

Breast cancer

**Breast Cancer:
Overview
Prevention, Diagnosis, Treatment**

Farah Zia, MD

Medical Officer

Division of Cancer Treatment & Diagnosis

Attending Physician & Clinical Research:

Center for Cancer Research

Women's Malignancies Branch



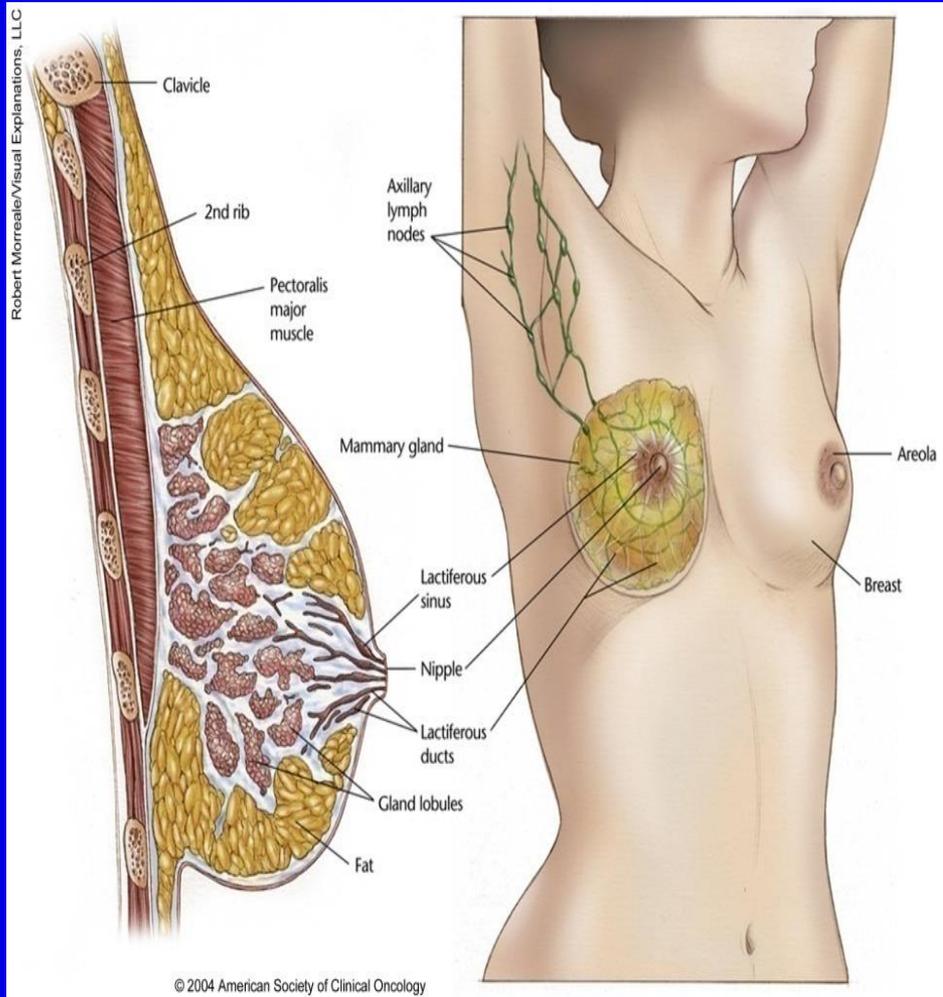
Breast Cancer
AWARENESS MONTH

Breast cancer

WHAT IS 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.

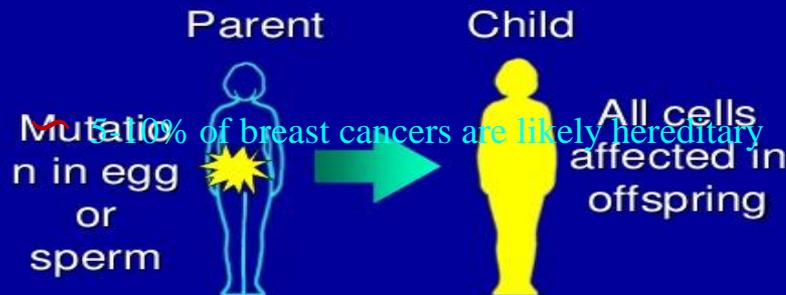
Known Breast Ca Risk Factors

- 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

Somatic mutations

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



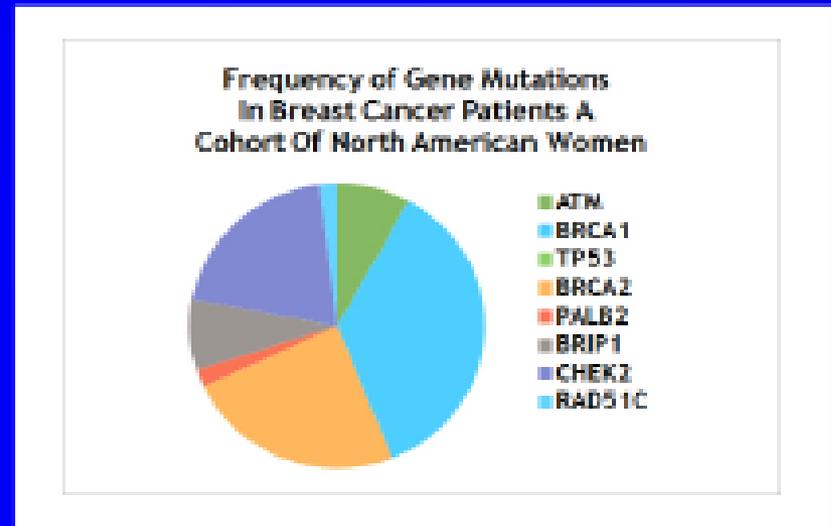
Somatic mutation (eg, breast)

- | Occur in nongermline tissues
- | Are nonheritable
- | Later onset

Gene mutations

Gene Mutations

- **ATM:** Helps repair damaged DNA.
- **BRCA 1/2:**
 - 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.
- **RAD51C:** Codes protein that



Statistics

Statistics 2019 - 2020 Predictions for the U.S.

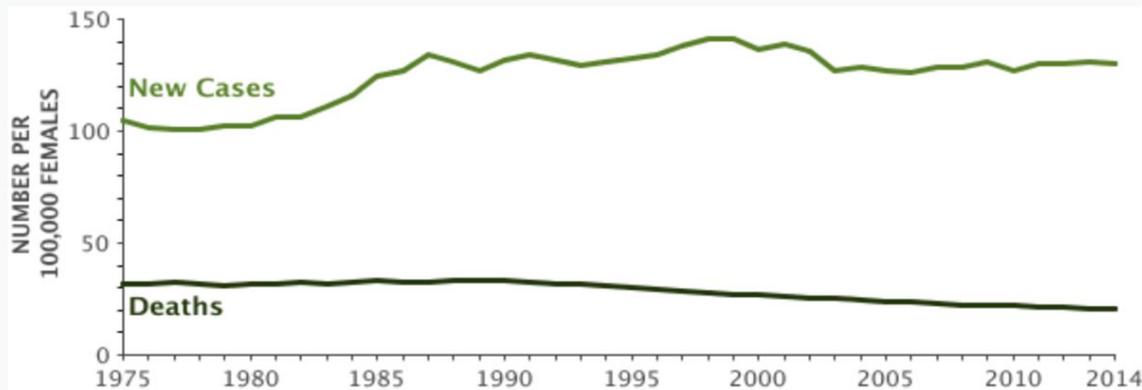
- About 1 in 8 U.S. women will develop invasive breast cancer over the course of her lifetime (**12.4% lifetime risk**).
- About 1 in 1000 men will develop invasive breast cancer over their lifetime (**0.1% lifetime risk**).

BREAST CANCER.

The breast cancer **incidence rate in the U.S** has been steadily **increasing since the 1970's**, which can be attributed to the strong push for screening among women age 40+, resulting in better early detection. **The breast cancer death (mortality) rate in the U.S.** has been **declining steadily since 1989**, when it peaked at a rate of 33 deaths for every 100,000 women, and the survival rate has been steadily increasing. These changes are more prominent for women < 50: treatment advances, early detection, increased awareness.

New Cases, Deaths and 5-Year Relative Survival

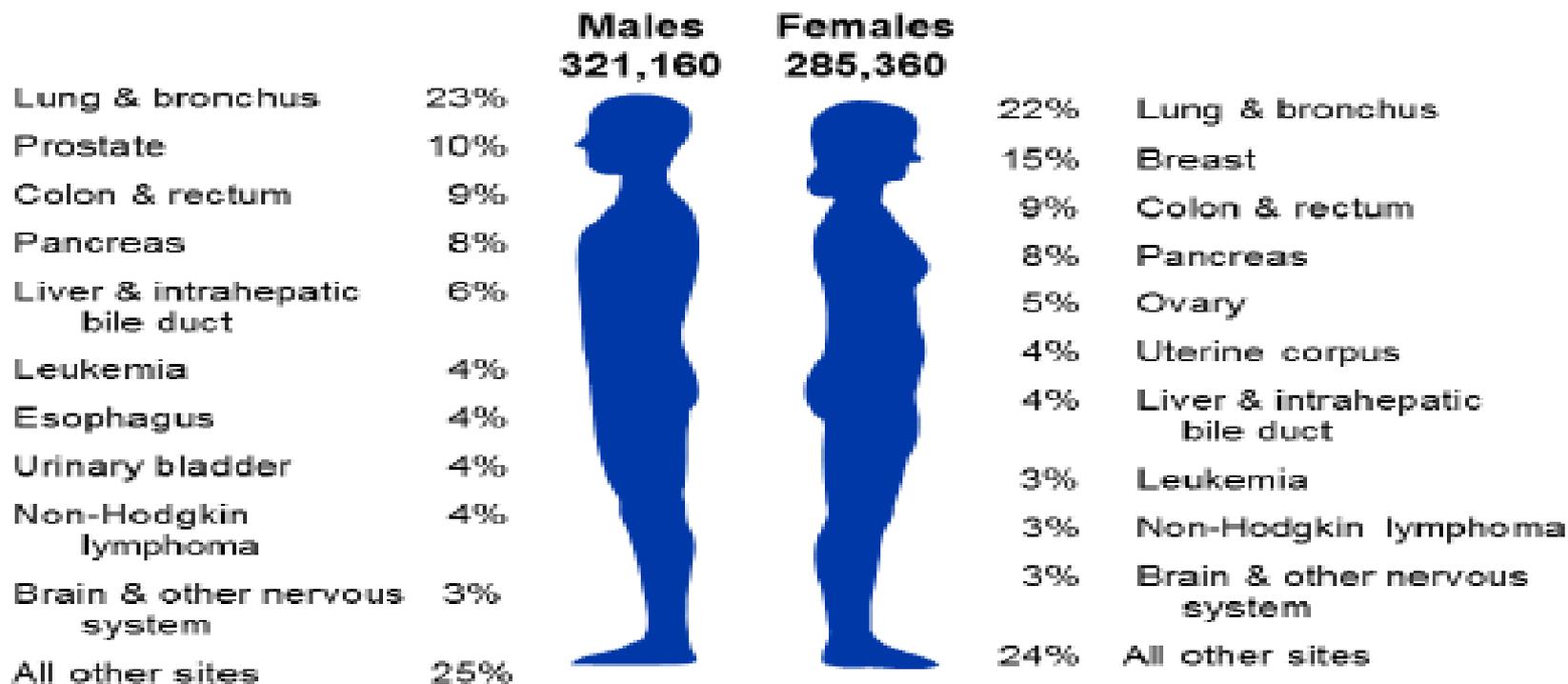
[View Data Table](#)



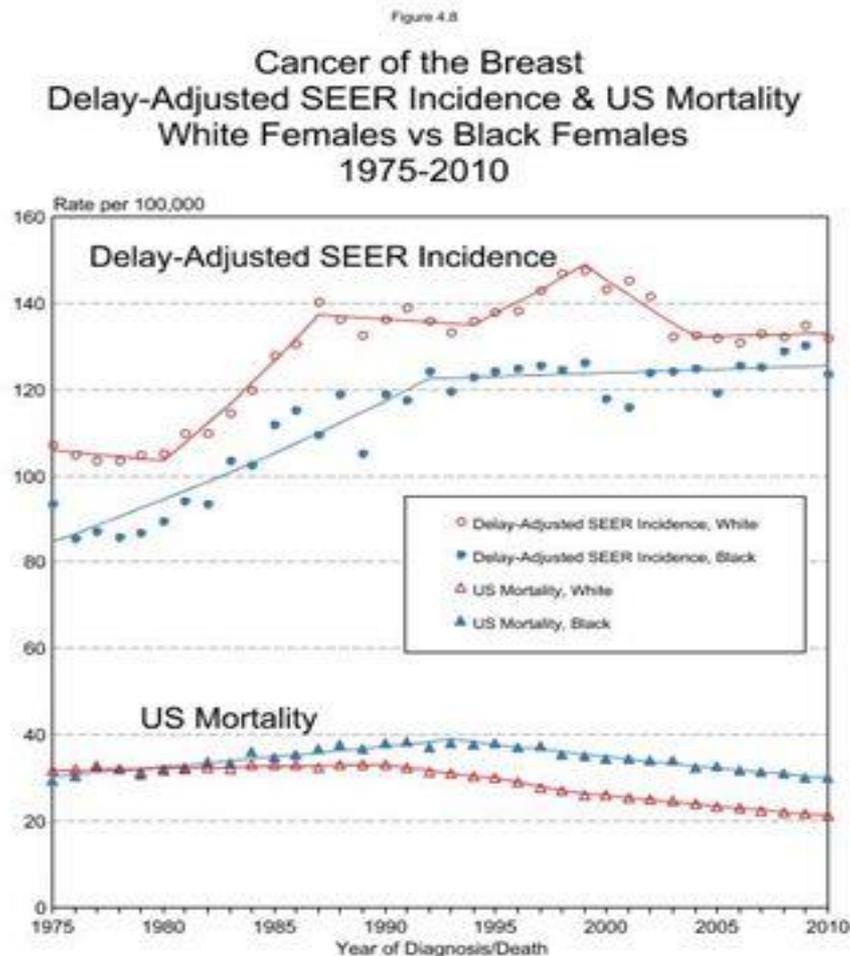
Year	1975	1980	1985	1990	1995	2000	2005	2009
5-Year Relative Survival	75.2%	74.9%	78.4%	84.6%	86.8%	90.2%	90.5%	91.3%

Cancer deaths in the US

Estimated Cancer Deaths in the US in 2020



Incidence & Mortality 1975 – 2010 By Race

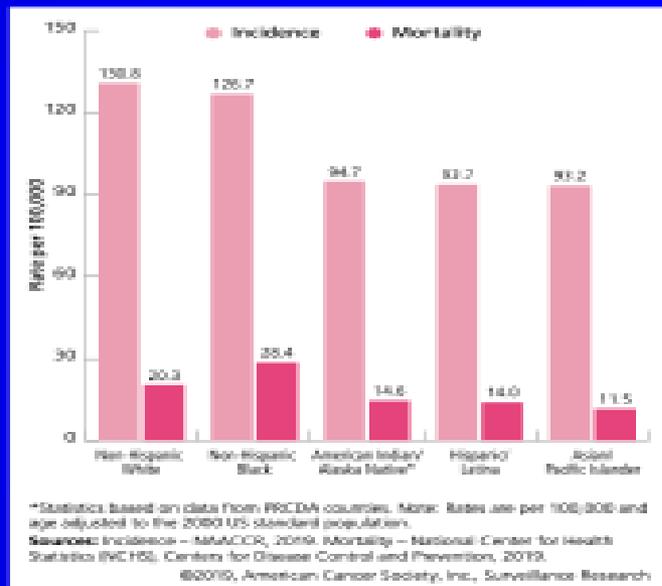


Source: SEER 9 areas and US Mortality Files (National Center for Health Statistics, CDC). Rates are age-adjusted to the 2000 US 5th Population (19 age groups - Census P25-1100). Regression lines are calculated using the Joinpoint Regression Program Version 4.0.3, April 2013, National Cancer Institute.

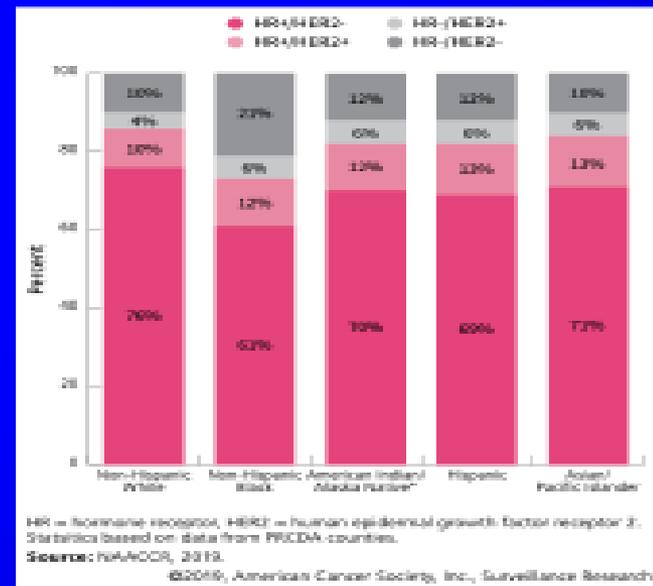
Statistics

Statistics

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



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

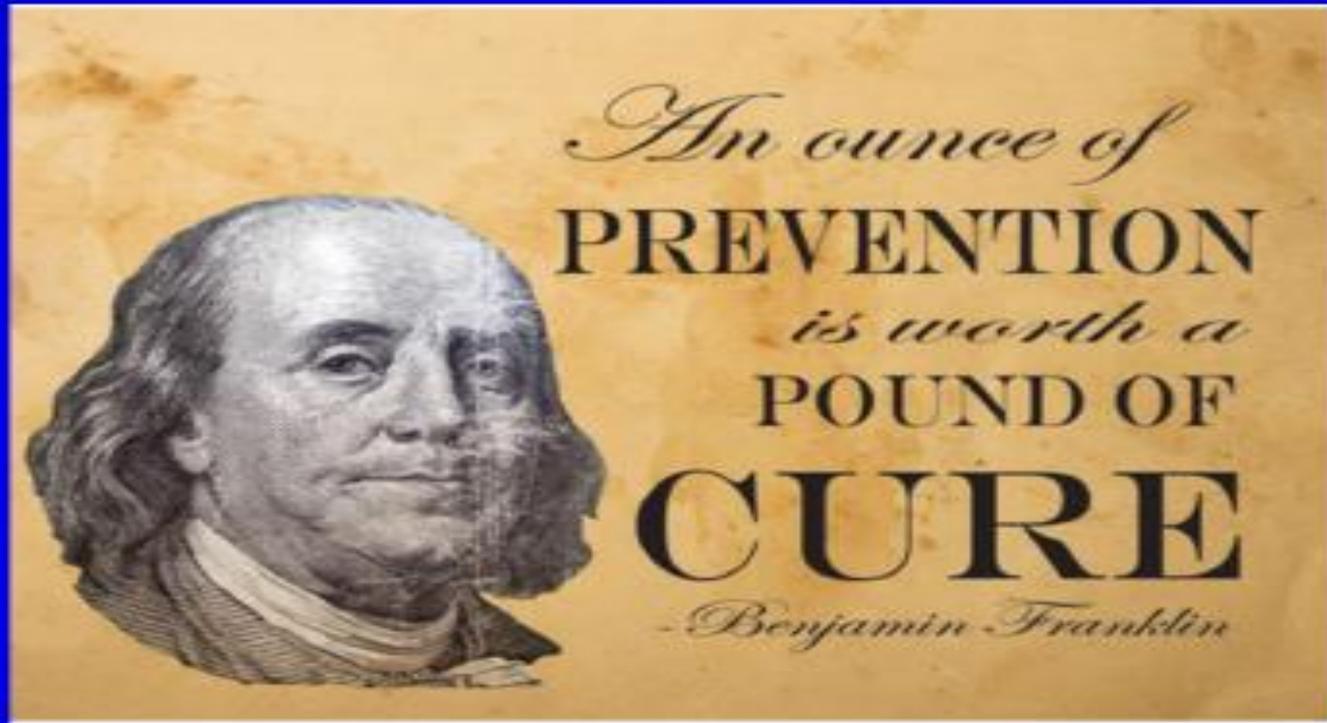


Early Detection



Breast Cancer
AWARENESS MONTH

Prevention



Mammograms 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



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 $\geq 20-25\%$ 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 the Early 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

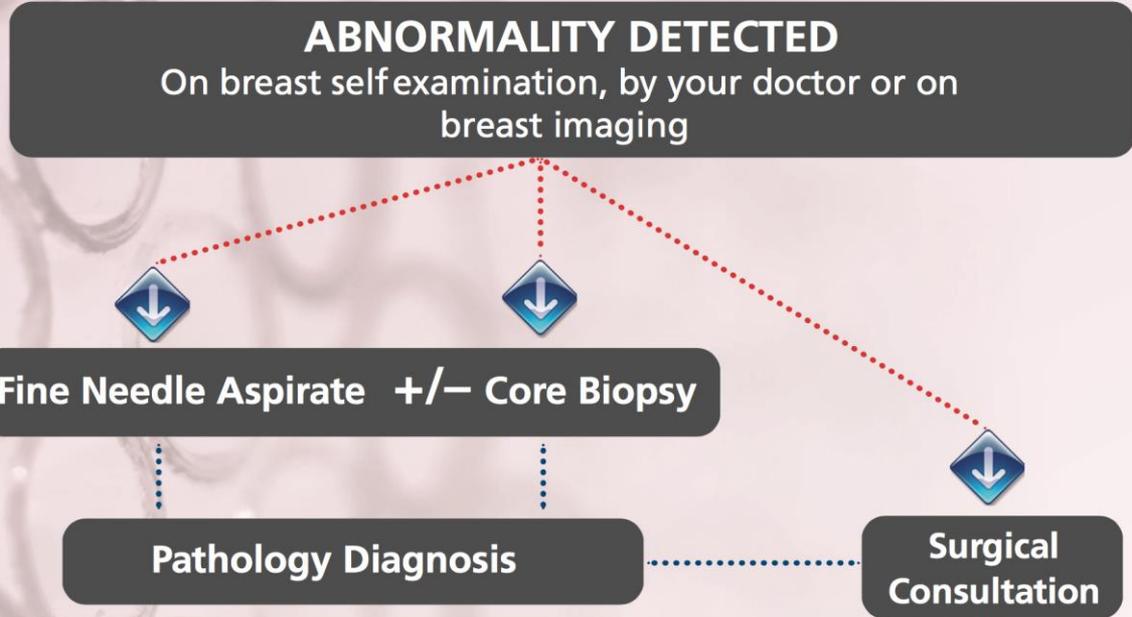


Examine upright

Pre-operative

The Breast Cancer Journey

PRE-OPERATIVE



Operative

OPERATIVE

Intraoperative Pathology

Frozen Section

Lymph node imprint

Surgical Procedures

Breast operation

Lumpectomy

Wire localised excision

Mastectomy

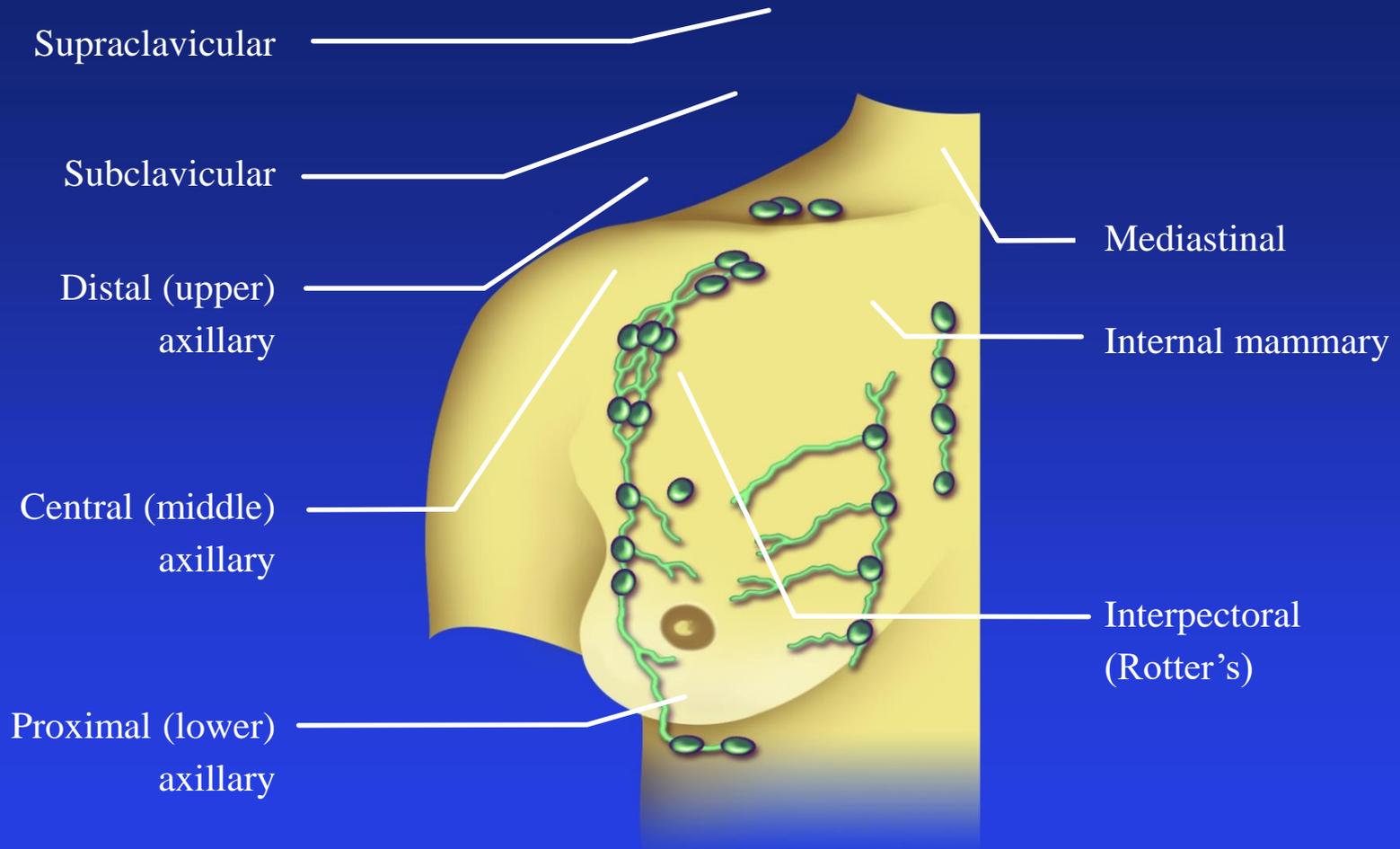
Lymph node operation

Sentinel nodes

Axillary nodes



Structure of the Breast : Lymph Nodes



Post-operative

POST-OPERATIVE

Final Tissue Pathology Report

Breast - includes ORIPRI/HER2

Lymph Nodes - includes full sentinel node protocol

Possible Genetic Workup

Pathology Monitoring Tests

FBC

LFT



Surgeon

Medical Oncologist

Radiation Oncologist

Decisions about radiation, chemotherapy, further surgery and monitoring.

Breast cancer staging

Breast cancer staging		
Stage	Tumor size	Axillary lymph nodes
In situ		
0	Tiny clusters of cells in a breast duct (in situ); no invasive cancer seen	No spread
Invasive		
I	Up to 2 cm	No spread
II	Smaller than 2 cm	Has spread
	Between 2 and 5 cm	May or may not have spread
	Larger than 5 cm	No spread
III	Any size	Has spread
Metastatic		
IV	Any size that has spread to other organs in the body	May or may not have spread

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 $\geq 1/3$ 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



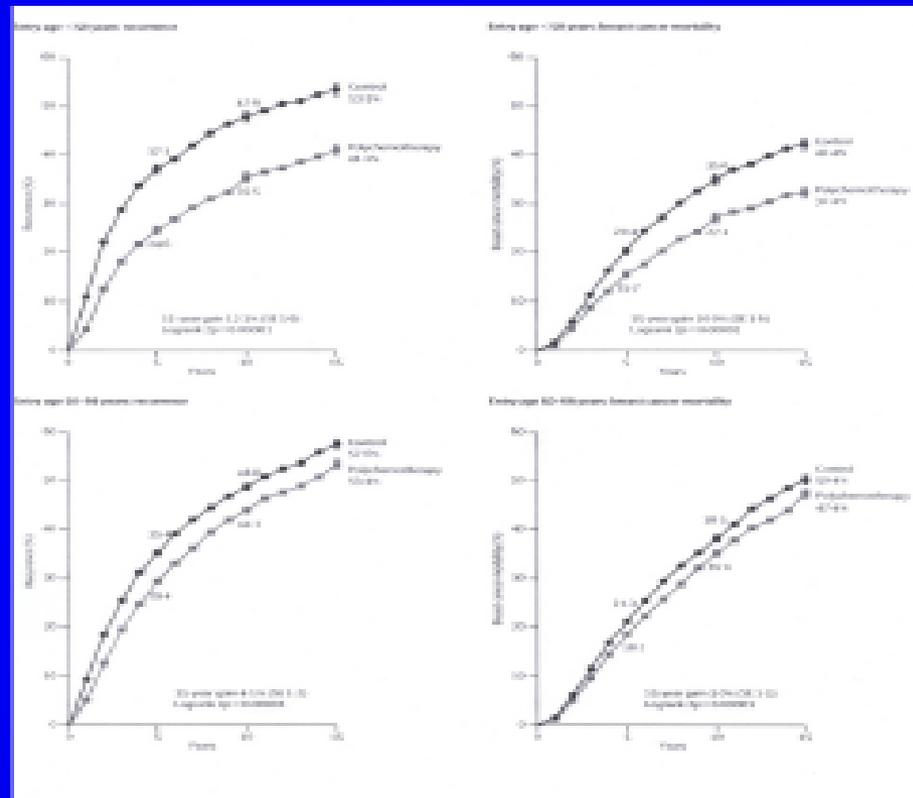
Prognosis and Selection of Therapy Influenced By:

- 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

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

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	Arimidex	Post	Pill	Aromatase Inhibitor (AI) Blocks Aromatase, enzyme that converts other hormones to estrogen
Letrozole	Femara		Pill	
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

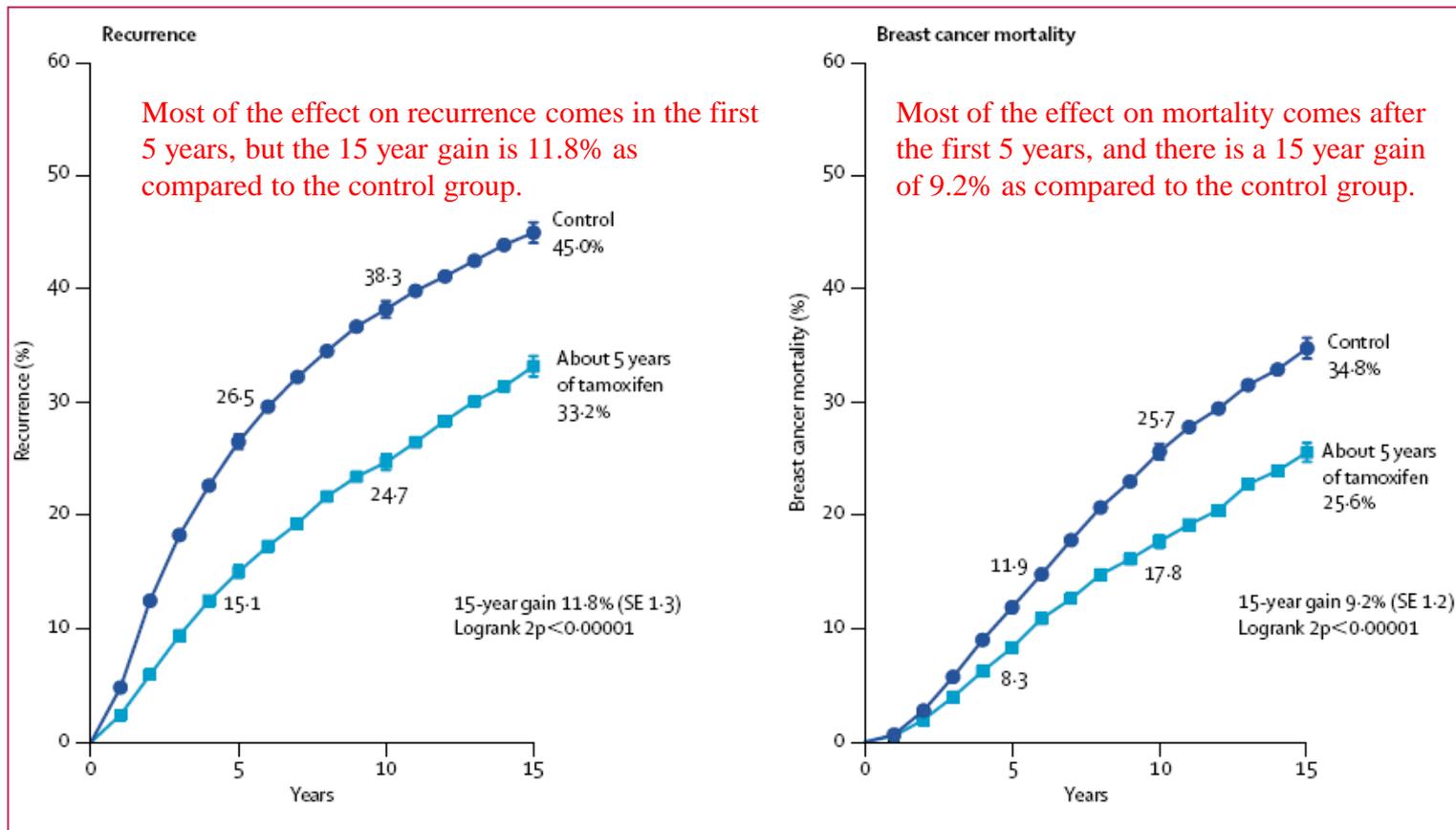
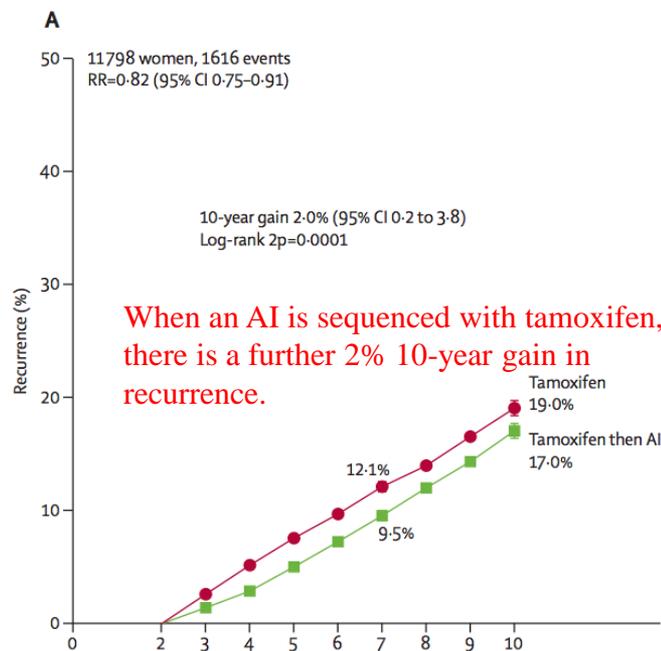


Figure 8: About 5 years of tamoxifen versus not in ER-positive (or ER-unknown) disease: 15-year probabilities of recurrence and of breast cancer mortality 10 386 women: 20% ER-unknown, 30% node-positive. Error bars are $\pm 1SE$.

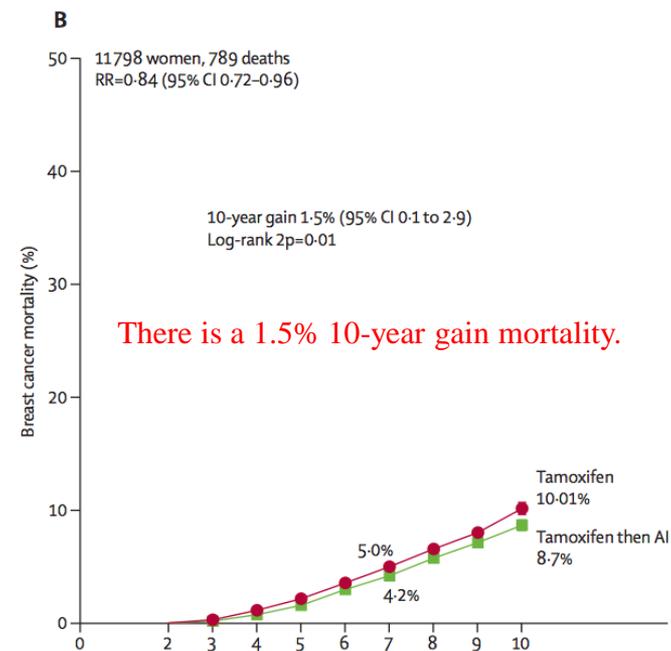
EBCTCG Lancet, 2014

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) from (O-E)/V	0.56 (0.46-0.67) -65.3/111.5	0.97 (0.86-1.11) -5.9/234.0	0.92 (0.68-1.25) -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) from (O-E)/V	0.65 (0.44-0.96) -11.0/25.8	0.91 (0.77-1.08) -11.9/132.0	0.69 (0.48-1.00) -10.6/28.9

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

Tucatinib

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

FEBRUARY 13, 2020

VOL. 382 NO. 7

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

R.K. Murphy, S. Lo, A. Clines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.H. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Sachdev, S.S. Shachar, V. Miller, S. Bragg, F.P. Duhaime, R. Gray, D. Cameron, L.A. Carey, G. Curigliano, R. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Waller, W. Fang, and S.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.

Targeted therapies

More Targeted Therapies ...

Chemical Name	Trade Name	Mechanism	Indication
Lapatinib	Tykerb	<p>Human EGFR type 1 and type 2 tyrosine kinase inhibitor.</p> <p>It binds to the intracellular phosphorylation domain to prevent receptor auto-phosphorylation upon ligand binding.</p>	<p>Lapatinib + Xeloda to treat advanced stage HER2+ breast cancer that has stopped responding to anthracyclines, taxanes, and Herceptin.</p> <p>Lapatinib + Letrozole for the treatment of postmenopausal HR+ HER2+ metastatic breast cancer</p>
Everolimus	Afinitor	<p>mTOR inhibitor</p> <p>Interacts with MTORC1 and inhibits downstream signaling.</p>	<p>Postmenopausal advanced HR+ HER2- breast cancer in combination with exemestane after progression on letrozole and anastrozole.</p>

Targeted therapies

Chemical Name	Trade Name	Mechanism	Indication
Palbociclib	Ibrance	<p>CDK4/6 Inhibitor</p> <p><i>Abserrations in the CDK-RB pathway are common in breast cancer. Consequently, inhibition of this pathway is an attractive therapeutic strategy.</i></p> <p>Inactivation of CDK4/6-cyclin D1 complexes helps control cell growth by inducing G1 arrest and reducing cell cycle progression.</p>	<p>HR+ HER2- advanced or metastatic breast cancer in combination with an aromatase inhibitor</p> <p>Or</p> <p>With fulvestrant in women with disease progression following endocrine therapy.</p>
Ribociclib	Kisqali	CDK4/6 inhibitor	<p>Ribociclib + AI for initial endocrine therapy in postmenopausal HR+ HER2- advanced/metastatic breast cancer.</p> <p>Ribociclib + Fulvestrant in HR+ HER2- advanced/metastatic breast cancer as initial Rx, or following progression on endocrine Rx</p>
Abemaciclib	Verzenio	CDK4/6 inhibitor	<p>HR+ HER2 – advanced metastatic BrCa in combination with an AI or fulvestrant.</p>

Targeted therapies

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

Targeted therapies

Chemical Name	Trade Name	Mechanism	Indication
Alpelisib	Piqray	<p>Inhibits PIK3 in the PI3K/AKT signaling pathway, ultimately inhibiting pathway activation.</p> <p>This results in inhibition of cell growth and survival.</p> <p>** PIK3CA missense mutations occur in about 40% of ER+ breast cancers</p>	<p>Approved in combination with fulvestrant for postmenopausal women with <u>HR+</u>, <u>HER2 negative</u>, <u>PIK3CA mutated</u>, advanced or metastatic breast cancer.</p> <p>Approved May 24, 2019, based on the phase 3 Solar-1 study.</p>

Chemotherapy

How do clinicians make well-informed decisions about which patients to treat with chemotherapy and what to choose?

Treating Breast Cancer in the Genomics Era

Selection of Chemotherapy Regimens for Patients	Selection of Patients for Chemotherapy Regimens
Tumor size, molecular subtype, histology, pathological grade, nodal status, hormone receptor expression, patient's age, co-morbidities, and performance status.	Tumor size, molecular subtype, histology, pathological grade, nodal status, hormone receptor expression, patient's age, co-morbidities, and performance status.
Use Gene Expression Profiling of the primary tumor to predict response to particular agents.	Use Gene Expression Profiling of the primary tumor to predict and treat only those patients who are most likely to recur and who, will therefore, benefit most from the addition of chemotherapy.

What are Genomic Tests?

- The difference between genomic and genetic testing:

Genetic testing involves sequencing a person's DNA

- using blood or saliva

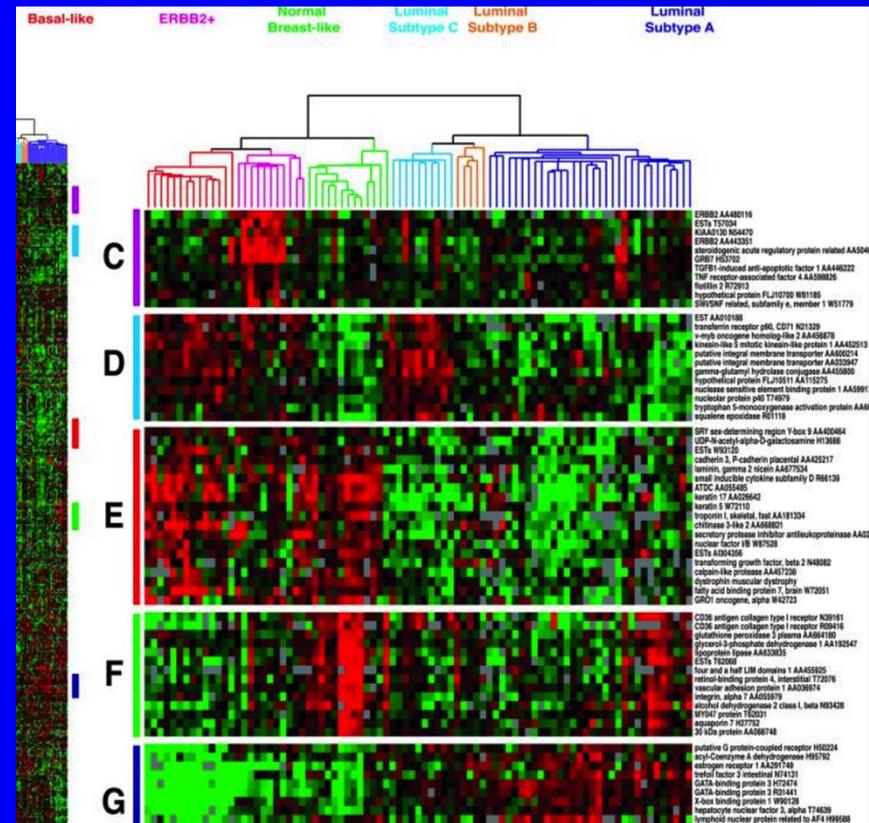
Genomic testing analyzes the tumor tissue itself

Emergence of **genomic profiling assays** of tumor tissue

- ❖ risk prognostication (recurrence)
- ❖ predictive benefit of adjuvant chemotherapies
- ❖ information on the likelihood of a cancer rapidly growing and metastasizing
- ❖ identifying actionable mutations.

The Use of Molecular Profiling in Determining Breast Cancer Prognosis & Treatment Strategies, Sorlie, PNAS 2001

- Gene expression patterns of 85 samples were analyzed by clustering using the 476 intrinsic cDNA clone set.
- The tumor specimens were divided into 5 (or 6) subtypes based on differences in gene expression.
- The cluster dendrogram shows the subtypes as luminal subtypes A, B, C, normal breast like, basal like, and ERB B2+
- This would provide a means for identifying expression motifs that represent important clinical phenotypes, such as:
 - resistance to specific therapies
 - sensitivity to specific therapies
 - tumor invasiveness
 - metastatic potential

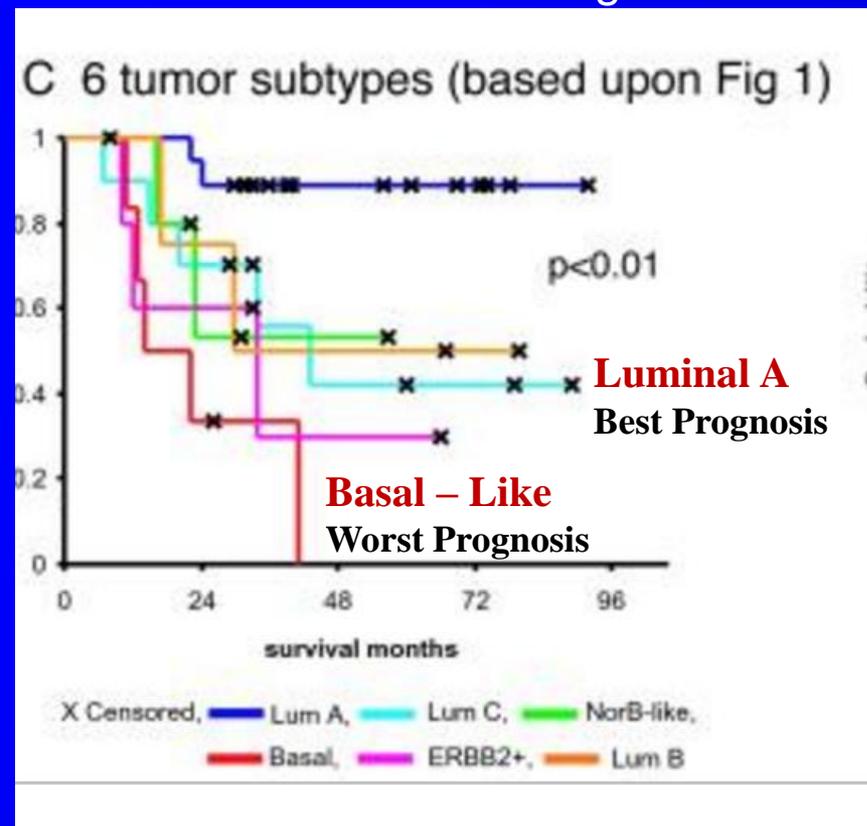


Is Molecular Profiling Useful in Determining Breast Cancer Prognosis & Treatment Strategies?

YES!!

- Significantly different outcomes for the patients belonging to the various groups.
- Luminal A subtype appears to have the best prognosis, and Basal-Like, the worst prognosis.

2. Then those with prognostic significance were identified using three independent clinical studies of breast ca involving 447 patients to test the relationship between expression of the 250 candidate genes and



Recurrence

FDA Approved Genomic Tests, Used by Clinicians to Predict Recurrence

- The **EndoPredict test** is used to predict the risk of distant recurrence of early-stage, hormone-receptor-positive, HER2-negative breast cancer that is either node-negative or has up to three positive lymph nodes.
- The **MammaPrint test** is used to predict the risk of recurrence within 10 years after diagnosis of stage I or stage II breast cancer that is hormone-receptor-positive or hormone-receptor-negative.
- The **Oncotype DX test** is used to predict the risk of recurrence of early-stage, hormone-receptor-positive breast cancer, as well as how likely it is that a woman diagnosed with this type of cancer will benefit from chemotherapy after surgery. The **Oncotype DX DCIS test** is used to predict the risk of recurrence of DCIS and/or the risk of a new invasive cancer developing in the same breast, as well as how likely it is that a woman diagnosed with DCIS will benefit from radiation after surgery.
- The **Prosigna Breast Cancer Prognostic Gene Signature Assay** (formerly called the **PAM50 test**) is used to predict the risk of distant recurrence for postmenopausal women within 10 years of diagnosis of early-stage, hormone-receptor-positive disease with up to three positive lymph nodes after 5 years of hormonal therapy.

Molecular assay

Onco-type DX : Molecular Assay in Clinical Practice

It is a **prognostic test** in that it provides information about how likely or unlikely the breast cancer is to come back.

It is a **predictive test**, in that it predicts the likelihood of benefit from chemo or radiation therapy treatment. This is the feature that makes this test stand out from the others.

Method of Development

1. RT-PCR method was designed to quantify gene expression and prognostication. It was initially validated for ER+ HER2- node negative invasive cancer; however, it has recently been extended to node-positive (1-3) disease as well.
2. 250 candidate genes were selected from published literature, genomic databases, and experiments based on DNA micro-arrays.
3. Then those with prognostic significance were identified using three independent clinical studies of breast ca involving 447 patients to test the relationship between expression of the 250 candidate genes and the recurrence of breast cancer.

Gene panel

Three Breast Cancer Studies Used To Select 21 Gene Panel

16 Cancer and 5 Reference Genes

4. Sixteen Cancer Related Genes were identified falling into 3 groups:

- proliferation group
- ER-related group
- invasion-related group
- several misc. genes
- 5 reference/housekeeping genes

An algorithm based on the levels of expression of these genes was used to compute a **recurrence score** for each tumor sample being tested.

PROLIFERATION

Ki-67
STK15
Survivin
Cyclin B1
MYBL2

GSTM1

CD68

BAG1

HER2

GRB7
HER2

ESTROGEN

ER
PR
Bcl2
SCUBE2

INVASION

Stromolysin 3
Cathepsin L2

REFERENCE

Beta-actin
GAPDH
RPLPO
GUS
TFRC

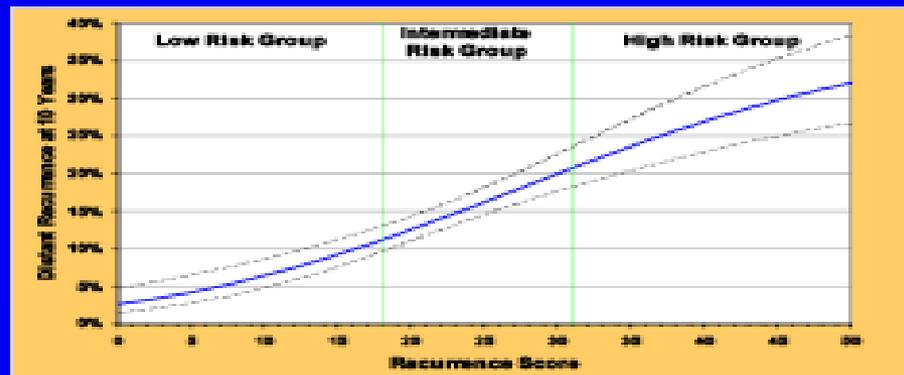
Oncotype DX

Oncotype DX

Prognostic for Likelihood of Recurrence Validation Study

- Assay and recurrence score were validated based on retrospective analysis of tissue samples from the NSABP-14 Study

- The tissue samples were from patients who were tamoxifen treated, node negative, ER+ and used to assess both the prognostic and predictive value of the assay.



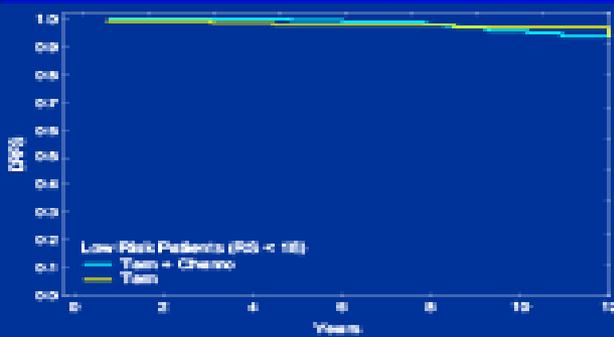
338 pts
149 pts
181 pts

- Low Risk Group (RS 0-20) = 2-12% DR @ 10 yrs
- Intermediate Risk Group (RS 20-30) = 12-21% DR @ 10 yrs
- High Risk Group (RS 30-50) = 20-33% DR @ 10 yrs

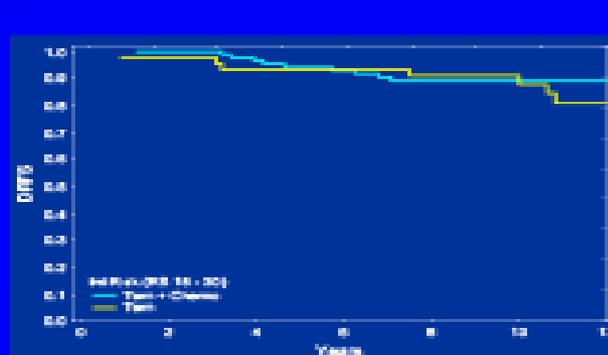
Validation study

Oncotype Dx: Predictive of Chemotherapy benefit Validation Study

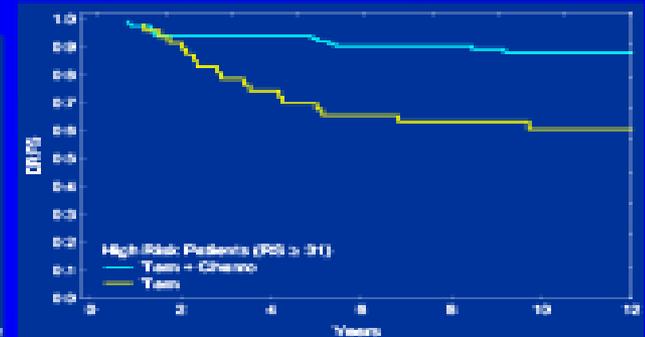
RS < 18



RS 18-30



RS ≥ 31



Assessing **Disease Recurrence Free Survival** in **Years**:

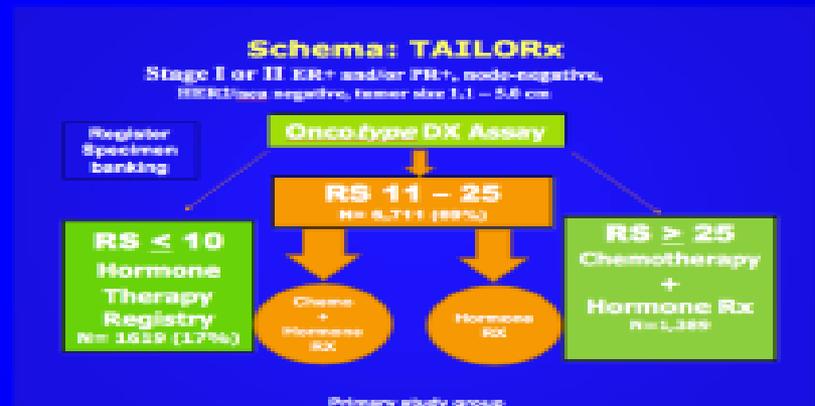
- Patients with tumors that have high Recurrence Scores have a large absolute benefit of chemotherapy (similar results with CMF and MF)
- Patients with tumors that have low Recurrence Scores derive minimal, if any, benefit from chemotherapy

TAILORx

TAILORx

Trial Assigning Individualized Options for Treatment

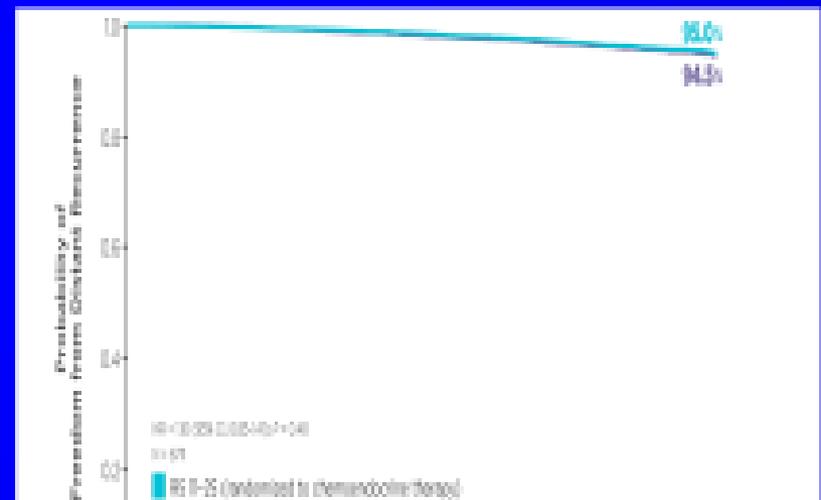
- Landmark clinical Trial supporting the use of the oncoTypeDX Breast Recurrence Score.
- It enrolled > 10,000 women with HR+, HER2-, node negative, early stage breast cancer, in over 1,000 trial sites in 6 different countries.
- It was a trial led by the ECOG-ACRIN Cancer Research Group, and sponsored by the NCI.
- Goal: spare the toxicity of chemo in women who do not need it.
- It was clear that women with a high score would benefit from chemotherapy, where as those with low scores would not.
- The gray zone encompassed those women with a mid-range score.



Adjuvant therapy



No Statistically significant difference between treatment groups (RS 11-25, chemo-endocrine v endocrine alone) in the probability of distant recurrence at 9y follow up.



TAILORx

TAILORx The Bottom Line

Excellence and Success in Translational Research in Clinical Oncology!!

In early stage ER+, HER2-, NO breast cancer, who benefits from chemotherapy?



25% of patients with a low Recurrence Score (RS) result (0-25) had high clinical risk* and would have been overtreated without the RS result

*High clinical risk: Grade 1, >3 cm; Grade 2, >2 cm;
Grade 3, >1 cm.

43% of patients with a high Recurrence Score (RS) result (26-100) had low clinical risk** and would have been **undertreated** without the RS result

**Low clinical risk: Grade 1, ≤3 cm; Grade 2, ≤2 cm;
Grade 3, ≤1 cm.

- Adjuvant chemotherapy, in early stage breast cancer, may now be guided

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

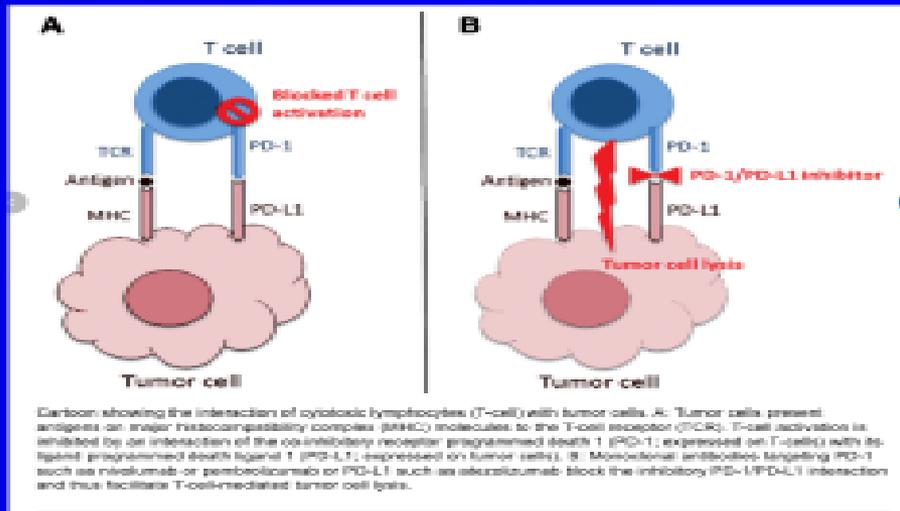
- Treatment is becoming more personalized for patients, with tumor genomic profiling that could lead to optimal treatment.
- Clinical Next Generation Sequencing (NGS or Tumor Profiling) is increasingly being used to identify potentially actionable mutations in tumor tissue.
- What we don't yet know is 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.

BREAST CANCER CLINICAL TRIALS

**Center For Cancer Research
Women's Malignancies Branch**

IMMUNOTHERAPY

The Role of PD-L1 Pathway Inhibition in Immunotherapy



- **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!!

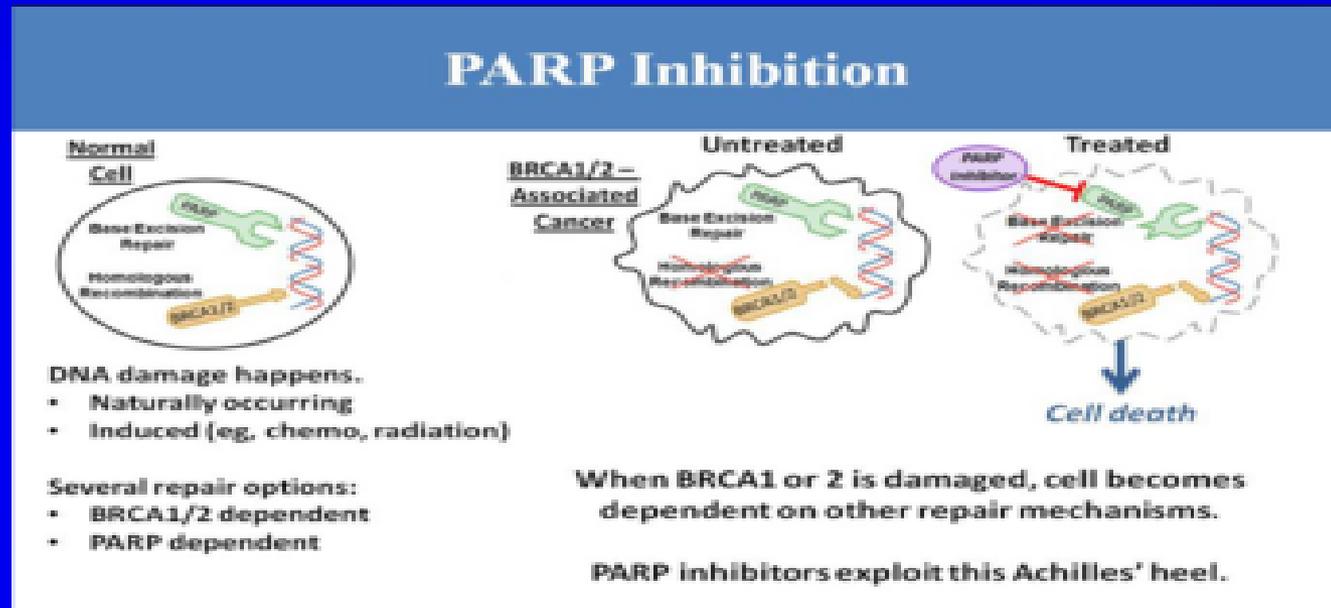
Immunotherapy + Small Molecules

- One approach in immuno-oncology:
 - 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.
- **MEDI-O (15-C-0145)**
Durvalumab (Medi-14736) + Olaparib for Advanced or Recurrent TNBC

PARP inhibition

PARP Inhibitors in Somatic and/or Germline Mutated Breast CA

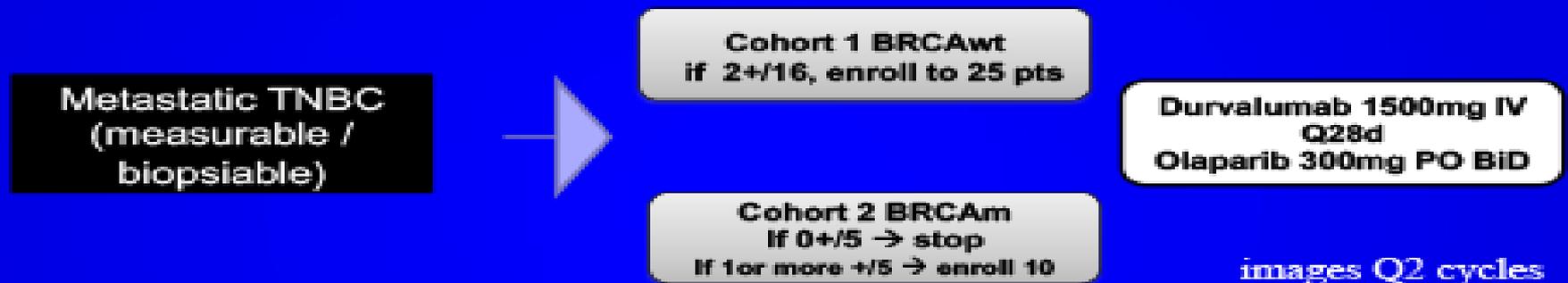
- PARP: Base Excision Repair
- BRCA1: Checkpoint Activation and DNA Repair
- BRCA2: Homologous Repair



- **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 nodes 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

Baseline 11/2/2018

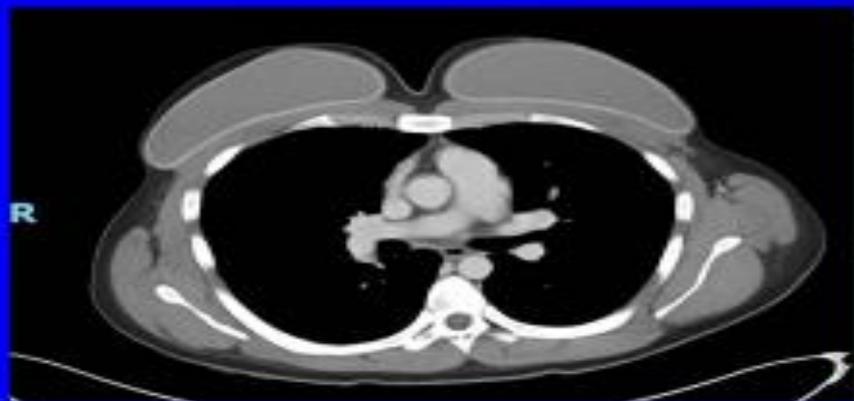
Left Subpectoral/Axillary Mass

4.4 x 3.3 cm

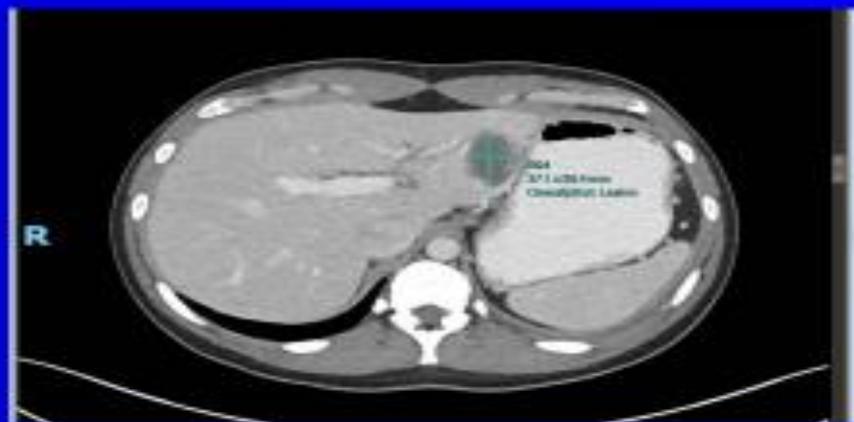


Post 10 cycles 9/16/2019

No mass noted in left axilla/subpectoral area



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



Baseline 11/2/2019
Multiple Lung Nodules
Mediastinal Lymphadenopathy

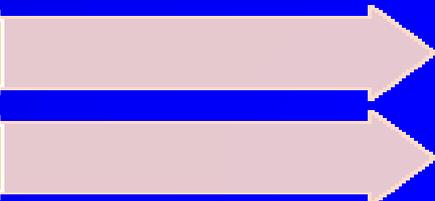


Post 10 cycles 9/16/2019
Sub-centimeter lung nodules
No mediastinal LAD

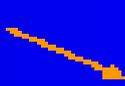


TNBC
BRCA WT

TNBC
BRCA Mut



PDL-1 Mo Ab
+
PARPi



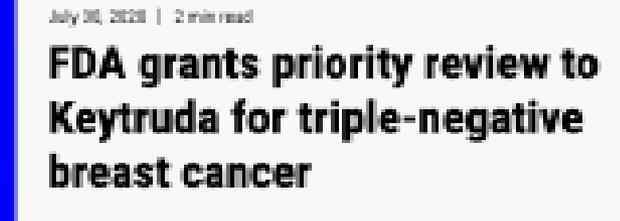
**Best
Response**

1. Durvalumab upregulates PDL-1 expression on APC
2. "Double Hit" to the DNA Repair Mechanism.
3. TNBC has higher TIL's in micro-environment.

Current Status of Immunotherapy for TNBC



- Approved March 2019 in combination with nab-paclitaxel, based on results of Impassion130 Trial
- 40% Risk Reduction in progression or death with addition of PDL-1 inhibitor



- Pembrolizumab + Chemotherapy for those with locally recurrent, unresectable or metastatic disease AND PD-L1 expression.
- Review granted based on results of Phase 3 KEYNOTE-355 trial – significantly approved PFS with combination

Thank You!