BREAST CANCER TREATMENT UPDATE 2023

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Disclosure

- Advisory Board : Gilead, Hologic Inc

Objectives

- Epidemiology, Risk factors.
- Types distribution of breast cancer,
- Inflammatory breast cancer treatment, prognosis,
- Recent development in treatment of breast cancer

EPIDEMIOLOGY

- Breast cancer is the most commonly diagnosed cancer worldwide.
- In USA breast cancer accounts for approximately 300,000 cases each year
- Responsible for 40,000 death.
- Incidence rate decreased from 1999 to 2007 by 1.8 %
- Decline is likely reflective of the end of prevalence peak of screening (when women are screened for first time there is a "prevalence peak" that is due to cancers that have been building up in the population added to the cancers detected earlier due to the screening) peaked in mid 1980s to 1999.
- Breast Cancer mortality have been decreasing due to screening and improvement in adjuvant therapy.

- Siegel et al Cancer statistics 2023 CA Cancer J Clin. 2023;73(1):17

EPIDEMIOLOGY II

- Hormone replacement therapy discontinuation had previously been touted as the major reason for decline
- WHI indicate HRT is safe in many postmenopausal women
- A study from Denmark showed incidence of breast cancer was unrelated to HRT use.

RISK FACTORS

- Age/Gender: 100 times more frequently in women than in men.
- 85% of breast cancers after women reach 50 years of age.
- 0.8% in women < 30 year old.
- 6.5 % in women between 30 and 40 year old.
- Race: Caucasian women have a higher rate than African American women .
- Asian and Hispanic less than white (approximately half).

- Jamal A et al Cancer statistics 2010 CA Cancer J Clin 2010;60:277

RISK FACTORS II

- Geography: Significantly lower in Japan, Thailand, Nigeria and India than USA, Denmark, Netherlands and Switzerland.
- Socioeconomic status: Higher in women of higher socioeconomic back ground.

Dense Breast Tissue

- The risk of breast cancer is four to five times greater in women with mammographically dense breasts (defined as >75% density) compared with women of similar age with less dense breasts.
- Breast density does not appear to a specific breast cancer subtype.
- Although breast density is a largely inherited trait, exogenous hormones can influence density.

- Boyd NF et al Mammographic density and the risk and detection of breast cancer N Engl J Med 2007;356:227

GENETIC FACTORS

- Accounts for 5-7 % of all breast cancer cases.
- BRCA1 gene: tumor suppressor gene located on chromosome 17 inherited in an autosomal-dominant fashion, more than 1000 deleterious mutations identified. 85% life time risk of breast cancer, 45% life time risk of ovarian cancer .
- BRCA2 gene: located on chromosome 13 also 85% life time risk of breast cancer, 6% male breast cancer, increased risk of ovarian, pancreatic, prostate cancer and melanoma
- Foulks WD et al N Engl J Med 2008;359:2143

Li-Fraumeni Syndrome

- Germline mutations in the TP53 gene on chromosome 17p inherited as autosomal dominant with penetrance of at least 50% by age 50.
- Premenopausal breast cancer, childhood sarcoma, brain tumors, leukemia and adrenocortical carcinoma.

Cowden's Syndrome

- Germ line mutations in the PTEN gene located on chromosome 10q23.
- Inherited as an autosomal dominant trait.
- Skin lesion trichilemmoma, mucocutaneous lesions, GI polyps,
- Life time risk of breast cancer 25 – 50%.

Family History

- Risk increased almost twofold if a woman had one affected first degree-relative.
- Increased threefold if she had two affected first degree relatives.
- Age at diagnosis of the affected first-degree relative influences the risk of breast cancer i.e. threefold higher if the first degree relative was diagnosed before age 30. But 1.5 fold increase if the affected relative was diagnosed after age 60.

- Collaborative Group on hormonal factors in breast cancer Lancet 2001; 358 :1389

Proliferative breast disease

- Moderate to florid ductal hyperplasia increases risk by 1.5 -2 times.
- Atypical ductal or lobular hyperplasia increases risk by 4 – 5 times.
- Lobular carcinoma in situ (LCIS) increases risk by 8 – 11 times.

Personal cancer history

- Significant risk factor for subsequent development of a second new breast cancer
- 1% per year from the time of diagnosis of an initial sporadic breast cancer.

Menstrual and reproductive factors

- Early onset of menarche (< 12 year old) associated with two fold increase risk.
- Menopause before 30 two fold reduction in breast cancer risk compared to women who undergo menopause after age 55.
- A first full term pregnancy before age 30 appears to have protective effect against breast cancer .
- Late first full-term pregnancy or nulliparity may be associated with a higher risk.

Lifestyle Factors

- Physical inactivity: regular exercise appear to provide modest protection against breast cancer.
- Alcohol: dose-response relationship between alcohol consumption and increased risk of breast cancer (as low as 3 drinks/week).
- Smoking: modestly increased risk of breast cancer.
- No association between passive smoking and breast cancer risk among a cohort of 1800 women (920 diagnosed with breast cancer).

Dietary Factors

- Dietary pattern: the influence of diet on breast cancer risk is not clear .
- A 2010 meta-analysis reported that high consumption of fruits and vegetables resulted in a lower risk of breast cancer.
- Fat intake: While there is an association between fat intake and breast cancer risk, it does not appear to be a strong one.
- Red meat and processed meat. >5 servings/week weak link.

Dietary Factors II

- Soy/phytoestrogens: naturally occurring plant substances with a chemical structure similar to 17-beta estradiol. They consist mainly of isoflavones (found in high concentrations in soy beans and other legumes) and fruits, vegetables , cereal products).
- A 2008 meta-analysis of 8 studies reported among Asian women a high intake of isoflavones > 20 mg/day was associated with a 29% reduction in breast cancer risk with a dose-response relationship. Among western women no association with soy intake (the highest level of soy intake 0.8 mg/daily .
- Wu AH et al Epidemiology of soy exposures and breast cancer risk Br J Cancer 2008;98:9

Environmental Factors

- Geographic residence: within USA Cape Cod, Massachusetts, Long Island, New York and Marin County California.
- Exposure to ionizing radiation: i.e. of chest at a young age for treatment of Hodgkin disease, survivors of atomic bomb or nuclear plant accidents. (age 10-14 or as late as 45).
- Night shift work: A 2005 meta-analysis exploring the relationship between night work and breast cancer risk included 13 studies of airline cabin attendants and nighttime shift worker relative risk 1.48. (this association may be related to nocturnal light exposure which result in the suppression of production of melatonin by the pineal gland.
- Whittemore AS et al breast cancer in marine county Breast cancer research 2003; 5:232

Medications

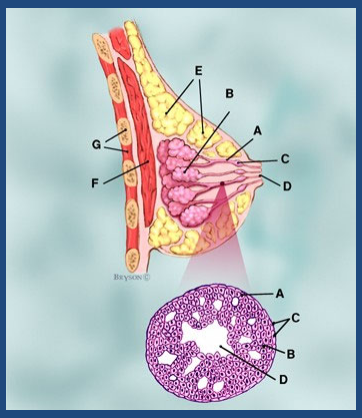
- Antioxidants: No effect.
- Non steroidal anti-inflammatory: No association .
- Low dose of vitamin D plus calcium no effect.
- Bisphosphonates: Potentially protective effect in adjuvant setting of women diagnosed with breast cancer .(post menopausal)

Reducing Breast Cancer Risk

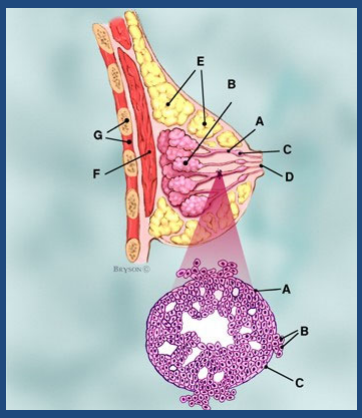
- Planning for the first birth before the age of 30.
- Breastfeeding for at least six months
- Avoidance of unnecessary exposure to radiation (avoid inappropriate use of CT scans).
- Avoidance or cessation of smoking.
- Limiting alcohol intake.
- Maintenance of a healthy weight and exercise.
- Limiting nocturnal shift work.

Pathology of Breast Cancer

Ductal carcinoma in situ

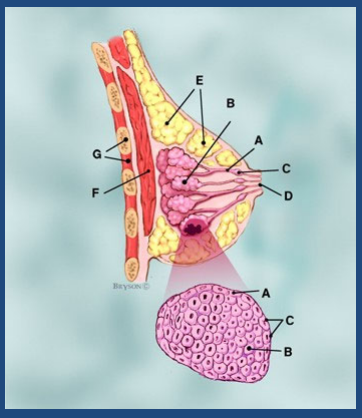


Invasive ductal carcinoma
76% of all breast cancer

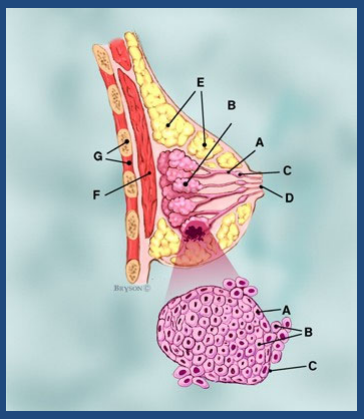


Lobular Carcinoma

Lobular carcinoma in situ



Invasive lobular carcinoma 8% of breast cancer

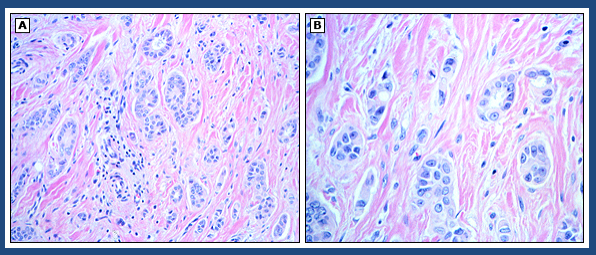


Pathology of Breast Cancer

- Less common types including mixed Ductal/Lobular 7%.
- Mucinous (colloid) 2.4%.
- Tubular 1.5%.
- Medullary 1.2%.
- Papillary 1%.
- Other subtypes including metaplastic and invasive micropapillary less than 5%.

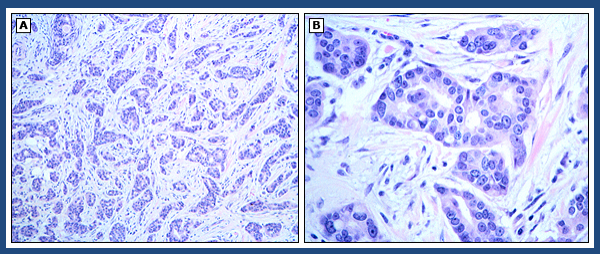
Invasive Ductal Carcinoma Grade I

Well differentiated ductal carcinoma



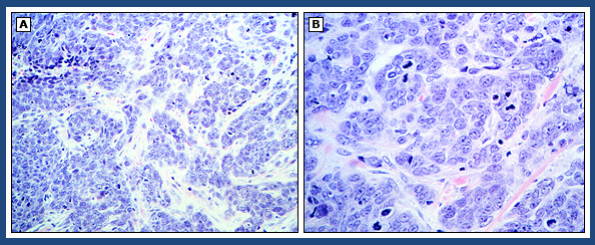
Invasive Ductal Carcinoma Grade II

- Moderately differentiated ductal carcinoma



Invasive Ductal Carcinoma Grade III

- Poorly differentiated ductal carcinoma



Molecular Intrinsic subtypes of breast Cancer

- Luminal subtypes: Luminal A and luminal B which express genes associated with luminal epithelial cells of normal breast tissue .
- Luminal A: the most common subtype make up 40% of all breast cancers , High expression of ER, low expression of HER 2 . Carry the best prognosis.
- Luminal B: Less common 20% relatively lower expression of ER, variable expression of HER2 and higher expression of proliferation cluster. Worse prognosis

HER2 enriched

- 15 – 20 % of breast cancer.
- Characterized by high expression of the HER2 and proliferation gene clusters.

Basal – Like (Triple negative breast cancers)

- 15-20% of breast cancers.
- Low expression of the luminal and HER2 gene clusters ER/PR- and HER2 -.
- High expression of proliferation cluster of genes .
- High grade and contain widespread genomic instability
- High expression of a unique basal cluster which include basal epithelial cytokeratins 5, 14, and 17.
- Strong association with BRCA1

Claudin-low

- 5-10% of breast cancers had triple negative.
- Expression of epithelial-mesenchyme transition genes and characteristics reminiscence of stem cells.
- Low or absent expression of epithelial cell-cell adhesion genes (Claudine 3,4 and 7 and E cadherin)..
- Slower growing and with features of mesenchyme and mammary stem cells.

Interferon-rich/immunomodulatory

- Better prognosis.
- High gene expression of complement and immune response pathway genes.

Androgen receptor-driven

- High expression of hormonally mediated pathways in spite of low estrogen receptor expression with AR protein detectable by immunostains.

Normal-like

- One of the initial subtype of triple negative identified by gene expression array and consistently appears in breast cancer clusters.
- Characterized by similar gene expression pattern as normal breast.
- Low tumor cell composition of the sampled specimen.

Inflammatory Breast Cancer

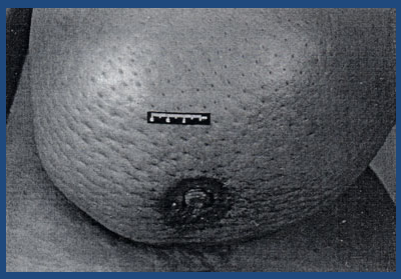
- Incidence 0.5 – 2 % of invasive breast cancer diagnosed in USA.
- Incidence appears to be increasing .
- Age incidence median 59 – 66 years of age.
- Higher in black American compared to white.

Clinical features

- Rapid onset of breast pain or rapidly growing breast lump.
- Lymph nodes involvement in almost all patients
- Distant metastasis in nearly 1/3 of patients.
- O/E Skin thickening Peau d'orange.
- Skin color range from pink flushed discoloration initially to redness or purplish hue (ecchymosis)
- Nipple retraction, flattening, erythema crusting blistering
- Discretely palpable lump may not be present.

Clinical presentation
Peau d'orange

Up to Date



Clinical presentation II

Up to Date

Diagnostic criteria

- IBC is designated as T4d in the American joint committee on cancer AJCC TNM staging system all the following criteria must be met.
- Rapid onset of breast erythema, edema/Peau d'orange, warm breast with or without palpable mass.
- Duration of history no more than 6 months.
- Erythema occupying at least one-third of the breast.
- Pathologic confirmation of invasive carcinoma.

Staging and pretreatment evaluation

- Labs. CBC,CMP CT scan, bone scan (if Alkaline phosphatase is elevated)
- Core needle biopsy of palpable LN.
- Echocardiogram for base line EF .

Treatment of Inflammatory Breast Cancer

- Neoadjuvant therapy based on biomarkers.
- HER2 overexpressing: TCHP Docetaxel/carboplatin/trastuzumab/pertuzumab x 6 cycles or A/C dose dense : doxorubicin/Cyclophosphamide q 2 weekly x 4 followed by weekly paclitaxel/trastuzumab/pertuzumab x 12 weeks
- Triple negative Keynote 522 Weekly paclitaxel/carboplatin x 12 along with pembrolizumab Q 3 or 6 weekly followed by 4 cycle of A/C
- Peter Schmid MD., et al N Eng J Med 2020;382:810-821

Treatment of IBC II

- Mastectomy Axillary lymphadenectomy
- Adjuvant radiotherapy
- Adjuvant endocrine therapy if ER positive
- Adjuvant anti HER2 for HER 2 positive,
- Adjuvant immunotherapy with Pembrolizumab if triple negative (as per KEYNOTE 522)

Prognosis

- With neoadjuvant chemotherapy followed by surgery and adjuvant radiotherapy overall five-year survival between 30-70%.
- SEER (Epidemiology and end results database demonstrated 20 –year cancer specific survival of 20 vs 9 % for patient with IBC treated in 1995 compared with 1975 .
- SEER between 2004 and 2007 two-year breast cancer – specific survival rate of patients with IBC vs non inflammatory breast cancer 84 vs 91 %

Management of Hormone Receptor – Positive Metastatic Breast Cancer

- First line therapy:
- Aromatase inhibitors (only post menopausal women) i.e. anastrozole, letrozole, and exemestane. Plush CDK 4/6 inhibitor ribociclib, abemaciclib or Palbociclib.
- Premenopausal Tamoxifen/ ribociclib (abemaciclib or Palbociclib) and ovarian suppression.
- The second line : Fulvestrant + CDK4/6 inhibitor or PIK3CA mutant Alplisib Check for ESR1 mutation by liquid biopsy if present consider Elacestrant.
- Third line therapy exemestane and everlolimus.
- Phase III BOLERO- 2 (Breast cancer trials of oral Everolimus) ER positive metastatic breast cancer who progressed or recurred after treatment with non steroidal aromatase inhibitor were randomizes to exemestane 25 mg po daily plus Everolimus (mTOR) inhibitor (n= 485) or placebo (n=239)

Management of Hormone Receptor Positive Metastatic Breast Cancer II

- PFS 11.0 months for Everolimus vs. 4.1 months for placebo group. (HR 0.38; 95% CI P<0.0001).
- Adverse effects including pneumonitis and interstitial lung disease observed with Everolimus but not with placebo arm.

- M Piccart et al San Antonio Breast cancer symposium 2012 poster P6-04-02

Management of Hormone Receptor Positive Metastatic Breast Cancer III

- Fulvestrant at a higher dose 500 mg I.M.
- Phase III CONFIRM Trial: 500 mg (n= 362) versus 250 mg (n= 374) .
- PFS 6.5 months versus 5.5 months (HR 0.80 : 95% CI).
- Overall survival 25.1 months vs. 22.8 months not statistically significant.
- The rate of adverse effects were similar in both arms

- Angelo Di Leo et al San Antonio Breast cancer symposium Dec, 4-8 2012 Abstract S1-4

Management of Hormone Receptor Positive Metastatic Breast Cancer IV

- Randomized phase II study of palbociclib a Cycline-Dependent Kinase (CDK) 4/6 Inhibitor in combination with letrozole Vs letrozole alone for first line treatment of ER+/HER2 – advanced breast cancer (N= 666 randomize 2:1). PALOMA-2
- CDK play a critical role in regulating cell cycle progression and novel target in cancer therapy .
- Palbociclib 125 mg po daily (day 1-21/28 days) plus letrozole 2.5 mg po daily (n=66)
- PFS 24.8 moths Vs. 14.5 months for letrozole .

- RS Finn et al N Engl J Med Nov 17/2016; 375: 1925-1936

Ribociclib

- MONALEESA-2 Phase III trial
- N = 668 postmenopausal women with advanced hormone positive HER2 NEU negative breast cancer randomized to ribociclib/letrozole or placebo/letrozole
- Median follow up of 6.6 years
- Overall survival 63.9 months with ribociclib vs 51.4 months with placebo.

- Gabriel N. Hortobagy et al N Engl J Med 2022;386:942-950

Future directions (ASCO 2023)

- Addition of ribociclib to endocrine therapy improves outcomes in early stage HR+ /HER2 negative breast cancer
- NATALEE phase III trial : N 5101 pre and post menopausal patients stage II and III HR+/HER2-
- Randomized 1:1 ribociclib 400 mg po daily 3 weeks on 1 week off for 3 years AI Letrozole or anastrozole alone . Premenopausal or med add goserelin for 5 years
- Absolute improvement of 3.3% in iDFS

- Slamon DJ D. Yardley et al LBA 5001. J Clin Oncol.2023;41(17)(suppl)

Future directions II

- SONIA trial support delay of CDK4/6 inhibitors until second-line in advanced HR+/HER2- breast cancer.
- 1050 pre-and post menopausal women with advanced breast cancer from 74 Dutch hospitals randomized 1:1 to receive first-line therapy with a CDK4/6 inhibitor plus an AI followed on progression by fulvestrant or first line treatment with an AI followed on progression by fulvestrant plus a CDK 4/6 inhibitor
- Median PFS or OS were not significantly better with either arms.

- Sonke GS et al [ASCO abstract LBA1000] J Clin Oncol.2023;41(17) (suppl)

Abemaciclib

- MONARCH2 phase III trial second line therapy for post menopausal women who progressed on AI
- N= 669 randomized 2:1 for Abemaciclib/fulvestrant or fulvestrant/placebo
- PFS 16.4 months for Abemaciclin/fulvestrant vs 9.3 Placebo/fulvestrant

- ASCO June/2017. George Sledge et al.

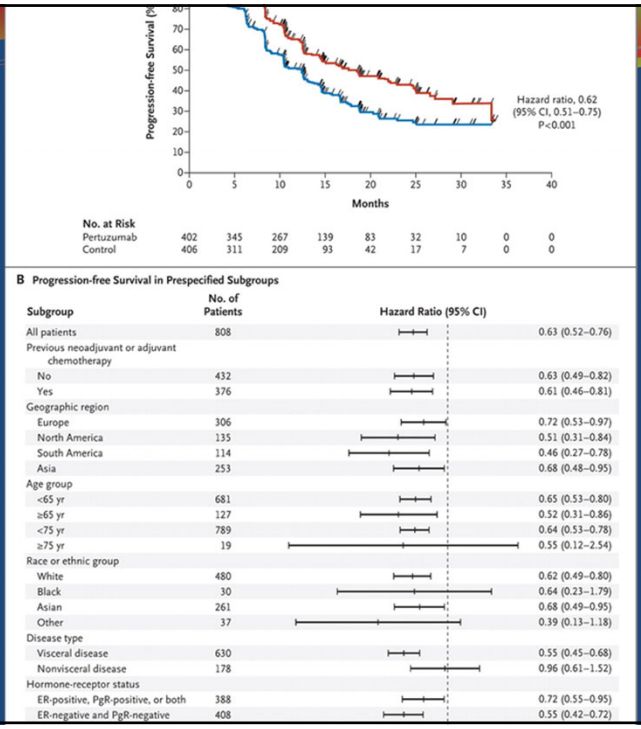
Management of HER2-Positive Metastatic Breast Cancer

- First line therapy: CLEOPATRA clinical trial (Clinical Evaluation of Pertuzumab and Trastuzumab for metastatic HER2 NEU overexpressing Breast cancer.
- Randomized double-blind placebo-controlled phase III clinical trial involving 808 patients (1:1 Ratio) To receive placebo+trastuzumab+docetaxel (control group) or pertuzumab+trastuzumab+docetaxel.
- Pertuzumab is a new humanized monoclonal antibody that binds HER2 at a different epitope of HER2 extracellular domain (subdomain I) than that at which trastazumab binds.

CLEOPATRA II

- Results: Progression-free survival was 12.4 months for the control group as compared to 18.5 months in the pertuzumab group.
- Hazard ratio of 0.62 .
- The safety profile was similar in the two groups with no increase in left ventricular systolic dysfunction.

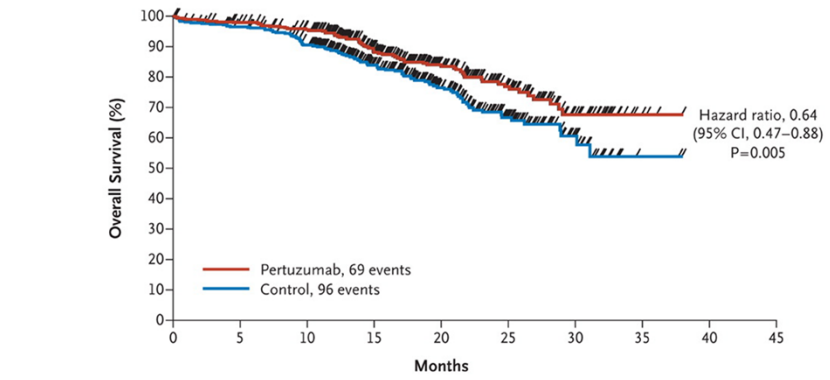
- Jose Baselga et. Al N Engl J Med 2012; 366:109-119



B Progression-free Survival in Prespecified Subgroups

Subgroup	No. of Patients	Hazard Ratio (95% CI)
All patients	808	0.63 (0.52–0.76)
Previous neoadjuvant or adjuvant chemotherapy		
No	432	0.63 (0.49–0.82)
Yes	376	0.61 (0.46–0.81)
Geographic region		
Europe	306	0.72 (0.53–0.97)
North America	135	0.51 (0.31–0.84)
South America	114	0.46 (0.27–0.78)
Asia	253	0.68 (0.48–0.95)
Age group		
<65 yr	681	0.65 (0.53–0.80)
≥65 yr	127	0.52 (0.31–0.86)
<75 yr	789	0.64 (0.53–0.78)
≥75 yr	19	0.55 (0.12–2.54)
Race or ethnic group		
White	480	0.62 (0.49–0.80)
Black	30	0.64 (0.23–1.79)
Asian	261	0.68 (0.49–0.95)
Other	37	0.39 (0.13–1.18)
Disease type		
Visceral disease	630	0.55 (0.45–0.68)
Nonvisceral disease	178	0.96 (0.61–1.52)
Hormone-receptor status		
ER-positive, PgR-positive, or both	388	0.72 (0.55–0.95)
ER-negative and PgR-negative	408	0.55 (0.42–0.72)

CLEOPATRA trial



Second line therapy

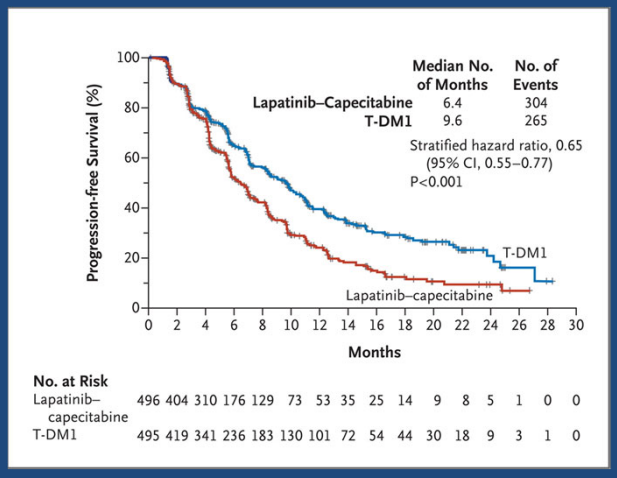
- Fam –trastuzumab deruxtecan Dxd is an antibody-drug conjugate.
- Phase III DESTINY – Breast 03 second line after progression on trastuzumab-taxane-containing regimen.
- Median PFS 28.8 months for Dxd compared to 6.8 months for T-DM1 (hazard ratio 0.33 CI 0.26-0.43)

Hurvitz SA Hegg R, Chung WP, et al Lancet 2022 online on 12/7/2022.

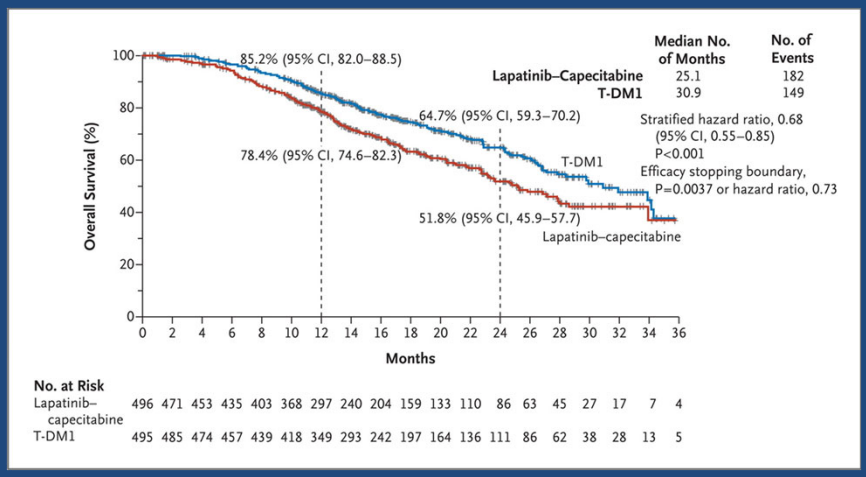
Third Line Therapy

- EMILIA Clinical Trial (phase III)
- Randomized (open-lable) clinical trial involving 991 patients who had previously been treated with trastuzumab and a taxan to trastuzumab emtansine (T-DM1) or lapatinib plus capecitabine.
- Progression –free survival was 9.6 months with T-DM1 versus 6.4 months with lapatinib/capecitabine
- Hazard ratio 0.65; 95% confidence interval.
- Trastuzumab T- DM1 is FDA approved in Feb./2013.
- Verma et. Al N Eng J Med 2012; 367 : 1783-91

EMILIA trial



EMILIA trial



ANTIBODY-DRUG CONJUGATES (ADCs)

ngoing Challenge in Cancer Treatment: Balancing Benefit vs. Side Ef

EMERGENCE OF CANCER TREATMENT OPTIONS[1]

EARLY 1900s	MID 1900s	1990s	EARLY 2000s
Radiation therapy	Chemotherapy and hormone treatments	Targeted medicines +/- chemotherapy or hormone treatments	Combinations of targeted medicines +/- chemotherapy or hormone treatments

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of ADCs is to help
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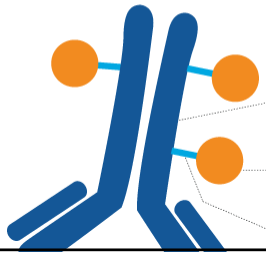

The **antibody** targets and binds
proteins (or receptors) on the su

The **chemotherapy** is delivered
is designed to destroy the cells o

The **linker** binds the antibody to

Beyond third line

- Tucatinib,capecitabine, and trastuzumab.
- 480 heavily pretreated patients HER2 positive metastatic breast cancer (median of 4 lines of therapy)
- 1 year PFS 33% patients receiving tucatinib-capecitabine-trastuzumab vs. 12% capecitabine-trastuzumab.
- Margetuximab SOPHIA phase III 536 patients (at least 2 lines of therapy) PFS 5.8 months for margetuximab plus chemo vs 4.9 months trastuzumab plus chemo.

Triple negative breast cancer

- Immunotherapy role in neoadjuvant
- Keynote 522 Phase III clinical trail 1174 patients previously untreated stage II or stage III neoadjuvant chemotherapy randomly assigned to pembrolizumab vs placebo q 3 weekly during NACT weekly paclitaxel/ carboplatin followed by 4 cycles of doxorubicin/cyclophosphamide q 3 weekly
- PCR 65 % with pembrolizumab 51% in placebo arm (HR0.63, 95% CI 0.48-0.82)

- Peter Schmid Javier Cortes et. Al . N Eng J Med 2020;382:810-821

Management of Triple-Negative Breast Cancer

- Chemotherapy remains the mainstay of therapy.
- Combination chemotherapy is associated with higher response rate, improved overall survival with increase toxicity.
- Anthracyclines : doxorubicin, epirubicin, Doxil.
- Taxans: paclitaxel, docetaxel, NAB paclitaxel.
- Antimetabolites : capecitabine, 5 FU. and Gemcitabine
- Antitubulins : vinorelbine, eribuline. Ixabepilone.
- Target therapy and gene sequencing.

Management of Bone metastasis

- Median survival for bone only disease if 24 months with 20 % of patients alive in 5 years .
- Some patients may have a longer survival at 72 months.
- Local therapy: External beam radiotherapy , Surgery to stabilize the long bone, Systemic therapy.
- Bone-targeting agents: bisphosphonates and denosumab

Skeletal-Related Events SREs

- Bone metastasis can be associated with skeletal complications SREs .
- Bone fracture, need for surgery or radiation, spinal cord compression, and hypercalcemia of malignancy.
- 70% of patients dying of breast cancer have evidence of bone metastasis.

- Coleman RE et al Clin cancer RES 2006; 12:6243

Bisphosphonates

- Zoledronic acid: a high potency parenteral bisphosphonate effectively decreases the risk of SREs and osteolytic and osteoblastic metastasis.
- Zoledronic acid was compared to placebo in a trial that randomly assigned 228 women with bone metastasis from breast cancer to zoledronic acid 4 mg i.v. monthly for 15 months or placebo . The rate of SREs 30 versus 50 percent and the time to develop a first SRE was significantly improved in the treated group.

- Kohno N et al J Clin Oncol 2005; 23: 3314

Denosumab

- Osteoclast inhibition can also be accomplished by targeting the receptor activator of nuclear factor kappa B ligand (RANKL).
- Monoclonal antibody to RANKL denosumab has demonstrated efficacy in decreasing the risk of first and subsequent skeletal-related events.
- In a double blind placebo controlled phase III trial of 2046 patients with metastatic breast cancer involving the bone (NCT00321464) patients were randomly assigned to either denosumab 120 mg sq monthly , i.v. placebo and zoledronic acid 4 mg i.v. and sq. placebo
- Stopeck AT et al J Clin Oncol 2010; 28: 5132

Denosumab II

- Denosumab extended the median time to first SRE (32.4 months versus 26.4 months).
- No statistical difference between denosumab and zoledronic acid in overall survival (HR 0.95, 95% CI 0.81- 1.11) or time to disease progression (HR 1.00, 95%CI 0.89-1.11).
- Side effects including osteonecrosis of the jaw 2% (similar to zoledronic acid) less renal toxicity , hypocalcaemia , and fatigue.

Whom to treat

- ASCO recommend that osteoclast inhibition with denosumab or bisphosphonate be considered in the management of patients with metastatic breast cancer with bone destruction on plain radiographs, CT or MRI .
- Duration of therapy: is unknown .
- Prevention of skeletal complications and palliation of symptoms have been seen with up to 3.6 years of continued therapy.

Palliative Care

- Should be part of interdisciplinary management.
- Focuses on preventing and relieving suffering .
- Promoting the best possible quality of life for patients and their families facing serious illness.
- When to stop therapy??
- Poor performance status.
- Extensive liver metastasis affecting liver functions .
- Patient and family request.

QUESTIONS?