Breast cancer

Breast Cancer:
Overview
Prevention, Diagnosis, Treatment

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TRACO Lecture
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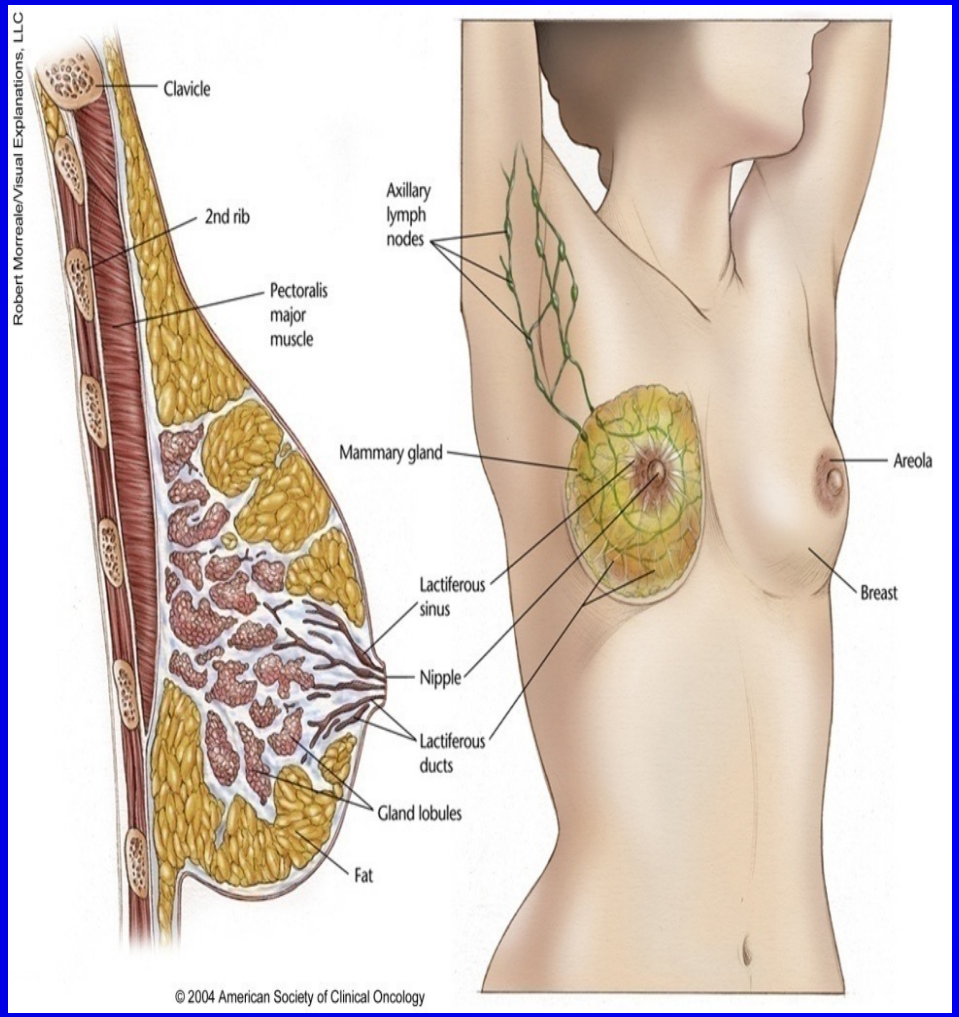
Breast cancer

Structure of the Breast



- The breast is composed mainly of **fatty tissue**, which contains a network of lobes made up of tiny, tube-like structures called lobules that contain milk glands
- **Tiny ducts connect the glands, lobules, and lobes**, and carry the milk from the lobes to the nipple
- Blood and lymph vessels run throughout the breast
- About **90% of all breast cancers** start in the **ducts** or **lobes** of the breast

Breast Cancer

- *Precise* reasons why a woman develops breast cancer are difficult to specify.
- Genetic + environmental + lifestyle factors
- Hormones seem to have an important role. Research has shown a link between estrogen levels and the risk of developing *HR+ breast cancers.*

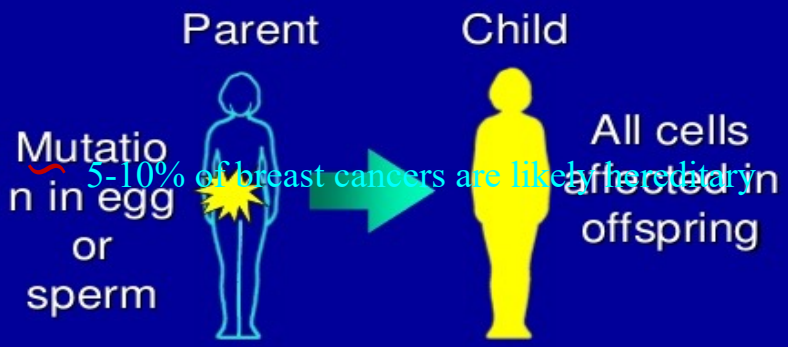
Known Breast Ca Risk Factors

- Age (80% of breast cancers occur after menopause)
  1/8 → age < 45
  2/3 → age ≥ 55
- History of Prior breast cancer
  3- 4 X more likely to develop a new cancer (same or other breast)
- History of benign breast conditions with atypia (4X Risk) or without (2X Risk).
- Exposure to excess endogenous or exogenous hormones:
  1. Early menarche
  2. Late menopause
  3. Use of Hormone Replacement Therapy
  4. No pregnancies or age >35 at birth of first child
- Radiation exposure before age 40
  (breast ca after xrt for Hodgkin's lymphoma)
- Dense breast tissue on mammogram
  glands > fat
- lifestyle factors (alcohol [↑ estrogen, DNA damage], lack of exercise [exercise consumes blood sugar and limits IGF, a hormone that can effect breast cell growth], also obesity ➤ (BMI > 25) ➤ extra fat cells = more estrogen in the body.

Gene mutations

Cancer Arises From Gene Mutations

Germline mutations



- Present in egg or sperm
- Are heritable
- Cause hereditary cancer syndromes

5-10% of breast cancers are likely hereditary

Somatic mutations

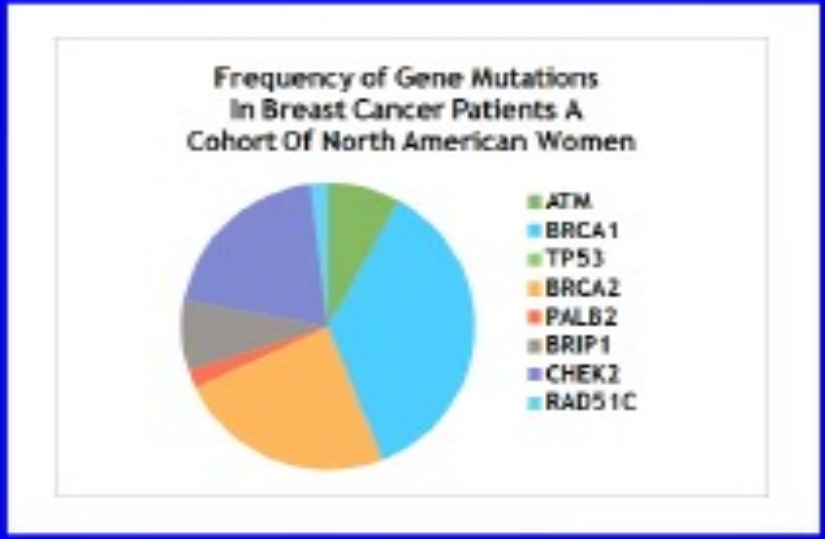
result of the natural aging process, or exposure to environmental carcinogens

- Occur in nongermline tissues
- Are nonheritable
- Later onset

Gene mutations

Gene Mutations

- **ATM:** Helps repair damaged DNA
- **BRCA ½:**
  - Helps repair damaged DNA.
  - up to 72% lifetime risk br ca
- **TP53:**
  - tumor suppressor gene
  - cancer risk nearly 100%
- **PALB2:** codes for protein that works with BRCA2 protein to repair damaged DNA. Mutation = 33% - 58% lifetime risk.
- **BRIP1:** codes protein that helps repair DNA.
- **CHEK2:** Codes protein that stops tumor growth. Mutation can double breast cancer risk.



Breast cancer statistics

Female Breast Cancer Stat Facts

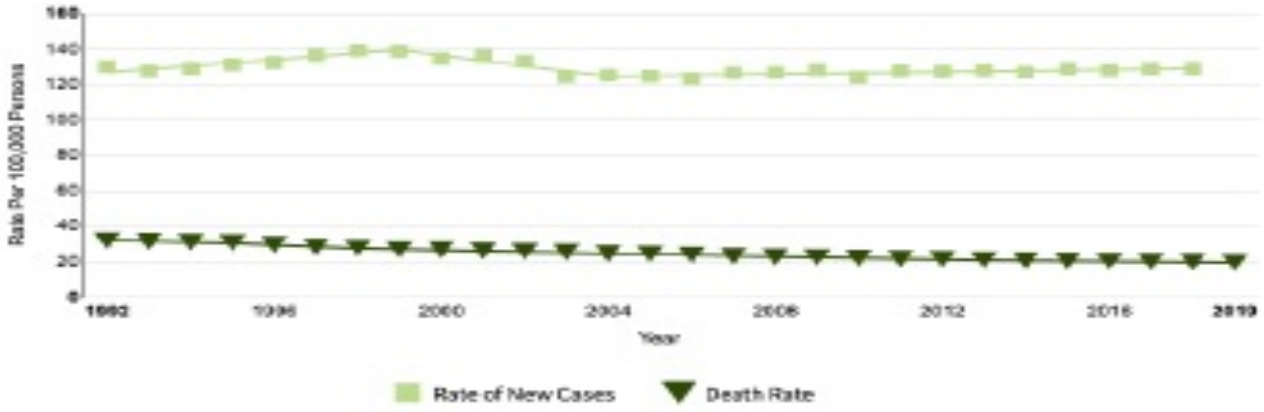
At a Glance

Estimated New Cases in 2021	281,550
% of All New Cancer Cases	14.8%
Estimated Deaths in 2021	43,600
% of All Cancer Deaths	7.2%

5-Year Relative Survival

90.3%

2011–2017



New cases come from SEER 13. Deaths come from U.S. Mortality.
All Races, Females. Rates are Age-Adjusted.

- Estimates of new cases and deaths for 2021 are projections made by the American Cancer Society, based on earlier reported data.

MEN:

- Lifetime Risk: 1 in 833
- About 2,650 new cases of invasive disease are projected to be diagnosed in 2021

Breast cancer cases

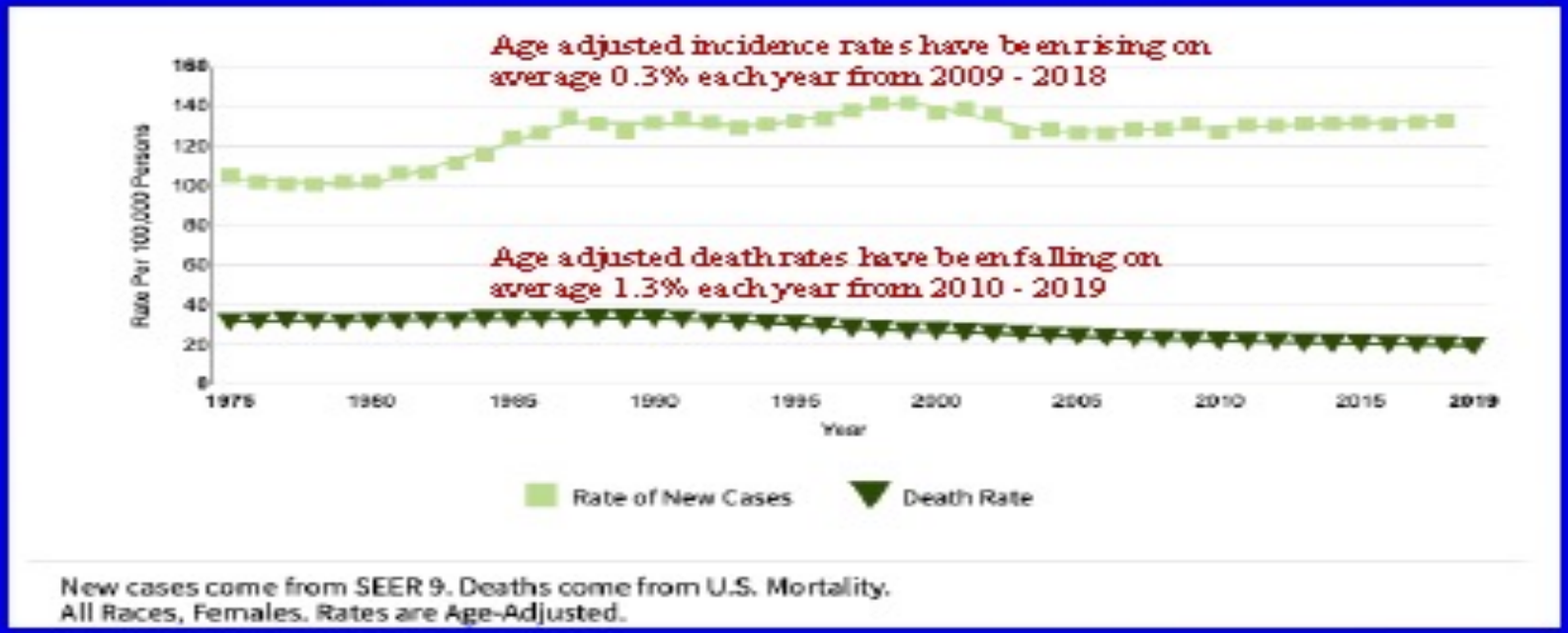
How Common is This Cancer?

	Common Types of Cancer	Estimated New Cases 2021	Estimated Deaths 2021
1.	Breast Cancer (Female)	281,550	43,600
2.	Prostate Cancer	248,530	34,130
3.	Lung and Bronchus Cancer	235,760	131,880
4.	Colorectal Cancer	149,500	52,980
5.	Melanoma of the Skin	106,110	7,180
6.	Bladder Cancer	83,730	17,200
7.	Non-Hodgkin Lymphoma	81,560	20,720
8.	Kidney and Renal Pelvis Cancer	76,080	13,780
9.	Uterine Cancer	66,570	12,940
10.	Leukemia	61,090	23,660

Female breast cancer represents 14.8% of all new cancer cases in the U.S.

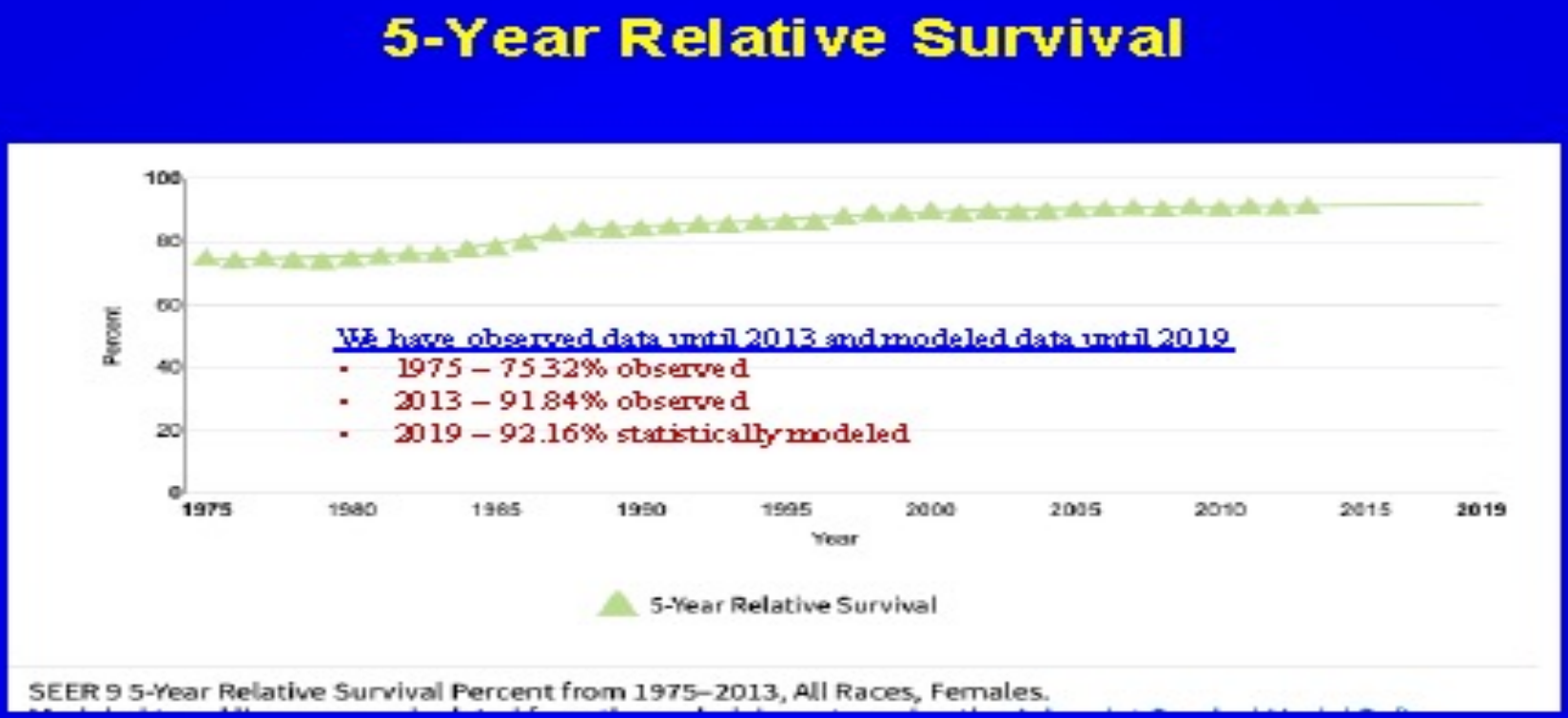
Breast cancer incidence

1. Incidence Rate of New Cases of Female Breast Cancer
2. Death Rate



New cases come from SEER 9. Deaths come from U.S. Mortality.
All Races, Females. Rates are Age-Adjusted.

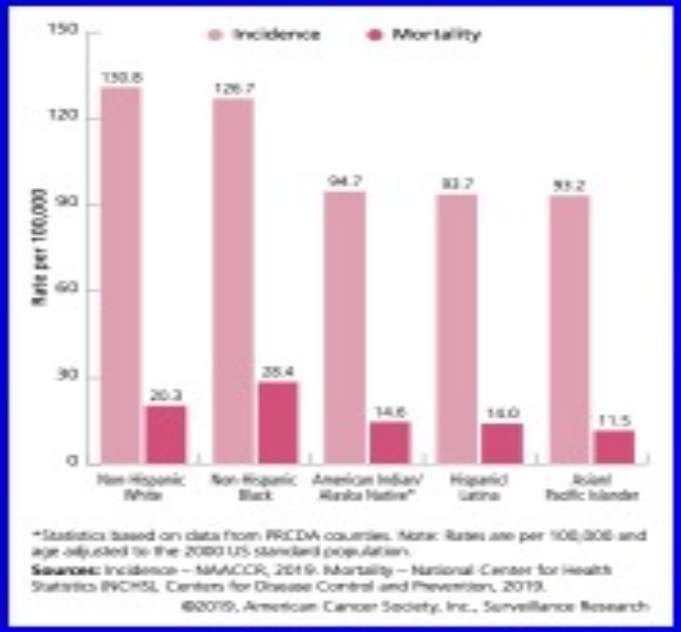
Breast cancer survival



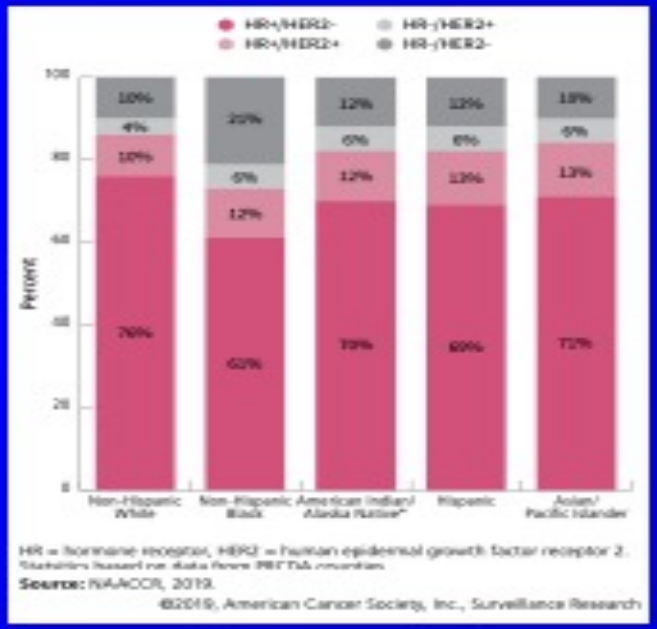
Breast cancer statistics

Statistics

Incidence & Mortality By Race/Ethnicity (2013-2017)

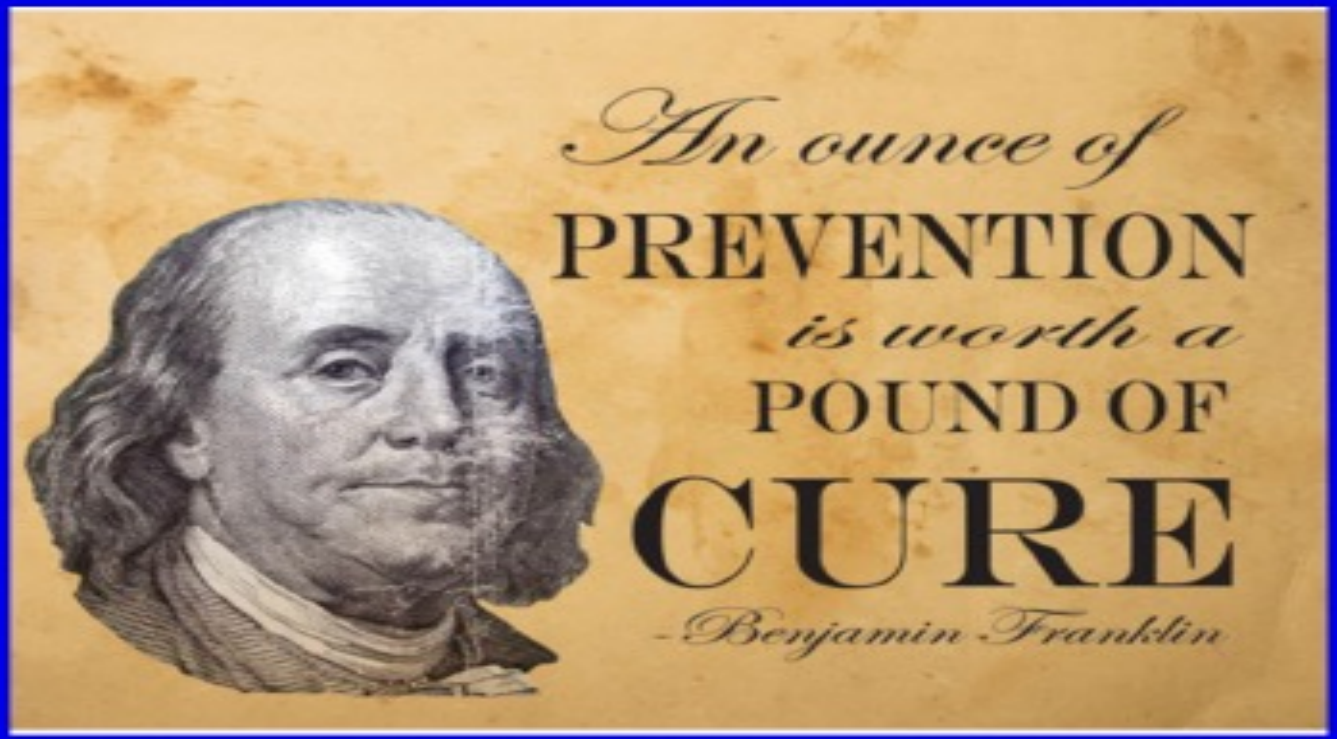


Distribution of Cancer Subtypes by Race/Ethnicity (2012-2016)



Early Detection

Prevention


An ounce of
PREVENTION
is worth a
POUND OF
CURE
-Benjamin Franklin

Mamograms save lives

- Mammograms can be used as **screening** tools to detect early breast cancer in women experiencing no symptoms
- Mammograms can also be used to **detect and diagnose** breast disease in women experiencing symptoms such as a lump, pain, or nipple discharge.
- Reduces mortality by:
  26% aged 50-74
  17% aged 40-49

*American Cancer Society

3 types of mammograms

3 Types of Mammograms

1. Film Mammography
   - X-Ray Picture of the breast
   - Antiquated Method!

2. Digital Mammography
   - Computer Picture of the breast

3. Digital Breast Tomosynthesis (DBT)
   - uses x-rays to take a series of pictures of the breast from many different angles. Then, a computer is used to make 3-D pictures of the breast

Approved by the FDA in 2018 & now in use in 3 out of 4 facilities. One study found that DBT reduced false positive results. Studies are on-going comparing digital mammography to DBT.

American Cancer Society Guidelines for the Early Detection of Breast Cancer

Average Risk

- Age 40-44: women have the choice to begin annual mammograms. Risks and benefits should be considered.
- Age 45-54: annual mammograms are recommended.
- Age 55 and older: switch to biannual mammograms, or have the choice to continue an annual schedule based on risks/benefits.

Screening should continue as long as a woman is in good health, and life expectancy is 10 years or more.

High Risk

Annual MRI + Mammogram *(as long as a woman is in good health and life expectancy is >/= 10 years)*

- Have a lifetime risk of breast cancer of >/= 20-25% using risk-assessment tools based mainly on family history.
- Have a known BRCA 1 or BRCA 2 Gene Mutation.
- Have a first degree relative with BRCA 1 or BRCA 2 gene mutation, but have not had testing themselves.
- Had radiation to the chest between AGES 10-40.

American Cancer Society Guidelines for theEarly Detection of Breast Cancer

Use of MRI For Early Detection:

- While MRI is more sensitive than mammogram, it also has a higher false positive rate. This may lead to unnecessary biopsies and other procedures.

- The American Cancer Society recommends *against* use of MRI for women whose lifetime risk of breast cancer is < 15%.

- For women who have a moderately increased lifetime risk of breast cancer (15-20%) there is not enough evidence to make a recommendation for or against use of annual MRI.

- If MRI is used, it should be in addition to, and not in place of a screening mammogram.

American Cancer Society Guidelines for the Early Detection of Breast Cancer

Clinical Breast Exam & Breast Self Exam:

- There is no solid clinical trial evidence that a physical breast exam done either by a health care professional or by the women themselves, provides any clear benefit in early detection or reducing breast cancer mortality.

- Due to this lack of evidence, regular clinical breast exams and breast self exams are not part of the ACS guidelines.

- However, all women should be familiar with how their breast look and feel, and report any changes to their physician ASAP.

Self Breast Exam

Self Breast Exam (SBE)

- Size
- Shape
- Color
- Dimpling
- Puckering
- Retraction
- Thickening
- Inverted nipple
- Nipple discharge

Step 1

Shoulders straight, arms on hips

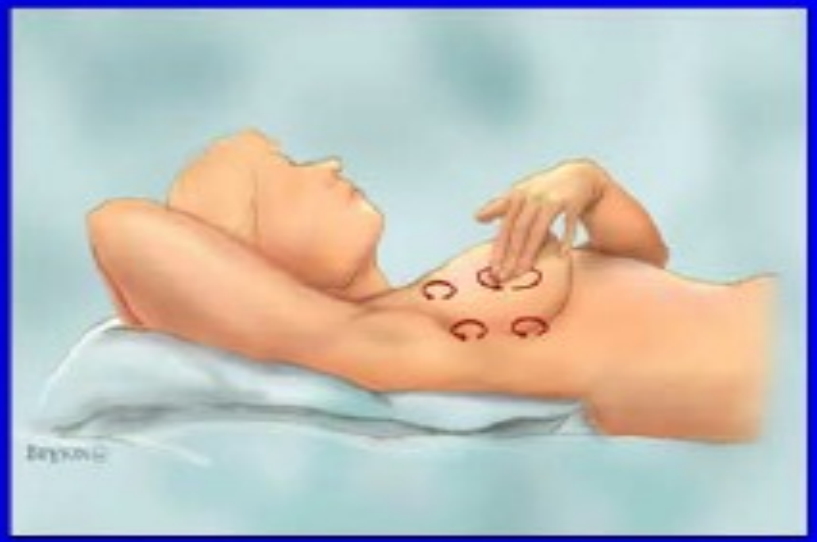
Step 2

Arms over head

Self Breast Exam

Self Breast Exam

Step 3



Examine lying down

Firm, smooth touch

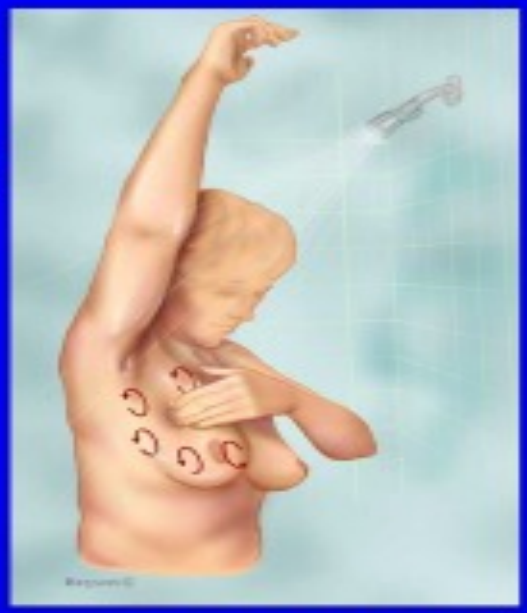
Fingers flat & together

Circular Motion

Follow a pattern

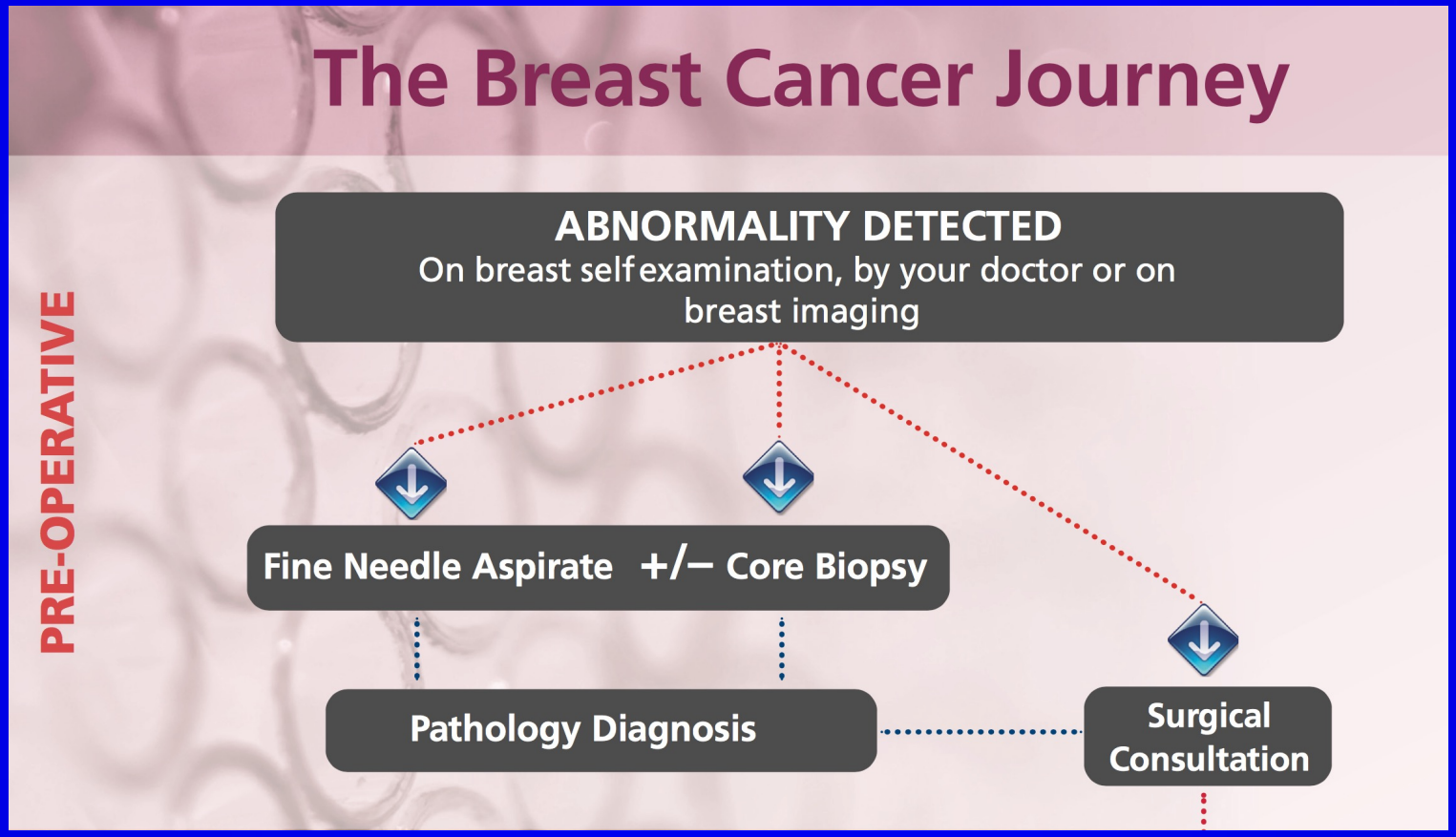
Cover whole breast

Step 4

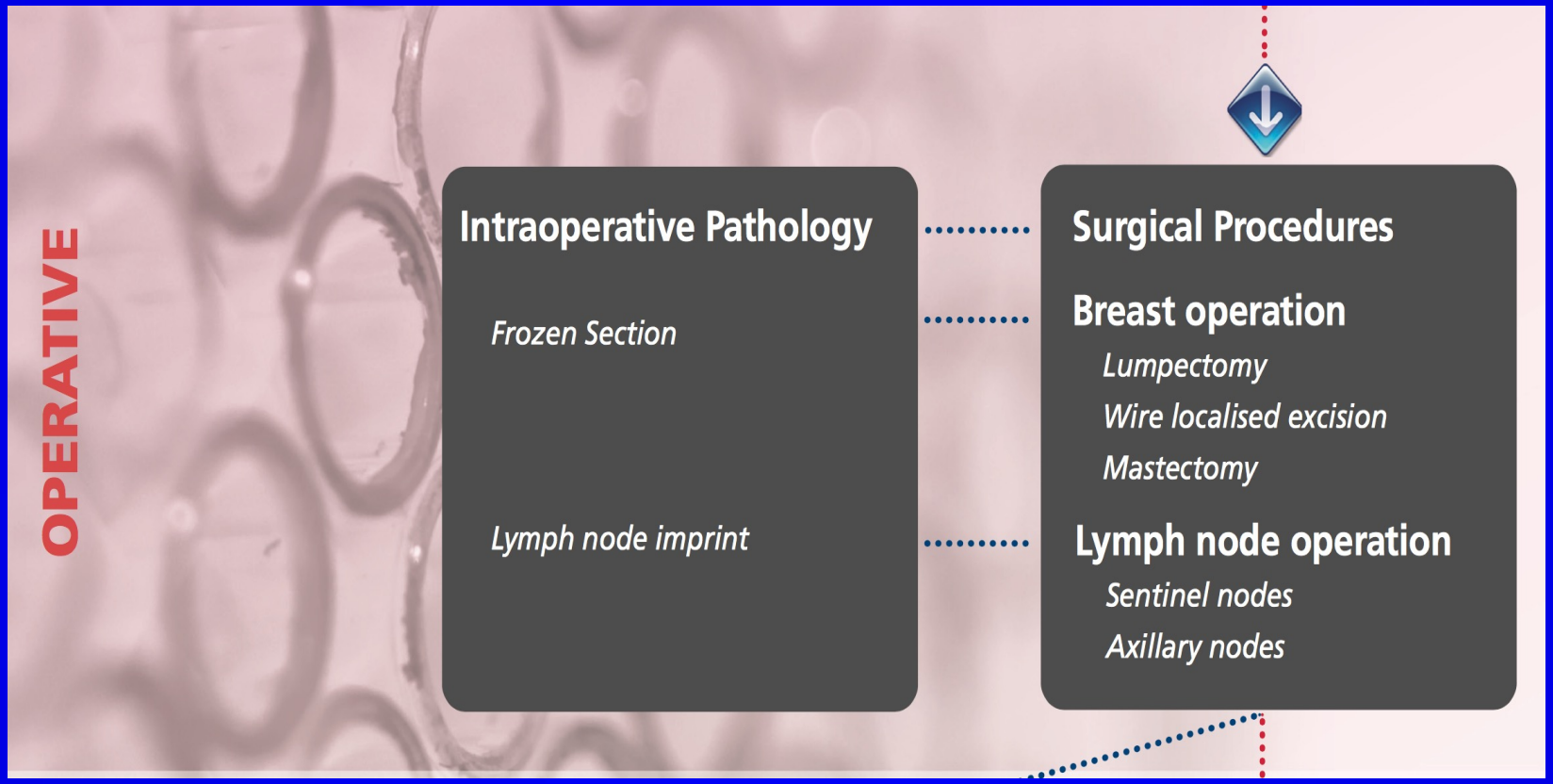


Examine upright

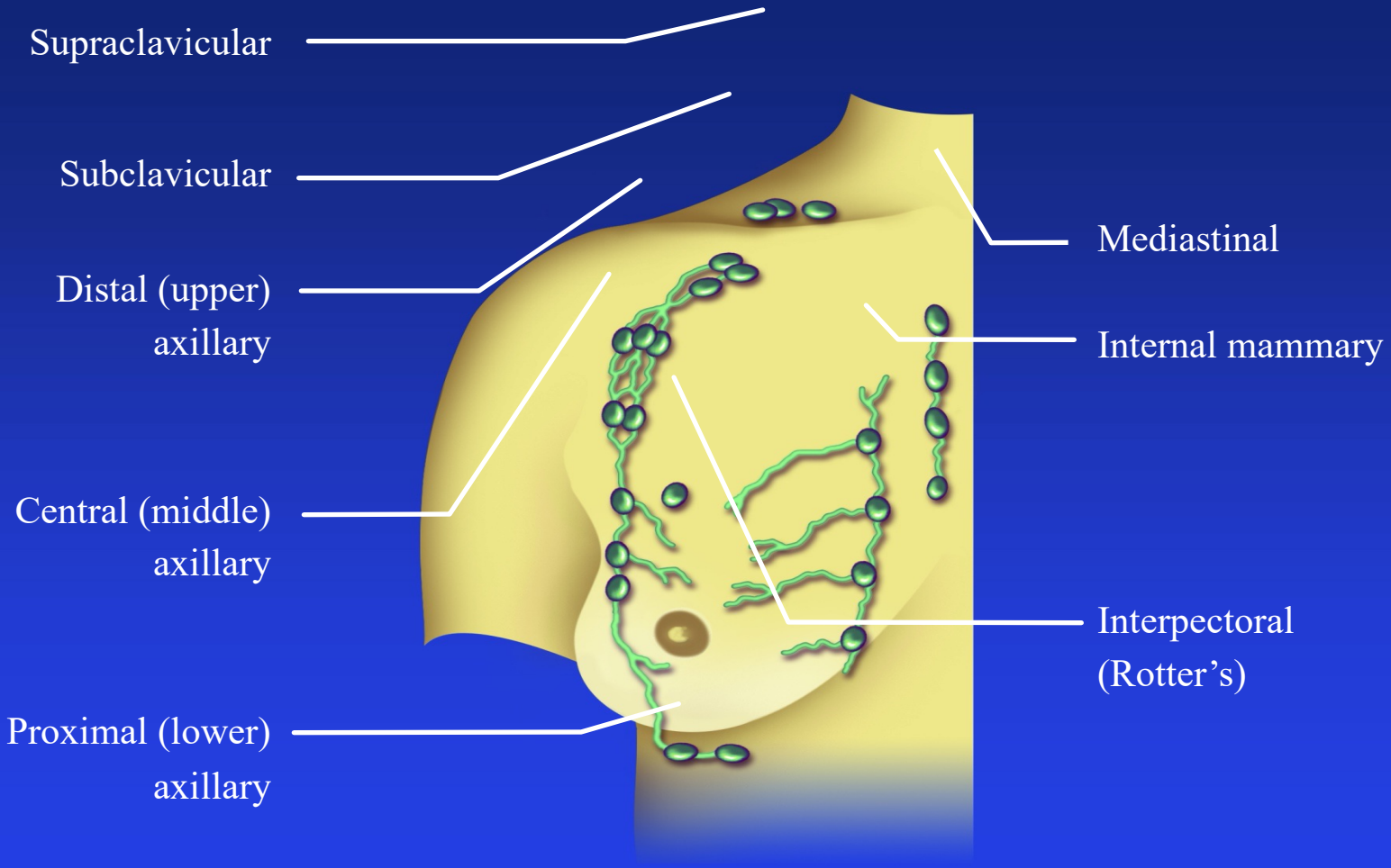
Pre-operative



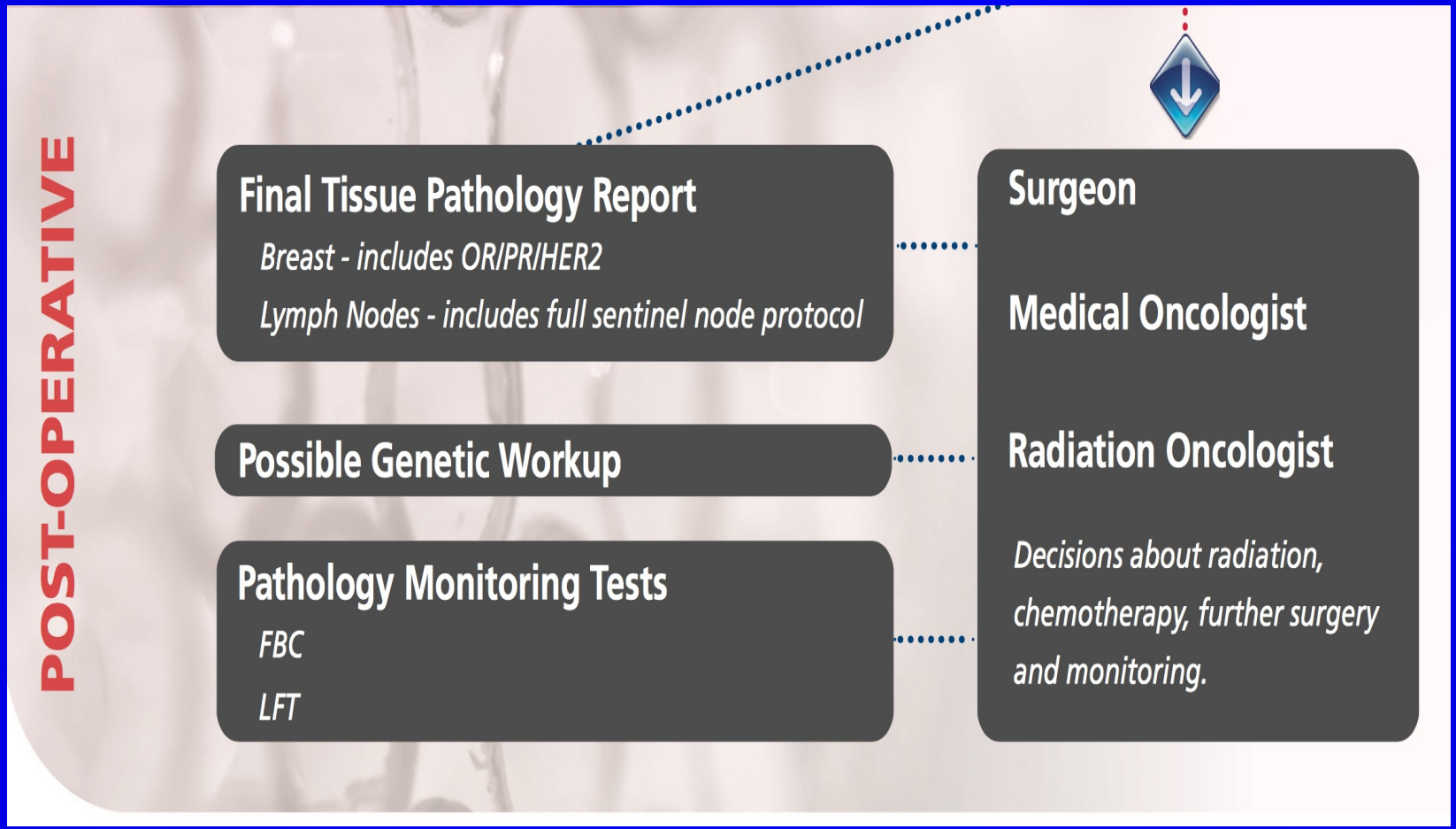
Operative


OPERATIVE
Intraoperative Pathology
Frozen Section
Lymph node imprint
Surgical Procedures
Breast operation
Lumpectomy
Wire localised excision
Mastectomy
Lymph node operation
Sentinel nodes
Axillary nodes

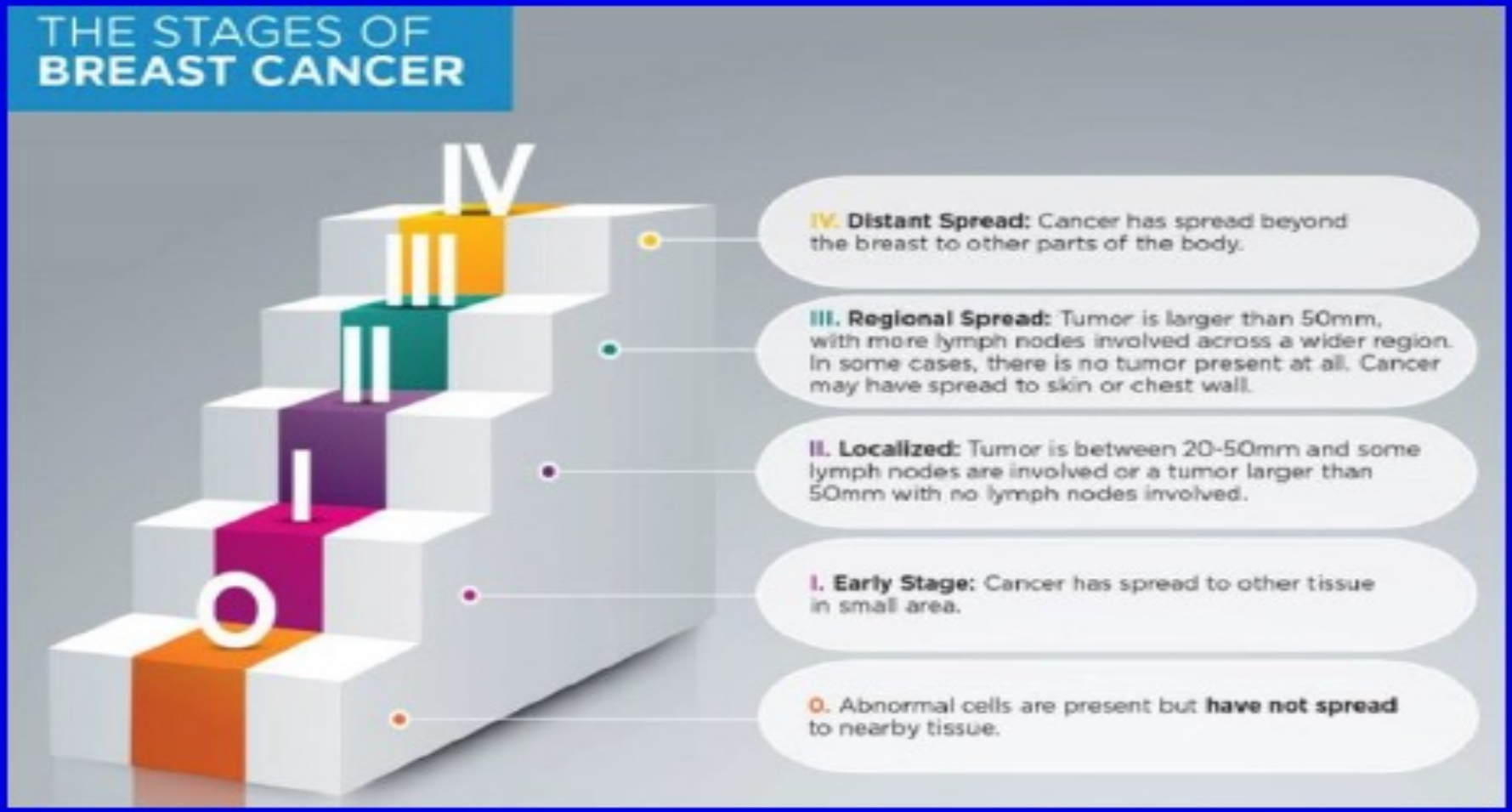
Structure of the Breast : Lymph Nodes



Post-operative



Breast cancer stages



Inflammatory Breast Cancer

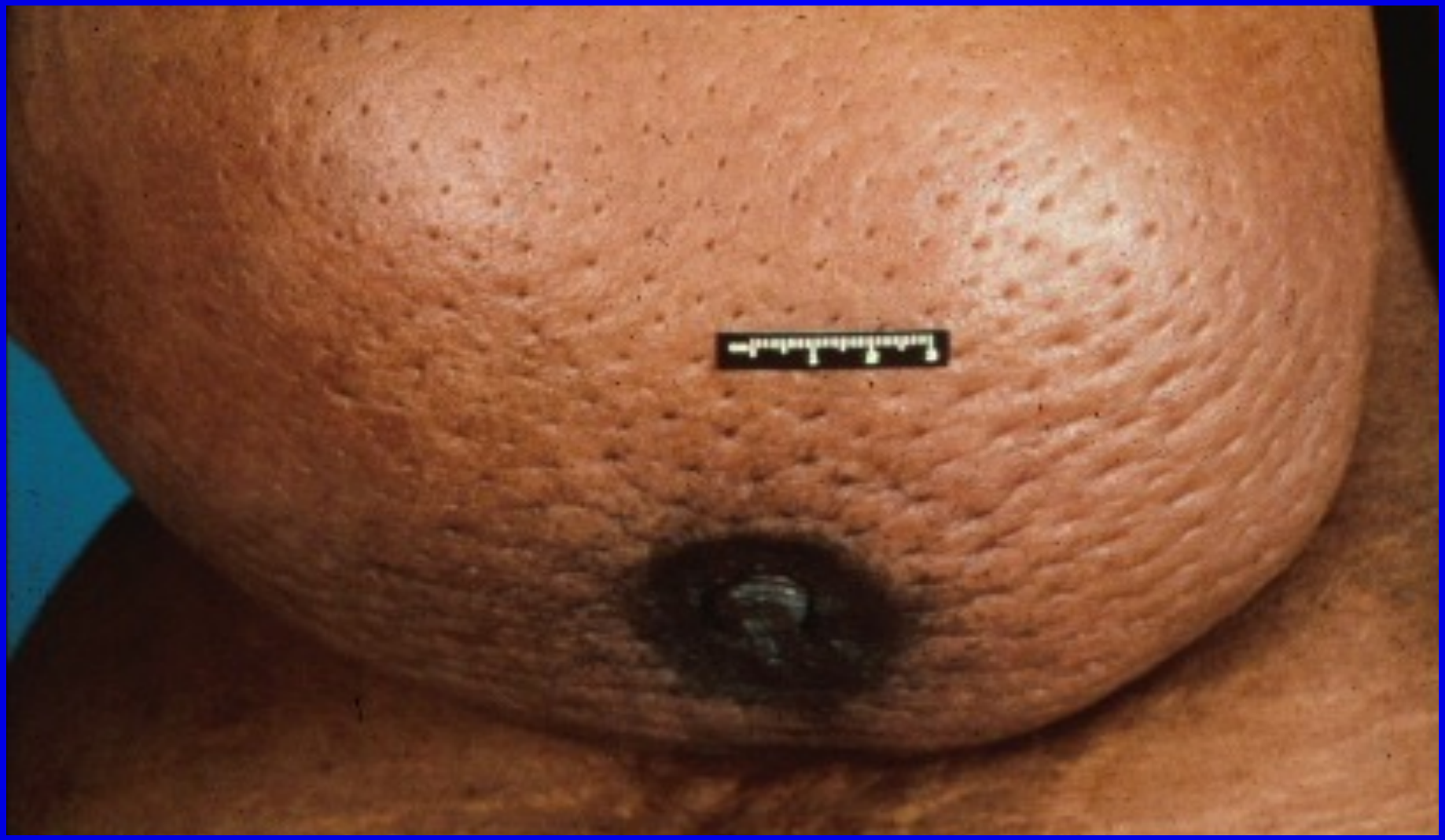
Definition

- A rare form of breast cancer
- Incidence in US ~ 1-5%
- Difficult to track because of variation in diagnostic criteria.
- Malignant cells infiltrate and clog the dermal lymphatics; However, this is NOT a diagnostic criteria for IBC
- The diagnosis is mainly clinical along with confirmed invasive cancer.

Clinical Presentation

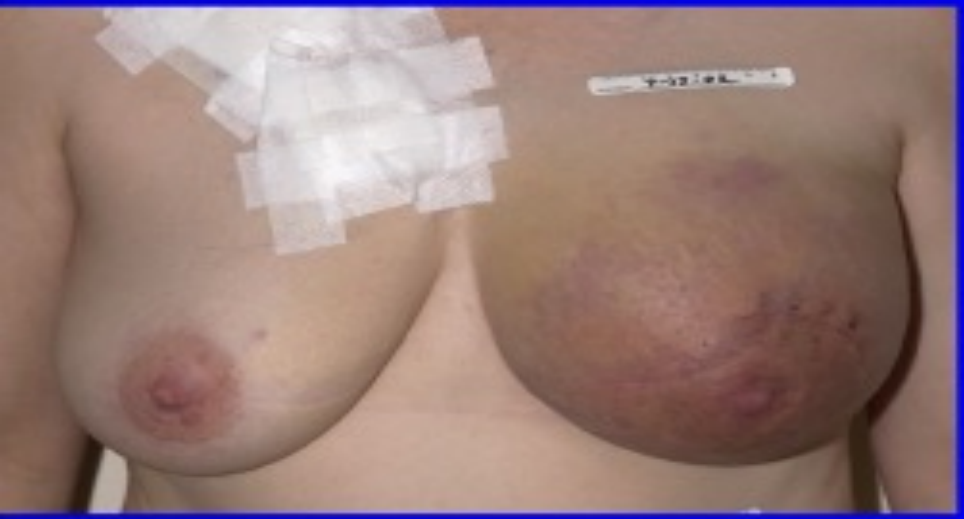
- Confirmed biopsy of invasive breast cancer .
- Rapid onset 3-6 months
- Erythema over ≥ 1/3 of the breast
- Edema (peau d'orange)
- Breast enlargement, often w/o a mass.

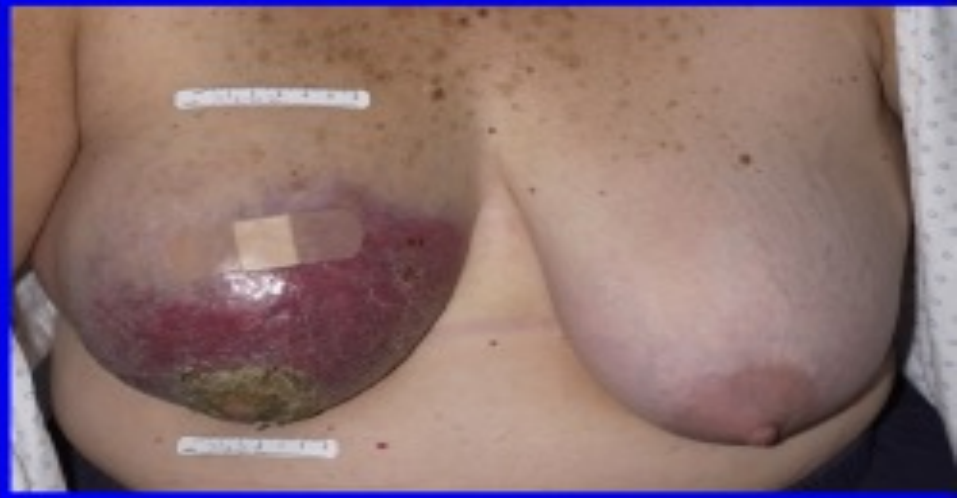
IBC

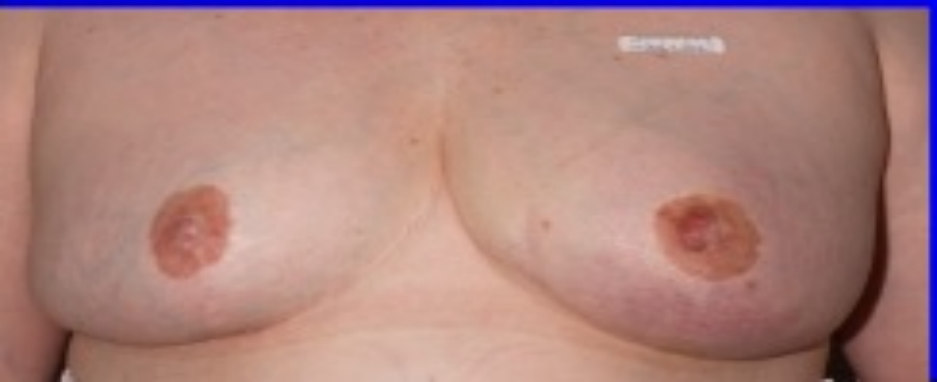


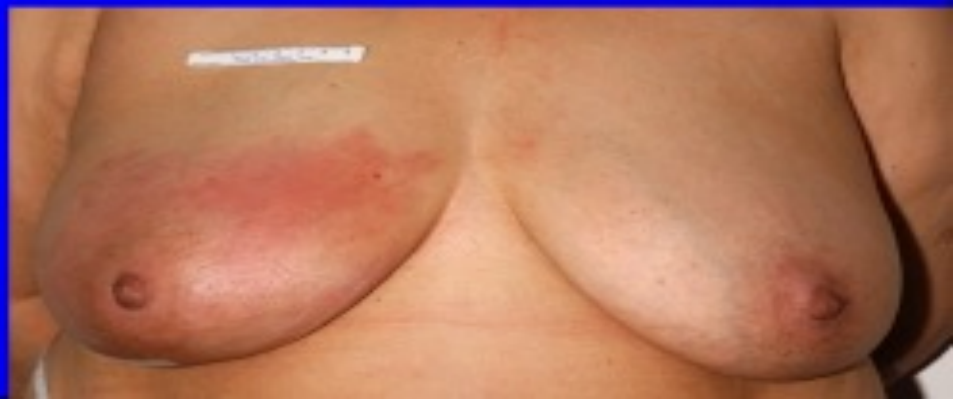
IBC

Clinical Presentations of IBC









Prognostic and Predictive Factors influencing Treatment Decisions

Treatment

- Breast Cancer is commonly treated with various combinations of:
  - surgery
  - radiation therapy
  - chemotherapy
  - hormone therapy
  - targeted therapies

Molecular Profiling

Prognosis and Selection of Therapy Influenced By:

- Menopausal status
- Stage of disease
- Grade of the tumor
- ER/PR status
- HER2/neu amplification
- Histologic type
  favorable histologies:
  - mucinous
  - medullary
  - tubular
- Patient's age and general health
- Presence of known mutations

Molecular diagnostics

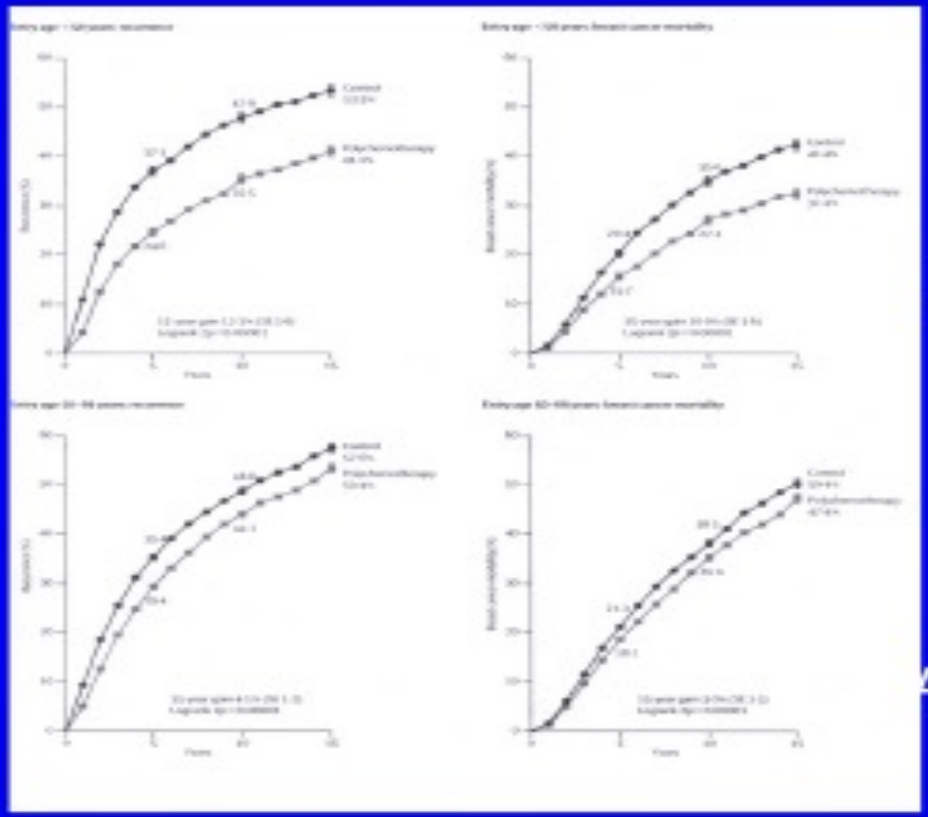
What are the Clinical Implications of Molecular Diagnostics in Breast Cancer?

- Treatment is becoming more personalized for patients, with tumor genomic profiling that could lead to optimal treatment.
- Clinical Next Generation Sequencing (NGS or Tumor Profiling) is increasingly being used to identify potentially actionable mutations in tumor tissue.
- What we don't yet know is if assigning treatment based on specific gene mutations can provide clinical benefit (increasing overall survival) to patients with metastatic tumors.
- Most tumors have multiple mutations and it is often not clear which one to target to achieve maximal benefit. This is an avenue of ongoing investigation

Risk reductions

Absolute Risk Reductions of Relapse and Mortality with Polychemotherapy

Though both age groups do benefit from polychemo the greatest reduction in recurrence and mortality is in those <50.



Age<50

Age 50-69

Recurrence Mortality

EBCTCG, Lancet 2005

Some examples of the many chemotherapies that may be used to treat invasive ductal carcinoma ….

Chemical Name	Trade Name
Doxorubicin	Adriamycin
Epirubicin	Ellence
Cyclophosphamide	Cytoxan
Docetaxel	Taxotere
Paclitaxel	Taxol
Capecitabine	Xeloda
Ixabepilone	Ixempra
Methotrexate	Methotrexate
5-Flourouracil (5-FU)	Flourouracil

Example of the many hormonal therapies approved for early stage and locally advanced breast cancer:

Drug	Brand Name	Menopausal Status	IM Pill	Class or Mechanism
Tamoxifen	Nolvadex	Pre & Post	Pill	SERM: antagonist (breast) partial agonist (endometrium)
Anastrozole Letrozole	Arimidex Femara	Post	Pill Pill	Aromatase Inhibitor (AI) Blocks Aromatase, enzyme that converts other hormones to estrogen
Exemestane	Aromasin	Post	Pill	AI
Fulvestrant	Faslodex	Post	IM	Pure Anti-estrogen
Goserelin	Zoladex	Pre	IM	Ovarian Suppression
Leuprolide	Lupron	Pre	IM	Ovarian Suppression

EBCTCG: Benefit of Tamoxifen as Adjuvant *Treatment*

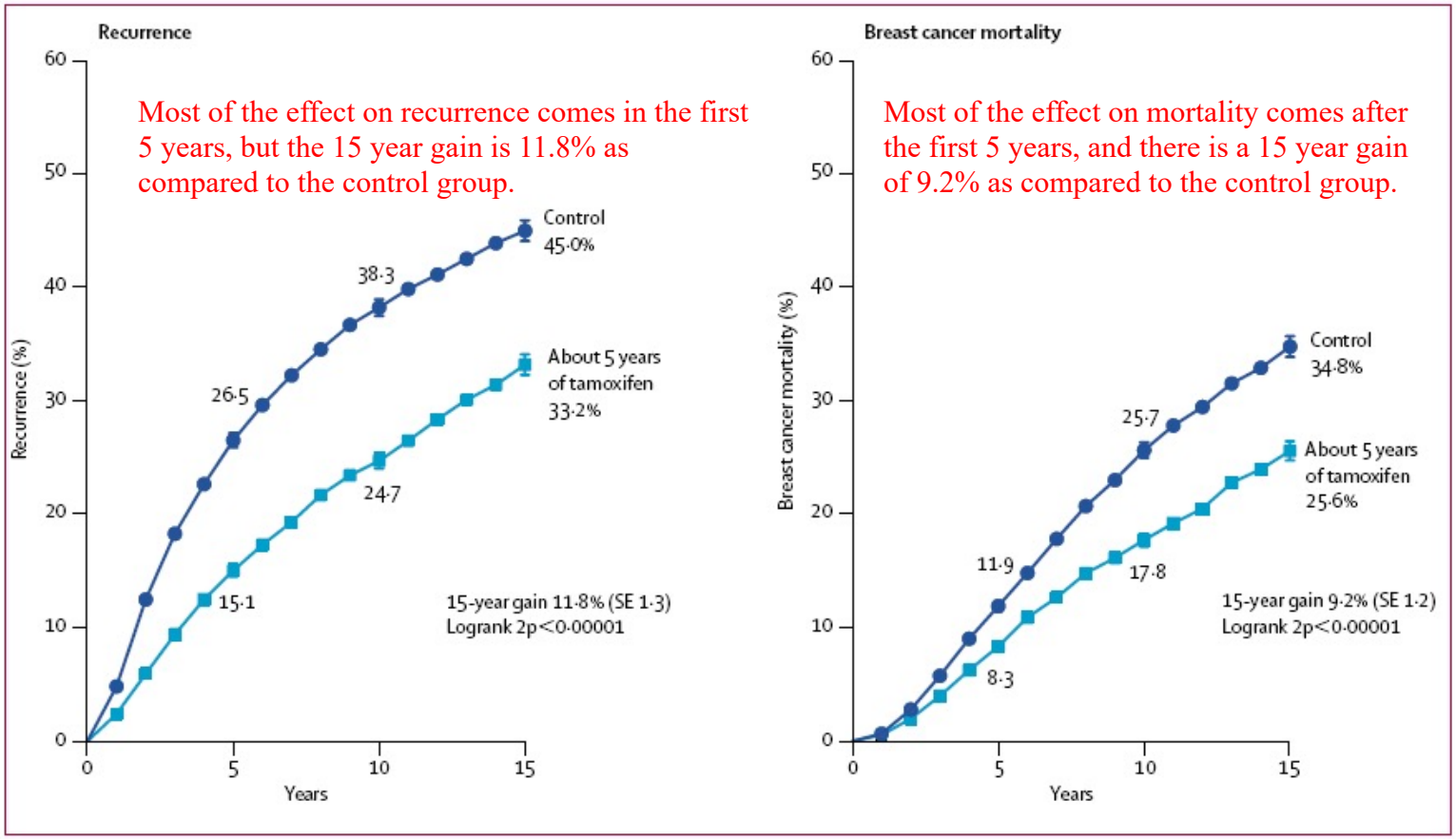


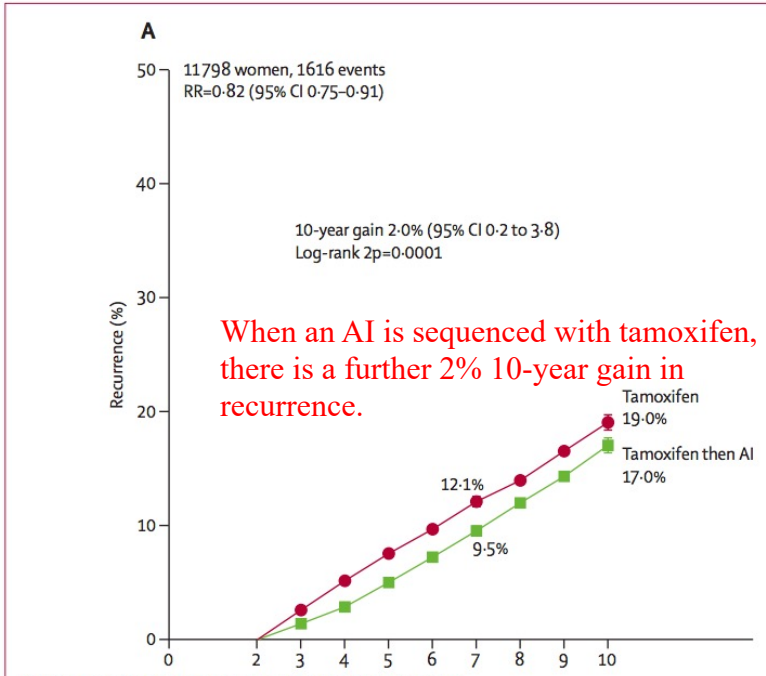
Figure 8: **About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality**
10 386 women: 20% ER-unknown, 30% node-positive. Error bars are ±1SE.

EBCTCG

Lancet, 2014

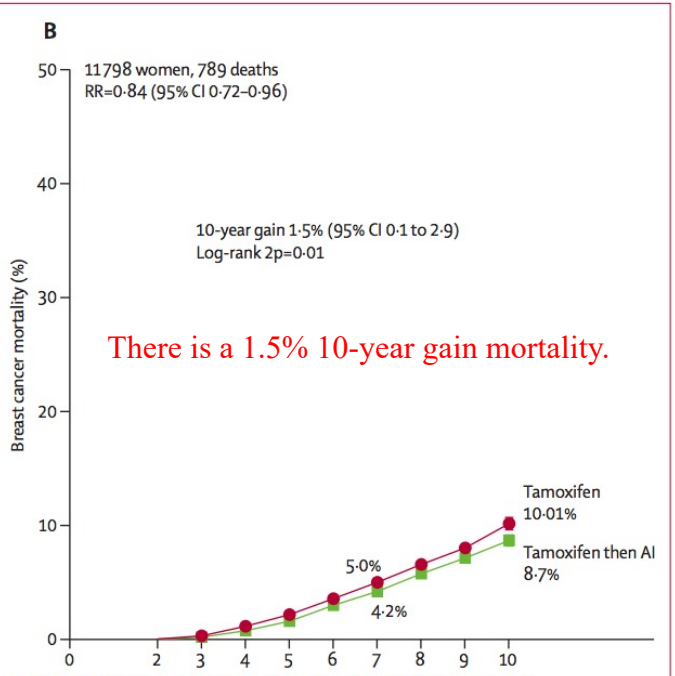
Tamoxifen followed by AI in Adjuvant Setting

Benefit of Sequencing Hormonal Therapies



Recurrence rate/year (%), events/woman-years and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	1·48 (170/11515)	2·48 (495/19920)	3·26 (88/2696)
Tamoxifen	2·64 (300/11360)	2·51 (479/19101)	3·35 (84/2505)
Rate ratio (95% CI)	0·56 (0·46–0·67)	0·97 (0·86–1·11)	0·92 (0·68–1·25)
from (O-E)/V	−65·3/111·5	−5·9/234·0	−3·3/40·8



Death rates (%/year: total rate minus rate in women without recurrence) and log-rank statistics

Allocation	Years 2–4	Years 5–9	Year 10+
Tamoxifen then AI	0·37 (0·25–0·48)	1·28 (1·12–1·44)	1·68 (1·63–1·72)
Tamoxifen	0·56 (0·43–0·70)	1·40 (1·26–1·56)	2·54 (2·45–2·59)
Rate ratio (95% CI)	0·65 (0·44–0·96)	0·91 (0·77–1·08)	0·69 (0·48–1·00)
from (O-E)/V	−11·0/25·8	−11·9/132·0	−10·6/28·9

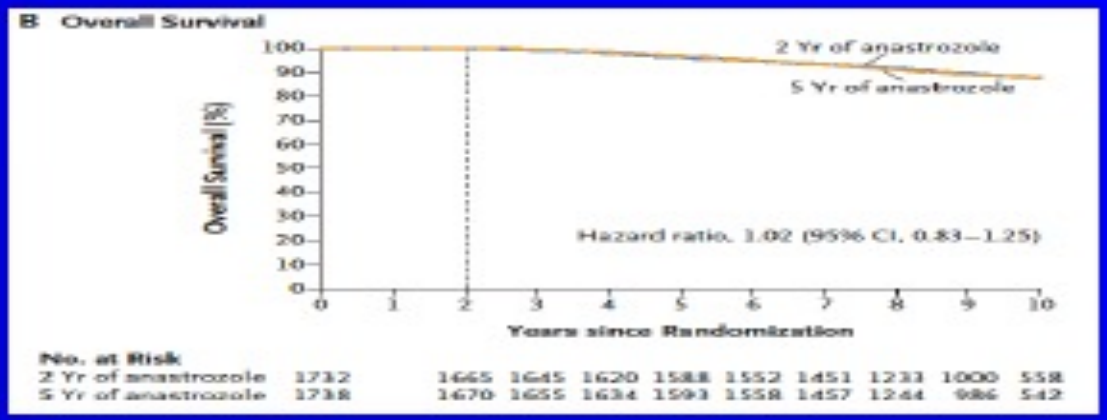
Aromatase-inhibitor therapy

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 29, 2021 VOL. 385 NO. 5

Duration of Adjuvant Aromatase-Inhibitor Therapy in Postmenopausal Breast Cancer

M. Gnant, F. Fitzal, G. Rinnerthaler, G.G. Steger, S. Greil-Ressler, M. Balic, D. Heck, R. Jakesz, J. Thaler, D. Egle, D. Manfreda, V. Bjelic-Radisic, U. Wieder, C.F. Singer, E. Melbinger-Zeinitzer, F. Haslbauer, P. Sevelda, H. Trapl, V. Wette, K. Wimmer, S.P. Gampenrieder, R. Bartsch, S. Kacerovsky-Strobl, C. Suppan, C. Brunner, C. Deutschmann, L. Soelkner, C. Fesl, and R. Greil, for the Austrian Breast and Colorectal Cancer Study Group*



- OS = 87.5% in the 2-year Group
- OS = 87.3% in the 5-year Group

(95% CI, 0.83 – 1.25)
Hazard Ratio for Death from any cause 1.02 *

* No Difference in Survival Between the 2 Groups

Examples of Targeted Therapies

Chemical Name	Trade Name	Mechanism	Indication
Trastuzumab	Herceptin	Humanized MoAb that binds selectively to the HER2 protein, and suppresses activity that would lead to cell proliferation	Adjuvant therapy along with chemo in HER2+ breast cancer; Neoadjuvant therapy in large HER2+, also used in metastatic HER2+ breast cancers
Pertuzumab	Perjeta	Humanized MoAb that binds to the extracellular domain II of HER2. it inhibits ligand dependent HER2 – HER3 Dimerization, reduced signalling through PI3K/AKT	Indicated for use in combination with trastuzumab and docetaxel for the neoadjuvant treatment of patients with HER2+ locally advanced inflammatory or early stage breast cancer.
Ado-trastuzumab Emantasine	Kadcyla	Herceptin + Emantasine. Delivers Emantasine to cancer cells in a targeted way.	Approved to treat HER2 positive metastatic breast cancer, previously treated with Herceptin and Taxane

Targeted therapies

Examples of Targeted Therapies (HER2+ Disease): Ab-Drug Conjugates

Chemical Name	Trade Name	Mechanism	Indication
Ado-trastuzumab Emantasine (T-DM1)	KADCYLA	Trastuzumab (MoAb) + Emantasine (cytotoxic agent) Delivers Emantasine to cancer cells in a targeted way.	Approved (Feb. 2013) to treat HER2 positive metastatic breast cancer, previously treated with Herceptin and Taxane
Fam-Trastuzumab Deruxtecan-Nxki (T-DXd)	Enhertu	Trastuzumab (MoAb) + deruxtecan-nxki (topoisomerase inhibitor)	Approved (Dec. 2019) to treat: • Unresectable HER-2 positive breast cancer. • Metastatic HER-2 positive breast cancer that has been treated with two or more anti-Her2 therapies

Targeted therapies

Examples of Targeted Therapies (HER2+ Disease) – TKI's

Chemical Name	Trade Name	Mechanism	Indication
Lapatinib	Tykerb	Small Molecule Tyrosine Kinase Inhibitor Human EGFR type 1 and type 2 tyrosine kinase inhibitor. It binds to the intracellular phosphorylation domain to prevent receptor auto-phosphorylation upon ligand binding.	Lapatinib + Xeloda to treat advanced stage HER2+ breast cancer that has stopped responding to anthracyclines, taxanes, and Herceptin. Lapatinib + Letrozole for the treatment of postmenopausal HR+ HER2+ metastatic breast cancer
Neratinib	Nerlynx	Small Molecule Tyrosine Kinase Inhibitor	• Approved to treat Her2-positive breast cancer: (by FDA July 2017) ✓ As a single agent for the treatment of early stage disease after trastuzumab (Herceptin) based therapy ✓ In combination with capecitabine (Xeloda) as a 3rd line HER2 agent to treat advanced or metastatic disease
Tucatanib	Tukysa	Small Molecule Tyrosine Kinase Inhibitor	Approved by FDA April 2020 ✓ In combination with Trastuzumab (Herceptin) and Capecitabine (Xeloda) in unresectable or metastatic disease, including when cancer has spread to the brain. ✓ Given when other treatments have failed.

Tucatinib


The NEW ENGLAND JOURNAL of MEDICINE

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Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murphy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

NewsMaker 2020!


FDA Approves Tucatinib Plus Trastuzumab/Capecitabine in HER2-Positive Breast Cancer

April 17, 2020

- Tucatinib: oral, small molecule tyrosine kinase inhibitor of HER-2
- Approval based on HER2CLIMB Trial with highly significant and clinically important results.
- Tucatinib added to trastuzumab and capecitabine achieved a 46% reduction in the risk of progression or death in a cohort of patients that was heavily pre-treated and had advanced or metastatic disease +/- brain metastasis.
- 2 year OS 44.9% in tucatinib arm vs 26.6% in placebo arm.

ASCO post

The ASCO Post

Presented:
ESMO Congresss
September 2021
Javier Cortes, MD, PhD

NewsMaker 2021!

DESTINY Breast03: Second-Line Fam-Trastuzumab Deruxtecan-nxki for Metastatic HER2-Positive Breast Cancer

By Caroline Helwick

Posted: 9/18/2021 10:58:00 AM
Last Updated: 10/4/2021 1:28:27 PM

This study will lead to a paradigm shift in the treatment of Her-2 positive metastatic breast cancer!

- This open-label, randomized trial was the first global phase III head to head trial of T-DXd against an active control in patients with HER2-positive, metastatic breast cancer following initial treatment with trastuzumab and a taxane

KEY POINTS

- T-DXd led to a highly significant and clinically meaningful improvement in progression-free survival.
- The rate of interstitial lung disease was 10.5%, almost all grade 1 or 2, which is notably less than seen in earlier studies of more heavily pretreated patients.

- 524 previously treated patients were randomly assigned to receive either T-DXd at 5.4 mg/kg or T-DM1 at 3.6 mg/kg every 3 weeks.
- The primary end-point was progression free survival measured by blinded central review, as this was a global trial.
- Confirmed response was seen in 79.1% vs 34.2% receiving T-DM1 (p,.0001)
- This translates to a highly significant 72% reduction in the risk of disease progression.

Benefit was seen across subgroups, including patients with brain metastasis.

Targeted therapies

More Targeted Therapies ...

Chemical Name	Trade Name	Mechanism	Indication
Alpelisib	Piqray	Inhibits PIK3 in the PI3K/AKT signaling pathway, ultimately inhibiting pathway activation. This results in inhibition of cell growth and survival. ** PIK3CA missense mutations occur in about 40% of ER+ breast cancers	Approved in combination with fulvestrant for post-menopausal women with HR+, HER2 negative, PIK3CA-mutated, advanced or metastatic breast cancer. **Approved May 24, 2019, based on the phase 3 Solar-1 study**
Everolimus	Affinitor	mTOR inhibitor Interacts with MTORC1 and inhibits downstream signaling.	Postmenopausal advanced HR+ HER2- breast cancer in combination with exemestane after progression on letrozole and anastrozole. **Approved April 10, 2018**

Targeted therapies

Chemical Name	Trade Name	Mechanism	Indication
Palbociclib	Ibrance	CDK4/6 Inhibitor Aberrations in the CDK-RB pathway are common in breast cancer. Consequently, inhibition of this pathway is an attractive therapeutic strategy. Inactivation of CDK4/6-cyclin D1complexes helps control cell growth by inducing G1 arrest and reducing cell cycle progression.	HR+ HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor Or With fulvestrant in women with disease progression following endocrine therapy.
Ribociclib	Kisqali	CDK4/6 inhibitor	Ribociclib + AI for initial endocrine therapy in postmenopausal HR+ HER2- advanced/metastatic breast cancer. Ribociclib + Fulvestrant in HR+ HER2- advanced/metastatic breast cancer as initial Rx, or following progression on endocrine Rx
Abemaciclib	Verzenio	CDK4/6 inhibitor	HR+ HER2 – advanced metastatic BrCa in combination with an AI or fulvestrant.

Targeted therapies

Chemical Name	Trade Name	Mechanism	Indication
Olaparib	Lynparza	PARP inhibitor Inhibits enzyme involved in DNA Repair Since BRCA mutated cells are incapable of homologous repair of DS DNA breaks, additional PARP inhibition causes genomic instability and cell death.	1st targeted therapy approved for gBRCAm breast ca (HER2 – and metastatic ***Approved Jan. 2018***
Talazoparib	Talzenna	PARP inhibitor Inhibits enzyme involved in DNA Repair	germline-BRCAm, HER2 – locally advanced or metastatic breast cancer. *(Based on germline testing by Myriad Genetic Laboratories)* ***Approved Oct. 2018***

ASCO post

The ASCO Post

NewsMaker 2021!

OlympiA Trial: Adjuvant Olaparib Extends Disease-Free Survival in *BRCA*-Mutated Early Breast Cancer

- The double blind OlympiA trial included 1,836 patients with high-risk early breast cancer that was HER2-negative and BRCA 1/2 positive, including both, triple negative and hormone receptor positive breast cancers.
- Following standard treatment with surgery, chemo, and, radiation (as needed per individual patient), patients were randomly assigned to receive either 1 year of adjuvant Olaparib or placebo.

Key Points:

- ✓ Adjuvant Olaparib reduced the risk of invasive disease-free recurrence by 42% compared with placebo (p<.0001)
- ✓ At 3-years, the rate of invasive disease-free survival was 85.9% with Olaparib vs 77.1% with placebo, an absolute difference of 8.8%

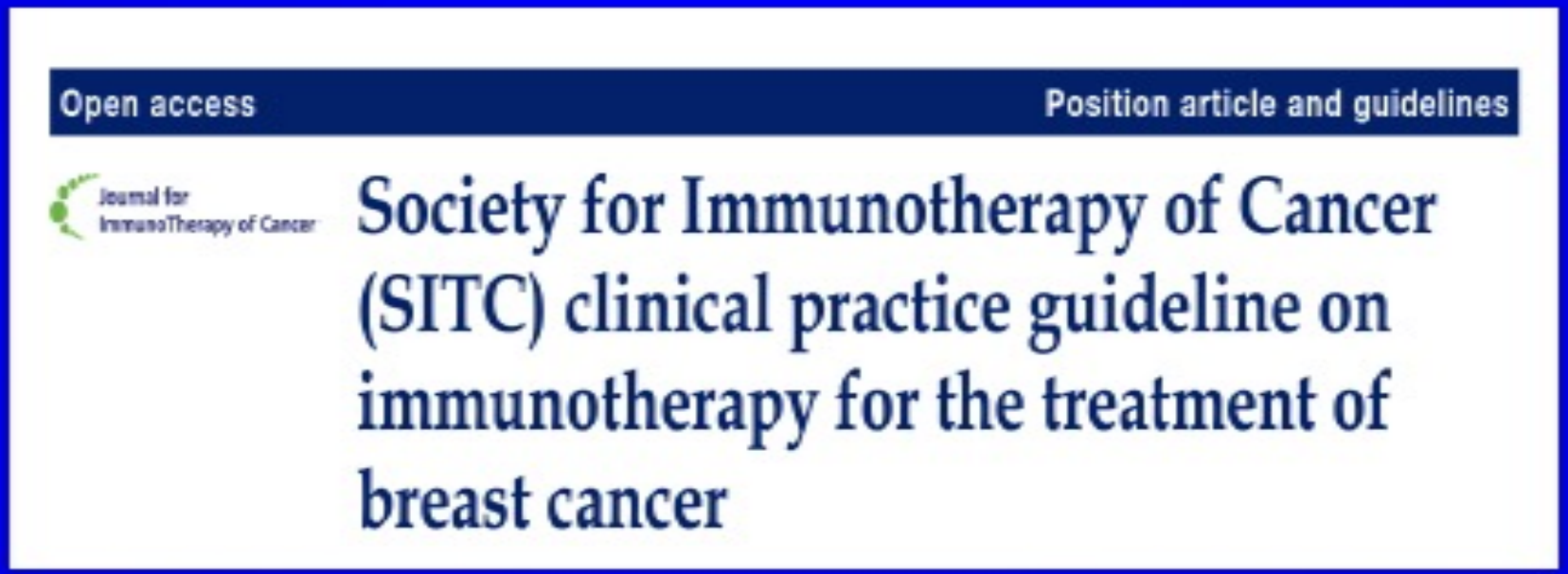
- ✓ Overall survival is still immature, but fewer deaths occurred in the Olaparib arm. Follow up for survival is still on-going.

This study is the first reporting the effect of a PARP inhibitor as adjuvant therapy on survival endpoints in early BRCA 1/2 mutated breast cancer.

- ➢ These findings support the use of adjuvant Olaparib for 1 year after SOC treatment in high-risk BRCA mutated disease.

Immunotherapy

Immunotherapy for Breast Cancer



Immunotherapy and chemotherapy

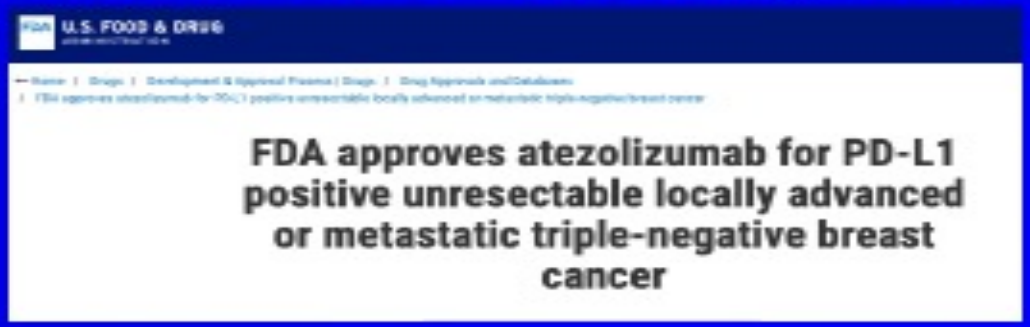
- Breast Cancer has historically been a disease for which immunotherapy was largely unavailable.
- Recently – immune checkpoint inhibitors (ICI's) in combination with chemotherapy have shown efficacy for the treatment of advanced/metastatic triple negative breast cancer (TNBC).
- In certain subsets of patients, we have seen

  → longer progression-free survival (PFS)
  → Increased overall survival (OS)

- Based on the clinical benefit seen in randomized trials, ICI's in combination with chemotherapy have been approved by the US FDA for the treatment of some patients with advanced or metastatic triple negative breast cancer (TNBC) – expanding options for patients (atezolizumab, pembrolizumab)
- Given that immunotherapy combinations are becoming available in breast cancer, including TNBC, SITC reviewed the existing data and published guidelines in August 2021 to help physicians make decisions.

Immunotherapy and TNBC

Current Status of Immunotherapy for TNBC


U.S. FOOD & DRUG

FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer

- Approved March 2019 in combination with nab-paclitaxel, for those patients with PD-L1 positive unresectable, locally advanced or metastatic triple negative breast cancer (TNBC) based on the results of the Impassion130 Trial
- 40% Risk Reduction in progression or death with addition of PDL-1 inhibitor

July 30, 2020 | 2 min read

FDA grants priority review to Keytruda for triple-negative breast cancer

- Approved Nov 2020
- Pembrolizumab + Chemotherapy for those with locally recurrent, unresectable or metastatic disease AND PD-L1 expression (>/= 10 on FDA approved test)
- Review & Approval was granted based on results of Phase 3 KEYNOTE-355 trial – significantly approved PFS with combination

Pembrolizumab and TNBC

FDA approves pembrolizumab for high-risk early-stage triple-negative breast cancer

On July 26, 2021, the Food and Drug Administration approved pembrolizumab (Keytruda, Merck) for high-risk, early-stage, triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

- Approval based on Keynote-522 - a randomized, multicenter, double-blind, placebo controlled trial conducted in 1174 patients with newly diagnosed, untreated high-risk early stage TNBC.
- Patients were enrolled regardless of PDL-1 expression.
- Patients were randomized to either pembro + chemo or placebo + chemo

- Measures of efficacy: pCR, EFS
- The pathological complete response (pCR) was 63% for patients who received pembro + chemo compared with 56% for patients who received placebo + chemo
- The number of patients who experienced an EFS "event" was 16% in pembro arm and 24% in placebo arm.

Treatments

- The review and summarization of the existing pre-clinical and clinical data by the SITC committee is extensive, and presented in the recently published position paper.
- A few of the key take away points are the following:

- **Given the limited activity with currently available single-agent immunotherapy, the efficacy of immunotherapeutic strategies will likely be enhanced with combination therapy, adding chemotherapy, targeted therapies, radiotherapy, or other immunotherapy agents.**
- **Based on current evidence, the majority of combinations are still investigational, and should only be considered in. context of a clinical trial.**
- **The optimal dose of radiation to combine with ICI's in the pre-operative setting, is the subject of an on-going clinical trial (NCT04443348). Data from this trial will permit design of larger phase II trials examining radiation and immunotherapy combinations in the neo-adjuvant (pre-operative) setting.**
- **In on-going and planned studies involving combination approaches with immunotherapy, both short and long-term toxicities should be a careful consideration.**
- **Biomarkers that predict clinical benefit and / or toxicity are essential in the development of these strategies.**

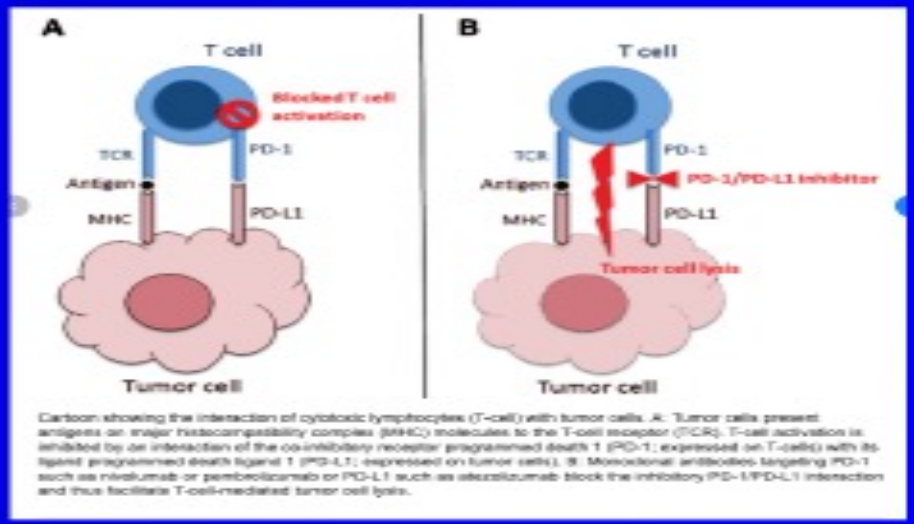
Women's malignancy branch

Center For Cancer Research
Women's Malignancies Branch

- Brief Description of on-going ICI Clinical Trial
- Short Case Report of patient on trial

IMMUNOTHERA

The Role of PD-L1 Pathway Inhibition in Immunotherapy



Cartoon showing the interaction of cytotoxic lymphocytes (T-cell) with tumor cells. A: Tumor cells present antigens on major histocompatibility complex (MHC) molecules to the T-cell receptor (TCR). T-cell activation is inhibited by an interaction of the co-inhibitory receptor programmed death 1 (PD-1; expressed on T-cell(s)) with its ligand programmed death ligand 1 (PD-L1; expressed on tumor cells). B: Monoclonal antibodies targeting PD-1 such as nivolumab or pembrolizumab or PD-L1 such as atezolizumab block the inhibitory PD-1/PD-L1 interaction and thus facilitate T-cell-mediated tumor cell lysis.

- **Programmed Cell Death Ligand -1 (PD-L1)**: biomarker and target for immunotherapy.
- **PDL-1**: frequently expressed on tumor cells as well as immune cells within the tumor microenvironment.
- **When PD-L1 binds to PD-1, which is expressed on activated T-cells, it induces T-cell exhaustion or a state of ineffective T-cell activity**
- **PD-L1** expressed on antigen presenting cells can also inhibit T-cell activity by binding to CD80 on T-cells.

Blocking the PD-1 / PDL-1 Pathway Reverses T-Cell Exhaustion and Strengthens Anti-tumor Activity!!

IMMUNOTHERAPY PLUS SMALL MOLECULES

- combination blockade of multiple immune checkpoints with small molecule targeted therapies.

•In our branch, we have a trial for triple negative breast cancer that combines Durvalumab (PD-L1 inhibitor) with a PARP inhibitor (Olaparib).

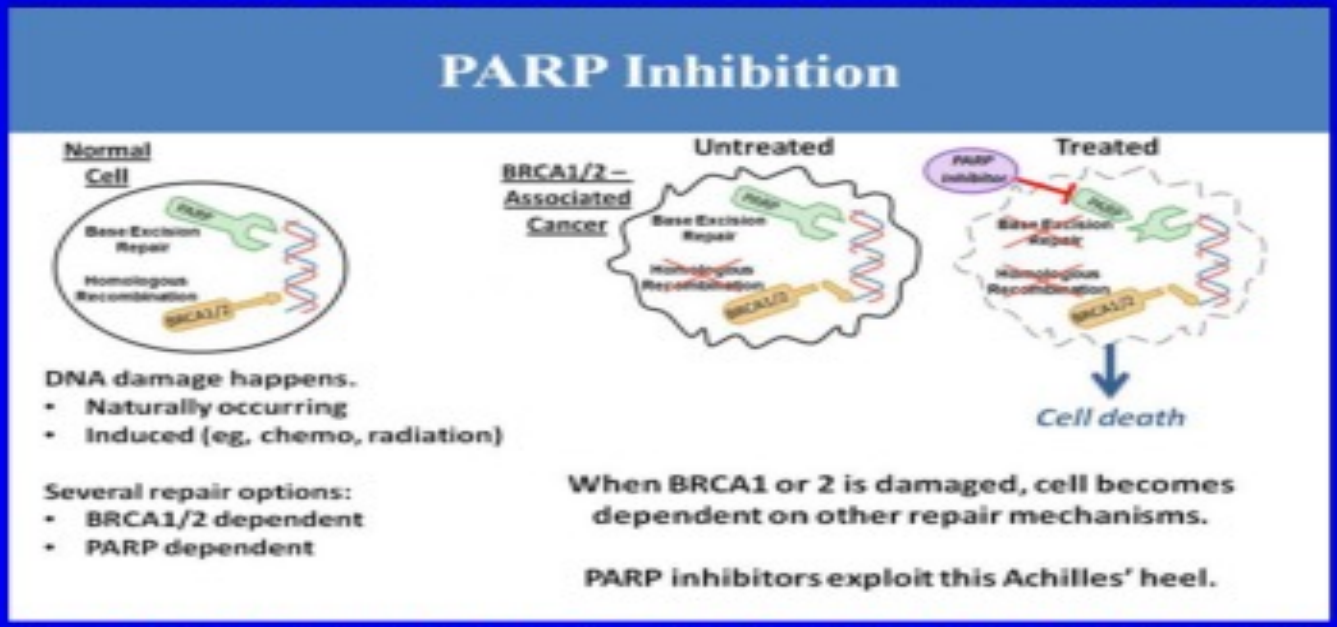
•Pre-clinical justification for the combination is that studies have shown that PARPi upregulated PD-L1 expression in breast cancer cell lines and animal models

•The combination of PARPi + anti-PD-L1 therapy increased the therapeutic efficacy in vivo, compared to either agent alone.

PARP inhibition

- PARP: Base Excision Repair
- BRCA1: Checkpoint Activation and DNA Repair
- BRCA2: Homologous Repair

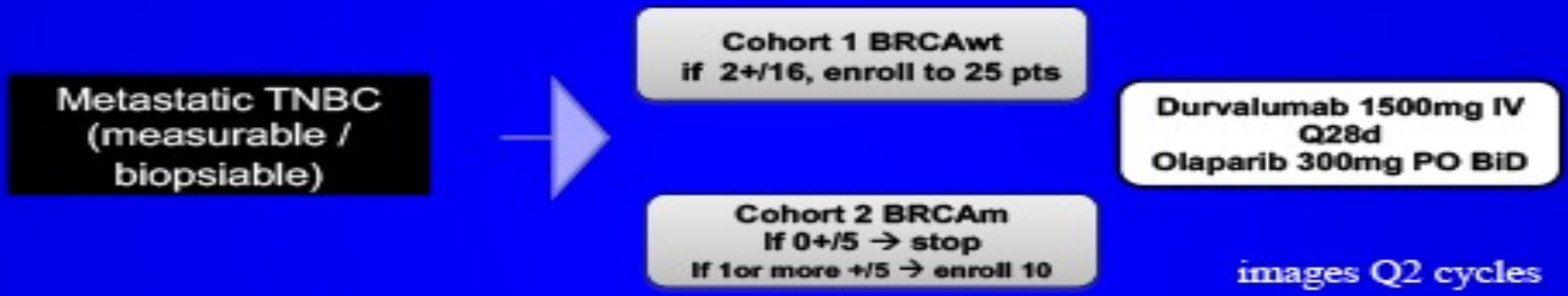
PARP Inhibitors in Somatic and/or Germline Mutated Breast CA



- **Normal Cell: Response to naturally occurring or induced DNA damage can be through either BRCA 1 and 2 enzymes or PARP enzymes.**
- **When BRCA 1 or 2 is mutated, the cell is dependent on other mechanisms (PARP)**
- **In this instance PARP inhibitors will cause a double hit to the cells repair mechanisms.**
- **The cells will then accumulate damage, and die.**

MEDI-O

MEDI-O (15-C-0145)
Durvalumab (Medi-14736) + Olaparib for Advanced or Recurrent TNBC
Phase II



- Primary endpoint: Response Rate
- Secondary endpoints: duration response, PFS, OS, toxicity

STATUS:
OPEN and Accruing

Case Report

History

- Patient is a 37 year old female of Dominican origin who noted a left breast mass on self-exam, Oct. 2016.
- Subsequent ultrasound showed a 2.6 x 1.6 x 2.5 cm irregular, hypoechoic mass, no pathologic lymph noted were noted.
- US guided fine needle biopsy revealed infiltrating ductal carcinoma (IDC), pathologic grade 3, IHC negative for ER/PR, HER2 negative by FISH (triple negative breast cancer, TNBC).
- Genetic testing indicated she had a germline BRCA 1 mutation.
- She was diagnosed with clinical stage IIb breast cancer (cT2N0M0).

CASE REPORT.

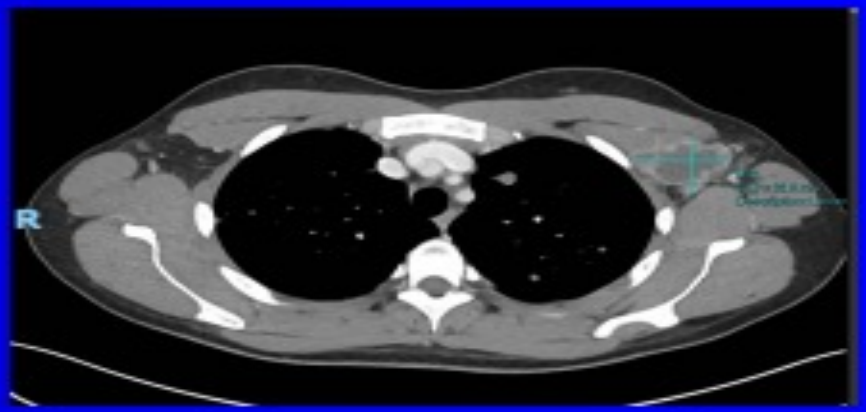
She began neoadjuvant chemotherapy with dose dense Adriamycin/Cytoxan (q 2 week) x 4 cycles followed by carboplatin/taxol (q 3 week) x 4 cycles.
July 2017 → underwent bilateral mastectomy and left sentinel node dissection.
She did not have a pathologic CR from the neoadjuvant chemotherapy, pathology showed residual IDC, ER/PR/HER2 negative, sentinel LN negative, pathologic stage T1bN0M0
Follow up CT Sept. 2018 showed progression, with a large mass in her left subpectoral region measuring 5.5 x 2.6 cm, left axillary LN measuring 1.9 x 1.3 cm, right hilar lymphadenopathy, and innumerable bilateral pulmonary nodules, and a 1.6 x 1.2 cm left hepatic lobe nodule, and bone metastasis.
PET CT showed all the lesions to be intensely FDG avid (high metabolic rate).
US guided biopsy of left subpectoral mass was consistent with recurrence of her breast cancer, still triple negative.
October 2018 she screened for our protocol, Durvalumab + Olaparib
She began cycle 1 on Nov. 5th 2018:

Durvalumab 1500 mg IV on D1 28 day cycle
Olaparib 300 mg PO q 12, daily 28 day cycle

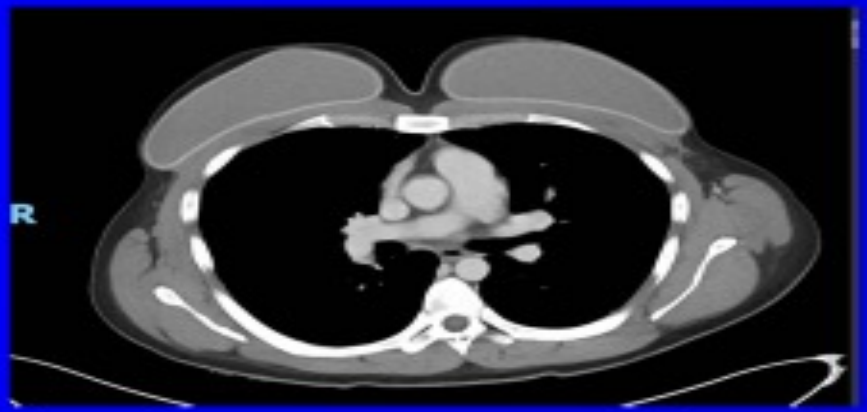
CT scan performed after 2 cycles (Jan. 7th, 2019) showed a dramatic partial response, with a 50% reduction of size of target lesions in lung and liver.
After 10 cycles of treatment, she continues to have a dramatic response, with the last CT 9/16/2019 showing an 82% decrease in size of her target lesions from baseline.

CT scan

Baseline 11/2/2018
Left Subpectoral/Axillary Mass
4.4 x 3.3 cm

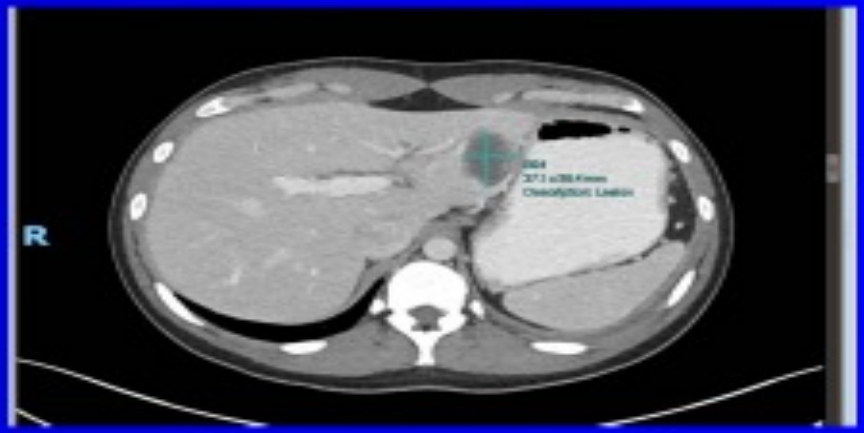


Post 10 cycles 9/16/2019
No mass noted in left axilla/subpectoral area

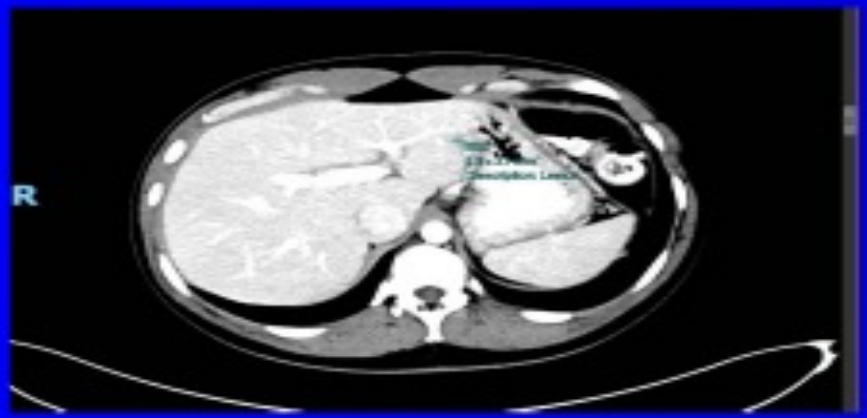


CT scan

Baseline: 11/2/2018
Left Lobe Liver Mass 3.7 x 2.8 cm

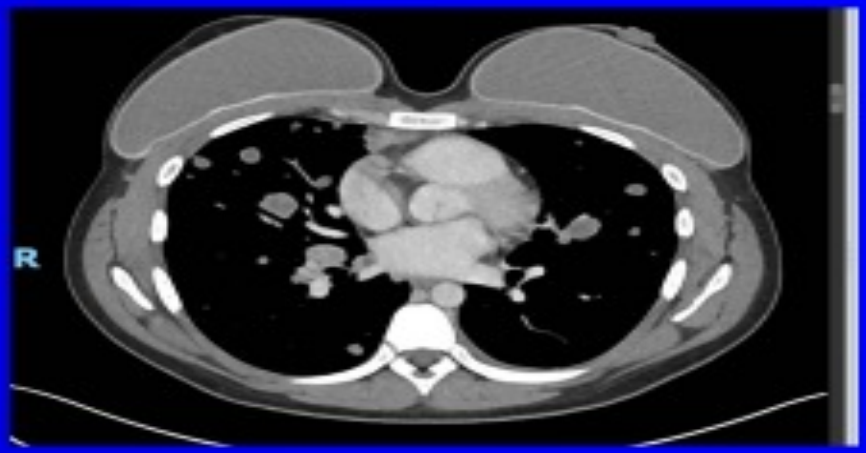


Post 10 cycles 9/16/2019
0.5 x 0.3 cm Left Lobe Liver

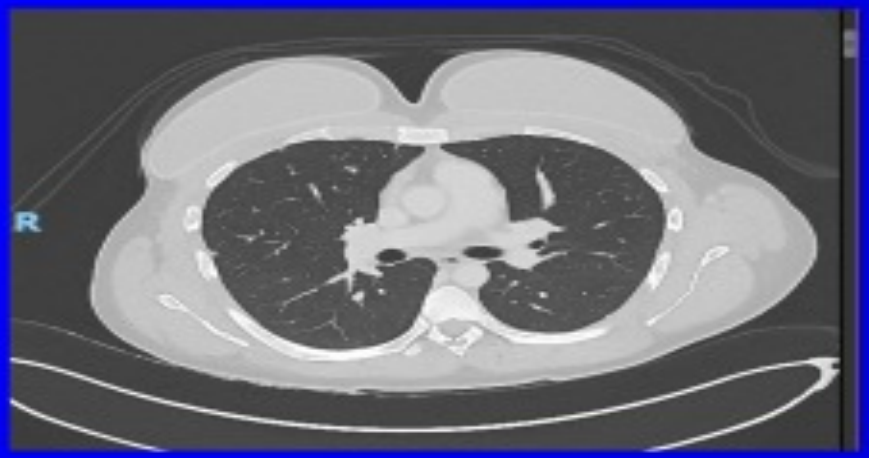


CT scan

Baseline 11/2/2019
Multiple Lung Nodules
Mediastinal Lymphadenopathy



Post 10 cycles 9/16/2019
Sub-centimeter lung nodules
No mediastinal LAD



Thank You!