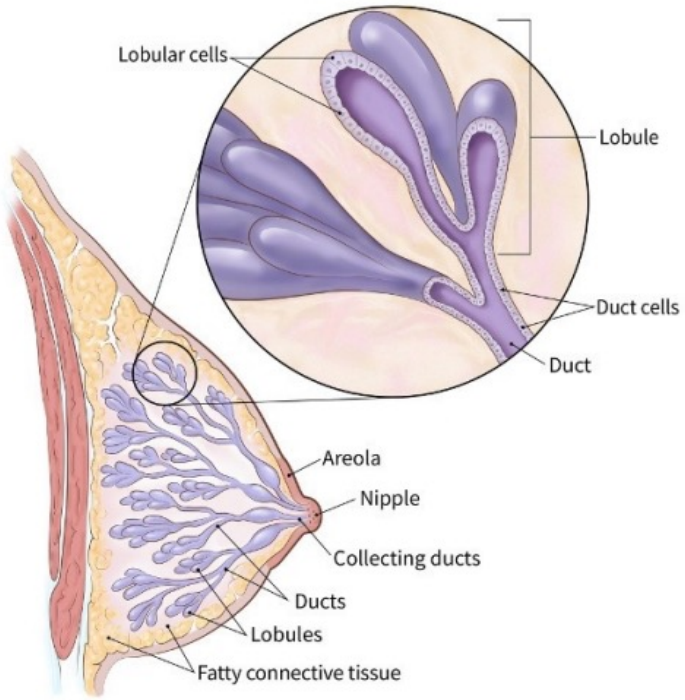
TNBC Introductory Lecture

Breast Cancer Pathology

Breast Cancer Pathology

Breast cancer cells develop into malignant cells from normal breast cells

Cancer cells come from either breast **lobules (10%)** where milk is made or breast **ducts (70%)** where milk is channeled



American Cancer Society

Lobular Carcinoma

Ductal Carcinoma

Breast Cancer Pathology

Breast cancer cells develop into malignant cells along a spectrum

Atypical Ductal/Lobular Hyperplasia (ADH/ALH)

Abnormal High-Risk Cells
Portend higher risk of future cancer

Ductal/Lobular Carcinoma in Situ (DCIS/LCIS)

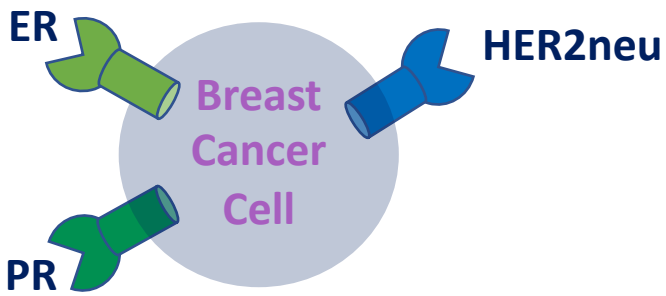
Pre-Cancerous Cells (Stage 0)
"in situ" = stuck "in place"
Does not have the ability to invade outside the breast

Invasive Ductal/Lobular Carcinoma (IDC/ILC)

Invasive Cancer (Stage I-III)
Has the potential to invade outside the breast

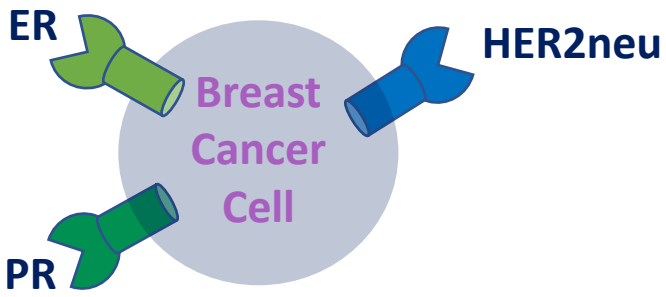
Breast Cancer Receptors

Hormone receptors (estrogen and progesterone) & HER2 receptors
= expressed on <u>some</u> breast cancer cells



Types of Breast Cancer	
HR+/HER2-	HR Positive
HR-/HER2+ HR+/HER2+	HER2 Positive Triple Positive
HR-/HER2-	Triple Negative

Breast Cancer Subtypes



Types of Breast Cancer		Incidence
HR+/HER2-	HR positive	70%
HR-/HER2+ HR+/HER2+	HER2 positive Triple Positive	20%
HR-/HER2-	Triple negative	10%

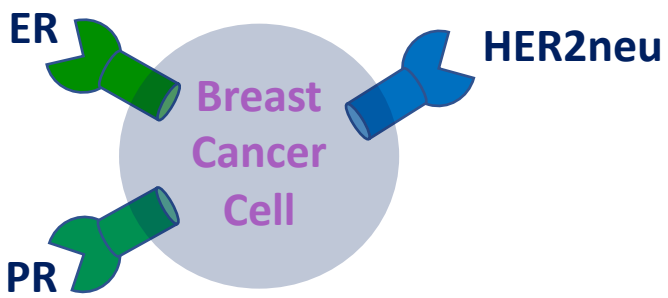
Positivity determined by tests of biopsy sample:

IHC = immunohistochemistry
FISH = fluorescence in situ hybridization

Receptors always written in order:

ER → PR → HER2
ER+/PR+/HER2- or +/+/-

Breast Cancer Receptors



Definition of HR+ (ER+ or PR+)

Hormone Receptor positive = HR+

Estrogen Receptor (ER)
Progesterone Receptor (PR)

HR "Low"
1-10% ER or PR = HR "low" but still positive
> 10% ER or PR = positive

either ER or PR > 1% = HR+

Definition of HER2+

HER2+ IHC is graded 1+ to 3+ (1+ = weak; 3+ = strong)

HER2 IHC 1+ = negative
HER2 IHC 2+ = equivocal, requires confirmatory FISH
HER2 IHC 3+ = positive

FISH Tests: HER2/CEP17 and HER2 CN

HER2/CEP17 > 2 = Positive
HER2/CEP17 = HER2 gene/chromosome 17 centromere expression

HER2 CN > 6 = Positive
HER2 CN = HER2 copy number

Breast Cancer Staging & Prognosis

Staging

Receptors:
Staging includes HR and HER2 receptor status, grade, as well as TNM

Notable T Sizes:
T1a: < 0.5 cm
T1b: 0.5 – 1 cm
T1c: 1-2 cm
T2: 2-5 cm
T3: > 5 cm
T4: chest wall or skin

Notable lymph Nodes:
N1 = 1-3 axillary LN
N2 = 4-9 axillary LN or Internal mammary LN
N3 = 10+ axillary LN or supraclavicular LN

M1 = mediastinal or cervical LN

Prognosis varies significantly based on: staging (early vs late) and receptor status

Early Stage Breast Cancer:

Stage I-III BC 5Y OS around 80-95%

HR+	5Y OS 95%
HER2+	5Y OS 85%
TNBC	5Y OS 75%

Metastatic Breast Cancer:

Stage IV HR+	5Y OS around 30%
Stage IV HER2+	5Y OS around 20%
Stage IV TNBC	5Y OS around 10%

Stage IV HR+	median OS 57 months
Stage IV HR-	median OS 31 months

TNBC Early Stage Treatment

Early Breast Cancer Treatment Paradigm

Local Control

Goal = remove cancer locally

Surgery

+/- Radiation Therapy

Systemic Therapy

Goal = reduce risk of local & distant recurrence

(1) Destroy any microscopic cells not removed in local resection
(2) Modify hormonal environment to reduce risk of recurrence

\+ Chemotherapy

+/- Immunotherapy

TNBC Receptor Based Therapy

Chemotherapy

+

Immunotherapy

TNBC requires chemotherapy

Immunotherapy is used for large or node positive breast cancers

Adjuvant vs. Neoadjuvant Therapy

SURGICAL INDICATIONS FOR NEOADJUVANT TX

(1) Down-Sizing of Surgery

ex: can allow for lumpectomy instead of mastectomy or spare an axillary LN dissection

(2) Rendering Inoperable Tumors Operable

ex: Inflammatory breast cancer (T4)

Adjuvant vs. Neoadjuvant Therapy

MEDICAL INDICATIONS FOR NEOADJUVANT TX

(3) Allow for Pathologic Assessment of Response to Neoadjuvant Therapy
→ Change of Adjuvant Therapy

TNBC w/ pathologic complete response (PCR) → no adjuvant chemo

TNBC w/ residual disease (RD) → adjuvant **capecitabine (Xeloda)**

TNBC Front Line Therapy

T1N0: often adjuvant chemo

* Can observe if T1a. Consider adjuvant therapy if T1bN0, T1cN0

Surgery → **ddACT**
(A) Doxorubicin
(C) Cyclophosphamide
(T) Taxol
→ +/- RT

T2 or N1: often neoadjuvant chemo

* Consider neoadjuvant in T1cN0

TC-AC-Pembrolizumab
(T) Taxol
(C) Carboplatin
(A) Doxorubicin
(C) Cyclophosphamide
(P) Pembrolizumab
→ Surgery

→ **PCR**
pathologic complete response → **Pembrolizumab**

→ **RD**
residual disease → **Capecitabine + Pembrolizumab**

+/- RT

* Consider Olaparib (PARP inhibitor) in place of capecitabine if RD and gBRCA+

Early Breast Cancer Front Line Therapies Overview

HR+ Breast Cancer:

Adjuvant Therapy
Low Oncotype (≤ 25): ET +/- OFS
High Oncotype (≥ 26): TC (N-) or ACT (N+) + ET

HER2+ Breast Cancer:

Neoadjuvant Therapy: TC-HP
Adjuvant Therapy RD: TDM1
Adjuvant Therapy PCR: HP

HR+/HER2+: Triple Positive Breast Cancer

Neoadjuvant Therapy: TC-HP
Adjuvant Therapy RD: TDM1 + ET
Adjuvant Therapy PCR: HP + ET

HR-/HER2-: Triple Negative Breast Cancer

Neoadjuvant Therapy: ACT or AC-TC + Pembrolizumab
Adjuvant Therapy RD: Capecitabine + Pembrolizumab
Adjuvant Therapy PCR: Observation + Pembrolizumab

TNBC Metastatic Treatment

MBC TNBC: Treatment Schema

Tx Line	Regimen
1st	PDL1 >10% = pembrolizumab + chemo
	PDL1 <10% = single agent chemo
2nd	gBRCA = PARP inhibitor (Olaparib, Talazoparib) * consider in sBRCA, PALB2
	BRCA WT = single agent chemo
3rd	Sacituzumab * approved after 2 systemic lines of therapy, at least 1 for MBC

★	Clinical Trial

Chemotherapy

Choose based on Efficacy and Toxicity

Efficacy:
typically highest RRs
pending prior usage

Taxanes:
paclitaxel (Taxol)
docetaxel (Taxotere)
nab-paclitaxel (Abraxane)

Anthracyclines:
doxorubicin (Adriamycin)
liposomal doxorubicin (Doxil) slower RR

Common Agents	Toxicities	Benefits
Anthracycline	Cardiotoxicity, Capped lifetime dose	Q3W Doxil Alopecia sparing
Taxanes	Neuropathy	Weekly or Q3W
Capecitabine	Mucositis, GI, PPE	Oral Alopecia sparing
Gemcitabine +/- Carbo		Q3W Alopecia sparing Consider doublet for large burden of disease
Eribulin	Neuropathy	Weekly

Toxicity Considerations:

Alopecia Sparing
Gemcitabine (Gemzar)
Capecitabine (Xeloda)
Liposomal doxorubicin (Doxil)

PO
Capecitabine (Xeloda)

Q3 Week Dosing
Docetaxel (Taxotere)
Paclitaxel (Taxol)
Liposomal doxorubicin (Doxil)
Gemcitabine

Other TNBC Drugs

Antibody Drug Conjugates

Sacituzumab (Trodelvy)
Antibody: Trop-2
Payload: SN-38 (active metabolite irinotecan)

* Also used in HR+ MBC

PARP Inhibitors (used in BRCA mutated)

Olaparib (Lynparza)
Talazoparib (Talzenna)

* Ongoing investigations regarding whether they can be used for other germline/somatic DNA repair mutations such as PALB2

Metastatic Breast Cancer: Front Line Therapy Overview

HR+ Breast Cancer:

Hormone Therapy: SERM or AI

with

CDK4/6 Inhibitor: palbociclib, ribociclib, abemaciclib

HER2+ Breast Cancer:

HER2+ Therapy: trastuzumab + pertuzumab

with

Chemotherapy: docetaxel

HR+/HER2+: Triple Positive Breast Cancer

HER2+ Therapy: trastuzumab + pertuzumab

with

Chemotherapy: docetaxel
** or with hormone therapy: SERM or AI*

HR-/HER2-: Triple Negative Breast Cancer

CPS+ (>10%): pembrolizumab + chemotherapy

or

Chemotherapy: single-agent chemotherapy

Breast Cancer Reference Handout

Breast Cancer Dx

Atypical Ductal/Lobular Hyperplasia (ADH/ALH)

Abnormal "high-risk" lesions
+/- Surgery
+/- ET (not stained for HR)

Ductal/Lobular Carcinoma in Situ (DCIS/LCIS)

Non-invasive cancerous lesions
Stage 0, "Pre-Cancer"
Surgery
+- ET if HR+

Invasive Ductal/Lobular Carcinoma (IDC/ILC)

Invasive cancerous lesions
Stage I-III
Surgical resection +/- RT
Receptor-based neoadjuvant or adjuvant therapy

Definition of HR+

ER or PR > 1%
(1-10% = low)

Definition of HER2+

IHC: HER2 2+ AND +FISH
HER2 3+

Types of Breast Cancer	Incidence
HR+/HER2-	70%
HR-/HER2+ HR+/HER2+	20%
HR-/HER2-	10%

Local vs Systemic Tx

Local Control:
Lumpectomy + RT or Mastectomy +/- RT

Receptor-Based Systemic Therapy:
Chemotherapy, Antibody Therapy, Endocrine Therapy

Receptor Based Tx

Chemo/Immunotherapy

HR+ Chemo	HER2+ Chemo	TNBC Chemo
ddACT	ACT-HP	ddACT
TC	TC-HP	TC-AC-Pembro "Keynote 522"
CMF	TH	

* All EBC requires chemo EXCEPT low-risk HR+

HR+ — **Endocrine Therapy [5-10 years]**
Pre-menopausal = SERM (tamoxifen)
Post-menopausal = AI (anastrozole, letrozole, exemestane)

HER2+ — **HER2+ Antibody Therapy [1 year]**
Trastuzumab (Herceptin) +/- Pertuzumab (Perjeta)

Important Side Effects:

Adriamycin → cardiotoxicity
Paclitaxel → neuropathy
Trastuzumab → cardiotoxicity
A, C, T, M, F → myelosuppression, hair loss, neuropathy, infertility
SERM → DVT, endometrial cancer, hot flashes/sweats, vaginal dryness
AI → hot flashes/sweats, vaginal dryness, arthritis, osteoporosis

Early Stage Breast Cancer Tx

Common Front Line Approach
for tumors >T1a

HR+ BC:

Adjuvant Therapy
Low Risk Oncotype (≤ 25): ET +/- OFS
High Risk Oncotype (≥ 26): TC (N-) or ACT (N+) + ET

HER2+ BC:

Neoadjuvant Therapy: TC-HP
Adjuvant Therapy RD: TDM1
Adjuvant Therapy PCR: HP (dual antibodies)
* Adjuvant TH if <2 cm, N-

HR+/HER2+ BC: Triple Positive

Neoadjuvant Therapy: TC-HP
Adjuvant Therapy RD: TDM1 + ET
Adjuvant Therapy PCR: HP (dual antibodies) + ET

HR-/HER2- BC: Triple Negative

Neoadjuvant Therapy: ACT or ACTC + Pembro
Adjuvant Therapy RD: Capecitabine + Pembro
Adjuvant Therapy PCR: Observation + Pembro
* Adjuvant ddACT if <2 cm, N-

HR+ Early Breast Cancer Risk

Oncotype
21 gene recurrence score sent on tumor to determine need for chemotherapy

When to send Oncotype:
- T1b-T2, N0-N1

When not to send Oncotype:
- Too small (T1a < 5mm)
- Too large (T3 > 5 cm, N2 ≥ 4 LN)
- Good prognosis histology (mucinous, tubular)

Oncotype

Menopausal Status	Node Negative	Node Positive (N1 = 1-3+ LN)
POST	≤ 25: ET	≤ 25: ET
	≥ 26: Chemo + ET	≥ 26: Chemo + ET
PRE	< 16: ET	≤ 25: Chemo + ET
	16-25: Chemo + ET * Can consider AI/OFS	
	≥ 26: Chemo + ET	≥ 26: Chemo + ET

Menopause Definition
1. Age >60
2. Age <60 and no menses >1Y OFF ET
3. BSO

ET

For 5-10Y

Pre-Menopausal
1. Tamoxifen (SERM)

Post-Menopausal
1. Aromatase Inhibitors (AI)
 --> anastrozole, letrozole, exemestane
2. Tamoxifen (SERM)

Important Side Effects:

AI + SERM → hot flashes/sweats, vaginal dryness, mood/weight changes
SERM → 1% DVT, 1% endometrial cancer
AI → 10-30% arthritis, osteoporosis

Chemo

Node Negative Chemo	Node Positive or High Risk Chemo
TC (TC, Q3 week) (T) Docetaxel (C) Cyclophosphamide	**ddACT (AC → T, Q2 week)** (A) Doxorubicin (C) Cyclophosphamide (T) Taxol

Rarely consider neoadjuvant chemotherapy
- Give if unresectable tumor
- Controversial for downstaging tumors as HR+ BCs respond less robustly to chemo

Additional Tx

1. Extended ET
7-10Y ET

2. CDK4/6
2Y Abemaciclib if N2 or N1 + (T3, G3 or Ki67 >20%)

3. OFS
If premenopausal + high risk (young, N+, required chemo)

4. PARP
If BRCA+ and RD

HR+ Early Breast Cancer Tx

Small
T1-T2, N0-N1

Surgery →

Low Oncotype →
ET: SERM (Tamoxifen)$^{PRE-MEN}$ or AI (Anastrozole)$^{POST-MEN}$
(5-10Y)
+/- RT: Radiation Therapy

High Oncotype →
TC
(T) Docetaxel
(C) Cyclophosphamide
→ **ET** (5-10Y)
+/- RT

Large or Unresectable
T3-T4, N2-N3

ddACT: AC → T Q2W
(A) Anthracycline
(C) Cyclophosphamide
(T) Paclitaxel
→ Surgery →
ET (5-10Y)
RT

HER2+ Early Breast Cancer Tx

Small
T1N0

Surgery →
T-H
(T) Docetaxel
(H) Herceptin
→
H (1Y HER2AB)
+/- ET (5-10Y)
+/- RT

Large
T2 or N+, consider T1c

TC-HP
(T) Docetaxel
(C) Carboplatin
(H) Herceptin
(P) Perjeta
→ Surgery →

PCR → **HP +/- ET**
To complete 1Y HER2 AB
For 5-10Y
+/-RT

RD → **TDM1 +/- ET**
To complete 1Y HER2 AB
For 5-10Y

TN Early Breast Cancer Tx

Small
T1N0

Surgery →
ddACT
(A) Doxorubicin
(C) Cyclophosphamide
(T) Taxol
→ **+/-RT**

Large
T2 or N+, consider T1c

TC-AC-Pembrolizumab
(T) Taxol
(C) Carboplatin
(A) Doxorubicin
(C) Cyclophosphamide
(P) Pembrolizumab
→ Surgery →

PCR → **Pembrolizumab**
+/-RT

RD → **Capecitabine + Pembrolizumab**
* if RD and gBRCA+ consider Olaparib in place of cape

Metastatic Breast Cancer Tx

Front Line Therapy

HR+ Breast Cancer:

Hormone Therapy: Tamoxifen or AI
WITH
CDK4/6 Inhibitor: Palbociclib, Ribociclib, Abemaciclib

HER2+ Breast Cancer:

HER2+ Therapy: Trastuzumab +/- Pertuzumab
WITH
Chemotherapy: Docetaxel

HR+/HER2+: Triple Positive Breast Cancer

HER2+ Therapy: Trastuzumab +/- Pertuzumab
WITH
Chemotherapy: Docetaxel

HR-/HER2-: Triple Negative Breast Cancer

CPS+ (>10%): Pembrolizumab + chemotherapy
OR
PDL1-: Chemotherapy: anthracyclines, taxanes, anti-metabolites, anti-tubulins, platins, etc

Metastatic Breast Cancer Tx

Additional Lines of Therapy: No SOC 2nd line therapy

Tx Line	HR+ Breast Cancer
1st	AI + CDK4/6 Inhibitor (palbociclib, ribociclib, abemaciclib)
2nd – 3rd ET Sensitive	PIK3CA - = Elacestrant or Fulvestrant +/- Everolimus or CDK4/6 PIK3CA + = Fulvestrant + Alpelisib
2nd – 3rd ET insensitive	BRCA - = single agent chemo or Enhertu (HER2 low) BRCA + = PARP inhibitor (olaparib, talazoparib)

Tx Line	HER2+ Breast Cancer
1st	Taxane + Trastuzumab + Pertuzumab
2nd	Trastuzumab Deruxtecan = TDXd (*Enhertu*)
3rd -4th	Trastuzumab Emtansine = TDM1 (*Kadcyla*)
3rd- 4th	Tucatinib + Trastuzumab + Capecitabine * consider 2nd line if brain mets

Tx Line	Triple Negative Breast Cancer
1st	PDL1 >10% = pembrolizumab + chemo PDL1 <10% = single agent chemo
2nd – 3rd	BRCA + = PARP inhibitor BRCA - = single agent chemo
2nd – 3rd	Sacituzumab * approved after 2 lines of systemic therapy, at least 1 for MBC