 ± 4</td>
</tr>
<tr>
<td></td>
<td>60-69 y/o</td>
<td></td>
<td></td>
<td>13 ± 3</td>
<td>9 ± 4</td>
</tr>
<tr>
<td></td>
<td>≥ 70 y/o</td>
<td></td>
<td></td>
<td>12 ± 11</td>
<td>13 ± 12</td>
</tr>
</tbody>
</table>

Abbreviations: y/o = years old; No. = number.
Data from: Early Breast Cancer Trialists’ Collaborative Group (EBCTCG).87

TABLE 11: Impact of Adjuvant Taxane plus Anthracycline Regimens versus Non-Taxane Chemotherapy for Breast Cancer

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>No. of Randomized Trials</th>
<th>No. of Patients Randomized</th>
<th>Reduction in Annual Odds of Recurrence (%)</th>
<th>Death with recurrence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>33</td>
<td>44,000</td>
<td>14 ± 2</td>
<td>13 ± 3</td>
</tr>
<tr>
<td>&lt; 45 y/o</td>
<td></td>
<td></td>
<td>12 ± 4</td>
<td>9 ± 5</td>
</tr>
<tr>
<td>45-54 y/o</td>
<td></td>
<td></td>
<td>13 ± 4</td>
<td>11 ± 5</td>
</tr>
<tr>
<td>55-69 y/o</td>
<td></td>
<td></td>
<td>17 ± 4</td>
<td>18 ± 5</td>
</tr>
<tr>
<td>≥ 70 y/o</td>
<td></td>
<td></td>
<td>36 ± 14</td>
<td>37 ± 16</td>
</tr>
</tbody>
</table>

Abbreviations: y/o = years old; No. = number.
Data from: Early Breast Cancer Trialists’ Collaborative Group (EBCTCG).105

3) Summary of Consensus Guidelines: (many international guidelines, NCCN v.3.2014 most commonly utilized in US, but can also be controversial)

a) CMF
   i. Inferior to anthracycline-based regimens with cumulative anthracycline doses > 240 mg/m² or
epirubicin doses > 360 mg/m²; 4 cycles of AC appear to be equivalent to standard CMF.105

b) Anthracyclines-containing regimens (see TABLE 12)

i. Anthracycline-based regimens with cumulative anthracycline doses > 240 mg/m² or epirubicin doses > 360 mg/m² are superior to standard CMF.105

ii. Inferior to anthracycline/taxane combination regimens (see below).

c) Taxane-containing regimens (see TABLE 13)

i. EBCTCG update included taxane data105

(a) Incorporation of a taxane reduced the risk of distant recurrence (RR 0.87, SE 0.03), any recurrence (RR 0.86, SE 0.02, 2p<0.00001), breast cancer mortality (RR 0.87, SE 0.03, 2p<0.00001), and overall mortality (RR 0.89, SE 0.03, 2p<0.00001).

(b) Proportional reductions in recurrence and breast cancer mortality largely independent of age, nodal status, tumor size, tumor differentiation, or ER status.

(c) Mean follow-up only 5 yrs, mostly node positive patients.

ii. Standard of care for node-positive disease; consider for node-negative disease.

d) Trastuzumab-containing regimens (with or without pertuzumab-see TABLE 14)

i. In a meta-analysis of 6 RCT, DFS (OR 0.69, 95%CI 0.59-0.80, p<0.001) and OS (OR 0.78, 95%CI 0.69-0.88, p<0.001) were prolonged in patients who received chemotherapy with adjuvant trastuzumab compared to chemotherapy alone.106

(a) No differences in DFS based on lymph node status (none vs. 1-3 lymph nodes vs. >4 lymph nodes).

(b) Sequential and concomitant use of trastuzumab + chemotherapy both prolonged DFS compared to chemotherapy alone; however concomitant trastuzumab also improved OS, whereas sequential trastuzumab did not.

ii. For all HER2-overexpressed patients with tumors > 1 cm.

iii. According to the NCCN guidelines, trastuzumab should be considered in HER2-overexpressed patients with tumors 0.6 to 1 cm due to poor recurrence-free survival in this patient population who did not receive trastuzumab in retrospective...
analyses (see FIGURES 2 and 3). These patients were not included in the prospectively conducted randomized clinical trials of adjuvant trastuzumab.

(a) A single arm study with paclitaxel + trastuzumab weekly followed by every three week trastuzumab for a total of one year has been evaluated in lymph node negative HER2+ tumors less than 3 cm\textsuperscript{107}

(i) 50% of patients enrolled in the study had tumors 1 cm or less in size

(ii) 3-year DFS was 98.7%, 3-year RFS was 99.2%

(iii) Symptomatic CHF occurred in 0.5% of patients, asymptomatic declines in CHF occurred in 3.2% of patients

• The benefit of this regimen compared to standard trastuzumab-based regimens listed in table 14 is unknown.

• May be reasonable in carefully selected patients.

iv. Concurrent with taxane portion of regimen or sequentially after completion of chemotherapy.

v. Should not be given concurrent with an anthracycline due to cardiac toxicity seen in patients with metastatic breast cancer. See neoadjuvant therapy section for additional details on combination FEC and trastuzumab.

vi. Trastuzumab has been given for a total of one year in the majority of clinical trials, and is considered to be the standard of care in the U.S.

vii. Trastuzumab was given for 9 weeks in combination with docetaxel followed by FEC in the FinHER trial. However, this shortened course of trastuzumab was not compared to a regimen that included trastuzumab administered for one year.\textsuperscript{108}

viii. In the HERA trial, no differences in DFS or OS were seen with one year of trastuzumab compared to two years of trastuzumab after adjuvant chemotherapy in patients with HER2-positive breast cancer after 8 years of follow-up.\textsuperscript{109}

ix. In the PHARE study, 6 months of adjuvant trastuzumab did not meet the criteria for noninferiority for DFS compared to 1 year of adjuvant trastuzumab.\textsuperscript{110}
x. Other trials evaluating different lengths of adjuvant trastuzumab are ongoing.

xi. Cardiac monitoring should be performed.

xii. Trastuzumab can be administered either weekly or every 3 weeks.

5) Other information

a) Taxane frequency (weekly vs. Q 3 week) and comparison (paclitaxel vs. docetaxel).\textsuperscript{111}

i. Overall, there was no difference in which taxane was administered (paclitaxel vs. docetaxel) nor the frequency of administration (weekly vs. Q 3 week).

ii. Subsequently, weekly paclitaxel, weekly docetaxel, and Q 3 week docetaxel were compared to Q 3 week paclitaxel and found:

(a) Improved DFS with weekly paclitaxel and Q 3 week docetaxel compared to Q 3 week paclitaxel.

(b) Improved OS with weekly paclitaxel compared to Q 3 week paclitaxel.

(c) Higher incidence of febrile neutropenia with Q 3 week docetaxel and higher incidence of G3/4 neuropathy with weekly paclitaxel.

b) Dose-dense therapy

i. Node-positive breast cancer patients in the CALGB 9741 study were randomized after surgery to sequential versus concurrent chemotherapy (AC → Pac vs. A → P → C), and standard dose versus dose density (AC → Pac).\textsuperscript{112}

(a) Patients receiving every-2-week chemotherapy had a significantly prolonged DFS (85% vs. 81%, $p = 0.01$) and OS (92% vs. 90% $p = 0.013$) vs. every 3-week chemotherapy.

(b) Sequential versus concurrent chemotherapy was not significantly different in terms of DFS or OS.

(c) Very toxic regimen (AC → Pac); morbidity and risks of transfusions should be considered with this regimen.

(d) Less toxic when given as sequential single agents (A → P → C).

ii. Many studies with anthracyclines (without taxanes) appear to indicate no benefit from a dose-dense approach to drug administration.
iii. Data with the taxanes, especially paclitaxel, appear to support a dose dense approach, with weekly therapy producing optimal outcomes.

iv. Although other trials have attempted to investigate dose-dense regimens, they also have other variables that were altered that could potentially impact the outcomes.

v. No significant differences in 5-year DFS or OS with DDAC x 4 → DDPac x 4 vs. TAC x 6 in NSABP B-38.\textsuperscript{113}

vi. No significant differences in 5-year PFS or OS with DDAC x 4 → DDPac x 6 vs DDAC x 4 → weekly pac x 12 with more musculoskeletal pain, allergic reaction, and neurologic toxicity with DDPac.\textsuperscript{114}

vii. Must consider risks vs. benefits.

c) Adjuvant capecitabine is inferior to standard chemotherapy (CMF x 6 cycles or AC x 4 cycles) in women older than 65 yrs.\textsuperscript{115}

6) Risks associated with chemotherapy

a) Anthracycline-containing regimens: myelosuppression, nausea/vomiting, cardiotoxicity, mucositis/diarrhea, alopecia, leukemia (may be higher risk with cumulative epirubicin doses of > 720mg/m\textsuperscript{2}), amenorrhea (mainly due to cyclophosphamide).

b) Taxane-containing regimens: myelosuppression, hypersensitivity reactions, peripheral neuropathy, myalgias/arthralgias, fluid retention, skin/nail changes, total body alopecia.

c) Trastuzumab-containing regimens: increased cardiotoxicity, interstitial pneumonitis (only combined analysis of NCCTG/NSABP).

d) All attempts to maintain chemotherapy schedule should be made; dose-reductions should be made only when other measures (e.g., growth factor support) have failed.

e) Some leeway exists with anthracycline regimens in terms of dose-reductions (e.g., lowest effective dose appears to be 400/40/400 with FAC) and higher doses with these regimens does not improve efficacy.

7) See TABLE 12, 13 & 14 and NCCN guidelines for selected adjuvant chemotherapy regimens.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Doses</th>
<th>Schedule</th>
<th>Frequency</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CAF</strong></td>
<td>Cyclophosphamide</td>
<td>100 mg/m²/d PO</td>
<td>D 1-14</td>
<td>Q 28 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>30 mg/m² IV</td>
<td>D 1&amp;8</td>
<td>Q 28 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D 1&amp;8</td>
<td>Q 28 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>FAC</strong></td>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D 1&amp;8</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>50 mg/m² IV (CI)</td>
<td>D 1 (72h)</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>AC</strong></td>
<td>Doxorubicin</td>
<td>60 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td><strong>EC</strong></td>
<td>Epirubicin</td>
<td>100 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>830 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>8</td>
</tr>
<tr>
<td><strong>CEF</strong></td>
<td>Cyclophosphamide</td>
<td>75 mg/m²/d PO</td>
<td>D 1-14</td>
<td>Q 28 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>60 mg/m² IV</td>
<td>D 1&amp;8</td>
<td>Q 28 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D 1&amp;8</td>
<td>Q 28 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>FEC</strong></td>
<td>Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>100 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV</td>
<td>D1</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
</tbody>
</table>

* No anthracycline-based chemotherapy regimens are designated as a preferred regimen.

a If doxorubicin is given as a continuous infusion, the 5-fluorouracil is given on day 1 and at the end of the infusion. For example, if doxorubicin is given over 72 hours, then the 5-fluorouracil is given on day 1 and 4.

b Given with growth factor support or prophylactic antibiotics.

Reference 32.
### TABLE 13: Selected Taxane-Containing Regimens for the Adjuvant Therapy of Breast Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Doses</th>
<th>Schedule</th>
<th>Frequency</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AC ⇒ Paclitaxel</strong></td>
<td>Doxorubicin</td>
<td>60 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>80 mg/m² IV over 1h</td>
<td>Weekly</td>
<td>Q 7 days</td>
<td>12 wks</td>
</tr>
<tr>
<td><strong>Pac ⇒ FAC</strong></td>
<td>Paclitaxel</td>
<td>80 mg/m² IV over 1h</td>
<td>Weekly</td>
<td>Q 7 days</td>
<td>12 wks</td>
</tr>
<tr>
<td></td>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D 1 &amp; 8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>50 mg/m² IV (CI)</td>
<td>D 1 (48-96h)</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td><strong>FEC ⇒ Docetaxel</strong> (total of 6 cycles)</td>
<td>5-Fluorouracil</td>
<td>500 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Epirubicin</td>
<td>100 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>100 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>3</td>
</tr>
<tr>
<td><strong>TAC&lt;sup&gt;b&lt;/sup&gt;</strong></td>
<td>Docetaxel</td>
<td>75 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>50 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>500 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>TC&lt;sup&gt;a,b&lt;/sup&gt;</strong></td>
<td>Docetaxel</td>
<td>75 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td><strong>Dose-Dense&lt;sup&gt;b&lt;/sup&gt; AC Followed by</strong></td>
<td>Doxorubicin</td>
<td>60 mg/m² IV</td>
<td>D 1</td>
<td>Q 14 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>D 1</td>
<td>Q 14 days</td>
<td>4</td>
</tr>
<tr>
<td>**Dose-Dense&lt;sup&gt;b&lt;/sup&gt; Pac&lt;sup&gt;<em>b&lt;/sup&gt; OR Weekly Pac&lt;sup&gt;<em>a&lt;/sup&gt;</em></em></td>
<td>Paclitaxel</td>
<td>175 mg/m² IV over 3h</td>
<td>D 1</td>
<td>Q 14 days</td>
<td>4</td>
</tr>
</tbody>
</table>

<sup>*</sup> Designated as a preferred regimen

<sup>a</sup> If doxorubicin is given as a continuous infusion, the 5-fluorouracil is given on day 1 and at the end of the infusion. For example, if doxorubicin is given over 72 hours, then the 5-fluorouracil is given on day 1 and 4.

<sup>b</sup> Given with growth factor support.

Reference 32
### TABLE 14: Selected Trastuzumab-Containing Regimens for the Neoadjuvant/Adjuvant Therapy of Breast Cancer

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Doses</th>
<th>Frequency</th>
<th>Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AC ⇒ PH ⇒ H</strong></td>
<td>Doxorubicin</td>
<td>60 mg/m² IV</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td><strong>(NCCN preferred)</strong></td>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>175 mg/m² IV over 3h</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>80 mg/m² IV over 1h</td>
<td>Q 7 days</td>
<td>12 wks</td>
</tr>
<tr>
<td></td>
<td>with Trastuzumab</td>
<td>followed by</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>4 mg/kg IV → 2 mg/kg IV</td>
<td>Q 7 days</td>
<td>12 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TCH</strong></td>
<td>Docetaxel</td>
<td>75 mg/m² IV</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>(BCIRG 006)</strong></td>
<td>Carboplatin</td>
<td>AUC 6 IV</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>(NCCN preferred)</strong></td>
<td>Trastuzumab</td>
<td>4 mg/kg IV → 2 mg/kg IV</td>
<td>Q 7 days</td>
<td>18 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>AC ⇒ TH</strong></td>
<td>Doxorubicin</td>
<td>60 mg/m² IV</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td><strong>(BCIRG 006)</strong></td>
<td>Cyclophosphamide</td>
<td>600 mg/m² IV</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>100 mg/m² IV</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab</td>
<td>4 mg/kg IV → 2 mg/kg IV</td>
<td>Q 7 days</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TCH + pertuzumab</strong></td>
<td>Docetaxel</td>
<td>75 mg/m² IV</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>(TRYPHAENA)</strong></td>
<td>Carboplatin</td>
<td>AUC 6 IV</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td><strong>(NCCN preferred)</strong></td>
<td>Trastuzumab</td>
<td>8 mg/kg IV → 6 mg/kg IV</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pertuzumab</td>
<td>840 mg → 420 mg</td>
<td>Q 21 days</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TH + pertuzumab</strong></td>
<td>Neoadjuvant</td>
<td>Docetaxel</td>
<td>75 mg/m² IV</td>
<td>Q 21 days</td>
</tr>
<tr>
<td><strong>⇒ FEC</strong></td>
<td>Trastuzumab</td>
<td>8 mg/kg IV → 6 mg/kg IV</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td><strong>(NEOSPHERE)</strong></td>
<td>Pertuzumab</td>
<td>840 mg → 420 mg</td>
<td>Q 21 days</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Pertuzumab may be incorporated into regimen per NCCN breast cancer guidelines

Reference 32
Patient case #3 (continued): HA has Stage IIB (pT2 N1 M0), node-positive, hormone-receptor negative, and HER2-normal breast cancer. Options for her adjuvant systemic therapy would then include any of the regimens listed in Table 12 or 13. Inclusion of an anthracycline and a taxane would be the standard of care, since she is lymph node-positive (e.g., TAC, AC → pac/doc, etc.). This would then be followed by radiation therapy. Endocrine therapy is not indicated since her tumor was hormone-receptor negative. She would be carefully followed for the rest of her life for recurrence and/or new primary breast cancers.

If this patient is started on AC chemotherapy, what antiemetic regimen should she receive?

VIII. Antiemetic use in patients with breast cancer [further discussion in Symptom Management, CINV section]

A. Neurokinin-1 (NK-1) Receptor Antagonists (aprepitant or fosaprepitant) with AC regimens in patients with breast cancer

1. Chemotherapy-naïve breast cancer patients receiving cyclophosphamide plus either doxorubicin or epirubicin were randomized to either an aprepitant regimen or a control regimen over multiple cycles of chemotherapy.121
   a. Aprepitant regimen:
      1) Aprepitant 125 mg PO, ondansetron 8 mg PO, dexamethasone 12 mg PO prior to chemotherapy on day 1 and ondansetron 8 mg PO 8 hours later
      2) Aprepitant 80 mg PO daily on days 2 and 3
   b. Control arm:
      1) Ondansetron 8 mg, dexamethasone 20 mg prior to chemotherapy on day 1 and ondansetron 8 mg 8 hours later
      2) Ondansetron 8 mg PO twice daily on days 2 and 3
   c. Complete response (CR) defined as no emesis or use of rescue therapy
   d. Results
      1) 866 patients randomized with 744 (86%) entering the extension phase and a total of 650 (75%) finishing all 4 cycles
      2) Aprepitant group had a higher CR rate across all four cycles of chemotherapy versus the standard group
         a) Cycle 1: 50.8% vs. 42.5% (p=0.015)
         b) Cycle 2: 53.8% vs. 39.4%
         c) Cycle 3: 54.1% vs. 39.3%
         d) Cycle 4: 55% vs. 38.4%
   e. Adverse effects similar between both groups

2. A single dose of 150 mg of IV fosaprepitant was compared to the three-day oral regimen of aprepitant 125 mg on Day 1 followed by 80 mg on Days 2 & 3 (non-breast cancer population).122
   a. All patients were chemo naive and received cisplatin ≥ 70 mg/m² plus ondansetron and dexamethasone and were randomized to IV fosaprepitant or PO aprepitant.
   b. A total of 2,322 patients were randomized and 2,247 were evaluable.
c. Antiemetic protection was equivalent between aprepitant and fosaprepitant; therefore, efficacy irrespective of route.

According to the ASCO guidelines, HA should receive prophylactic antiemetics for acute and delayed CINV associated with AC (doxorubicin and cyclophosphamide) chemotherapy. Her acute prophylaxis should include a serotonin antagonist (ondansetron, granisetron, dolasetron, or palonosetron), a corticosteroid (dexamethasone), and a neurokinin-1 receptor antagonist (oral aprepitant or IV fosaprepitant). According to the ASCO guidelines, her delayed prophylaxis should include aprepitant orally for two days (if fosaprepitant 150 mg IV on day 1 not given) and dexamethasone. Of note, dexamethasone was not utilized in the delayed setting in the clinical trial which evaluated aprepitant in women with breast cancer who received AC, and may be omitted according to provider preference. Antiemetics for breakthrough nausea such as prochlorperazine or promethazine should also be given. The patient should be evaluated for signs or symptoms of nausea and/or vomiting for this and subsequent cycles.

What if HA had HER2-overexpressed breast cancer? Since her tumor is HER-overexpressed, she would be eligible for any of the trastuzumab-based chemotherapy regimens in TABLE 14. It does appear that concurrent chemotherapy with trastuzumab is optimal, but the benefits should be weighed against the higher risks of cardiotoxicity (especially with an anthracycline in the regimen). The duration of trastuzumab is controversial, but therapy should be consistent with the treatment regimen used in the majority of clinical trials (which was generally 1 year of therapy). Pertuzumab has been evaluated in the neoadjuvant setting only, and therefore incorporation of pertuzumab in the adjuvant setting is controversial. This would then be followed by radiation therapy, which could occur concurrently with trastuzumab therapy.

What is this patient’s risk of heart failure with an anthracycline-based and/or trastuzumab-based chemotherapy regimen?

IX. Cardiotoxicity [further discussion in Symptom Management, cardiotoxicity section]

A. Type-1 Chemotherapy-Related Cardiac Dysfunction (anthracyclines)

1. Mechanism of toxicity
   a. Formation of iron-dependent oxygen free radicals due to stable anthracycline-iron complexes, which cause catalysis of electron transfer.
   b. Damage to myocardial mitochondria occurs through peroxidation of membrane-bound lipids by the oxygen free radicals.
   c. Myocardium is more susceptible due to lower levels of enzymes capable of detoxifying oxygen free radicals compared with other tissues.
   d. Mechanism of antitumor effects (topoisomerase II inhibitor) of anthracyclines is different than the mechanism of toxicity.

2. Acute
   a. Occurs immediately after a single dose or course of therapy with an anthracycline.
   b. Uncommon and transient.
   c. May involve abnormal ECG findings, including QT-interval prolongation, ST-T wave changes, and arrhythmias.
   d. Rarely, CHF and/or pericarditis are observed.
   e. May be caused by an inflammatory response.
3. Chronic
   a. Onset usually within a year of receiving anthracycline therapy.
   b. Rapid onset and progression.
   c. Common and life threatening.
   d. Related to cumulative dose patient received\textsuperscript{127} - estimated incidences are:
      1) < 5\% incidence with a cumulative doxorubicin dose of 400 mg/m\textsuperscript{2}
      2) 15\% incidence with a cumulative doxorubicin dose of 500 mg/m\textsuperscript{2}
      3) 25\% incidence with a cumulative doxorubicin dose of 550 mg/m\textsuperscript{2}
      4) 50\% incidence with a cumulative doxorubicin dose of 700 mg/m\textsuperscript{2}
   e. Can be resistant to treatment.
   f. Symptoms include tachycardia, tachypnea, exercise intolerance, pulmonary and venous congestion, ventricular dilatation, poor perfusion and pleural effusion.
   g. Exact mechanism is unknown; but may reflect progressive injury and loss of cardiomyocytes.
      1) Onset may be masked initially as the initial loss of function is compensated by remaining myocytes.
      2) However, will become apparent, usually as a decreased left ventricular ejection fraction (LVEF) and CHF, as patient receives increasing cumulative doses of anthracyclines.

4. Late-onset
   a. Develops several years or even decades after therapy.
   b. Manifests as ventricular dysfunction, CHF, conductile disturbances and arrhythmias.
   c. Occurs more often in childhood / adolescence cancer survivors who received anthracyclines.

5. The anthracycline antibiotics (daunorubicin, doxorubicin, idarubicin, epirubicin) can cause a dose-related, cumulative cardiomyopathy.

B. Primary Prevention (avoidance)\textsuperscript{128}

1. Risk Factors
   a. Age > 65 years or < 4 years
   b. Female gender
   c. Hypertension
   d. Preexisting cardiac disease
   e. Mediastinal radiation
   f. Treatment with cyclophosphamide, paclitaxel, or trastuzumab
   g. Higher individual anthracycline dose
   h. Cumulative anthracycline dose
      1) Cumulative dose of chemotherapy agent (rapid IV administration)
Cumulative lifetime doses of doxorubicin > 450 mg/m²

Cumulative lifetime doses of doxorubicin are safely increased with continuous infusion over 96-hours to 800 - 1000 mg/m²

Cumulative lifetime doses of epirubicin > 935 mg/m²

Schedule of delivery - administering anthracyclines by continuous infusion over 24 to 92 hours versus IV bolus can reduce the cardiotoxicity.

Product formulation – liposomal formulations of doxorubicin has been shown to decrease the cardiotoxicity of doxorubicin compared to conventional doxorubicin formulations.

Table 15: Anthracycline Conversion Factors (doses listed are for rapid IV administration)

<table>
<thead>
<tr>
<th>Anthracycline</th>
<th>Conversion Factor</th>
<th>% Cardiotoxicity at Cumulative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>1</td>
<td>5% risk at 450 mg/m²</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>0.5</td>
<td>5% risk at 900 mg/m²</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>0.5</td>
<td>5% risk at 935 mg/m²</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>2</td>
<td>5% risk at 160 mg/m²</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>2.2</td>
<td>5% risk at 200 mg/m²</td>
</tr>
</tbody>
</table>

2. Cochrane database of systematic reviews on different dosage schedules to reduce cardiotoxicity in cancer patients receiving anthracycline chemotherapy
   a. 7 randomized, clinical trials were identified which looked at different anthracycline infusion durations
   b. Statistically significant lower rate of clinical heart failure was found with infusion durations of > 6 hours versus shorter infusion duration, i.e. maximal duration of 1 hour (RR = 0.27, 95% CI, 0.09 to 0.81; 5 studies; n = 557)
   c. Infusions > 6 hours reduce risk of clinical heart failure and seems to reduce the risk of subclinical cardiac damage
   d. Occurrence of clinical heart failure in patients receiving doxorubicin > 60 mg/m² versus < 60 mg/m² was not significantly different

C. Secondary prevention – Dexrazoxane (Zinecard®)
   1. Acts as an intracellular metal chelating agent
      a. Proposed mechanism of action is via metal-chelation (free iron and iron bound in anthracycline complexes), which leads to a decrease of anthracycline-induced free radical damage
   2. Approved for use in metastatic breast cancer patients who are responding to doxorubicin-containing chemotherapy and have received 300 mg/m² by IV bolus
   3. Two meta-analyses have been completed to date, which have shown that treatment with dexrazoxane significantly decreases the relative risk of anthracycline-induced cardiac toxicity in cancer patients by 72% to 76% when compared to no treatment and
      a. Dexrazoxane plus anthracyclines may not increase the relative risk of chemotherapy failure and may not decrease patient survival.
   4. Dosing is based on a ratio of 10:1 (dexrazoxane-to-doxorubicin, i.e. 500 mg/m² dexrazoxane and 50 mg/m² doxorubicin).
a. Must administer doxorubicin within 15 to 30 minutes of dexrazoxane injection, due to a short half-life of approximately 2 hours.

b. Should be administered by slow IV push or short IV infusion over 15 minutes.

c. A dose ratio of 10:1 may be reasonable with epirubicin, however, the optimal dose ratio has not been determined.

5. Difficult to determine side effects of dexrazoxane versus the chemotherapy agent it is co-administered with, but generally well tolerated and lacks additive toxicity with anthracycline-based chemotherapy except for a small, but significant increase in leukopenia and/or thrombocytopenia seen in some trials.

a. Higher doses (20:1) also appear to be well tolerated.

6. ASCO guidelines for use of dexrazoxane

a. Recommendations for use in patients with metastatic breast cancer:

1) Do not use routinely in women who are receiving initial doxorubicin therapy.
   a) Not proven to increase overall or disease free survival.
   b) May increase hematologic toxicity.
   c) May decrease tumor response rates – single clinical trial.

2) Consider use in women who have received ≥ 300 mg/m² of doxorubicin in the past and who may benefit from continued doxorubicin therapy.

3) Must consider the following:
   a) Dexrazoxane may decrease response rates
   b) The patient’s risk for cardiotoxicity with continued use of doxorubicin
   c) This has not been studied in clinical trials
   d) Dexrazoxane administration not helpful with continuous administration of anthracyclines

b. Use in patients receiving adjuvant chemotherapy for breast cancer is not recommended, unless patient enrolled in a clinical trial

c. Use with other anthracycline doses and schedules:

1) Dexrazoxane may be considered in patients responding to anthracycline-based chemotherapy for advanced breast cancer in whom continued dosing of epirubicin is recommended.

2) No evidence currently exists regarding the use of dexrazoxane with liposomal anthracyclines, idarubicin, or mitoxantrone.

d. Use in patients with cardiac risk factors: insufficient evidence to base a recommendation for this group of patients.

e. Monitoring of therapy:

1) Patients should undergo continual cardiac monitoring
   a) After a cumulative dose of doxorubicin ≥ 400 mg/m² the monitoring should be frequent, i.e. repeat after dose reaches
500 mg/m² and then repeat after every 50 mg/m² of doxorubicin.

2) Panel recommends discontinuation be strongly considered in anyone who develops a decrease in LVEF to < lower limits of normal (LLN) or who develop clinical signs of CHF

7. Cochrane database of systematic reviews on the use of cardioprotective interventions in cancer patients receiving anthracyclines

a. Objective was to assess the efficacy of different cardioprotective medications in the prevention of cardiac damage in cancer patients who received anthracyclines

1) Identified randomized, controlled trials for eight cardioprotective agents: n-acetylcysteine, phenethylamines, coenzyme Q10, combination of vitamin E, vitamin C, and N-acetylcysteine, L-carnitine, carvedilol, amifostine, and dexrazoxane

2) First seven agents had insufficient data to pool and none of the single studies showed a cardioprotective effect

3) Ten studies were included for the dexrazoxane analysis with a total of 1619 patients:
   a) Dexrazoxane had a statistically significant benefit for preventing the occurrence of heart failure (RR 0.29, 95% CI 0.20 to 0.41).
   b) No significant difference was observed in survival or response rates between dexrazoxane group and control groups.
   c) Results were ambiguous for differences in adverse events.
   d) Authors conclude that if risk of cardiac damage is expected to be high, dexrazoxane use may be justified in cancer patients receiving anthracyclines

8. Carvedilol, statins, and ACE inhibitors have been evaluated for prevention of chemotherapy-induced cardiotoxicity, with mixed results. An excellent review on this subject is available.

a. Type II Chemotherapy-Related Cardiac Dysfunction

1) Does not appear to be dose-related or occur in all patients

2) Ranges widely in severity and has not been identified with myocardial damage, to date

3) Mechanism appears to involve epidermal growth factor receptor pathway which normally blunts the effects of stress-signaling pathways that are required to maintain cardiac function, structure, and contractility

4) Appears to be largely reversible and short-lived after therapy discontinuation

5) Trastuzumab
   a) Acceptable rate of cardiotoxicity with most regimens tested in the adjuvant setting (see TABLE 16).
   b) Appears to be responsive to heart failure medical therapy; however, few patients recover their LVEF to baseline; may
recover to a normal LVEF (> 50%), but some residual damage
evident and may not have reserve to adequately respond to
subsequent stressors; need to follow for longer to determine
long-term risks.135

c) Serial prospective cardiac monitoring with MUGA scans or
echocardiograms was performed in all studies, but definitions
for cardiac events differ.

d) Cardiac function should be assessed every 3 months during
adjuvant trastuzumab-based therapy.

e) If trastuzumab is given concurrently with an anthracycline the
rate of cardiac toxicity increases substantially to 27% (16%
NYHA class III/IV)136

f) Pertuzumab and ado-trastuzumab emtansine – see Biologic
Therapy section for details

### TABLE 16: Cardiotoxicity Associated with Adjuvant Trastuzumab Clinical Trials

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>B-31 N=1964</th>
<th>N9831 N=1610</th>
<th>HERA N=3401</th>
<th>BCIRG 006 N=3222</th>
<th>FinHer N=232</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AC → TH vs.</td>
<td>H vs. no H</td>
<td>AC → T</td>
<td>AC → TH</td>
<td>TCH</td>
</tr>
<tr>
<td>Cardiotoxicity</td>
<td>4.0% vs.</td>
<td>0.8% vs.</td>
<td>0.7%</td>
<td>2.0%</td>
<td>0.4%</td>
</tr>
<tr>
<td></td>
<td>1.3%</td>
<td>0.3%</td>
<td>0.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median F/U</td>
<td>7 years</td>
<td>3 years</td>
<td>8 years</td>
<td>5.4 years</td>
<td>5.2 years</td>
</tr>
</tbody>
</table>

Definition of cardiotoxicity differs:
B-31/N9831: NYHA Class III/IV CHF or cardiac death.
HERA: Symptomatic CHF, including severe.
BCIRG: Cardiac death, symptomatic CHF, and asymptomatic decreases in LVEF.
FinHer: Symptomatic HF.

**D. Monitoring of Therapy**

1. No definite guidelines have been adopted for adult patients - endomyocardial biopsy
   remains the most sensitive and specific way to monitor and diagnosis anthracycline
   cardiotoxicity, but invasiveness of procedure limits its use in clinical practice.

2. Methods to determine cardiac function include:
   a. Left ventricular (LVEF) systolic function can be evaluated via either
echocardiography (ECHO) or multigated acquisition scans (MUGA), but neither
are sensitive enough to detect early preclinical cardiac dysfunction.
   b. Monitoring diastolic function may be useful in detecting early anthracycline-
      induced cardiac dysfunction.
   c. Exercise or dobutamine echocardiography have also been used to assess early
      anthracycline cardiotoxicity.
   d. Measurement of myocardial strain and strain rate by speckle-tracking imaging.
   e. Troponin T and Troponin I may also be useful in early detection of
      cardiotoxicity before changes develop in LV ejection fraction.134

1) Dolci analysis included 7 studies which monitored troponin I and T in
   almost 1,500 patients141
   a) The authors summarized the clinical evidence from these
      studies as:
i. Measuring troponin predicts the occurrence of clinically significant left ventricle (LV) dysfunction at least 3 months in advance

ii. Early increases of troponin levels also predicts the degree and severity of future LV dysfunction

iii. Patients who have positive troponin levels that persist 1 month after the last dose of chemotherapy have an 85% probability of a major cardiac event within the 1st year of follow up

iv. Continually negative troponin tests can identify patients with the lowest cardiotoxicity risk at least within 1 year of follow up, with a negative predictive value of 99%

2) Natriuretic peptides (ANP, BNP, NT-proBNP) have also been studied in early detection of cardiotoxicity, but the results have been less consistent than troponins.

3) None of these serological markers of cardiotoxicity are routinely recommended.

3. Recommendations

a. Any patient with a risk factor for cardiotoxicity should have a baseline evaluation of cardiac function by ECHO or MUGA scanning.

b. For patients with a LVEF >50% at baseline:
   1) Consider repeating after reaching 250-300 mg/m²
   2) Repeat after reaching 400 mg/m² in patients with known risk factors of cardiac failure or after 450 mg/m² in the absence of risk factors
   3) Discontinue doxorubicin if:
      a) Functional signs of cardiotoxicity and/or
      b) Absolute decrease in LVEF ≥ 10% associated with a decline to a level of < 50% of normal.

c. NSABP and NCCTG trials evaluated LVEF serially in breast cancer patients receiving doxorubicin/cyclophosphamide (AC regimen) at the following time points:
   1) Prior to initiation of therapy (baseline)
   2) Every 3 months during and on completion of trastuzumab
   3) Every 6 months for at least 2 years after completion of trastuzumab

d. Pertuzumab and ado-trastuzumab emtansine – see Biologic Therapy section for monitoring details

e. If receiving anthracyclines and dexrazoxane, ASCO guideline on the use of chemoprotectants recommend cardiac monitoring for patients who have received a cumulative dose of 400 mg/m², repeat monitoring when reaching a cumulative dose of 500 mg/m² and then repeat monitoring after every 50 mg/m² thereafter
f. Patients who develop heart failure secondary to anthracyclines or HER2-targeted agents should be treated according to standard heart failure guidelines.

**Patient case #3:** HA's risk of cardiotoxicity is dependent on the specific trastuzumab-based chemotherapy regimen chosen. The TCH regimen is associated with a lower risk of cardiotoxicity (0.7% at 5.4 years) compared to anthracycline and trastuzumab-based regimens (2.0% at 5.4 years with AC followed by docetaxel-trastuzumab). See TABLE 16 for further details. HA would be monitored by signs and symptoms of heart failure during therapy and undergo evaluation of LVEF with an ECHO or MUGA scan prior to initiation of therapy, every 3 months and on completion of trastuzumab, and every 6 months for at least 2 years after completion of trastuzumab.

**Patient case #4:** CO is a 41 y/o premenopausal woman with new onset left breast erythema, with a heavy, thick feeling in the breast. She has also experienced left breast swelling and erythema. This occurred within the last few weeks and is getting worse despite the antibiotics her primary physician gave her 3 weeks ago. She comes to the clinic for further work up. A mammogram is performed, indicating skin edema without a discrete mass. An ultrasound is performed, indicating similar findings, with lymph nodes suspicious for metastatic disease. A core needle biopsy of the breast is performed indicating an invasive ductal carcinoma, involving the skin with extensive lymphatic invasion and a high Ki-67 (90%). This tumor was ER/PR negative and HER2 normal. FNA confirms breast cancer in the axilla consistent with the breast primary. She is otherwise healthy.

**What would be the most appropriate therapy for this patient at this time?**

X. **Stage IIIA, IIIB & IIIC Invasive Breast Cancers (locally advanced, non-inflammatory)**

A. **Summary:**

1. Operable stage IIIA (T3, N1, M0)
   a. See guidelines for early stage breast cancer (listed above).
   b. Primary surgery is an option for those who do not wish to have BCS.
   c. Primary (preoperative, neoadjuvant) systemic chemotherapy is an option if BCS is preferred by the patient (see Figure 5).

2. All other stage IIIA, IIIB, IIIC (non-inflammatory) (see Figure 5)
   a. Primary (preoperative, neoadjuvant) systemic anthracycline-containing chemotherapy with a taxane is standard therapy; trastuzumab should be incorporated if HER2-overexpressed.
   b. If response is demonstrated, then local therapy would be performed.
      1) Mastectomy or lumpectomy may be considered, depending on clinical situation.
      2) Axillary lymph node dissection would be required (all node positive patients).
      3) Radiotherapy would be required in all patients regardless of surgical procedure.
   c. If no response to preoperative chemotherapy, then proceed to mastectomy.
Abbreviations: RT = radiation therapy.
* If treated with endocrine therapy, aromatase inhibitors are preferred in postmenopausal women.

Patient case #4: CO has T4d, N1, M0, inflammatory breast cancer. She would be considered inoperable due to her extensive skin involvement and lack of a discrete mass. Primary/preoperative chemotherapy would be indicated for CO. If she had a non-inflammatory locally advanced breast cancer, primary/preoperative chemotherapy would also be considered standard of care.

What systemic regimen would be most appropriate?

3. Primary (preoperative, neoadjuvant) systemic chemotherapy.
   a. General principles of primary systemic chemotherapy
      1) Goals of therapy:
         a) Decrease the size of the tumor to minimize surgery.
         b) Determine response to chemotherapy in vivo (an important prognostic indicator).
         c) Theoretical advantages: early initiation of systemic therapy, delivery of drugs through intact vasculature, opportunity to study the biologic effects of chemotherapy.
      
      b. Neoadjuvant (primary, preoperative) vs. adjuvant systemic therapy
         1) Meta-analysis of neoadjuvant vs. adjuvant systemic treatment*142
a) Nine trials included in analysis (n=3861)

b) No significant difference:
   i. Death (RR = 1.00, 95% CI 0.90-1.12)
   ii. Disease progression (RR = 0.99, 95% CI = 0.91-1.07)
   iii. Distant recurrence (RR = 0.94, 95% CI = 0.83-1.06)

c) Only significant difference found:
   i. Loco-regional recurrences greater with neoadjuvant treatment (RR 1.22, 95% CI = 1.04-1.43, p=0.015)
   ii. Difference driven by 3 trials that used radiotherapy alone without surgery as definitive local therapy
   iii. Authors recommend avoiding the use of radiotherapy alone; patients should undergo BCS instead with the use of radiotherapy after definitive surgery

2) Emerging data on OS from NSABP B-18 (16 year follow-up) may indicate a benefit with neoadjuvant therapy for women < 50 years of age and the opposite for women 50 years old and older (difference still not statistically significant).143

c. Choice of neoadjuvant regimen

1) Chemotherapy
   a) NCCN guidelines recommend that in general, those chemotherapy regimens recommended in the adjuvant setting may also be considered in the preoperative setting. This is a consensus recommendation, not an evidence-based one. (See TABLE 12, 13, & 14 for adjuvant regimens.)

   b) Many trials incorporating the taxanes have not yet reported survival data, but for the largest of these (NSABP B-27) survival results are now available.143

      i. Three-arm randomized study design:
         (a) Arm 1: Preoperative AC x 4 cycles → surgery
         (b) Arm 2: Preoperative AC x 4 cycles → preoperative Docetaxel x 4 cycles → surgery
         (c) Arm 3: Preoperative AC x 4 cycles → surgery → Docetaxel x 4 cycles

      ii. Significant increases in clinical complete response (cCR) (63% vs 40%, p<0.001) and pathologic complete response (pCR) (26% vs 13%, p<0.001) in arm 2 compared to arms 1 and 3.

      iii. No significant differences in DFS or OS rates (median follow-up 8.5 years).
         (a) Relapse-free interval (RFI) was significantly improved with AC/Docetaxel vs AC only, but
was the difference due to more chemotherapy or inclusion of taxane? (b) May suggest that giving all chemotherapy prior to surgery optimal vs splitting before and after surgery.

c) Dose-dense chemotherapy regimens in neoadjuvant setting

i. Studies investigating this question are limited and included more than one variable in the regimens between the 2 arms of the study (differing number of cycles of chemotherapy, concurrent vs. sequential taxane administration).

ii. Clearly more trials are needed to fully understand the role of dose density in neoadjuvant chemotherapy.

d) Triple-negative breast cancer specific regimens

i. Carboplatin has been evaluated in the neoadjuvant setting incorporated into an anthracycline and taxane-based regimen144

(a) Compared weekly pac x 12 doses followed by DD AC x 4 doses with or without carboplatin AUC 6 every 3 weeks during the taxane portion of the regimen (n=443)

(b) Included stage II and III breast cancers, ER/PR 10% or less. Inflammatory breast cancers were excluded.

(c) pCR rate in breast and axilla was superior in patients who received carboplatin (54% vs 41%, p=0.0029)

(d) Bevacizumab also evaluated, but did not significantly increase pCR rates in the breast and axilla and added toxicity

(e) Consistent with carboplatin benefit in TNBC reported in GeparSixto145

ii. Carboplatin-based regimens have not yet been incorporated into national breast cancer guidelines32

**Patient case #4 (continued):** CO has T4d, N1, M0, inflammatory breast cancer. She should receive neoadjuvant chemotherapy initially. Regimens used in the adjuvant setting are generally considered to be appropriate for use in the neoadjuvant setting as well. The regimen should include an anthracycline with a taxane (since she has positive lymph nodes), either concurrently or sequentially administered. Since her tumor is triple-negative, addition of carboplatin to paclitaxel followed by dose-dense AC could be considered based on the results of the study by Sikov et al (although patients with IBC were excluded from the clinical trial). Response to this regimen should be monitored closely, followed by locoregional therapy. Consideration of further systemic therapy post-operatively is complicated and very controversial (e.g., additional chemotherapy may be considered if pathologic response was poor or if the initial chemotherapy regimen was not completed). She would not be a candidate for endocrine therapy given the ER/PR-negative status of her tumor. She would require local radiation therapy post-operatively.
d. Regimens for patients with HER2-positive disease

1) In general, those chemotherapy regimens recommended in the adjuvant setting may also be considered in the preoperative setting.\textsuperscript{32}

2) Several studies have been published with anthracyclines and trastuzumab administered concomitantly.

3) There is an important distinction between studies that have compared trastuzumab-based chemotherapy vs. chemotherapy alone and studies that have compared two trastuzumab-based chemotherapy regimens either concomitantly or concurrently with anthracyclines.

e. Trastuzumab-based chemotherapy vs. chemotherapy alone

1) Stage II-IIIA (non-inflammatory) breast cancer; HER2-overexpressed (IHC 3+) or gene amplified by FISH.\textsuperscript{146}

   a) Chemotherapy alone vs chemotherapy + trastuzumab weekly (n=42); chemotherapy was paclitaxel 225 mg/m\textsuperscript{2} IV over 24 hours q 3 weeks followed by FEC (epirubicin 75 mg/m\textsuperscript{2}) q 3 weeks.

   b) pCR: chemo alone (n=19) 26.3% vs chemo + trastuzumab (n=23) 65.2% (p=0.016).

   c) Required conformation in a larger study population

   d) Adverse events: grade 4 neutropenia higher with trastuzumab (11 vs 21 patients, p=0.03), but not neutropenic fever (8 vs 8 patients); no cases of clinical CHF; > 10% reduction in LVEF similar (5 patients chemotherapy alone vs 7 patients chemotherapy + trastuzumab), no treatment-related deaths.

2) A large randomized study (NOAH) has also described increased event-free survival rates, pCR rates, and acceptable cardiac toxicity with the addition of neoadjuvant and adjuvant trastuzumab (total of one year) to anthracycline- and taxane-based chemotherapy for patients with HER2-overexpressed locally advanced or inflammatory breast cancer compared to patients that received neoadjuvant chemotherapy alone.\textsuperscript{147}

f. Trastuzumab-based chemotherapy regimens either concomitantly or concurrently with anthracyclines

1) Results from the GeparQuattro trial supports the use of neoadjuvant trastuzumab in combination with anthracycline and taxane-based chemotherapy, but HER2-overexpressed patients were not randomized to receive chemotherapy without trastuzumab.\textsuperscript{148}

2) Patients in ACOSOG Z1041 (n=282) were randomized to FEC-75 x 4 → weekly pac x 12 or weekly pac + trastuzumab x 12 → FEC-75 + trastuzumab\textsuperscript{149}

   a) No difference in pCR rates were seen between the two groups (56.2% vs. 54.2%, OR 0.90; 95% CI 0.55-1.49)

   b) LVEF was decreased below the lower limit of normal in 0.8% of patients in the sequential arm and 2.9% of patients in the concurrent arm at week 12; with 7.1% and 4.6% of patients at week 24, respectively.
3) **Summary:** patients with HER2-positive ESBC or LABC should receive trastuzumab-based chemotherapy, but concomitant administration of trastuzumab and anthracycline-based chemotherapy is controversial.

4) Based on the results from the ACOSOG Z1041 study; the Pac/H → FEC/H regimen has been removed from the NCCN guidelines for preoperative regimens.\(^{32}\)

g. **Pertuzumab**

1) On September 30, 2013, pertuzumab received accelerated approval from the FDA in combination with docetaxel and trastuzumab for patients with HER2+, locally advanced, inflammatory, or early stage breast cancer (either greater than 2 cm or lymph node positive) based on results from the NeoSphere and TRYPHAENA studies.\(^{150}\)

a) Appropriate regimens include:

i. Docetaxel + trastuzumab + pertuzumab (THP) every 3 weeks x 4 cycles prior to surgery, then FEC every 3 weeks x 3 cycles after surgery

ii. FEC every 3 weeks x 3 cycles → THP every 3 weeks x 3 cycles prior to surgery

iii. TCH + pertuzumab (TCHP) every 3 weeks x 6 cycles prior to surgery

iv. See Table 14 for regimen details

2) NCCN breast cancer guidelines state that a pertuzumab-containing regimen can be administered to patients with T2 or N1, HER2-positive ESBC. NCCN guidelines also extend use of pertuzumab-containing regimens to the adjuvant setting, although no data with pertuzumab in the adjuvant setting is currently available.\(^{32}\)

3) In the Neosphere study\(^{120}\), 417 women with HER2+, locally advanced, inflammatory, or early stage breast cancer were randomized to one of four treatment arms:

a) Arm A: Docetaxel + trastuzumab q3wks x 4 cycles prior to surgery, then FEC q3wks x 3 cycles after surgery

b) Arm B: THP q3wks x 4 cycles prior to surgery, then FEC q3wks x 3 cycles after surgery

c) Arm C: Trastuzumab + pertuzumab q3wks x 4 cycles prior to surgery, then docetaxel + trastuzumab q3wks x 4 cycles and FEC q3wks x 3 cycles after surgery

d) Arm D: Docetaxel + pertuzumab q3wks x 4 cycles prior to surgery, then FEC q3wks x 3 cycles after surgery

e) pCR rates in the breast (primary endpoint) were: Arm A 29%, Arm B 46%, Arm C 17%, Arm D 24%

4) In the TRYPHENA study\(^{119}\), 225 women with HER2+, locally advanced, inflammatory, or early stage breast cancer were randomized to one of three treatment arms:

a) Arm A: FEC q3wks x 3 cycles followed by THP q3wks x 3 cycles prior to surgery
b) **ARM B: FEC + trastuzumab + pertuzumab q3wks x 3 cycles followed by THP q3wks x 3 cycles prior to surgery**

c) **Arm C: TCH + pertuzumab (TCHP) every 3 weeks x 6 cycles prior to surgery**

d) **Primary endpoint of the study was safety and tolerability during neoadjuvant treatment**

e) **pCR rates in the breast and axilla were: Arm A 50.7%, Arm B 45.3%, Arm C 51.9%**

h. There is conflicting data regarding the addition of lapatinib to trastuzumab-containing chemotherapy regimens in the neoadjuvant setting, and therefore use of neoadjuvant lapatinib should not be considered outside of a clinical trial at this time.

i. **Preoperative endocrine therapy**

1) Routine use is limited by the slow response (6-8 weeks for any clinical response, longer for potential pCR; cytostatic drugs, not cytotoxic).

2) Historically, utilized for locally advanced breast tumors in elderly patients, patients with poor performance status or comorbid conditions precluding the use of chemotherapy, or patients who refuse chemotherapy.

3) Some emerging thoughts that this may be more effective than chemotherapy in HR-positive, postmenopausal patients; however, clinical evidence is lacking to support this theory.

4) Historically, studied in postmenopausal women with tamoxifen with some benefit; limited data in premenopausal women.

5) **Aromatase inhibitors preferred over tamoxifen in postmenopausal women.**

   a) Four randomized phase III clinical trials comparing an AI to tamoxifen; overall rates of pCR with endocrine therapy 1-3%.

   b) **Anastrozole:**

      i. IMPACT trial (A vs Tam vs Combination); 3 months of therapy; clinical CR+PR=37% vs 36%; numerically, more patients became eligible for BCS with anastrozole compared to tamoxifen (44% vs 31%, p=0.23).\(^{151}\)

      ii. PROACT trial (A vs T); 3 months of therapy; clinical CR+PR=39.5% vs 35.4% (p=0.29); numerically, more patients became eligible for BCS with anastrozole compared to tamoxifen (38.1% vs 29.9%, p=0.11).\(^{152}\)

   c) **Letrozole:** 4 months of letrozole or tamoxifen; clinical CR+PR=55% vs 36%, respectively (p<0.001); more patients became eligible for BCS with letrozole compared to tamoxifen (45% vs 35%, p=0.022).\(^{153}\)

   d) **Exemestane:** 12 weeks of exemestane or tamoxifen; clinical CR+PR=76% vs 40%, respectively (p=0.05); more patients became eligible for BCS with exemestane compared to tamoxifen (37% vs 20%, p=0.05).\(^{154}\)
e) Randomized phase II study (ACOSOG Z1031) compared 4 months of preoperative anastrozole, letrozole, and exemestane (n=377). \(^{155}\)

i. Eligibility restricted to high ER expression (Allred score 6 to 8).

ii. Primary endpoint was clinical response rate

iii. Clinical CR+PR = 69% (A), 75% (L), and 63% (E); low rates of grade 3 to 4 toxicity with all agents.

iv. Results should be confirmed in a Phase III randomized clinical trial.

j. Local therapy following primary/preoperative systemic therapy consists of:

1) Total mastectomy + surgical axillary staging ± delayed reconstruction OR
2) Lumpectomy + surgical axillary staging
3) All patients should receive chest wall/breast and supraclavicular XRT to reduce the risk of local recurrence.
4) Patients with involved internal mammary chain lymph nodes should receive XRT to this lymph node basin.
5) DO NOT recommend radiation alone as the only local therapy (based on the Mauri meta-analysis).
6) Markers should be placed early (prior to or shortly after starting preoperative systemic therapy); allows for minimal surgical resection in the face of no gross tumor upon inspection.

k. Nonresponders to primary/preoperative systemic therapy or less than operable tumors

1) Change to non-cross-resistant chemotherapy OR
2) XRT to breast and supraclavicular area
3) If no response to non-cross-resistant chemotherapy, then go to XRT
4) Adjuvant therapy after surgery?
5) NCCN states that there is no role for postoperative chemotherapy if a full course of preoperative chemotherapy was administered.
6) Hormone-receptor positive (stage I, II, III): see Adjuvant Hormone Therapy section.
7) Inflammatory breast cancer (Any T4c) (separate algorithm in NCCN guidelines)\(^32\)
8) Distinct clinical entity; rare (1-6% of all breast cancer cases in US); poor prognosis; extremely aggressive; often ER-negative, HER2-overexpressed.
9) Historically, >95% mortality at 5 years.
10) With combined modality approach, DFS at 5 years were 35% for IBC vs 50% for non-IBC patients; 50% of patients are alive at 5 years and 35% alive at 10 years; late relapses are uncommon.
11) Incorporation of new agents into chemotherapy regimens may improve outcomes.
12) Some studies with neoadjuvant taxanes included inflammatory breast cancer patients.

13) No standard of care; clinical trials are most appropriate for these patients.

14) Treat as locally advanced disease (see Figure 5), but they are not candidates for breast conserving therapy and local radiation is more extensive.

15) Chemotherapy regimens are similar to patients with locally advanced disease and trastuzumab should be considered for HER2-overexpressed disease.

**Patient case #4 (continued):** What if CO’s tumor was HER2-overexpressed? In this case, a trastuzumab-chemotherapy regimen with or without pertuzumab would be preferred. The NeoSphere and TRYPHAENA studies both included patients with locally advanced and inflammatory breast cancer. Therefore, incorporation of neoadjuvant trastuzumab and pertuzumab-based regimens listed in Table 14 would be appropriate options. The best treatment would be to consider a clinical trial, incorporating standard agents with newer therapies.

**Patient case #5:** DM is a 58 y/o postmenopausal woman with newly diagnosed bone metastases. She was originally diagnosed 3 years ago with stage IIIB right breast cancer (T2N1M0, invasive ductal carcinoma, ER/PR positive, HER2 normal by IHC and Ki-67=7%), underwent a modified radical mastectomy followed by adjuvant chemotherapy with TAC for 6 cycles. Since she was premenopausal prior to starting chemotherapy, she was started on adjuvant tamoxifen therapy and continues on that therapy now. She returns to clinic with new bone pain in her lower back, which is well controlled with over the counter pain medication. A bone scan was performed that indicated suspicious areas of uptake in her lumbar spine, which were confirmed with x-rays of those areas to represent metastatic breast cancer. Biopsy of the lumbar spine confirms metastatic breast cancer consistent with the initial breast primary (ER/PR positive, HER2 normal by FISH). The rest of her staging studies demonstrated no other sites of metastases.

What would be the most appropriate therapeutic option for DM at this time?

**XI. Systemic therapy for metastatic/recurrent breast cancer**

A. General considerations

1. Goals of therapy: palliation, prolongation of life (if possible) and to maximize quality of life; cure is not likely (< 5% at 10 years).

2. Median survival 3 years; however, in some selected patients disease is controlled for many years with good quality of life.

3. Bone and soft tissue metastases tend to have a better prognosis and are more likely to respond to endocrine therapy.

4. Symptomatic visceral metastases generally require chemotherapy due to need for rapid response.

5. Brain metastases generally do not respond to the standard chemotherapy regimens given for breast cancer; however, there are reports of responses to some chemotherapy and endocrine therapy regimens.

6. ER and PR positive breast cancers tend to be more indolent and respond better to endocrine therapy than cancers that are negative for these receptors.
Patient case #5 (continued): DM has bone-only metastases, her primary tumor was ER/PR positive, the Ki-67 was low, and she is relatively asymptomatic (pain controlled with OTC analgesics). All of these features suggest that she should receive endocrine therapy.

What specific endocrine therapy would be most appropriate?

B. Endocrine therapy
   1. General principles
      a. Targets:
         1) Inhibit or eliminate the production of estrogen
            a) Oophorectomy or LHRH agonist (premenopausal women).
            b) Aromatase inhibitors (postmenopausal women).
         2) Block the effect of estrogen at the cellular level (pre- and postmenopausal)
            a) Selective estrogen receptor modulators (SERMs).
            b) Selective estrogen receptor down-regulators (SERDs).
      b. If a patient responds to an endocrine therapy, it predicts response to another endocrine agent; the number of patients who respond decreases with each subsequent line of therapy.
1) Because many patients have bone disease, difficult to determine response.

2) Data indicate that patients who achieve stabilization of disease for \( \geq 24 \) weeks have a similar OS compared to those patients who achieve an objective response. "Clinical benefit" often one of the primary endpoints in trials (CB = complete response (CR) + partial response (PR) + stable disease (SD) \( \geq 24 \) weeks).

2. Combination vs. sequential single agents
   a. Combinations have never been shown to be superior to single agent endocrine therapy in terms of efficacy; more toxicity related to combinations.
   b. Only exception may be LHRH agonists for ovarian suppression.

3. Definition of menopause
   a. See Adjuvant Endocrine Therapy section.

4. Treatment Decisions in Metastatic Breast Cancer - Endocrine Therapy

---

FIGURE 7: Treatment Algorithm: Endocrine Therapy for Metastatic Breast Cancer

* Limited data supports an improvement in PFS with the use of trastuzumab or lapatinib in combination with an aromatase inhibitors for postmenopausal women with ER+, HER2+ metastatic breast cancer. No difference in overall survival was noted.

b Conflicting data exists regarding the combination of an AI plus fulvestrant in postmenopausal women with hormone receptor-positive MBC in the first-line setting. See the Selective Estrogen Receptor Down-regulators (SERDs) section for further details.

c The combination of exemestane and everolimus can be considered in women who fulfill the eligibility criteria of BOLERO-2.
Aromatase inhibitors

1) Mechanism of action: inhibit cytochrome P450 enzyme(s) responsible for estrogen production through peripheral aromatization.

2) Anastrozole (Arimidex®)
   a) Selective, nonsteroidal, competitive aromatase inhibitor; no intrinsic hormonal properties.
   b) Typically first- or second-line therapy (RR=20-40%); some efficacy after steroidal AI (exemestane).
   c) Also some data with fulvestrant (see Selective Estrogen Receptor Down-regulators section) and trastuzumab in HER2-overexpressing MBC (see Biologic therapy section).
   d) **Dose:** 1 mg PO daily; higher doses (10 mg) no better efficacy and more nausea.
   e) **Toxicity:** asthenia, myalgias/arthralgias, headaches, diarrhea, hot flashes, mild nausea, vaginal dryness, possible bone loss with long-term use.
   f) Ongoing trials include: use with LHRH agonists in premenopausal women or with fulvestrant in MBC (see Fulvestrant section for further details).
   g) Significant pharmacokinetic interaction with anastrozole and tamoxifen (decrease anastrozole levels by 27%). May be why ATAC trial combination arm had similar efficacy compared with tamoxifen alone.157

3) Letrozole (Femara®)
   a) Selective, nonsteroidal aromatase inhibitor; similar mechanism to anastrozole; no intrinsic hormonal properties.
   b) Typically first- or second-line therapy (RR=20-40%); some efficacy after steroidal AI (exemestane); also some data with lapatinib in HER2-overexpressing MBC (see Biologic therapy section).
   c) **Dose:** 2.5 mg PO daily
   d) **Toxicity:** hot flashes, mild nausea, headache, fatigue, arthralgias, possible bone loss with long-term use.
   e) Ongoing trials include: with LHRH agonists in premenopausal women.
   f) Significant pharmacokinetic interaction with letrozole and tamoxifen (decrease letrozole levels by 38%).158

4) Exemestane (Aromasin®)
   a) Steroidal aromatase inactivator; irreversibly binds to enzyme; requires production of new enzyme to overcome inhibition; similar structure to androstenedione (androgen).
   b) Similar efficacy to anastrozole and letrozole (no direct comparisons in MBC, see Adjuvant Hormone Therapy section); also data with everolims in patients with MBC (see Biologic therapy section).
c) Some efficacy after failing aminoglutethimide or non-steroidal aromatase inhibitors (27% and 21% CB, respectively).

d) Dose: 25 mg PO daily.

e) Toxicity: fatigue, hot flushes, nausea, dyspnea, anxiety, insomnia, pain at tumor sites, asthenia.

f) Ongoing trials include use with fulvestrant in MBC

g) Mild androgenic effects may be seen with long-term use?

5) One study comparing letrozole to anastrozole$^{159}$

a) Second-line treatment after tamoxifen.

b) Letrozole 2.5mg/day (n=356) vs anastrozole 1mg/day (n=357).

c) Only 48% of patients had ER/PR positive disease; no independent response review; multiple problems with concurrent therapies (e.g., estrogen) and other issues with the trial.

d) Overall response rate (ORR): Letrozole = 19% vs anastrozole = 12% (p=0.013).

e) CB: Letrozole = 27% vs anastrozole = 23% (p=0.218).

f) No difference in time to progression (TTP), time to recurrence (TTR), duration of response or durations of CB.

g) Similar side effect profile.

h) Poor study; severely flawed.

6) One study comparing anastrozole to exemestane$^{160}$

a) Randomized, open label, crossover phase II trial exemestane 25 mg/day (n=51) vs anastrozole 1mg/day (n=52).

b) Overall response rate (ORR): exemestane = 36% vs anastrozole = 46% (p=not reported).

c) CB: exemestane = 60% vs anastrozole = 68% (p=not reported).

d) Similar side effect profile.

e) No significant differences in clinical activity.

f. Antiestrogens

1) Selective estrogen receptor modulators (SERMs)

a) Tamoxifen (Nolvadex® , generic)

i. Tissue-specific activity; estrogenic - bones, lipids, endometrium; antiestrogenic - breast, vaginal mucosa.

ii. First-line therapy for metastatic premenopausal patients, typically utilized after failure of AIs in postmenopausal women; RR 16-52% .
iii. Some data in combination with everolimus (see Targeted Therapy section).

iv. **Dose:** 20 mg PO daily (available in 10 mg and 20 mg tabs); Europeans use up to 40 mg/day; no data supporting doses higher than 40 mg/day.

v. **Toxicity:** hot flashes, mild nausea, thromboembolic events, vaginal discharge, endometrial hyperplasia, endometrial cancer (long-term use), ocular effects (high doses), no hepatic carcinogenesis (only in animal models).

vi. **Benefits:** prevent bone loss in postmenopausal patients (not as effective as estrogen), decrease total cholesterol (no effect on HDL).

vii. Potential drug interactions with CYP2D6 inhibitors (see section VIII, Treatment of Hot Flashes).

b) Toremifene (Fareston®)

i. No advantage over tamoxifen; less data supporting its use long-term; RR similar in randomized, controlled comparative trials.

ii. Endometrial effects are questionable; in animals, no effect on endometrium; humans - similar effects compared to tamoxifen to date.

iii. **Dose:** 60 mg PO daily; higher doses did not provide better responses.

iv. **Toxicity:** similar to tamoxifen in all respects (animal data differs).

v. **Benefits:** effects on bones appear to be similar to tamoxifen; effects on lipids are still controversial between the two agents; both lower total cholesterol, toremifene may have a more substantial effect on lipids vs tamoxifen.

vi. Near complete cross-resistance between agents (0% response; 27% SDx4weeks); some patients may benefit if time has elapsed between therapies.

g. Selective Estrogen Receptor Down-regulators (SERDs) - Fulvestrant (Faslodex®)

1) Binds to ER, antagonizes receptor, also down-regulates receptor expression; no agonistic activity on ER.

2) Approved for use after tamoxifen failure in postmenopausal women only:

   a) Compared to anastrozole as second-line therapy for MBC. Two parallel studies (similar design to anastrozole vs tamoxifen).\(^\text{161, 162}\)

   b) Postmenopausal women only (due to anastrozole arm); limited data available in premenopausal women.

   c) Fulvestrant 250mg IM Q 28 days vs Anastrozole 1mg PO q day.
d) Similar outcomes with Fulvestrant vs Anastrozole (TTP, response rate, CB rate).

e) Similar tolerability issues (hot flashes); injection site reactions more frequent with 2 injection-dosing vs 1 injection-dosing.

3) Compared with tamoxifen as front-line therapy for metastatic, postmenopausal, hormone-receptor positive breast cancer.  \(^{163}\)

a) Fulvestrant 250 mg IM Q 28 days vs tamoxifen 20 mg PO daily

b) Did not meet endpoints for non-inferiority; basically inferior to tamoxifen as front-line therapy.

4) Compared with exemestane as second-line therapy for metastatic, postmenopausal, hormone-receptor positive breast cancer in women who progressed on a non-steroidal aromatase inhibitor.  \(^{164}\)

a) **Fulvestrant loading dose (500 mg IM on day 0, 250 mg IM on days 14 & 28; then 250 mg IM Q 28 days)** vs exemestane 25 mg PO daily (n=693)

b) Randomized, placebo-controlled, double-blind, double-dummy, multicenter, phase 3 trial.

c) Similar TTP (3.7 mo in both groups, p=0.65), duration of response (p-value not reported), clinical benefit rate (p=0.853), and toxicity

5) Compared with anastrozole as first-line therapy for metastatic, postmenopausal, hormone-receptor positive breast cancer.  \(^{165}\)

a) Randomized, open-label, multicenter, phase 2 trial

b) **High dose fulvestrant (500 mg IM on day 0, 500 mg IM on days 14 & 28; then 500 mg IM Q 28 days)** vs anastrozole 1 mg PO daily (n=205)

c) Similar clinical benefit rate (72.5% vs 67.0%, p=0.386) and toxicity

d) Improved TTP for patient with HD fulvestrant vs anastrozole (median TTP not reached with fulvestrant vs 12.5 months for anastrozole, p=0.0496)

6) Two dosing schedules compared after antiestrogen: 250 mg IM q28d vs 500 mg IM on day 0, 500 mg IM on days 14 & 28; then 500 mg IM Q 28 days  \(^{166}\)

a) Randomized, double-blind, placebo controlled phase 3 trial (n=736)

b) PFS (primary endpoint) was improved for patients who received high dose fulvestrant vs standard dosing (6.5 mo vs 5.5 mo, p=0.006)

c) Similar ORR, CBR, OS, and toxicities between the two groups

d) Final OS results with further follow-up show an improvement with high dose fulvestrant (26.4 months vs. 22.3 mo, p=0.02).  \(^{167}\)
e) Resulted in labeling changes to list higher dosing as the new standard: 500 mg IM on day 1, 15, & 29; then once monthly thereafter.¹⁶⁸

7) Recent Phase III RCT comparing anastrozole to anastrozole plus fulvestrant in postmenopausal women with HR+ MBC (first-line setting)¹⁶⁹

a) Fulvestrant loading dose (500 mg IM on day 0, 250 mg IM on days 14 & 28; then 250 mg IM Q 28 days) vs anastrozole 1 mg PO daily (n=707)

b) Crossover to fulvestrant after progression on anastrozole encouraged (crossover occurred in 41% of patients randomized to anastrozole)

c) PFS (15 mo vs 13.5 mo, HR=0.80 95% CI 0.68-0.94, p=0.007) and OS (47.7 mo vs 41.3 mo, HR=0.81 95% CI 0.65-1.00, p=0.049) were significantly longer for the combination of anastrozole plus fulvestrant than for anastrozole alone.

d) Adverse events not significantly different by treatment group

e) Results from the FACT¹⁷⁰ and SoFEA¹⁷¹ trials of similar study design were negative

f) One limitation of this study was that the new higher fulvestrant 500 mg dosing schedule not used in this study

g) Further study of this combination is needed

h. LHRH agonists (also see prostate cancer material)

1) Leuprolide (Lupron®)

a) Not approved in the US for breast cancer.

b) Use in premenopausal patients only; limited use secondary to fact that premenopausal patients tend to have more aggressive tumors and tend to be ER negative.

c) Similar to oophorectomy data; Europeans use quite often; studies ongoing in adjuvant setting; RR in MBC 44% (small study).

d) Dose: 3.75 mg IM Q4weeks; prolonged delivery formulations not tested.

e) Toxicity: hot flashes, injection site reaction, bone loss with long-term use.

f) Investigational use with aromatase inhibitors in premenopausal breast cancer (complete estrogen blockade, phase II data only).

g) Combination data with tamoxifen controversial; see adjuvant therapy section.

2) Goserelin (Zoladex®)

a) Use is similar to leuprolide; similar efficacy; RR 31-63% (more data available than with leuprolide).
b) Approved for advanced breast cancer in the U.S.; adjuvant trials ongoing.

c) **Dose:** 3.6 mg SQ Q4weeks; prolonged delivery formulations not tested.

d) Slightly different administration technique; subcutaneous pellet injected.

e) **Toxicity:** hot flashes, injection site reactions, bone loss with long-term use.

f) Investigational use with aromatase inhibitors in premenopausal breast cancer (phase 2 data only).

g) Combination data with tamoxifen controversial; see Adjuvant therapy section.

3) Triptorelin (Trelstar®)

   a) Approved for prostate cancer only.

   b) Phase 2 trials indicate significant response in HR-positive patients (70%) as first line therapy for metastatic breast cancer.

   c) **Dose:** 3.75 mg IM Q 28 days (tamoxifen was given for first 28 days to cover for flare reaction); prolonged delivery formulations not tested.

   d) **Toxicity:** hot flashes, injection site reactions, bone loss with long-term use.

   e) Phase 3 trials with combinations with aromatase inhibitors and antiestrogens ongoing.

i. Progestins

1) Megestrol acetate (Megace®)

   a) Mechanism is unknown; may involve direct effect on the cell through the progesterone receptor.

   b) RR 25-45%; overall survival rate is lower compared to new aromatase inhibitors.

   c) **Dose:** 40 mg PO QID or 80 mg PO BID; higher doses only contribute to more toxicity.

   d) **Toxicity:** weight gain, edema, vaginal bleeding (upon w/draw), thromboembolic events.

2) Medroxyprogesterone (Provera®)

   a) Mechanism is unknown.

   b) RR 40%; used in Europe extensively.

   c) **Dose:** 500 mg-1000 mg IM QD x 30 days then Q week (no depot formulation); poor oral bioavailability.

   d) **Toxicity:** weight gain, edema, uterine bleeding (upon w/draw), thromboembolic events.
j. Androgens

1) Fluoxymesterone (Halotestin®)
   a) Mechanism is unknown: may act through androgen receptors present on some breast cancers or may act through another indirect mechanism of cellular function.
   b) RR 20%; usually used as salvage.
   c) Dose: 10 mg PO BID.
   d) Toxicity: virilization (facial hair, deepening voice, hair loss, acne, increased libido), mild nausea.

2) Danazol (Danocrine®)
   a) Mechanism is unknown.
   b) RR 20%; usually used as salvage.
   c) Dose: 200 mg PO TID.
   d) Toxicity: edema, hot flashes, weight gain.

k. Estrogens

1) Diethylstilbestrol (DES®)
   a) Some institutions compounding from raw materials - used as salvage.
   b) Dose: 5 mg PO TID (high doses)
   c) Not well tolerated; nausea, edema, thromboembolic events.

2) Ethinyl estradiol (generics)
   a) Little information; mechanism unknown; may be a dose effect overcoming the estrogenic mechanisms of tumor growth.
   b) Dose: 3mg PO daily; high doses are required.
   c) Toxicity: fluid retention (usually give HCTZ with it), nausea, thromboembolic events.

Patient case #5 (continued): DM is now postmenopausal and has been taking adjuvant tamoxifen therapy. Postmenopausal status would be verified by asking the patient about her most recent menstrual cycle and through laboratory measurements (estradiol and FSH). The most appropriate therapy would be to stop tamoxifen and give an aromatase inhibitor. Anastrozole 1 mg PO daily, Letrozole 2.5 mg PO daily and Exemestane 25 mg PO daily all have data to support their efficacy and safety in this setting, compared with megestrol acetate. If she responds to this therapy (e.g., clinical response or shrinkage on diagnostic imaging, stabilization of disease for prolonged period), then subsequent endocrine therapies would be considered (e.g., fulvestrant or switching from non-steroidal AI to exemestane and everolimus). Data with frontline fulvestrant + anastrozole for hormone-receptor positive MBC is conflicting, and therefore controversial. Endocrine therapy would be continued sequentially until her disease became hormone-refractory, she exhausted all her endocrine therapy options, or she began having significant symptoms from her breast cancer. Chemotherapy would be considered in those circumstances.

Is any other supportive therapy indicated at this time?
BONE METASTASES

I. Epidemiology\textsuperscript{172}

A. Incidence is high in patients with advanced cancer
   1. 50% of breast cancer patients each year develop metastases and 65-75% of these patients develop bone metastases.

B. Skeletal-related events include:
   1. Pathologic fracture
   2. Spinal cord compression
   3. Surgery to bone
   4. Radiotherapy to bone
   5. +/- Hypercalcemia

II. Etiology & Pathophysiology\textsuperscript{172}

A. Adult bones undergo continuous bone remodeling by osteoclasts and osteoblasts. Osteoclasts first breakdown bone to form a resorption cavity, then this resorption stimulates osteoblasts to form new bone over the resorption cavity.

B. Radiographically lesions are described as osteolytic, osteoblastic or mixed.
   1. Osteolytic lesions (appear less dense on radiographs)
      a. Tumor cells activate osteoclast activity without any stimulation of osteoblastic activity.
      b. Parathyroid hormone related protein (PTHrP; secreted by tumor cells) thought to be important factor in breast cancer bone metastases.
   2. Osteoblastic lesions (appear more dense on radiographs)
      a. Tumor cells stimulate osteoclasts and osteoblasts with the new bone formation being deposited in sites unrelated to the resorption cavities.
      b. Factors related to osteoblast activation are largely unknown; may be related to similar mechanisms as seen with PTHrP.
   3. Mixed lesions (appear to have features of both osteolytic and osteoblastic lesions).
      a. Most common for patients with breast cancer
   4. Regardless of appearance, excess bone resorption is the hallmark of all malignant bone lesions and compromises the integrity of the bone matrix, resulting in skeletal complications of malignancy.
      a. Tumor cells secrete factors (autocrine and paracrine) that cause an imbalance in bone resorption and formation.
      b. Many of these factors are being investigated as potential therapeutic targets.
C. Biochemical markers of:

1. Bone resorption includes urinary calcium, acid phosphatase, hydroxyproline, n-telopeptide, and c-telopeptide (useful as study endpoints, but not clinically relevant at this time).

2. Bone formation includes bone-specific isoform of alkaline phosphatase (BAP) and procollagen peptide fragments formed during the conversion to mature collagen (investigational only).

III. Management

A. ASCO Update on bone modifying agents (BMA) in MBC

1. Patients with evidence of bone metastases by radiography, CT or MRI (but not only by abnormal bone scan) should be offered a BMA with concurrent anticancer treatment.
   a. Pamidronate 90 mg IV over at least 2 hours Q 3-4 weeks OR
   b. Zoledronic acid 4 mg IV over at least 15 minutes Q 3-4 weeks OR
   c. Denosumab 120 mg SQ every 4 weeks.

2. There is insufficient evidence regarding efficacy to support one bone modifying therapy over another.

3. BMA should be continued until evidence of a substantial decline in a patient’s general performance status.

B. Bisphosphonates

1. Inhibits osteoclast maturation and function – pamidronate and zoledronate approved for this indication in U.S; others being investigated (e.g., clodronate, ibandronate).

2. Affinity for bone with exposed minerals (areas of osteolysis).

3. Efficacy
   a. Cochraine review of bisphosphonates and other agents for breast cancer
   
   1) For patients with MBC to bone (n=2806), the use of bisphosphonates (zoledronic acid IV, pamidronate IV, ibandronate IV, clodronate PO) reduced the risk of SREs by 15% vs. placebo or no bisphosphonates (RR 0.85; 95% CI 0.77 to 0.94).

   b. Optimal duration of therapy unknown

   1) Patients generally on these therapies indefinitely; however, with growing concern over longer-term toxicities (especially ONJ; see next section), multiple studies are ongoing to better determine optimal duration of therapy (with zoledronic acid).

   2) ZOOM trial compared zoledronic acid 4 mg IV every 4 weeks vs. every 12 weeks for one year in 425 patients with MBC to bone
   a) Non-inferiority design
   b) Patients were enrolled after completing 12-15 months of monthly zoledronic acid.
c) The skeletal morbidity rate (primary endpoint) was 0.26 in the 12 week group and 0.22 in the 4 week group, which met the criteria for noninferiority.

3) The OPTIMIZE trial was a prospective, randomized, double-blind clinical trial that randomized patients to zoldronic acid 4 mg IV either every 4 weeks or every 12 weeks after receiving 9 or more doses of ZA for MBC to bone.\(^{177}\)
   a) 403 patients with metastatic breast cancer to bone were randomized to ZA every 4 weeks or ZA every 12 weeks.
   b) Rates of SREs were similar between the two arms, and met the criteria for non-inferiority.
   c) The incidence of treatment-emergent adverse events was similar between the two arms, but renal adverse events were numerically higher in patients who received every 4 week ZA.

4) The BISMARK trial (BISphosphonate therapy directed by bone resorption MARKers) is evaluating the benefit of using bone markers to tailor frequency of treatment and predict the patients' risk of bone metastases.

4. Safety considerations
   a. Renal dysfunction
      1) Patients with impaired renal function should receive reduced doses of zoledronate when being administered for bone metastases as noted below:

<table>
<thead>
<tr>
<th>Baseline Creatinine Clearance (mL/min)</th>
<th>Recommended Dose Zoledronate (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 60</td>
<td>4</td>
</tr>
<tr>
<td>50-60</td>
<td>3.5</td>
</tr>
<tr>
<td>40-49</td>
<td>3.3</td>
</tr>
<tr>
<td>30-39</td>
<td>3.0</td>
</tr>
</tbody>
</table>

2) Similar percent recommendations could be made for pamidronate; but no specific data in product information noted.

3) Lengthening the duration of the infusion has also been noted to help the renal clearance and minimize renal dysfunction related to these compounds.

4) These recommendations have not been well-studied and are only recommendations.

5) Patients with more severe renal dysfunction (Cr > 3.0) have not been sufficiently studied.

6) Generally do not dose reduce when treating hypercalcemia of malignancy (HCM).

7) Monitoring
   a) ASCO recommends checking serum Cr prior to each dose.
   b) Electrolytes, calcium, phosphorus, magnesium, Hg/HCT should be monitored periodically (interval not suggested).
b. Hypocalcemia, hypophosphatemia, hypomagnesemia
   1) Guidelines for zoledronic acid (product information) indicate calcium supplementation should be given to all patients (500mg + 400 IU vitamin D daily); would not supplement in a patient with a history of hypercalcemia or extensive bone metastases.
   2) No other guidelines for supplementation – close monitoring recommended.

c. Myalgias/arthralgias (flu-like symptoms including fever)
   1) Usually occurs within 48 hours of infusion with the first and possibly the second dose of bisphosphonate therapy.
   2) Usually managed with OTC NSAIDs or acetaminophen and/or transient increases in the patients’ current pain medication regimen.

d. Atrial fibrillation
   1) A meta-analysis evaluated six randomized clinical trials (n=43,375) and six observational trials (149,856) with bisphosphonates and the risk of atrial fibrillation.\textsuperscript{178}
   2) Risk for a-fib was increased with bisphosphonate users (OR 1.27 95% CI 1.16-1.39).
   3) Widely debated association due to multiple confounding variables; most reports appear to implicate zoledronic acid, with few reports with oral bisphosphonates.

e. Osteonecrosis of jaw\textsuperscript{179}
   1) More than 600 cases now reported with long-term use of pamidronate and zoledronic acid; cases have also been reported with oral bisphosphonates, alendronate and residronate.
   2) Common terminology to describe death of bone cells (osteocytes in the cortical bone and cells of the bone marrow organ residing in the hematopoietic compartment of trabecular bone); also destroys bone endothelial cells and vasculature leading to impaired blood flow within the bone; lesions exposing bone in the mouth (e.g., mandible, maxilla) do not heal due to lack of blood flow.
   3) Usually present as painful, soft tissue swelling and infection, loosening teeth, drainage, exposed bone, or it may be asymptomatic.
   4) Most cases were diagnosed after dental procedures such as tooth extractions, though a few cases occurred spontaneously.
   5) Causality is still questionable; many reviews into this phenomenon and whether it is related to bisphosphonate therapy or not (may be related to radiotherapy, chemotherapy, glucocorticoids, other factors).
   6) Proposed clinical staging and treatment strategies:
Table 18. Proposed Staging and Treatment for Bisphosphonate (BP)-Induced Osteonecrosis of the Jaw (ONJ)\textsuperscript{179}

<table>
<thead>
<tr>
<th>Stage</th>
<th>Pre-ONJ</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical features</td>
<td>• Patients treated with BP</td>
<td>• Exposed/necrotic bone</td>
<td>• Exposed/necrotic bone</td>
<td>• Exposed/necrotic bone with pain, infection, and one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>• No apparent exposed/necrotic bone</td>
<td>• Asymptomatic</td>
<td>• Infection as evidenced by pain, erythema in region of the exposed bone</td>
<td>• Pathologic fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No evidence of infection</td>
<td>• With or without purulent drainage</td>
<td>• Extra-oral fistula or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Osteolysis extending to the inferior border</td>
</tr>
<tr>
<td>Management</td>
<td>Patient education</td>
<td>• Antibacterial mouth rinses</td>
<td>• Symptomatic treatment with broad-spectrum oral antibiotics</td>
<td>• Antibacterial mouth rinses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Clinical follow-up on a quarterly basis</td>
<td>• Oral antibacterial mouth rinses</td>
<td>• Antibiotic therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Patient education</td>
<td>• Pain control</td>
<td>• Pain control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Review indications for continued BP therapy</td>
<td>• Only superficial debridement to relieve soft-tissue irritation</td>
<td>• Surgical debridement or resection for long-term palliation of infection and pain</td>
</tr>
</tbody>
</table>

7) Recommendations in product information include:
   a) Baseline dental examination prior to initiating a bisphosphonate.
   b) Periodic oral examination during bisphosphonate therapy, limiting invasive dental procedures if at all possible.

8) If ONJ does occur, a minimalistic approach appears to be the best course of action. Aggressive surgical debridement delays healing and worsens the condition.

C. Denosumab (Xgeva\textsuperscript{TM})
   1. Denosumab received FDA approval in November, 2010 to prevent skeletal-related events in cancer patients with breast cancer and bone metastases.
   2. This agent is a fully human IgG2 monoclonal antibody that binds to RANK ligand which is a protein found on osteoclasts and involved in bone breakdown.
   3. The approved dose is 120 mg SQ every 4 weeks.
   4. Denosumab is also marketed as Prolia\textsuperscript{TM} and indicated for postmenopausal osteoporosis at a dose of 60 mg SQ every 6 months.
   5. A randomized phase III trial compared denosumab to zoledronic acid in delaying or preventing skeletal-related events in patients with MBC to bone.\textsuperscript{180}
a. SREs were defined as pathologic fracture, radiation or surgery to bone, or spinal cord compression.
b. The primary endpoint of time to first on-study SRE (noninferiority comparison) was met (HR, 0.82; 95% CI, 0.71 to 0.95).
c. Secondary endpoints:
   1) Time to first on-study SRE was longer with denosumab vs. zoledronic acid (superiority comparison, HR, 0.82; 95% CI, 0.71 to 0.95) and the risk of multiple SREs was reduced with denosumab vs. zoledronic acid (RR 0.77; 95% CI, 0.66 to 0.89.)
d. Overall survival and progression free survival were similar between the two groups.
e. The risk of osteonecrosis of the jaw, hypocalcemia and hypophosphatemia with denosumab was similar to zoledronic acid.

6. Denosumab is administered subcutaneously and there are no major concerns about renal dysfunction as seen with the bisphosphonates however, severe hypophosphatemia may occur in patients with renal insufficiency.

7. The risk of osteonecrosis of the jaw, hypocalcemia and hypophosphatemia is similar to the bisphosphonates.

Patient case #5 (continued): Since this patient has new metastatic breast cancer to the bone, the addition of a supportive therapy for bone metastasis would also be discussed with the patient. Based on the ASCO Update on BMA in MBC, zoledronic acid, pamidronate, or denosumab would be an appropriate option. The patient should have a baseline dental evaluation prior to starting the BMA. Baseline renal function should be evaluated for all BMAs and prior to each dose of bisphosphonates. Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should be monitored regularly with bisphosphonates. Serum calcium and phosphate should be monitored regularly with denosumab. She would continue on a BMA for at least 2 years, or until there is a significant deterioration in her performance status.

Patient case #6: TP is a 45 y/o premenopausal woman with newly diagnosed lung metastases. She was originally diagnosed approximately 16 months ago with a stage IIIIB left breast cancer (T3, N1, M0, invasive ductal carcinoma, ER/PR negative, HER2 normal by FISH, Ki-67 30%), underwent preoperative chemotherapy with weekly paclitaxel for 12 weeks followed by FAC x 4 cycles followed by a segmental mastectomy with axillary lymph node dissection. She has done well since surgery, but now presents with a history of 4 - 6 weeks of persistent dry cough that has been treated with two courses of antibiotics prescribed by her local primary care physician. A chest x-ray was performed about 1 week ago and demonstrated new nodules in both lungs, which were biopsied under CT-guidance and found to be positive for metastatic carcinoma consistent with breast primary. She is also not able to walk very far without becoming short of breath and coughing.

What would be the most appropriate therapy for TP at this time?

This section is continued from XI. Systemic Therapy for Metastatic/Recurrent Breast Cancer

C. Chemotherapy
   1. General considerations
      a. No well-defined clinical characteristics to identify patients likely to benefit from chemotherapy.
1) HER2-overexpressed and ER-negative tumors have been looked at for predictive value with conflicting results.

2. Consider first-line chemotherapy for patients with:
   a. ER/PR negative tumors.
   b. Symptomatic, visceral sites of metastases (visceral crises).
   c. Faster growing; high ki-67.

3. Combination vs. sequential single agents
   a. Widely debated.
   b. Combination regimens are generally associated with higher response rates compared with single agent chemotherapy.
   c. Increases in OS have been demonstrated with few regimens; none of which were compared with sequential administration of the same agents.

1) Only 1 study prospectively designed to study combination therapy compared to both agents administered sequentially.\(^{181}\)
   a) \(A \rightarrow T\) vs \(T \rightarrow A\) vs \(AT\) (\(T\) = paclitaxel).
   b) Crossover to other single agent upon progression was part of study design.
   c) Response rates were higher with \(AT\) vs single agents (\(A=36\%\), \(T=34\%\), \(AT=47\%\); \(A\) vs \(AT\) \(p=0.017\); \(T\) vs \(AT\) \(p=0.006\)).
   d) TTF longer with \(AT\) vs single agents (\(A=6\) mo, \(T=6.3\) mo, \(AT=8.2\) mo; \(A\) vs \(AT\) \(p=0.0022\); \(T\) vs \(AT\) \(p=0.0567\)).
   e) OS was similar between all groups (\(A=19.1\)mo, \(T=22.5\)mo, \(AT=22.4\)mo; \(A\) vs \(AT\) \(p=0.82\); \(T\) vs \(AT\) \(p=0.49\)).

2) O’Shaughnessy J et al.\(^{182}\)
   a) Docetaxel vs docetaxel + capecitabine.
   b) **Only 18% of patients on docetaxel received capecitabine upon progression.**
   c) Response rates were higher with combination (42% vs 30%, \(p=0.006\)).
   d) TTP higher with combination (6.1 vs 4.2mo; HR=0.652; 95% CI=0.545-0.78; \(p=0.0001\)).
   e) OS higher with combination (14.5 vs 11.5mo; HR=0.775; 95% CI=0.634-0.947; \(p=0.0126\)).
   f) Did not adequately compare sequential use of these agents to combination.

3) Albain K et al. \textit{J Clin Oncol} 2008 26(24):3950-9.\(^{183}\)
   a) Paclitaxel vs paclitaxel + gemcitabine (\(n=529\)).
   b) Response rates were higher with the combination (41.4% vs 26.2%, \(p=0.0002\)).
   c) Median TTP = 6.14 mo vs 3.98 mo (HR 0.70; 95% CI=0.59-0.85; \(p=0.0002\)).
d) OS higher with combination (18.6 mo v 15.8 mo; HR=0.82; 95% CI=0.67-1.00; p=0.0489).

e) Safety: increased toxicity with combination, including anemia (increased RBC transfusions), neutropenia, febrile neutropenia, thrombocytopenia, motor neuropathy, fatigue and elevations in transaminases.

d. Widely accepted that combination chemotherapy regimens impart greater toxicity.

e. In metastatic setting, toxicities are not warranted with most combination regimens.

f. Patients who require a rapid response to chemotherapy (e.g., symptomatic, bulky disease) may benefit from a combination regimen, despite the added toxicity.

g. Very complex decision; made on an individual basis. No standard regimen.

4 Treatment Decisions in Metastatic Breast Cancer – Chemotherapy

<table>
<thead>
<tr>
<th>Preferred Agents</th>
<th>Preferred Combinations</th>
<th>Other Active Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines(a)</td>
<td>CAF/FAC/FEC</td>
<td>Cisplatin/carboplatin</td>
</tr>
<tr>
<td>Taxanes(b)</td>
<td>AC/EC</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>CMF</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Gemcitabine/carboplatin</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Docetaxel/capecitabine</td>
<td>Albumin-bound paclitaxel</td>
</tr>
<tr>
<td>Eribulin</td>
<td>Gemcitabine/paclitaxel</td>
<td>Ixabepilone</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel/bevacizumab(c)</td>
<td></td>
</tr>
</tbody>
</table>

FIGURE 8: Chemotherapy for Metastatic Breast Cancer\(^{32}\)
Clinical trials should always be considered. If no response to 3 sequential lines of chemotherapy or poor performance status, consider no further cytotoxic therapy.

\(a\) Includes doxorubicin and pegylated liposomal doxorubicin.

\(b\) Includes paclitaxel.

\(c\) Addition of bevacizumab to chemotherapy modestly improves time to progression but not survival.

a. Anthracyclines (doxorubicin, epirubicin, liposomal doxorubicin products)

1) Relative comparisons with single agents (doxorubicin to epirubicin ratios):

a) Efficacy: 75mg/m^2 dox \(\approx\) 90mg/m^2 epi OR 60mg/m^2 dox \(\approx\) 90mg/m^2 epi (2 different studies).

b) Myelosuppression (equimyelotoxic doses): 75mg/m^2 dox \(\approx\) 90mg/m^2
c) **Cardiotoxicity (cumulative lifetime maximum doses):** 450-500mg/m² bolus dox ≈ 900mg/m² bolus epi ≈ 900-1000mg/m² continuous infusion dox

d) **Mucositis:** at equimyelotoxic doses, epi and dox have similar mucositis

e) **Nausea/vomiting:** at equimyelotoxic doses, epi and dox have similar nausea/vomiting

2) **Liposomal doxorubicin products**

   a) Pegylated liposomal doxorubicin (not approved for breast cancer in US)

   b) Phase 3 trial comparing to conventional doxorubicin.\(^{184}\)

      i. Metastatic breast cancer patients; no prior chemotherapy for MBC; prior adjuvant anthracyclines were allowed (cumulative doxorubicin equivalents ≤300 mg/m\(^2\)). Non-inferiority analysis.

      ii. Peg-dox (50mg/m\(^2\) IV Q 4 weeks) vs Dox (60mg/m\(^2\) IV over 60 minutes Q 3 weeks)

      iii. Median PFS was similar (Peg-dox 6.9 mo vs Dox 7.8 mo; p= not reported)

      iv. Median OS was also similar (Peg-dox 21 mo vs Dox 22.0 mo; p=not reported)

      v. Side effects: less alopecia, myelosuppression, nausea/vomiting with Peg-dox; less cardiotoxicity despite a higher cumulative dose of Peg-dox (398 mg/m\(^2\) vs 421 mg/m\(^2\)); however, hand-foot syndrome (HFS) and infusion reactions are more common with Peg-dox.

3) **Cross-resistance with anthracyclines**

   a) Doxorubicin pretreated patients may respond to Peg-dox

      i. One Phase 2 trial – 70 patients with MBC more than 12 months after adjuvant anthracycline therapy.\(^{185}\)

      ii. Peg-dox + cyclophosphamide – ORR = 38%, CBR = 71%, median TTP = 12.2 months, no symptomatic cardiac events.

   b) Conversions for calculating cumulative doxorubicin dose have not been established for this agent; but it appears to be less cardiotoxic compared with equal bolus doses of conventional doxorubicin (perhaps similar to continuous infusion doxorubicin).\(^{186}\)

   c) Must consider risks and benefits of additional anthracyclines in anthracycline-pretreated patients.

b. **Taxanes**

   1) **Paclitaxel (Taxol\(^{®}\))**
a) Q 3 week dose for metastases is typically 175 mg/m² IV over 3 hours (FDA-approved)

b) Weekly schedules generally preferred (greater efficacy, better toxicity profile, however, also less convenient)
   i. May take advantage of cell cycle with more frequent smaller doses (80 mg/m² over 1 hour weekly without a break is the most commonly used dose)
   ii. Typically infused over 1 hour; but longer infusions may be necessary if hypersensitivity occurs
   iii. Side effects differ with weekly administration: less myelosuppression, alopecia (still significant), and myalgias/arthritis, and peripheral neuropathy is delayed. May see more nail/skin changes and edema with weekly compared with q 3 week.

2) Docetaxel (Taxotere®)
   a) Optimal dose
      i. Q 3 week dose: 60-100 mg/m² over 1 hour (FDA-approved dose)
         (a) Dose comparison trial\(^{187}\)
         (b) 60 vs 75 vs 100 mg/m² IV over 1 hour Q 3 weeks
         (c) Increased response rates with higher doses (60=22.1%; 75=23.3%; 100=36%; p=0.007)
         (d) Increased TTP with highest dose level (60=13.7 weeks; 75=13.9 weeks; 100=18.6 weeks; p=0.023 vs 60 mg/m² and p=0.033 vs 75 mg/m²)
         (e) Similar median survival between groups (60=11.3 mo; 75=10.1 mo; 100=14.7 mo; p=NS)
         (f) Dose may be important for patients with symptomatic or bulky disease
         (g) Side effects also significantly increased with higher dose (neutropenia, febrile neutropenia, infection, stomatitis, diarrhea, and neurosensory)
      ii. Weekly dosing
         (a) 30-35mg/m² weekly most common dose (more toxic compared w/ weekly paclitaxel)
         (b) Steroid regimen studied has been 3 doses of 8 mg (12h, 1h before and 12h after chemotherapy); other regimens may be used; consider rapid taper after third cycle
         (c) Compared with Q 3 week\(^{188}\)
- Q week 35 mg/m² (to 40 mg/m² if tolerated) vs Q3 week 75 mg/m² (to 100 mg/m² if tolerated)
- Increased response rates with Q3 week, but similar PFS and OS
- Higher overall toxicity rate (grade 3/4 toxicities: 88% vs 56%, \( p=0.0001 \)) with Q 3 week compared to weekly
- Asthenia/fatigue becomes dose limiting; skin and nail changes are still significant problem

**b)** Incomplete cross-resistance with paclitaxel\(^{189}\)

i. Response rate of 18% in patients progressing while on paclitaxel

ii. May have to start at a lower dose in patients who are heavily pretreated

**c)** Comparative efficacy (docetaxel vs paclitaxel)\(^{190}\)

i. Docetaxel 100 mg/m² vs Paclitaxel 175 mg/m² Q 3 week \( n=449 \)

ii. OR (CR + PR) = 32% vs 25% \( (p=0.10) \) – no difference

iii. Median TTP = 5.7 vs 3.6 months \( (p=0.0001) \) – docetaxel superior

iv. Median OS = 15.4 vs 12.7 months \( (p=0.03) \) – docetaxel superior

v. Grade 3/4 toxicities greater with docetaxel (55.4% vs 23.0%, \( p<0.001 \))

vi. Paclitaxel not maximally or optimally dosed (weekly paclitaxel superior to Q 3 week paclitaxel in the metastatic setting), but docetaxel was. Nonetheless, infers a benefit with docetaxel over paclitaxel if both agents are given every 3 weeks.

**3)** Paclitaxel protein-bound particles (Abraxane\(^{TM}\))

**a)** Microemulsion of human albumin with paclitaxel; nanoparticle albumin-bound paclitaxel (nab-paclitaxel); Cremophor-free suspension

**b)** Phase 3 clinical trial in MBC:

i. Nab-paclitaxel 260 mg/m² over 30 minutes (no premedications; \( n=229 \)) vs Paclitaxel 175 mg/m² IV over 3 hours every 3 weeks (standard premedications; \( n=225 \)).\(^{191}\)

ii. Response rates significantly better with nab-paclitaxel (33% vs 19%, \( p<0.001 \))

iii. Median TTP 23.0 weeks vs 16.9 weeks \( (p=0.006) \), OS not significantly different
iv. **Safety:** more grade 4 neutropenia (but not febrile neutropenia) with paclitaxel (p<0.001); more grade 2 flushing with paclitaxel (p<0.001); more grade 3 sensory neuropathy with nab-paclitaxel (p<0.001); slightly more grade 2/3 vomiting with nab-paclitaxel (p=0.022).

c) **Weekly administration:**
   i. Weekly x 3 doses Q 28 days (days 1, 8, 15)
   ii. MTD in lightly pretreated patients 150 mg/m²; DLT neuropathy – sensory
   iii. MTD in heavily pretreated patients 100 mg/m²; DLT neutropenia

d) **Phase 2 trials:**
   i. Heavily pretreated, taxane-refractory metastatic breast cancer
      (a) Some benefit in patients treated with prior taxane therapy

<table>
<thead>
<tr>
<th>Prior Taxane</th>
<th>ABX 100 mg/m²</th>
<th>ABX 125 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>21% (n=34)</td>
<td>21% (n=34)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>13% (n=30)</td>
<td>20% (n=20)</td>
</tr>
<tr>
<td>Both</td>
<td>7% (n=15)</td>
<td>0% (n=0)</td>
</tr>
</tbody>
</table>

(b) **Adverse effects (Grade 3/4):**
   - 100 mg/m² (n=106): neutropenia = 17%, sensory neuropathy 8%, nausea = 4%, vomiting = 3%
   - 125 mg/m² (n=75): neutropenia = 32%, sensory neuropathy = 19%, fatigue = 12%, nausea = 3%, vomiting = 1%

e) **Comparative trial - ABX vs Docetaxel randomized phase 2 trial, first-line chemotherapy for MBC.**
   i. Four arm trial:
      (a) ABX 300 mg/m² IV Q 3 weeks (n=76, Arm A)
      (b) ABX 100 mg/m² IV Q week x 3 Q 28 days (D 1,8,15) (n=76, Arm B)
      (c) ABX 150 mg/m² IV Q week x 3 Q 28 days (D 1,8,15) (n=74, Arm C)
      (d) Docetaxel 100 mg/m² Q 3 weeks (n=74, Arm D)
   ii. **Investigator-assessed response:** ABX Q week better than Q 3 week (B vs A, 63% vs 46%, p=0.024; C vs A, 74% vs 46%, p=0.002); ABX weekly schedules better than docetaxel (B vs D, 63% vs 39%, p=0.002; C vs D, 74% vs 39%, p<0.001).
(a) OS favored Arm C (33.8 mo, A=27.7 mo, B=22.2 mo, D=26.6 mo, overall p=0.047), Arm C also superior to Arm B (p=0.008).

(b) Docetaxel had significantly more grade 4 neutropenia (7%, 5%, 9% vs 75%; p<0.001) and grade 3 fatigue (5%, 0%, 4%, 19%, p<0.001) but less grade 3 neuropathy (21%, 9%, 22%, 12%, p=0.083).

iii. Administration issues:

(a) Can use non-PVC or PVC bags and tubing

(b) DO NOT FILTER

(c) No premedications required; may be safer for weekly administration if efficacy is established and safety confirmed in other aspects

c. Capecitabine (Xeloda®)

1) Approved as monotherapy for metastatic breast cancer resistant to paclitaxel and an anthracycline and in combination with docetaxel for MBC after failing an anthracycline-containing regimen. Also, data with ixabepilone + capecitabine (ixa approved in combination) and lapatinib + capecitabine (lapatinib approved in combination).

2) Single agent response rates of 20-30% (CR+PR) in this setting

3) Compared to paclitaxel (175 mg/m² IV Q 3 wk) in patients that failed an anthracycline-containing regimen; RR = Cape (36%) and Pac (26%); similar TTP.¹⁹⁴

4) Oral administration; metabolized to 5-FU through a three-step enzymatic process

5) Dosing:
   a) 2500mg/m²/day PO divided BID x 14 days, then 7 days rest Q 21 days
   b) Full dose often not tolerated; starting dose of 2000mg/m²/day may be a better starting dose with similar efficacy.¹⁹⁵, ¹⁹⁶

6) Available in 500mg tablets and 150 mg tablets (often use only one strength and round doses)

7) Take on a full stomach; avoid antacids; do not take with juices

8) Similar toxicity as seen with continuous infusion 5-fluorouracil; HFS, mucositis, diarrhea, etc.

d. Ixabepilone (Ixempra™)

1) Semisynthetic analogue of Epothilone B; first approved agent in class

2) Microtubule stabilizing agent (similar mechanism to taxanes, but effective in resistant cell-lines)

3) FDA-approved indications:
a) Monotherapy for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane and capecitabine.

b) In combination with capecitabine for the treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline and a taxane.

i. Of note, the ixabepilone + capecitabine combination regimen has been removed from the NCCN Breast Cancer Management guidelines.

4) Efficacy data:

a) Single agent (phase 2 trials)

i. Salvage in triple refractory patients (prior anthracycline, taxane, capecitabine)

ii. Ixa = 40 mg/m² IV D1 every 21 days; other regimens daily x 3 or daily x 5 less effective and more toxic (more neutropenia)

iii. RR = 12% (all PRs)

iv. TTP = 6 months

b) Combination trial (ixa + cape vs cape alone)¹⁹⁷

i. Patients had prior anthracycline and/or taxane therapy for neoadjuvant, adjuvant, or MBC.

ii. Ixa 40 mg/m² IV D1 + cape 2000 mg/m²/day divided BID PO x 14 days every 21 days vs cape 2500 mg/m²/day divided BID PO x 14 days every 21 days

iii. RR = 35 vs 14% (p<0.0001)

iv. Median PFS = 5.8 vs 4.2 months (p<0.0003)

v. OS not significantly different in a subsequent analysis. Several patients died in the combination arm of the trial (n=7); retrospective analysis indicate an association with liver dysfunction (black box warning). Update showed continued improvement in PFS (5.3 mo vs 3.8 mo, p=0.0011) but not OS (12.9 mo vs 11.1 mo, p:NS).¹⁹⁸

c) Larger confirmatory study (n=1,221).¹⁹⁹

i. Improved PFS (6.2 mo vs 4.4 mo, p=0.0005) with the combination, but not OS (primary endpoint, 16.4 mo vs 15.6 mo, p=NS)

5) Approved dose/schedule:

a) 40 mg/m² IV over 3 h every 3 weeks as a single agent

b) 40 mg/m² IV over 3 h every 3 weeks + capecitabine 2000 mg/m²/day PO Days 1-14 every 21 days

c) Premedicate with H1 and H2 antagonist only; add steroids with next cycles if patient has a reaction
d) Also dosing guidelines for liver dysfunction in product information:

i. Mild (ALT/AST ≤ 2.5 x ULN and TBili ≤ 1 x ULN) = 40 mg/m²

ii. Mild (ALT or AST ≤ 10 x ULN and TBili ≤ 1.5 x ULN) = 32 mg/m².

iii. Moderate (ALT or AST ≤ 10 x ULN & TBili > 1.5-≤ 3 x ULN) = 20-30 mg/m²

6) Adverse events: neutropenia (grade 3/4 50%); febrile neutropenia (rare); sensory neuropathy (grade 3/4 15-20%); fatigue; myalgias/arthritis; infusion-related hypersensitivity reactions (uncommon with premedications); combination has slightly more neutropenia, but similar capecitabine-related adverse events.

7) Administration issues:

a) Formulated in Cremophor EL + dehydrated alcohol (similar to paclitaxel)

b) Final dilution requires one of the following fluids (pH-dependent solubility)

- Lactate Ringers for Injection
- 0.9% Sodium Chloride Injection (pH adjusted with Sodium Bicarbonate for Injection)
- PLASMA-LYTE A Injection pH 7.4

c) Requires non-PVC bags and tubing

d) Requires an in-line filter also (similar to paclitaxel)

e) Optimal final concentration 0.2-0.6 mg/mL (concentration-dependent solubility)

f) Metabolized through CYP 3A4

i. If patient taking a strong inhibitor of CYP 3A4, company recommends empiric dose reduction to 20 mg/m²

ii. If patient taking a strong inducer of CYP 3A4, company recommends gradually increasing dose from 40 mg/m² to 60 mg/m² (depending on tolerance)

e. Eribulin mesylate (Halaven™)

1) Synthetic analogue of macrolide halichondrin B; first approved agent in class

2) Thought to work mainly through an end-poisoning mechanism that inhibits microtubule growth

3) FDA-approved indication:

a) Treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. Prior
therapy should have included an anthracycline and taxane in either the adjuvant or metastatic setting.

4) Efficacy data:
   a) Single agent (phase 2 trials)
      i. Studied in patients who failed an anthracycline and taxane\textsuperscript{201} and an anthracycline, taxane, and capecitabine\textsuperscript{202}
      ii. ORR = 9.3-11.5%
      iii. CBR = 17.1-17.2%
      iv. Median PFS = 2.6 months in both studies
      v. Most common treatment-related adverse events were asthenia/fatigue, alopecia, neutropenia, nausea, and anemia
   b) Phase 3 study - eribulin vs physician’s choice single agent therapy\textsuperscript{203}
      i. Open-label, randomized, multicenter trial (n=762)
      ii. Patients had prior anthracycline and/or taxane therapy for adjuvant or metastatic breast cancer
         (a) 1.4 mg/m\textsuperscript{2} intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle vs primarily single agent treatment (26% vinorelbine, 19% gemcitabine, 18% capecitabine, 15% taxane, 10% anthracycline, 10% other chemotherapy, 4% endocrine therapy).
      iii. OS (primary endpoint) = 13.1 mo vs 10.6 mo (HR 0.81 95%CI 0.66-0.99, p=0.041)
      iv. Investigator assessed PFS = 3.6 mo vs 2.2 mo (HR=0.76 95%CI 0.64-0.90, p=0.002)
      v. ORR = 12% vs 5% (p=0.002)

5) Approved dose/schedule:
   a) 1.4 mg/m\textsuperscript{2} intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle.
   b) Dose modifications
      i. Mild hepatic dysfunction (Child-Pugh A): 1.1 mg/m\textsuperscript{2} IV on Days 1 and 8 of a 21-day cycle
      ii. Moderate hepatic dysfunction (Child-Pugh B): 0.7 mg/m\textsuperscript{2} IV on Days 1 and 8 of a 21-day cycle
      iii. Severe (Child-Pugh C): not studied in this patient population
      iv. Moderate renal dysfunction (CrCl 30-50 mL/min): 1.1 mg/m\textsuperscript{2} IV on Days 1 and 8 of a 21-day cycle
v. Patients with CrCl less than 30 mL/min were not studied

6) Adverse events: neutropenia (grade 3/4 57%); febrile neutropenia (5%); sensory neuropathy (grade 3/4 8%); anemia; alopecia; asthenia/fatigue; nausea; constipation

7) Potential for QT-prolongation

8) Administration issues:
   a) **Not compatible with dextrose.** Administer undiluted or diluted in 100 mL NS.
   b) Undiluted and diluted eribulin stable for up to 4 hours at room temp or 24 hours refrigerated.

f. Vinorelbine (Navelbine®)
   1) Not approved for breast cancer, although activity has been demonstrated; being studied in combination with many other agents, especially with trastuzumab in HER2-positive disease.
   2) OR 16-47% in pretreated patients; 35-52% as first line therapy
      a) One study demonstrated 25% response in patients resistant to an anthracycline and taxane when given with filgrastim
      b) Another study demonstrated 25% response in a similar patient population without filgrastim, but the definition of resistance was not clearly defined
   3) Dosing varies – 25-30 mg/m² weekly, every 2 weeks, or days 1 and 8 every 3 weeks
   4) Sliding scale dosing also very effective (per package insert):
      a) 25mg/m²/week starting dose
      b) If ANC > 1250 cells/mm³, give 25mg/m²
      c) If ANC 750-1250 cells/mm³, give 15mg/m²
      d) If ANC < 750 cells/mm³, hold dose and repeat CBC/diff/plts in one week

g. Gemcitabine (Gemzar®)
   1) Approved in combination with paclitaxel as first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated.¹⁸³
   2) OR 18-37% in chemotherapy naïve patients as a single agent
   3) Dosing may be important factor affecting response:
      a) Chemotherapy naïve patients may be able to tolerate higher doses (1000-1250 mg/m²/week D1, 8, 15 Q 28 days), but nearly all patients require dose reductions after a few cycles due to myelosuppression or thrombocytopenia.
      b) Pretreated patients usually require a lower starting dose (e.g., 800 mg/m²/week) and/or a shortened cycle (e.g., D 1 and 8 only Q 21 days).
h. Other active agents (platinum agents, oral etoposide, vinblastine, fluorouracil CI)
   1) All have activity in MBC as single agents
   2) Combination regimens have demonstrated some utility with the platinum agents (e.g., with taxanes and/or trastuzumab)
   3) Response limited in light of other therapies now available; these agents often do not overcome chemoresistance.

i. Continuous vs intermittent chemotherapy
   1) No difference in OS
   2) Prolonged TTP with continuous chemotherapy if patient has responsive or stable disease – may improve QOL
      a) Randomized trial of intermittent vs continuous Epirubicin + Ifosfamide
         i. Superior QOL with intermittent chemotherapy.
         ii. Suggests a drug holiday for patients with significant treatment-related toxicity does not compromise outcomes
      b) Randomized trial of maintenance chemotherapy vs. observation
         i. Patients received six cycles of gemcitabine/paclitaxel
         ii. Those who achieved disease control were randomized to maintenance chemotherapy or observation (n=231)
         iii. Median PFS (7.5 mo. vs 3.8 mo, HR 0.73; 95% CI 0.55 to 0.97) and OS (32.3 mo vs. 23.5 mo, HR 0.65; 95% CI 0.42 to 0.99) were significantly longer in patients who received maintenance chemotherapy compared to observation.
         iv. The rate of grade ≥ 3 neutropenia was higher in the maintenance group vs the observation group (61% vs 0.9%, p < 0.001)
         v. QoL did not differ between the two groups
   3) Recommend:
      a) Titrating dose to allow for continuous treatment with least impact on QOL
      b) If significant treatment-related toxicity:
         i. Continue with single agent OR
         ii. Drug holiday

j. High-dose chemotherapy with BMT or PBSC support – very controversial; no demonstrated benefit in survival over standard dose chemotherapy to date.

k. Also see the ASCO guidelines for Chemotherapy and Targeted Therapy for Women with HER2-negative Advanced Breast Cancer for additional details.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Drugs</th>
<th>Dose</th>
<th>Schedule</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin + Paclitaxel</td>
<td>Doxorubicin</td>
<td>50-60 mg/m² IV (give 1ᵗʰ)</td>
<td>Bolus or over 15 min, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>200 mg/m² IV</td>
<td>Over 3h, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td>Doxorubicin + Docetaxel</td>
<td>Doxorubicin</td>
<td>60 mg/m² IV (give 1ᵗʰ)</td>
<td>Bolus or over 15 min, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>60 mg/m² IV</td>
<td>Over 1h, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Or</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>50 mg/m² IV (give 1ᵗʰ)</td>
<td>Bolus or over 15 min, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>75 mg/m² IV</td>
<td>Over 1h, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td>Epirubicin + Paclitaxel</td>
<td>Epirubicin</td>
<td>75-90 mg/m² IV (give 1ᵗʰ)</td>
<td>Bolus or over 15 min, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>175-200 mg/m² IV</td>
<td>Over 3h, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td>Epirubicin + Docetaxel</td>
<td>Epirubicin</td>
<td>70-90 mg/m² IV (give 1ᵗʰ)</td>
<td>Bolus or over 15 min, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>70-90 mg/m² IV</td>
<td>Over 1h, D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td>Docetaxel + Capecitabine</td>
<td>Docetaxel</td>
<td>75 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
<td>2500 mg/m²/d^ PO</td>
<td>Divide BID x 14 d then 7 days off</td>
<td>Q 21 days</td>
</tr>
<tr>
<td>Ixabepilone + Capecitabine</td>
<td>Ixabepilone</td>
<td>40 mg/m² IV</td>
<td>D 1</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
<td>2000 mg/m²/d PO</td>
<td>Divide BID x 14 d then 7 days off</td>
<td>Q 21 days</td>
</tr>
<tr>
<td>GT</td>
<td>Paclitaxel</td>
<td>175 mg/m² IV</td>
<td>D 1 (over 3 h)</td>
<td>Q 21 days</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>1250 mg/m² IV</td>
<td>D 1 &amp; 8</td>
<td>Q 21 days</td>
</tr>
<tr>
<td>Pac/Bev</td>
<td>Paclitaxel</td>
<td>90 mg/m² IV</td>
<td>D 1, 8, 15</td>
<td>Q 28 days</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>10 mg/kg</td>
<td>D 1, 15</td>
<td>Q 28 days</td>
</tr>
</tbody>
</table>

^ This is the approved dose for capecitabine. Most patients require dose reductions. Some clinicians prefer to use starting dose of 2000 mg/m²/day instead.
**Patient Case #6 (continued):** TP would not be a candidate for endocrine therapy due to the ER/PR negative characteristic of her tumor. She would be best served with chemotherapy at this point in time. Due to her symptomatic presentation, TP should receive a combination chemotherapy regimen initially. She received paclitaxel and FAC in the adjuvant setting more than 1 year ago. Usually, a patient is considered resistant if she recurs within 1 year of her adjuvant therapy. In her case, it has been more than a year. So, resistance would not necessarily dictate chemotherapy choice. Regimens to show benefit in terms of prolonging survival (although not compared to sequential single agents) are docetaxel + capecitabine and gemcitabine + paclitaxel. Ixabepilone + capecitabine has not been shown to improve survival compared to single agent capecitabine, but did result in improved TTP. Any of these would be an appropriate regimen for TP, given with other supportive measures (e.g., oxygen support, cough suppressants, etc.). Paclitaxel + bevacicuzumab is controversial in this setting. Additionally, an argument could be made for sequential single agent therapy for this patient as well.

**Patient Case #7:** CH is a 38 y/o premenopausal woman presenting with newly diagnosed left breast cancer. She has noticed a mass in her left breast for some time, but has neglected to have it evaluated. She now comes in with dimpling of the skin of the breast, erythema, and palpable lymph nodes in the axilla and supraclavicular areas on the left. She undergoes biopsy of this mass and staging and is found to have an invasive ductal carcinoma, ER/PR-negative, HER2 positive by FISH, Ki-67 60% with axillary and supraclavicular involvement and also bone metastases and questionable lung metastases. What would be the most appropriate therapy for CH at this time?

D. Biologic therapy

1. Trastuzumab (Herceptin®).
   a. Humanized monoclonal antibody to HER2 receptor protein.
   b. Activity in HER2-positive metastatic breast cancer as single agent or in combination with chemotherapy.
   c. Comparative trials demonstrating improved efficacy with trastuzumab + chemotherapy vs chemotherapy alone.

1) Pivotal trial chemotherapy ± trastuzumab.  
   a) Previously untreated MBC (n=469).
      i. No prior adjuvant anthracycline – AC ± trastuzumab.
      ii. Prior adjuvant anthracycline – Paclitaxel ± trastuzumab.

b) Survival advantage with trastuzumab + chemotherapy vs chemotherapy alone.

   c) Cardiotoxicity first identified in these early trials.
      i. Cardiomyopathy leading to CHF; clinically similar to anthracycline-induced CHF, but reversible with medication despite continuing trastuzumab therapy.
      ii. Rate extremely high with trastuzumab/anthracycline combination (28% any cardiotoxicity; 19% Class III-IV cardiotoxicity).
      iii. Lower rate with paclitaxel combination (11% any and 4% for Class III-IV cardiotoxicity).
      iv. Controversy over how to best monitor patients for the toxicity.
2) Docetaxel ± trastuzumab\textsuperscript{207}

d. Previously untreated metastatic breast cancer; IHC 3+ or FISH positive (n=186).
   a) Docetaxel 100 mg/m\textsuperscript{2} IV Q 3 week x 6 cycles
   2) With or without trastuzumab 4 mg/kg loading followed by 2 mg/kg weekly maintenance dose.
   3) OR = Doc/tras 61% vs Doc 34% (p=0.0002)
   4) Median TTP = Doc/tras 11.7mo vs Doc 6.1mo (p=0.0001)
   5) Median OS = Doc/tras 31.2mo vs Doc 22.7 mo (p=0.0325)
   6) Crossover to trastuzumab 57%; median OS 30.3 mo in those who crossed over vs those who did not (16.6mo)
   7) Side effects (G3/4): leukopenia and neutropenia more frequent with trastuzumab; Symptomatic CHF 1 patient in trastuzumab arm.

e. Selected trials of chemotherapy + trastuzumab demonstrating activity
   1) Vinorelbine + trastuzumab
      a) Salvage therapy; 71% response rates\textsuperscript{208}
      b) First-line therapy for MBC; 68% response rates\textsuperscript{209}
      c) Compared with docetaxel/trastuzumab in 284 patients with HER2+ MBC in the first-line setting.\textsuperscript{210}
         i. No difference in median TTP or OS; median TTF was shorter with docetaxel/trastuzumab (5.6 mo vs 7.7 mo, p=0.0001)
         ii. G3/4 toxicities were more common with docetaxel/trastuzumab (81% vs 51%, p<0.0001)
   2) Capecitabine + trastuzumab\textsuperscript{211}
      a) MBC patients who progressed on trastuzumab (n=156)
      b) Randomized to capecitabine dosed at 2500 mg/m\textsuperscript{2}/day x 14 days Q 21 days with or without trastuzumab 8 mg/kg loading followed by 6 mg/kg Q 3 week
      c) ORR = 48.1% with cape/H and 27.0% with cape alone (p=0.0115)
      d) Median TTP = 8.2 mo with cape/H and 5.6 mo with cape alone (p=0.038)
      e) OS was not significantly different
      f) \textbf{Provides evidence to support use of trastuzumab-based therapy after progression on trastuzumab}
   3) Gemcitabine + trastuzumab\textsuperscript{212}
      a) MBC (IHC 2+ or 3+)
      b) Gemcitabine 1200 mg/m\textsuperscript{2} D 1 and 8 Q 21 days + trastuzumab weekly
      c) ORR = 38%; TTP=5.8 mo.
4) Paclitaxel + carboplatin + trastuzumab
   a) Phase III trial Paclitaxel + trastuzumab vs Paclitaxel + trastuzumab + carboplatin
      i. MBC patients; HER2 positive by IHC 2+/3+; amended to include FISH positive for IHC 2+
      ii. ORR: TPC 52% vs TP 36% (p=0.04)
      iii. PFS: TPC 10.7 mo vs TP 7.1 mo (p=0.03)
      iv. OS: TPC 35.7 mo vs TP 32.2 mo (p=0.9)
      v. Increased incidence of grade 3/4 with TPC

5) Docetaxel + carboplatin + trastuzumab
   a) Phase III trial Doc + Trastuzumab vs Doc + Trastuzumab + Carboplatin
      i. MBC patients
      ii. Docetaxel 100 mg/m² + Trastuzumab weekly vs Doc 75 mg/m² + Trastuzumab weekly + Carboplatin AUC 6 (n=263)
      iii. Similar ORR, TTP and CB
      iv. More neutropenic infections with TH vs TCH, although 2 patients died due to sepsis in the TCH arm

f. Phase 3 trial of endocrine therapy + trastuzumab
1) Two trials reported to date
   a) Anastrozole vs Anastrozole + trastuzumab (n=207)
   b) Improved PFS (2.4 mo vs 4.8 mo, p=0.0016), CBR (28% vs 43%, p=0.026), and TTP (2.4 mo vs 4.8 mo, p=0.0007) with addition of trastuzumab
   c) Seventy percent of patients receiving anastrozole alone crossed over to trastuzumab upon progression; therefore OS was numerically higher with trastuzumab (23.9 mo vs 28.5 months), but did not reach statistical significance (p=0.325).
   d) Increased grade 3 and 4 toxicities as well as cardiac events in anastrozole + trastuzumab vs anastrozole alone
2) Second smaller trial (n=57) of patients received letrozole vs letrozole +trastuzumab in patients with ER+ HER2+ MBC showed a numerically improved TTP in patients who received trastuzumab (3.3 mo vs 14.1 mo, HR 0.67, p=0.23); OS was not different.

  g. Consider adding trastuzumab for patients with HER2+ and HR+ metastatic disease

h. Single agent trials with trastuzumab
1) Salvage (2nd or 3rd line therapy) – response rates 11-21%
2) First-line therapy for metastatic breast cancer – response rates 24-28%, CB = 34-42%
3) Very well tolerated; cardiotoxicity about 5% with single agent therapy; often reversible with medication and some patients may continue trastuzumab with medical management.

i. **Patient selection:** IHC 3+ or FISH positive - significant predictors for response to trastuzumab. IHC 0-1+ or FISH negative - no indication for trastuzumab; IHC 2+ must be confirmed by FISH. See previous section on HER2 testing guidelines.

j. **Dose:**
   1) Approved dose: 4mg/kg IV loading dose, followed by weekly 2mg/kg maintenance dose
   2) Other dosing schedules:
      a) Higher doses (8mg/kg load with 4mg/kg/week) no better than standard weekly dose
      b) **Q 3 week dosing (8mg/kg load with 6mg/kg Q 3 weeks)** similar efficacy and tolerability to standard weekly dosing\(^{217}\)

k. **Side effects:**
   1) Infusion-related effects:
      a) Fever, chills, rigors (first treatment (40%); subsequent doses (3%), somewhat dose-dependent)
      b) Hypersensitivity (allergic) reactions with dyspnea, hypotension, etc. (rare)
      c) Pulmonary events - Fatal respiratory events have occurred as far out as several days after administration. Most commonly seen in patients with pulmonary disease and oxygen dependent (rare).
   2) Cardiotoxicity (see pivotal trial discussion)
   3) Interstitial pneumonitis – rarely reported in adjuvant trials; ? significance
   4) In combination with chemotherapy, appears to slightly increase infections, myelosuppression, but not really a clinically significant difference

l. **Ongoing studies:**
   1) Metastatic breast cancer:
      a) Different combinations of chemotherapy ± trastuzumab; phase 3 trials to determine benefit of addition of trastuzumab to chemotherapy; other biologics in combination.
### TABLE 20: Comparative Clinical Trials with Chemotherapy and Trastuzumab\(^{134,205,211,212}\)

<table>
<thead>
<tr>
<th>Regimens</th>
<th>n</th>
<th>RR (%)</th>
<th>mTTP (mo)</th>
<th>mOS (Mo)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pivotal combination trial(^{236})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AC + trastuzumab</td>
<td>143</td>
<td>56**</td>
<td>7.8*</td>
<td>26.8</td>
<td>First-line metastatic breast cancer; HER2 positive by FISH or 2/3+.</td>
</tr>
<tr>
<td>AC alone</td>
<td>138</td>
<td>42</td>
<td>6.1</td>
<td>21.4</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel + trastuzumab</td>
<td>92</td>
<td>41*</td>
<td>6.9*</td>
<td>22.1</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel alone</td>
<td>96</td>
<td>17</td>
<td>3.0</td>
<td>18.4</td>
<td></td>
</tr>
<tr>
<td>Chemo + trastuzumab</td>
<td>235</td>
<td>50*</td>
<td>7.4*</td>
<td>25.1**</td>
<td></td>
</tr>
<tr>
<td>Chemo alone</td>
<td>234</td>
<td>32</td>
<td>4.6</td>
<td>20.3</td>
<td></td>
</tr>
<tr>
<td>Other combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel + trastuzumab(^{207})</td>
<td>94</td>
<td>61*</td>
<td>11.7*</td>
<td>31.2**</td>
<td>First-line metastatic breast cancer; HER2 positive by FISH or IHC 3+.</td>
</tr>
<tr>
<td>Docetaxel alone</td>
<td>94</td>
<td>34</td>
<td>6.1</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>Pac + carbo + trastuzumab(^{213})</td>
<td>92</td>
<td>52**</td>
<td>10.7**</td>
<td>35.7</td>
<td></td>
</tr>
<tr>
<td>Pac + trastuzumab</td>
<td>94</td>
<td>36</td>
<td>7.1</td>
<td>32.2</td>
<td></td>
</tr>
<tr>
<td>Doc + carbo + trastuzumab(^{214})</td>
<td>132</td>
<td>72</td>
<td>10.4</td>
<td>37.4</td>
<td></td>
</tr>
<tr>
<td>Doc + trastuzumab</td>
<td>131</td>
<td>72</td>
<td>11.1</td>
<td>37.1</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** n = number of patients; RR = response rate; mTTP = median time to progression; mOS = median overall survival; AC = anthracycline plus cyclophosphamide; chemo = chemotherapy.

*\(p\)-value < 0.01; **\(p\)-value < 0.05.

---

2. **Pertuzumab (Perjeta™)**

   a. **MOA:** Pertuzumab targets the extracellular domain of HER2 and blocks ligand-dependent heterodimerization with EGFR (HER1), HER3, and HER4.

   b. The binding site of pertuzumab is different from trastuzumab; pertuzumab binds to domain II on the HER2 receptor while trastuzumab binds to domain IV.

   c. The effect of weight and BSA on dosing is not considered to be highly contributable to overall drug exposure; therefore pertuzumab dosing is fixed (not weight-based).

   d. Pertuzumab has a low response rate as a single agent in patients with HER2-positive breast cancer (3.4%), and therefore has been studied in combination with other anti-HER2 agents.\(^{218}\)

   e. FDA approval based on a Phase III RCT, CLEOPATRA, which evaluated pertuzumab in combination with docetaxel and trastuzumab as first-line therapy for MBC.\(^{219}\)

1) Compared docetaxel 75 mg/m² IV every 3 weeks (could increase to 100 mg/m² if tolerated) + trastuzumab 8mg/kg load with 6mg/kg every 3 weeks + pertuzumab 840 mg IV load with 420 mg every 3 weeks or placebo.

2) Addition of pertuzumab to docetaxel and trastuzumab improved PFS (18.5 mo vs 12.4 mo, HR 0.62, 95% CI 0.51-0.75) compared to docetaxel and trastuzumab, and placebo.

3) Interim analysis of OS was immature (69 events vs 96 events, HR 0.64, \(p=NS\)); however a subsequent analysis showed an improvement in OS.
in favor of the pertuzumab group (HR 0.66; 95% CI, 0.52-0.84; 
P=0.0008). 220

4) Patients in the pertuzumab arm had more diarrhea, rash, mucosal 
inflammation, febrile neutropenia, and dry skin compared to control 
arm.
f. NCCN recommends the combination of trastuzumab plus pertuzumab in 
combination with docetaxel as a preferred first line option (Category I). 32

g. ASCO guidelines also recommend the combination of trastuzumab plus 
pertuzumab in combination with a taxane for first line therapy of advanced 
HER2-positive MBC. 221

h. Two phase II trials have also evaluated pertuzumab in combination with 
trastuzumab after prior progression on trastuzumab-based therapy.
1) ORR 24%, 26% SD, CBR 50%, PFS 5.5 months 222
2) ORR 18%, 27% SD, CBR 45%, PFS 6 weeks 223

i. Cardiotoxicity
1) Asymptomatic LVSD was 3.4% and 6.5% and symptomatic heart failure 
was 1.1% with pertuzumab/non-anthracycline based chemotherapy 
and pertuzumab/trastuzumab, respectively. 224
2) Pertuzumab should be withheld for at least 3 weeks if the left 
ventricular ejection fraction (LVEF) decreases to <40% or if the LVEF 
decreases to 40-45% with at least a 10% absolute decrease from 
baseline value.
3) Treatment with pertuzumab can be resumed if LVEF recovers to >45% 
or to 40-45% with <10% absolute decrease from baseline value within 
3 weeks.

j. Important pharmacy information 150
1) It is recommended to reload with 840 mg if the patient has not 
received a dose of pertuzumab for 6 weeks or longer.
2) The loading dose is administered over 60 minutes, with subsequent 
doses administered over 30 to 60 minutes.
3) No dose adjustments are required for patients with a CrCl > 30 
ml/min.
4) Reconstitute with 250 mL NS (not compatible with dextrose).
k. A number of interesting clinical trials with pertuzumab are ongoing including 
some in combination with trastuzumab emtansine as well as various 
chemotherapeutic agents.

Patient case #7 (continued): CH is a candidate for anti-HER2 therapy given her HER2 status and her metastatic 
disease. The most appropriate therapy would be the combination of trastuzumab, pertuzumab, and a taxane 
(either every 3 week docetaxel or weekly paclitaxel). The strongest data supports the use of docetaxel in 
combination with trastuzumab and pertuzumab. CH would require an assessment of her LVEF and periodic LVEF 
monitoring during treatment. She would continue this therapy until disease progression or intolerable toxicities.

Patient case #7 (continued): CH is placed on docetaxel, trastuzumab, and pertuzumab for several months with 
significant response. However, she then progresses with increased disease in her supraclavicular region and her 
lung masses are larger. What therapy would be appropriate at this time?
3. Ado-trastuzumab emtansine (Kadcyla™)
   a. Novel antibody drug conjugate that contains trastuzumab (a monoclonal antibody) connected via a stable linker to a maytansine derivative (a potent microtubule inhibitor).
   b. After binding to sub-domain IV of the HER2 receptor, ado-trastuzumab emtansine (TDM-1) undergoes receptor-mediated internalization and subsequent lysosomal degradation, resulting in intracellular release of DM1-containing cytotoxic catabolites, which results in microtubule inhibition and apoptosis. TDM-1 also inhibits HER2 receptor signaling, mediates ADCC, and inhibits shedding of the HER2 extracellular domain.
   c. FDA approval based on a Phase III RCT, EMILIA, which compared TDM-1 to the combination of capecitabine and lapatinib for MBC in patients who failed trastuzumab and a taxane.  
      1) Compared TDM-1 3.6 mg/kg IV every 3 weeks versus lapatinib 1,250 mg PO daily and capecitabine 2000 mg/m²/day for 14 days of a 21 day cycle.
      2) TDM-1 significantly improved PFS (9.6 mo vs 6.4 mo, HR 0.65, 95% CI 0.55-0.77) and OS (30.9 mo vs 25.1 mo, HR 0.68, 95% CI 0.55-0.85) compared to capecitabine and lapatinib.
      3) Patients in the capecitabine/lapatinib arm had more diarrhea, hand-foot syndrome, nausea, vomiting, and neutropenia; patients in the TDM-1 arm had more peripheral neuropathy, fatigue, anemia, elevated AST/ALT, and thrombocytopenia.
   d. Many dose reductions for toxicity, see package insert for details.
      1) Monitoring of AST/ALT, bilirubin, and platelets is recommended prior to each cycle.
      2) Starting dose: 3.6 mg/kg IV every 3 weeks
      3) First dose reduction: 3.0 mg/kg IV every 3 weeks
      4) Second dose reduction: 2.4 mg/kg IV every 3 weeks
      5) Discontinue treatment
      6) If dose reduction is made, the dose should not be re-escalated.
   e. T-DM1 has also been evaluated as monotherapy vs physician’s choice therapy.
      1) Open-label, randomized, multicenter trial (n=602).
      2) Patients had progressed on 2 or more anti-HER2 therapies, including trastuzumab and lapatinib for MBC and prior taxane in any setting.
         a) Physician’s choice included: trastuzumab + chemotherapy (68%), trastuzumab + lapatinib (10%), trastuzumab + endocrine therapy (2%), lapatinib + chemotherapy (3%), single agent chemotherapy (17%).
            i. PFS = 6.2 mo vs 3.3 mo (HR=0.53 95%CI 0.42-0.66, p<0.0001)
            ii. Interim OS was not significantly different.
f. Three phase II trials have also evaluated T-DM1 as monotherapy (3.6 mg/kg IV every 3 weeks)

1) ORR 25.9%, PFS 4.6 months \(^{228}\)
2) ORR 34.5%, PFS 6.9 months \(^{229}\)
3) T-DM1 vs. docetaxel 75-100 mg/m\(^2\) and trastuzumab 8 mg/kg 6 mg/kg every 3 weeks \(^{230}\)
   a) ORR 64.2% vs. 58.0% (p=NS); PFS 14.2 mo. vs. 9.2 months (HR 0.59; 95% CI 0.36-0.97).

g. Cardiotoxicity
1) LVSD occurred in 1.8% of patients who received TDM-1 and 3.3% in patients who received capecitabine/lapatinib.
2) LVEF should be monitored at baseline and regular intervals (e.g. every 3 months) during therapy.
3) TDM-1 should be withheld for at least 3 weeks if the left ventricular ejection fraction (LVEF) decreases to < 40% or if the LVEF decreases to 40-45% with at least a 10% absolute decrease from baseline value.
4) Treatment can be resumed if LVEF recovers to > 45% or to 40-45% with < 10% absolute decrease from baseline value within 3 weeks.
5) Discontinue for symptomatic heart failure.

h. A detailed safety analysis of T-DM1 in 884 patients is also available. \(^{231}\)

i. Important pharmacy information
1) The initial dose is administered over 90 minutes, with subsequent doses administered over 30 minutes if first dose was well tolerated.
2) No dose adjustments are required for patients with a CrCl > 30 mL/min.
3) Reconstitute with 250 mL NS (not compatible with dextrose).
4) Infuse with a 0.22 micron in-line non-protein adsorptive polyethersulfone (PES) filter.
5) If not used immediately, refrigerate for up to 4 hours after reconstitution.
6) Do not substitute TDM-1 for trastuzumab.
7) The use of strong CYP3A4 inhibitors should be avoided.

4. Bevacizumab (Avastin\textsuperscript{®})
1) Studied in combination with capecitabine; no benefit in terms of OS; but increased response rates were seen; these patients were previously treated patients (second- or third- line therapy).
2) Data with paclitaxel for patients with MBC (first-line) (See TABLE 19 for details of dosing). \(^{232}\)
   a) Paclitaxel weekly vs Paclitaxel weekly + bevacizumab Q 2 weeks (n=722)
      i. Paclitaxel weekly 90 mg/m\(^2\) IV D1, 8, 15 every 28 days (n=326) vs
ii. Paclitaxel same dose + Bevacizumab 10 mg/kg IV D1 and 15 every 28 days (n=347).

iii. Addition of bevacizumab to paclitaxel improved OR (36.9% vs 21.2%, p<0.001) and PFS (11.8 mo vs 5.9 mo, HR 0.60 (0.43-0.62), p<0.0001) compared to paclitaxel alone, but not OS (26.7 mo vs 25.2 mo, HR 0.84 (0.64-1.05), p=0.16)

b) Adverse events (grade 3/4):

- HTN – 0% vs 15% (p<0.001)
- Infection – 3% vs 9% (p<0.001)
- Bleeding – 0% vs 3% (p=0.02)
- Proteinuria – 0% vs 3% (p<0.001)
- Headache – 0% vs 2% (p=0.008)
- Neuropathy – 18 vs 23%
- Fatigue – 5 vs 9% (p=0.04)
- Neutropenia – 3 vs 4%
- Proteinuria – 0% vs 3% (p<0.001)
- ↓ LVEF – 0 vs <1%
- VTE – 4% vs 2%

3) Data from three phase 3 RCTs which evaluated chemotherapy with or without bevacizumab in the first line setting (E2100, AVADO, and RIBBON-1) were analyzed in a meta-analysis.233

a) PFS (HR 0.70, 95% CI 0.57-0.86) was significantly increased in patients who received bevacizumab in addition to chemotherapy compared to chemotherapy alone.

b) OS was not significantly different between the two groups (HR 0.95, 95% CI 0.85-1.06).

c) Addition of bevacizumab to chemotherapy increased grade 3/4 hypertension (OR 5.6, 95% CI 1.66-18.62), proteinuria (OR 5.4, 95% CI 2.8-10.20), sensory neuropathy (OR 1.48, 95% CI 1.11-1.99), and cardiac events including LV dysfunction and heart failure (OR 3.4, 95% CI 1.41-8.01).

4) Bevacizumab in combination with paclitaxel for patients with HER2-normal MBC in the first line setting was granted accelerated approval by the FDA in February 2008. FDA also took preliminary results from the AVADO trial into consideration.

5) FDA required that Genentech “conduct adequate and well-controlled studies to further define the degree of clinical benefit to patients.”

6) Results from confirmatory studies AVADO and RIBBON1 showed that bevacizumab marginally improved PFS (1 to 3 months), did not improve survival, and increased grade 3 - 5 toxicities compared to placebo.

7) FDA recommended removing breast cancer from drug labeling (ODAC voted 12-1 to remove the breast cancer indication), and revoked the breast cancer indication for bevacizumab on 11/18/11 after concluding it has not been shown to be safe and effective for that use.

8) Still included as an acceptable regimen in NCCN breast cancer guidelines.32

9) Unclear whether insurance companies will reimburse for bevacizumab after removal of drug labeling.
10) The decision to use bevacizumab in this setting is complex and very controversial.

5. Lapatinib (Tykerb®)
   
a. Dual tyrosine kinase inhibitor
   1) HER2
   2) EGFR (epidermal growth factor receptor)
   b. Small molecule works inside the cell to inhibit activation of these pathways.
   c. May also cross the BBB, although results in patients with brain metastases have been disappointing.234
   d. Daily oral medication
   1) Lapatinib 1250 mg PO daily in combination with capecitabine 2000 mg/m²/day PO divided BID x 14 days every 21 days.
   2) Single agent trials: up to 1500 mg PO daily.
   e. Combination trial (lap + cape vs cape alone)235
   1) Studied in patients previously treated with an anthracycline, taxane and trastuzumab.
   2) HER2 + tumors only.
   3) Median TTP 6.2 vs 4.3 months [HR = 0.57 (95% CI 0.43-0.77, p<0.001)]; combination superior.
   4) RR 24% vs 14% (p=0.017); combination superior.
   5) OS = 55 vs 64 deaths, p=0.177; no difference in survival.
   f. Other efficacy information
   1) Single agent efficacy modest with RR = 24% for first line treatment and 8% for trastuzumab-pretreated patients.
   2) Longer PFS (8.2 mo vs 3 mo, HR = 0.71, p=0.019) in ER +, HER2+ patients (n=219) that received letrozole + lapatinib compared to letrozole alone.236
   3) Longer PFS (11.1 weeks vs 8.1 weeks, HR 0.74, p=0.011) and OS (14 mo. vs 9.5 mo, HR 0.74, p=0.026) in HER2+ patients that received trastuzumab + lapatinib compared to lapatinib alone.237
   4) Under investigation in combination with several chemotherapy agents (paclitaxel, nab-paclitaxel, vinorelbine, etc.).
   5) Did not improve PFS or OS when added to fulvestrant in patients with ER-positive MBC (regardless of HER2 status) and increased toxicity.238
   g. Patient counseling points:
   1) Lapatinib taken on an empty stomach (increased absorption with food).
   2) Capecitabine taken on a full stomach (decreased rate of absorption with food).
   3) Lapatinib taken for the entire 21 days; no break when taken with capecitabine.
4) Significant drug/food interactions with lapatinib:

a) CYP3A4 – inducers may decrease efficacy; inhibitors may increase toxicity.

b) Strong inhibitors
   i. Should be avoided (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole).
   ii. Grapefruit may also increase plasma concentrations of lapatinib and should be avoided.
   iii. If patients must be coadministered a strong CYP3A4 inhibitor, based on pharmacokinetic studies, a dose reduction to 500 mg/day of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inhibitors and should be considered.
   iv. However, data exists with this dose adjustment in patients receiving strong CYP3A4 inhibitors.
   v. If the strong inhibitor is discontinued, a washout period of approximately 1 week should be allowed before the lapatinib dose is adjusted upward to the indicated dose.

c) Strong inducers
   i. The concomitant use of strong CYP3A4 inducers should be avoided (e.g., dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, St. John’s Wort).
   ii. If patients must be coadministered a strong CYP3A4 inducer, based on pharmacokinetic studies, the dose of lapatinib should be titrated gradually from 1,250 mg/day up to 4,500 mg/day based on tolerability.
   iii. This dose of lapatinib is predicted to adjust the lapatinib AUC to the range observed without inducers and should be considered.
   iv. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers.
   v. If the strong inducer is discontinued the lapatinib dose should be reduced to the indicated dose.

h. There are several exciting agents under investigation for HER2+ MBC, including trastuzumab emtansine and neratinib.
Patient case #7 (continued): CH would now be a candidate for TDM-1 or lapatinib + capecitabine therapy. TDM-1 improved PFS and OS compared to lapatinib + capecitabine in this patient population. There is also data to support the use of trastuzumab + capecitabine in this setting. Additional options include continuation of trastuzumab and changing the chemotherapy to vinorelbine. Continuation of pertuzumab after disease progression has not been evaluated. She should be evaluated for concurrent drug therapy with CYP 3A4 inhibitors or inducers if she receives lapatinib.

Patient case #5 (continued): DM was started on anastrozole 1 mg PO daily and zoledronic acid 4 mg IV monthly for her ER+ metastatic breast cancer. She has had a good response to this therapy, however after 6 months her disease has progressed.

What would be the most appropriate treatment option for this patient?

6. Everolimus (Afinitor®)
   a. Inhibits mammalian target of rapamycin (mTOR), blocking a pathway of resistance to endocrine therapy (and potentially HER2).
   b. FDA approval based on a Phase III RCT (BOLERO-2)  
      1) 724 patients with ER+ HER2-negative MBC after failure of a nonsteroidal AI (anastrozole or letrozole) were randomized to exemestane (EXE) 25 mg PO daily + everolimus (EVE) 10 mg PO daily vs EXE 25 mg PO daily + placebo (PLA) daily
      2) Nonsteroidal AI resistance was defined as recurrence during or within 12 months after the end of adjuvant treatment or progression during or within 1 month after the end of treatment for advanced disease.
      3) PFS based on radiographic studies (primary endpoint) was significantly longer in the EXE/EVE group compared to EXE/PLA (6.9 mo vs 2.8 mo, HR 0.43 (0.35-0.54; p<0.001)
      4) OS data was immature at the time of publication; OS was not significantly different in a subsequent analysis at 31 months of follow up.
      5) Serious adverse events occurred in 23% of EXE/EVE compared to 12% in the EXE/PLA group.
      6) Any grade of stomatitis (56% vs 11%), rash (36% vs 6%), diarrhea (30% vs 16%), hyperglycemia (13% vs 2%) were increased with EXE/EVE compared to EXE/PLA.
   c. Also phase II data with the combination of tamoxifen and everolimus  
      1) Tam/EVE improved TTP (8.6 mo vs 4.5 mo, exploratory p=0.002) and OS (not reached vs 32.9 mo exploratory p=0.007) compared to tam alone.
   d. Other unique toxicities
      1) Non-infectious pneumonitis: incidence approximately 3% (all grades), but higher in one trial in patients with breast cancer.
      2) Treatment may require dose interruption and subsequent dose reduction, permanent discontinuation, and/or administration of corticosteroids depending on severity.
3) Hyperglycemia/hypercholesterolemia/hypertriglyceridemia.
   a) Patients should be monitored at baseline and periodically during treatment.
   b) There are no specific guidelines available, but excellent reviews on the subject exist.241

e. Significant drug interactions with everolimus
   1) Avoid strong CYP3A4 inhibitors.
   2) Reduce dose from 10 mg daily to 2.5 mg daily with titration to 5 mg daily if tolerated with concomitant moderate CYP3A4 inhibitors and/or PgP inhibitors.
   3) With strong CYP3A4 inducers, increase in 5 mg increments to a maximum of 20 mg daily.

f. Dose modification not required for renal impairment

g. Dose modifications for hepatic impairment
   1) Reduce dose to 7.5 mg daily for mild hepatic impairment (Child-Pugh class A)
   2) Reduce dose to 5 mg daily for moderate hepatic impairment (Child-Pugh class B)
   3) If benefits outweigh risk, reduce dose to not more than 2.5 mg daily for severe hepatic impairment (Child-Pugh class C)

h. Other pharmacy information
   1) Tablets are supplied in individual foil-packed blister cards; remove each individual tablet immediately prior to administration.
   2) Available in multiple tablet strengths (2.5 mg, 5 mg, 7.5 mg, and 10 mg).
   3) Expensive, some insurance companies may require prior authorization.

i. Clinical trials with everolimus are ongoing for women with HER2-positive MBC in combination with paclitaxel/trastuzumab and vinorelbine/trastuzumab.

j. There is no role for temsirolimus in MBC based on the negative results of the HORIZON trial242

Patient case #5 (continued): Since DM has experienced disease progression on a nonsteroidal AI (anastrozole), she would be an appropriate candidate for exemestane and everolimus. Fulvestrant would also be an appropriate treatment option for this patient if she was concerned about side effects associated with everolimus ( stomatitis, infection, hyperglycemia, etc.) and was less concerned with having a monthly IM injection with fulvestrant. Zoledronic acid would be continued in either case. If she started on exemestane/everolimus, baseline lab work for blood glucose and a lipid panel and periodic monitoring of these would be necessary. Her medications would need to be evaluated for any strong or moderate CYP3A4 inhibitors or inducers. Endocrine therapy would be continued sequentially until her disease became hormone-refractory, she exhausted all her endocrine therapy options, or she began having significant symptoms from her breast cancer. Chemotherapy would be considered in those circumstances.
Patient case #2 (continued): LG is currently on adjuvant tamoxifen therapy, and presents to the clinic 3 months later complaining of severe hot flashes. She was given a prescription for paroxetine by her local physician, but wanted to check it out with her oncologist prior to taking this medication.

What are your recommendations?

IV. TREATMENT OF HOT FLASHES

A. Antidepressants

1. Venlafaxine - 75 mg PO Q day (extended-release) (1 placebo-controlled RCT in patients receiving tamoxifen); higher doses may be more effective (37.5mg vs 75mg vs 150mg; best results with 75mg and 150 mg vs 37.5 mg, but more toxicity with 150 mg vs 75 mg and 37.5 mg).
   a. A recent study compared venlafaxine 75 mg PO daily vs clonidine 0.1 mg PO daily vs placebo in patients with a history of breast cancer (n=80). Over the 12 week period of treatment, there was a reduction in hot flash scores by 41% with venlafaxine compared to placebo (p<0.001) and a reduction by 26% in the clonidine group compared to placebo (p=0.045).
   b. In a separate crossover study, 68% of patients chose venlafaxine over gabapentin (p=0.01)

2. Paroxetine - 10mg PO Q day (2 placebo-controlled RCT, included some pts receiving tamoxifen).

3. Fluoxetine – 20mg PO Q day (1 placebo-controlled RCT, included some pts receiving tamoxifen).

4. Sertraline – 50mg PO Q day (1 placebo-controlled RCT in pts receiving tamoxifen).

5. Citalopram – 10-20 mg PO Q day (1 placebo-controlled RCT, included some pts receiving tamoxifen, raloxifene, or AIs).

6. CAUTION:
   a. SSRIs and SNRIs have been shown to alter the PK of tamoxifen and its active metabolites (decrease concentrations of active metabolites through inhibition of CYP 2D6).
   b. Inherited genetic polymorphisms of CYP2D6 (specifically *4/*4 patients who are poor metabolizers) have been correlated with significantly shorter DFS and lack of hot flashes, but not with diminished OS.
   c. In a population-based cohort study, concomitant use of tamoxifen and paroxetine (but not other antidepressants) resulted in increased risk of breast cancer death.
   d. Strong to moderate inhibitors should be avoided during tamoxifen therapy if possible.
   e. More detailed information is available.
TABLE 21: Effects of Selected Antidepressants on CYP 2D6

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Fluoxetine</th>
<th>Paroxetine</th>
<th>Sertraline</th>
<th>Duloxetine</th>
<th>Citalopram</th>
<th>Bupropion</th>
<th>Venlafaxine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>±</td>
<td>+++</td>
<td>(-)</td>
</tr>
</tbody>
</table>

(-) = no inhibition; + = > 1.25-fold but < 2-fold x increase in AUC or 20-50% decrease in clearance; ++ = > 2-fold increase in AUC or 50-80% decrease in clearance; +++ = > 5-fold increase in AUC or > 80% decrease in clearance; ± = all other inhibition.

B. Gabapentin – 1 placebo controlled RCT in breast cancer patients (most receiving tamoxifen) improved control of hot flashes (at 900 mg/day, not 300 mg/day).

C. Pregabalin - 1 placebo controlled RCT (40% of pts with a history of breast cancer, some patients receiving tamoxifen, raloxifene, or an AI), both 75 mg bid and 150 mg bid superior to placebo249
   1. More dizziness with both pregabalin arms and more cognitive difficulties with the higher-dose arm compared with the placebo arm.

D. Bellergal-S® (belladonna, phenobarbital, ergotamine).

E. Clonidine – caution with hypotension.

F. Low-dose megestrol acetate 20mg PO daily or BID (controversial in breast cancer - effect on cancer).

G. Depo-medroxyprogesterone (Depo-Provera®) (controversial in breast cancer – effect on cancer).

H. Evening primrose oil (anecdotal reports only) – linoleic acid that may have phytoestrogens?

I. Vitamin E has been shown to benefit breast cancer patients with hot flashes; concern related to information regarding increased mortality?

J. Increasing soy in diet
   1. Phytoestrogens controversial in breast cancer patients; conflicting data in the literature regarding benefits for menopausal symptoms in general; benefits are minimal at best.

K. Acupuncture – compared to venlafaxine in one RCT, with similar reductions in the number of hot flashes, but resulted in fewer toxicities250

Patient case #2 (continued): LG should be instructed to not fill the prescription for paroxetine. Therapy for her hot flashes should begin with venlafaxine or citalopram. If this is not effective after 2 months, then gabapentin or clonidine therapy could be considered.

V. Survivorship

A. Breast cancer survivorship
   1. ASCO has recently updated its guidelines for breast cancer surveillance68
      a. Women should have a history and physical examination every 3 to 6 months for the first 3 years after primary therapy, then every 6 to 12 months for the next 2 years, then annually.
         1) Should be performed by a physician (or mid-level provider) experienced in surveillance of patients with breast cancer and in breast examination.
      b. Patients should be educated regarding the symptoms associated with breast cancer recurrence (new lumps, bone pain, chest pain, dyspnea, abdominal pain, or persistent headache.)
c. Women at high risk of familial breast cancer should be referred for genetic counseling.

d. Women should be counseled on how to perform breast monthly self-exams.

e. Women who undergo breast conserving surgery should have their first post-
treatment mammogram no earlier than 6 months after breast irradiation.

1) Subsequent mammograms should be obtained every 6-12 months for surveillance of abnormalities.

2) Mammograms should be performed yearly if mammographic finding are stable after locoregional therapy.

f. Regular gynecologic exams are recommended.

1) Patients who receive tamoxifen are at increased risk for endometrial cancer and should report any abnormal vaginal bleeding to their provider immediately (see Secondary Malignancy section).

g. Continuity of care is recommended and should be performed by a physician experienced in surveillance of patients with breast cancer and in breast examination.

1) Follow-up performed by a primary care provider seems to lead to equivalent health outcomes as a specialist with good patient satisfaction.

h. The following are not recommended:

1) Routine CBC bloodwork or blood chemistry.

2) Routine chest x-rays, ultrasound of the liver, bone scans, CT scans, PET scans, breast MRI.

3) Tumor markers (CA 15-3, CA 27.29, CEA).

2. Management of selected long-term or late effects

a. Bone health

1) Adult bones undergo continuous bone remodeling by osteoclasts and osteoblasts. Osteoclasts first breakdown bone to form a resorption cavity, then this resorption stimulates osteoblasts to form new bone over the resorption cavity.

2) Increased bone resorption can result from:

   a) Chemotherapy-induced ovarian failure
   
   b) Tamoxifen in premenopausal women
   
   c) LHRH agonists or oophorectomy in premenopausal women
   
   d) Aromatase inhibitors in postmenopausal women

3) Several guidelines are available for monitoring and treatment of cancer treatment induced bone loss (CTIBL) including from ASCO\textsuperscript{251}, NCCN\textsuperscript{252}, and others\textsuperscript{253}, primarily focusing on bone loss from aromatase inhibitors.

4) Screening and monitoring

   a) Screen for osteoporotic risk factors
   
   b) Consider use of FRAX algorithm\textsuperscript{252}
c) Baseline and periodic bone mineral density (every 1 to 2 years) in patients on an AI and who experience ovarian failure due to treatment.

5) Treatment algorithm from NCCN\textsuperscript{252}

a) Physical activity (all women).

b) Adequate calcium + vitamin D intake (all women).
   i. IOM report in 2010\textsuperscript{254}
      (a) Recommended 1000 mg of calcium and 600 IU of vitamin D per day in health adults
      (b) Recommended 1200 mg of calcium for women > 50 y/o.
      (c) Recommended 800 IU of vitamin D per day in adults > 70 y/o.
      (d) Defined 25-OH vitamin D levels of 20 ng/mL (50 nmol/L) as adequate, corresponding to 600 IU/day of vitamin D.

c) T-score > -1
   i. Repeat DEXA scan every 2 years

d) T-score between -1 and -1.5
   i. Consider checking a 25(OH) vitamin D level
   ii. Repeat DEXA scan every 2 years

e) T-score between -1.5 and -2.0
   i. Consider checking a 25(OH) vitamin D level
   ii. Consider pharmacologic therapy
   iii. Repeat DEXA scan every 2 years

f) T-score between > -2.0 OR FRAX 10 year risk >20% for major fracture or > 3% for hip fracture
   i. Consider checking a 25(OH) vitamin D level
   ii. Strongly consider pharmacologic therapy
   iii. Repeat DEXA scan every 2 years

6) Treatment options

a) Oral bisphosphonates (alendronate, ibandronate, risedronate)
   i. Consider a dental exam prior to starting bisphosphonate.

b) Intravenous agents (zoledronic acid) for bone loss refractory to oral bisphosphonates can be considered.
   i. Most studies in cancer patients evaluated zoledronic acid 4 mg IV every 3 to 6 months.
ii. Use of zoledronic acid 5 mg IV yearly (marketed as Reclast) may be necessary for reimbursement purposes.

c) Denosumab (Prolia) 60 mg SC every 6 months also an option for patients with bone loss refractory to oral bisphosphonates (FDA-approved in women at high risk of fracture receiving adjuvant AI therapy for breast cancer).
RECOMMENDED READING AND REFERENCES

Recommended Reading

Overview


Management of Breast Cancer

Adjuvant Endocrine Therapy

Adjuvant/Neoadjuvant Chemotherapy


Anti-HER2 Therapy


Therapy for Metastases


Cardiotoxicity from Anthracyclines

Cardiotoxicity from Trastuzumab

Bone modifying agents

**Chemotherapy-induced Nausea and Vomiting**


*Very good references to at least review. Others would be helpful, but not a must.

References


32 Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.3.2014 © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [December 1, 2014].


35 Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Screening and Diagnosis V.1.2014 © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [December 1, 2014]


37 Walter LC and Schonberg MA. Screening mammography in older women: A review. *JAMA.* 2014; 311(13):1336-47.


51 Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Risk Reduction V.1.2014 © National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [December 1, 2014].


152 Cataliotti L, Buzdar AU, Noguchi S et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: The pre-operative "arimidex" compared to tamoxifen (proact) trial. *Cancer.* 2006; 106(10):2095-103.


154 Semiglazov V KA, Zhiltzova E et al. Exemestane (e) vs tamoxifen (t) as neoadjuvant endocrine therapy for postmenopausal women with er+ breast cancer (t2n1–2, t3n0–1, t4n0m0). J clin onc 2005; 25:530. Abstract.


164 Chia S, Gradishar W, Mauriac L et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal


177 Hortobagyi GN LA, Chew HK et al. Efficacy and safety of continued zoledronic acid every 4 weeks versus every 12 weeks in women with bone metastases from breast cancer: Results of the optimize-2 trial. *J clin Oncol.* 2014; Iba9500. Abstract.


198 Hortobagyi GN PE, Vrdoljak E et al. Analysis of overall survival (os) among patients (pts) with metastatic breast cancer (mbc) receiving either ixabepilone (i) plus capecitabine (c) or c alone: Results from two randomized phase iii trials. Asco breast cancer symposium. 2008; 186. Abstract.


Burstein HJ, Cirrincione CT, Barry WT et al. Endocrine therapy with or without inhibition of epidermal growth factor receptor and human epidermal growth factor receptor 2: A randomized, double-blind, placebo-controlled phase iii trial of fulvestrant with or without lapatinib for postmenopausal women with hormone receptor-positive advanced breast cancer-calgb 40302 (alliance). J Clin Oncol. 2014.


