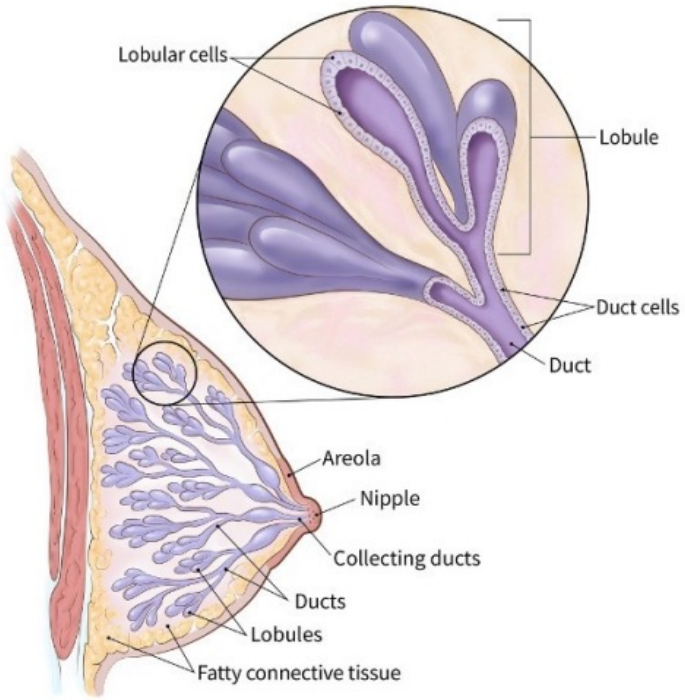
HER2+ Breast Cancer Introductory Lecture

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)

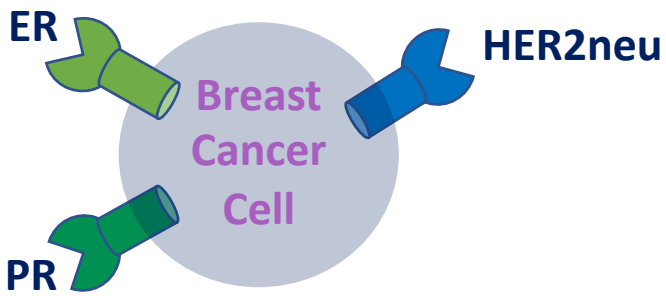
Pre-Cancerous Cells (Stage 0)
"in situ" = stuck "in place"
Does not have the ability to invade outside the breast

Invasive Ductal/Lobular Carcinoma (IDC/ILC)

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

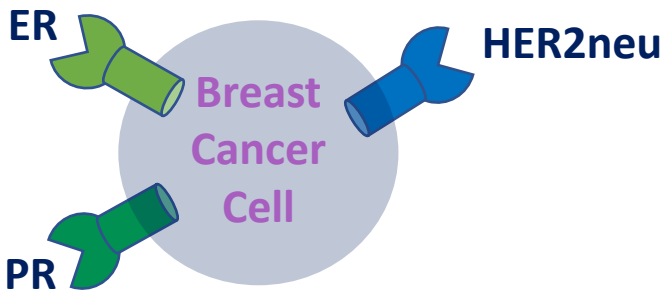
Breast Cancer Receptors

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%

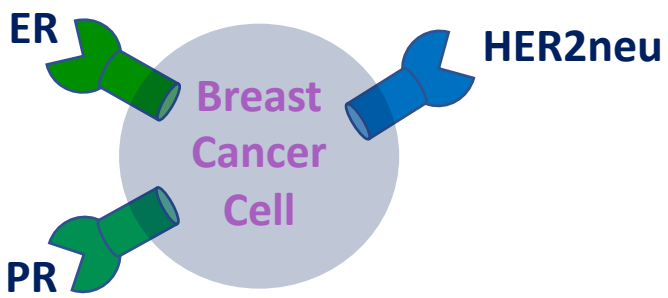
Positivity determined by tests of biopsy sample:

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

HER2+ Breast Cancer 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**

\+ **Antibody Therapy**

+/- **Endocrine Therapy** if HR+

HER2+ Receptor Based Therapy

Chemotherapy

+

HER2 AB Therapy

+

Endocrine Therapy

HER2+ breast cancer requires a combination of chemotherapy with HER2 antibody therapy

ET is used for HR+/HER2+ triple positive breast cancer

HER2+ Antibodies, Conjugated ABs, TKIs

HER2 Antibodies: 1 year total

trastuzumab (Herceptin): HER2 AB
always part of neo/adjuvant treatment

pertuzumab (Perjeta): HER2 AB
** Only used with trastuzumab for >T2 or N+ tumors*

TDM1 (Kadcyla): HER2 Conjugated AB
** Only used if residual disease after neoadjuvant trastuzumab*

neratinib: HER2 Tyrosine Kinase Inhibitor
** Can give after 1 year adjuvant HER2 AB if high-risk, often TPBC*

Important Side Effects:

trastuzumab/TDM1 → cardiotoxicity (Q3 month TTE during treatment)
pertuzumab → diarrhea
TDM1 → thrombocytopenia, transaminitis, neuropathy

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

HER2+ w/ pathologic complete response (PCR) → adjuvant **HP (Herceptin/Perjeta)**

HER2+ w/ residual disease (RD) → adjuvant **TDM1 (Kadcyla)**

Early Breast Cancer: HER2+ Front Line Therapy

T1N0: often adjuvant chemo/HER2 AB

* Can observe if T1a. Consider adjuvant therapy if < 2-3 cm, N0

Surgery → **T-H**
(T) Docetaxel
(H) Herceptin → **+/- RT**
H To complete 1Y HER2 AB
+/-ET For 5-10Y

T2 or N1: often neoadjuvant chemo/HER2 AB

* Consider neoadjuvant in T1cN0

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

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

→ **RD**
ANY residual invasive disease
*does not have to be HER2+ → **TDM1 +/- ET**
To complete 1Y HER2 AB
For 5-10Y

+/- RT

* Consider 1Y adjuvant neratinib after HER2 Abs if high risk w/ RD, especially HR+

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

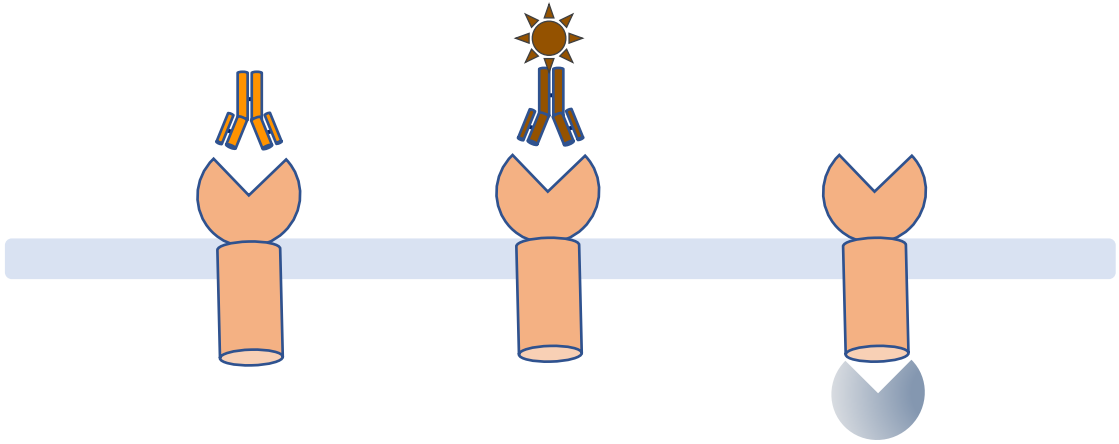
HER2+ Breast Cancer Metastatic Treatment

MBC: HER2+ Common Drug Options

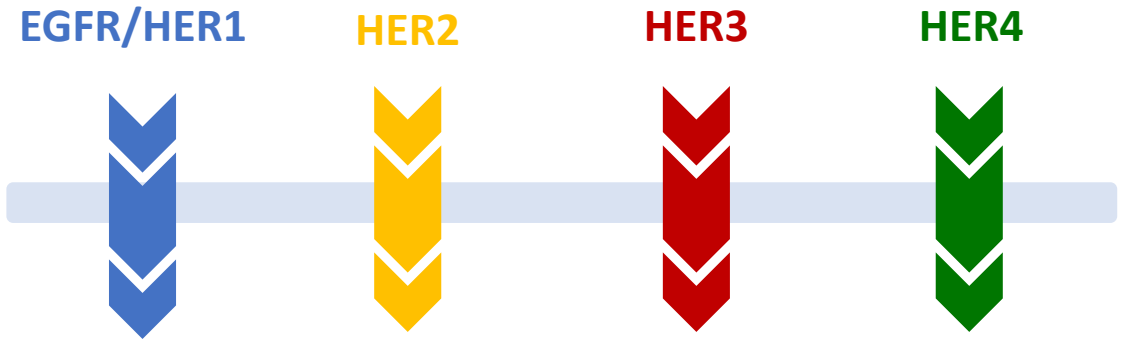
HER2+ Antibodies (ABs):
trastuzumab (Herceptin)
pertuzumab (Perjeta)

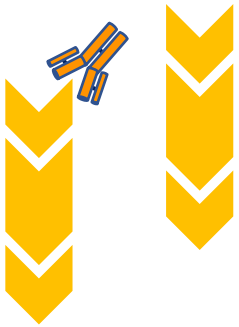
HER2+ Antibody Drug Conjugates (ADCs):
trastuzumab emtansine/TDM1 (Kadcyla)
trastuzumab deruxtecan/TDXd (Enhertu)

HER2+ Tyrosine Kinase Inhibitors (TKIs):
lapatinib
neratinib
tucatinib
* TKIs often combined with chemo +/- HER2 ABs



HER2 ABs & ADCs: Extracellular





Trastuzumab & Pertuzumab
Herceptin & Perjeta

HER2 monoclonal antibody

Trastuzumab has many mechanisms
Pertuzumab prevents dimerization

Trastuzumab Emtansine = TDM1
Kadcyla

HER2 conjugated monoclonal antibody
Trastuzumab linked to cytotoxic DM1

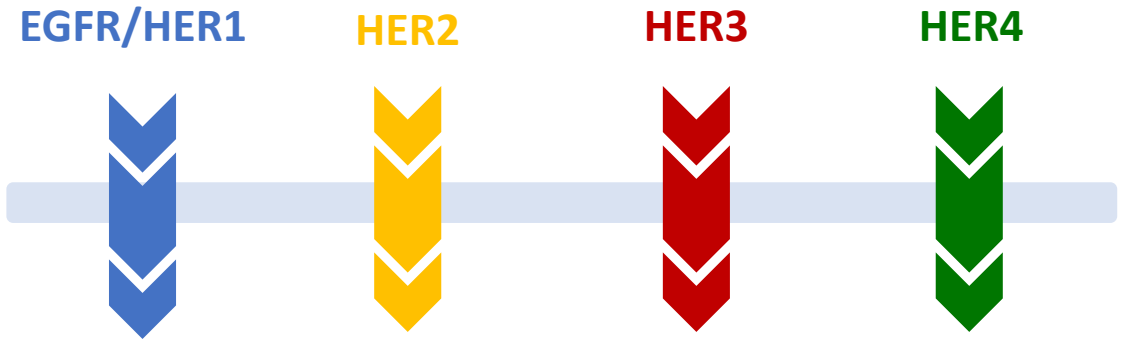
(DM1 = microtubulin toxin)

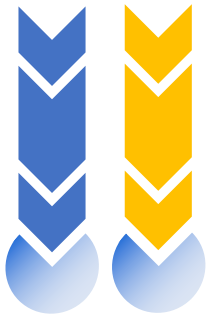
Trastuzumab Deruxtecan
Enhertu

HER2 conjugated monoclonal antibody
Trastuzumab linked to cytotoxic Dxd

(Dxd = topoisomerase I inhibitor)

HER2 TKIs: Intracellular





Lapatinib

reversibly inhibits **HER1/HER2**
Inhibits ATP binding to TK

Neratinib

irreversibly inhibits **HER1/HER2/HER4**
Inhibits ATP binding to TK

Tucatinib

irreversibly inhibits **HER2**
Inhibits ATP binding to TK

MBC HER2+: Treatment Schema

* Order can vary after 2nd line therapy

Tx Line	Regimen
1st	Taxane + Trastuzumab + Pertuzumab
2nd	**Trastuzumab Deruxtecan = TDXd (*Enhertu*)** * consider earlier if brain mets
3rd	**Tucatinib + Trastuzumab + Capecitabine** * consider earlier if brain mets
4th	**Trastuzumab Emtansine = TDM1 (*Kadcyla*)**
5th	**Margetuximab + Chemo** **Neratinib + Capecitabine**

★	**Clinical Trial**

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

HER2+ 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