

Medical Update: Her2-Positive Metastatic Breast Cancer

Rebecca Jaslow, MD
Clinical Assistant Professor
Thomas Jefferson University Hospital

Disclosures

I have no actual or potential conflict of interest in relation to this presentation

Goals

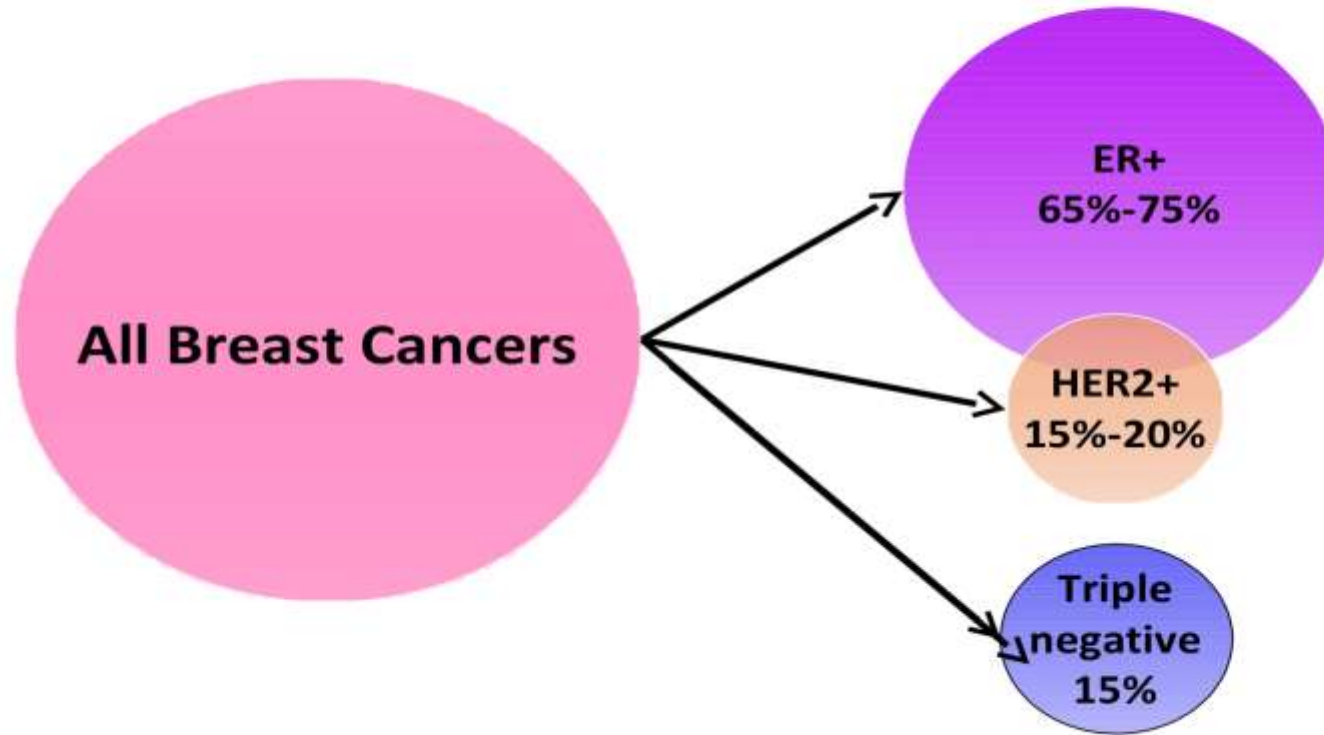
- What is Her2 positive breast cancer
- How do we treat Her2 positive metastatic breast cancer in 2019
- What are the targeted drugs and combinations considered standard
- What are the challenges we face with tumor resistance
- What are some of the new drugs on the way

Metastatic breast cancer

- Approximately 266,120 women in the U.S. were diagnosed with invasive breast cancer in 2018
- Estimates suggest that up to 154,000 patients are living in the U.S. with metastatic breast cancer
- Patients benefiting from targeted therapies to treat disease
- Problems have included development of tumor resistance mechanisms
- Novel targeted therapies are in development which will hopefully overcome tumor resistance and further improve outcomes

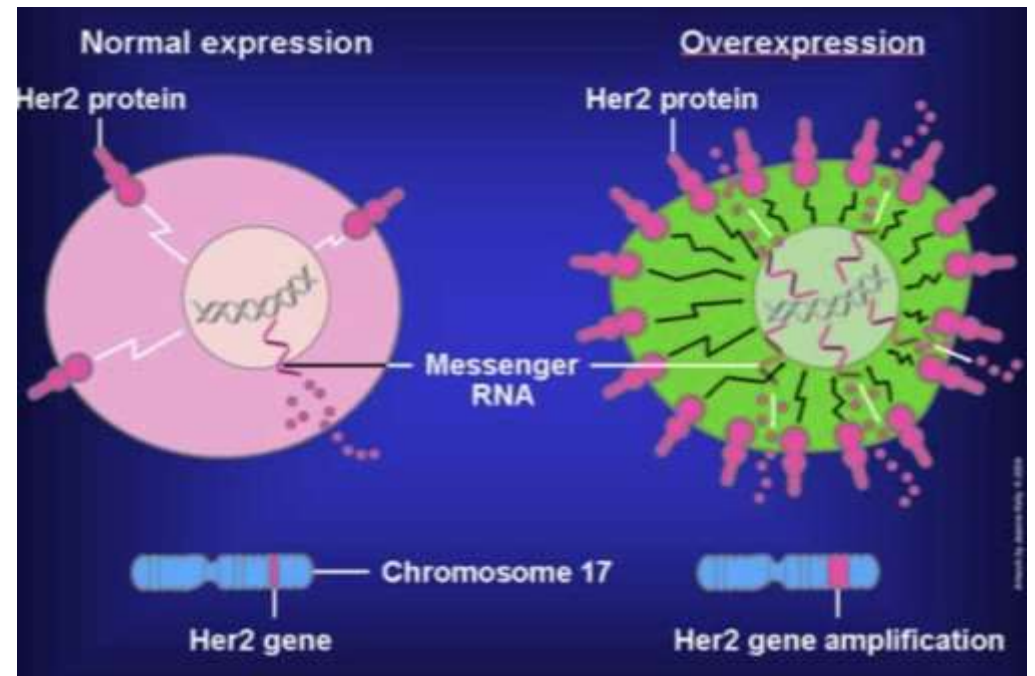
ACS Cancer facts and Figures 2018; NCI SEER

Clinical Breast Cancer Subtypes

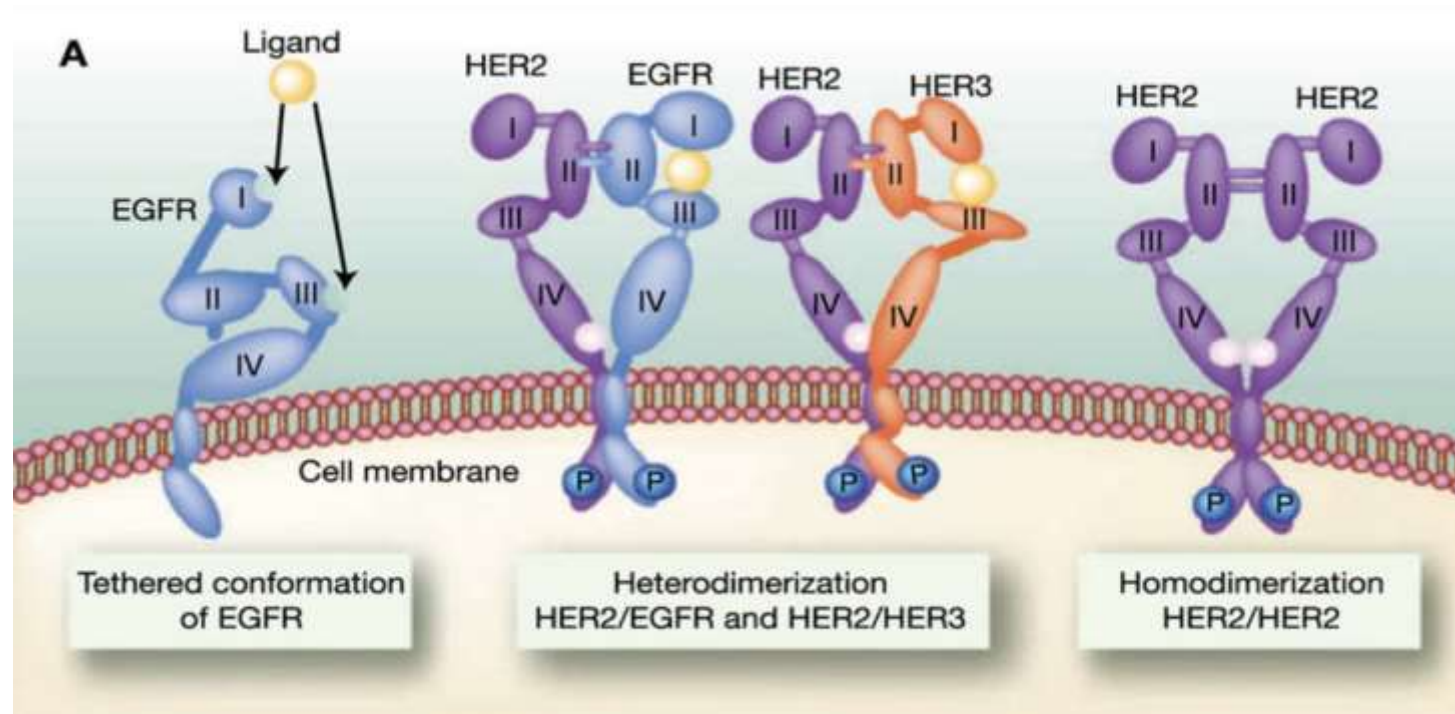


Her2 Overexpression

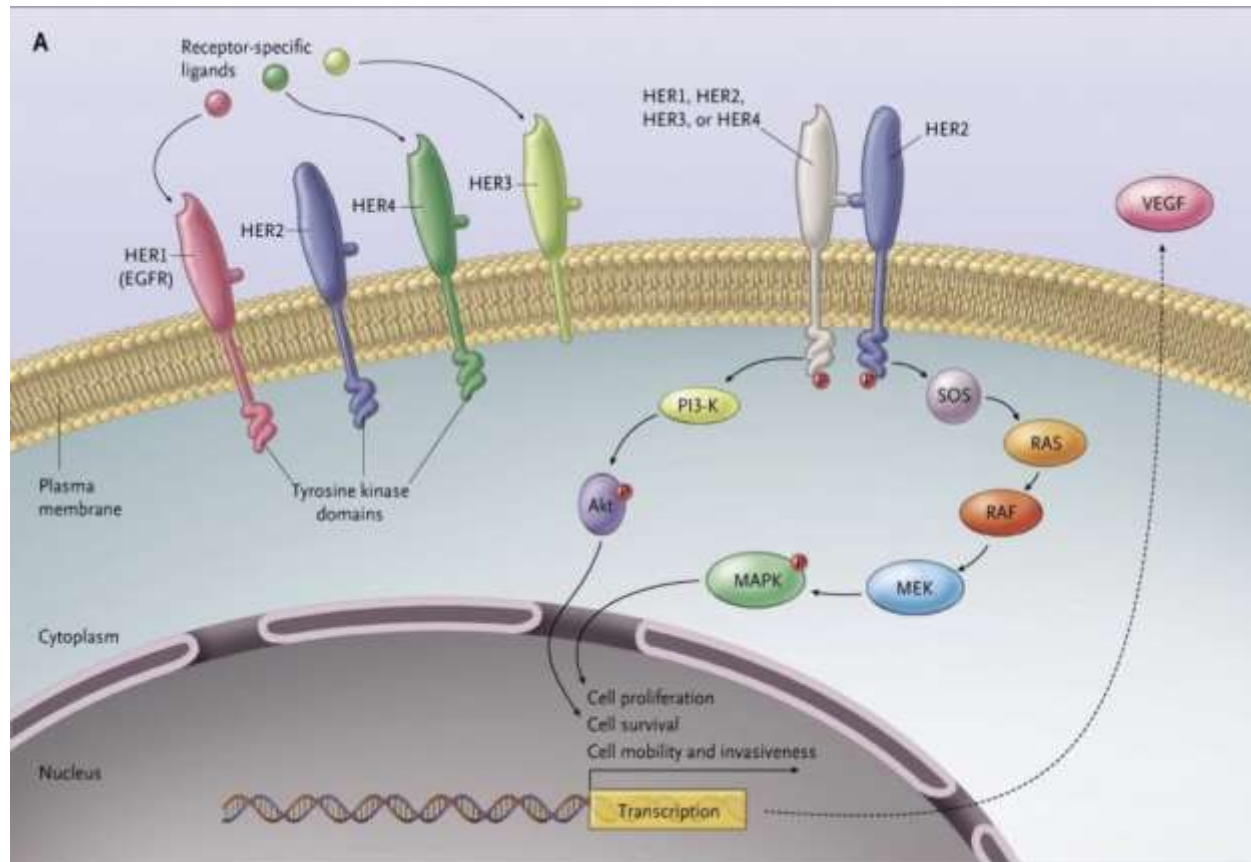
- Her2 is overexpressed in 15 to 20% of invasive breast cancer
- Associated with high grade disease, nodal metastases and tumor size
- Her2 overexpression occurs also in other forms of cancer including gastric, ovary, uterine serous endometrial carcinoma, colon, bladder, lung, uterine cervix, head and neck, and esophagus



Her Receptors



HER Family Signaling



Hudis C, NEJM
2007

How do we test for Her2neu

Immunohistochemistry test is done first:

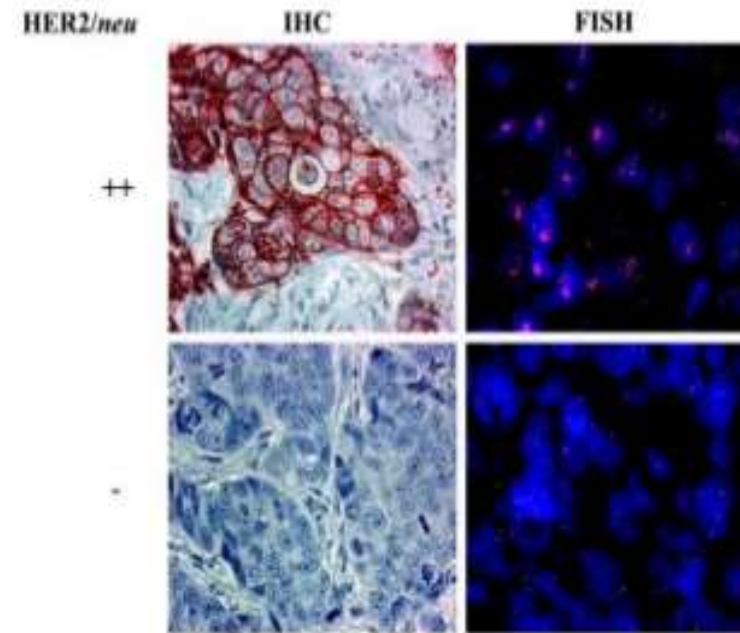
- If the result is 0 or 1+, the cancer is considered Her2-negative. These cancers do not respond to treatment with drugs that target Her2
- If the result is 3+, the cancer is Her2-positive. These cancers are usually treated with drugs that target Her2
- If the result is 2+, the Her2 status of the tumor is not clear and is called “equivocal” This means the Her2 status needs to be tested with in situ hybridization to clarify the result (weak to moderate complete membrane staining observed in >10% of tumor cells)

Her2neu testing

- If Her2 is 2+, then:
 - DISH
 - CISH
 - FISH
- Looks at the ratio of the Her2 gene to chromosome 17

What is the definition of HER2 positive?

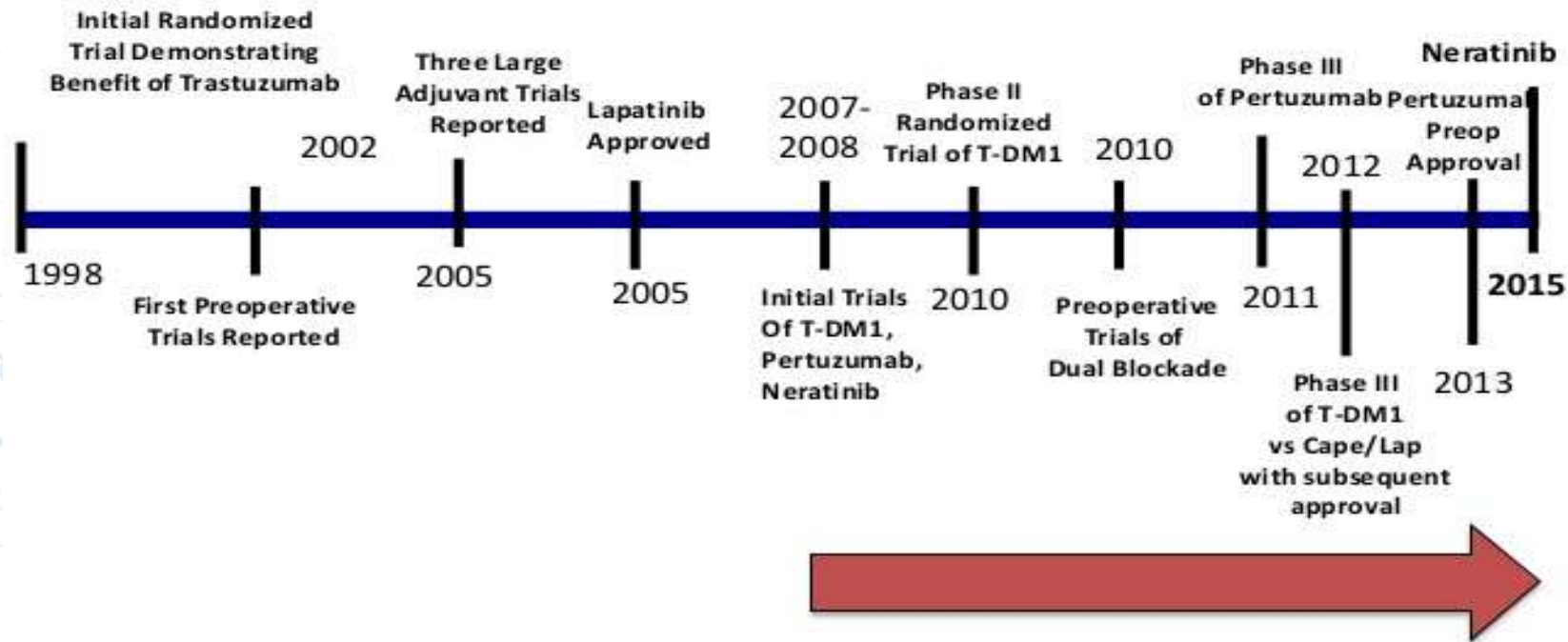
- HER2 positive defined by IHC that is **3+**
- HER2 positive defined by FISH (HER2/CEP17 ratio of **≥ 2**)



Receptor status over time

- Biology of breast cancer may evolve over time
- A discordance in ER, PgR, and HER2 receptor status has been reported between primary breast cancer and metastases
- It is important to re-biopsy if breast cancer recurs
- If pace of disease changes, can re-biopsy again

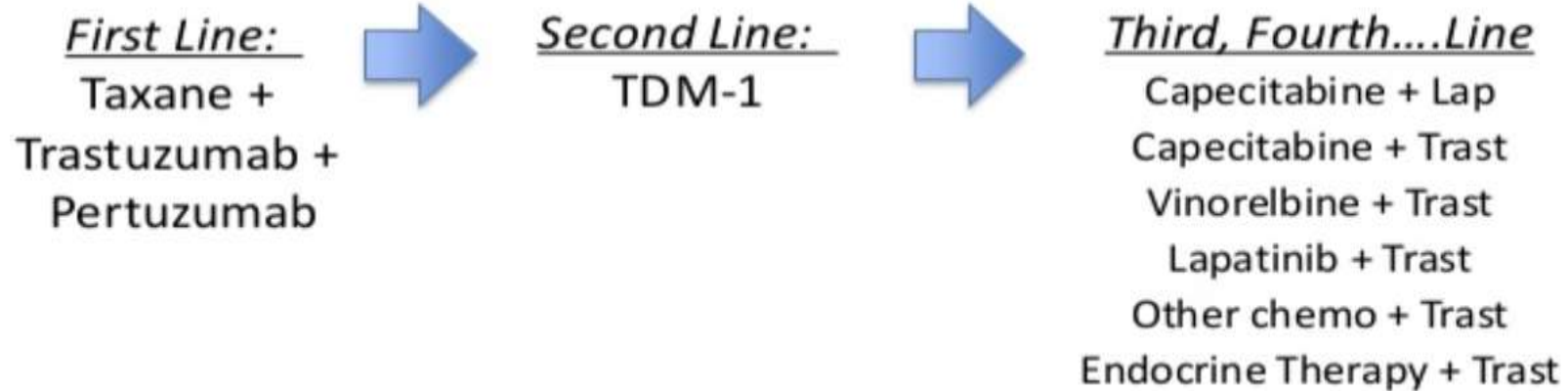
HER2+ Disease: Major Clinical Advances Over The Past 15+ Years



FDA approved Her2 targeted drugs

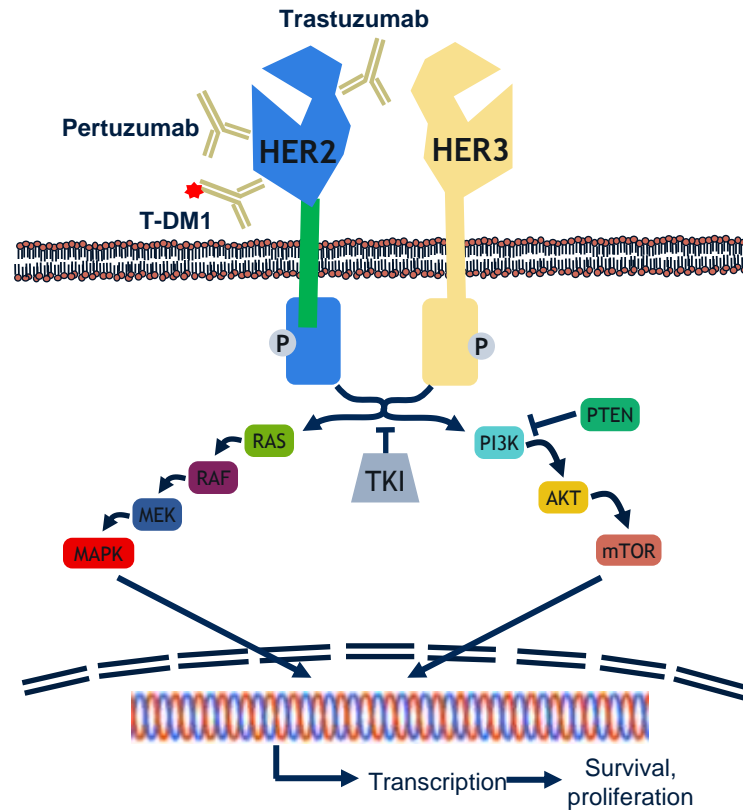
- Trastuzumab
- Pertuzumab
- Lapatanib
- T-DM1
- Neratinib

Treatment of Metastatic Her2 Positive Breast Cancer



***Important Exception:
Some patients with ER+/PR+ disease can be treated up front
with hormonal therapy +/- anti-HER2 therapy***

Targeting HER2 Receptors



Olson EM, et al. J Clin Oncol. 2012;30:1712-1714.

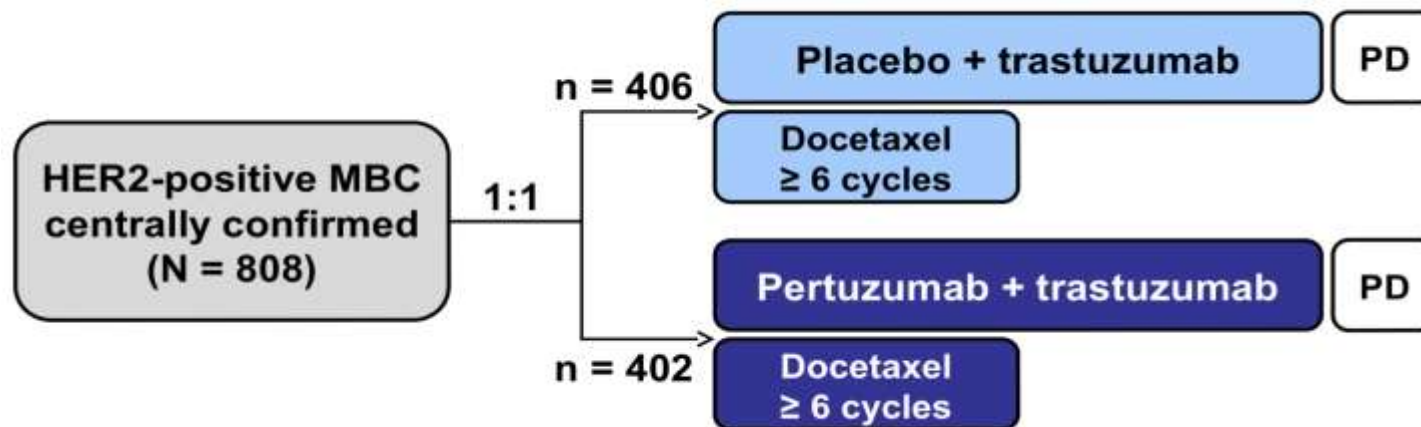
Trastuzumab

- Monoclonal antibody that targets Her2
 - Blocks downstream signaling pathways
 - Flags the tumor cell for destruction by the immune system (antibody dependent cellular cytotoxicity)
- Can be safely given together with many chemotherapies
- Side Effects: Fever, nausea/vomiting, infusion reactions, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, myalgia, infusion reactions, cardiac toxicity, lung toxicity

Pertuzumab

- Targets a different part of the Her2 receptor
- Monoclonal antibody - Her dimerization inhibitor
- When given with Herceptin provides dual blockade of Her2 pathways
- Usually coupled with taxane. Can be combined with other chemotherapies
- Side effects:
 - Infusion reactions, fatigue, diarrhea, cardiac dysfunction
- No data to continue this drug beyond progression

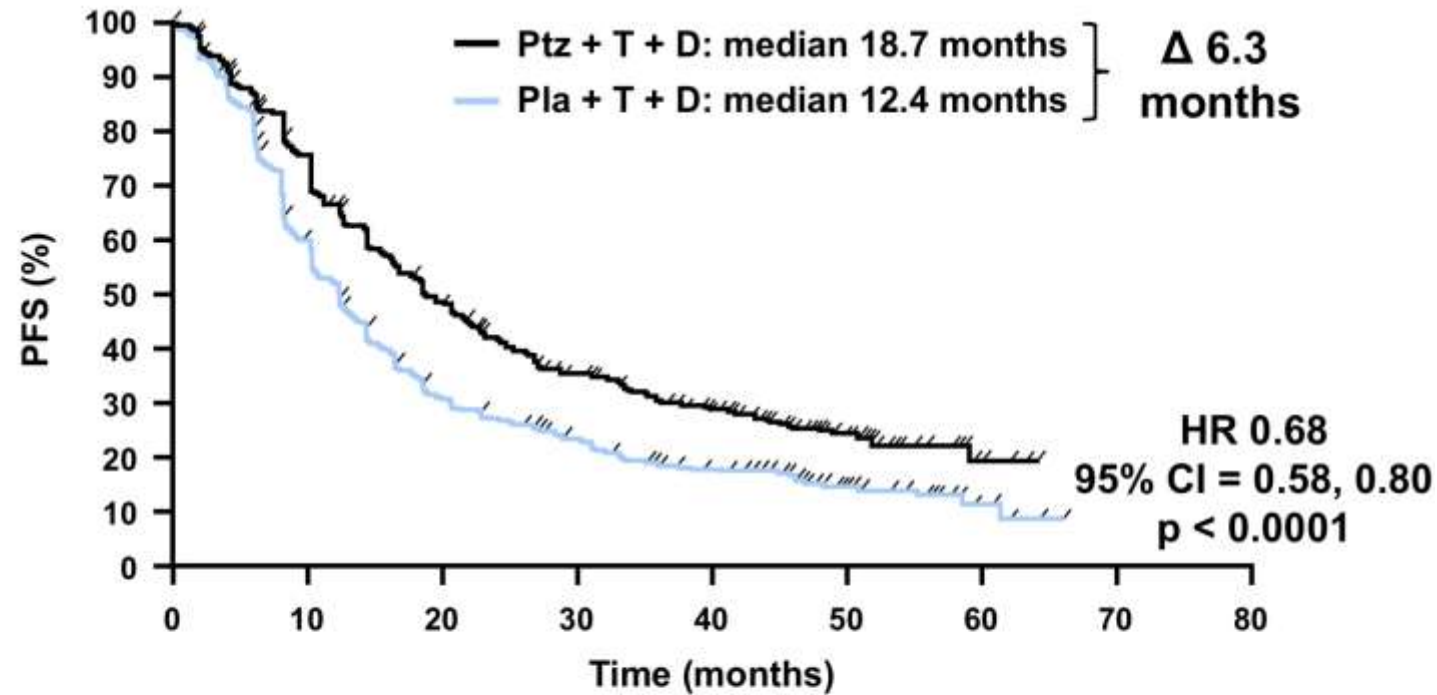
CLEOPATRA



- Randomization stratified by geographic region and neo/adjuvant chemotherapy
- Study dosing q3w:
 - Pertuzumab/placebo: 840 mg loading → 420 mg maintenance
 - Trastuzumab: 8 mg/kg loading → 6 mg/kg maintenance
 - Docetaxel: 75 mg/m² → 100 mg/m² escalation if tolerated

Baselga J, et al. *N Engl J Med* 2012; **366**:109–119.

Pertuzumab delays progression

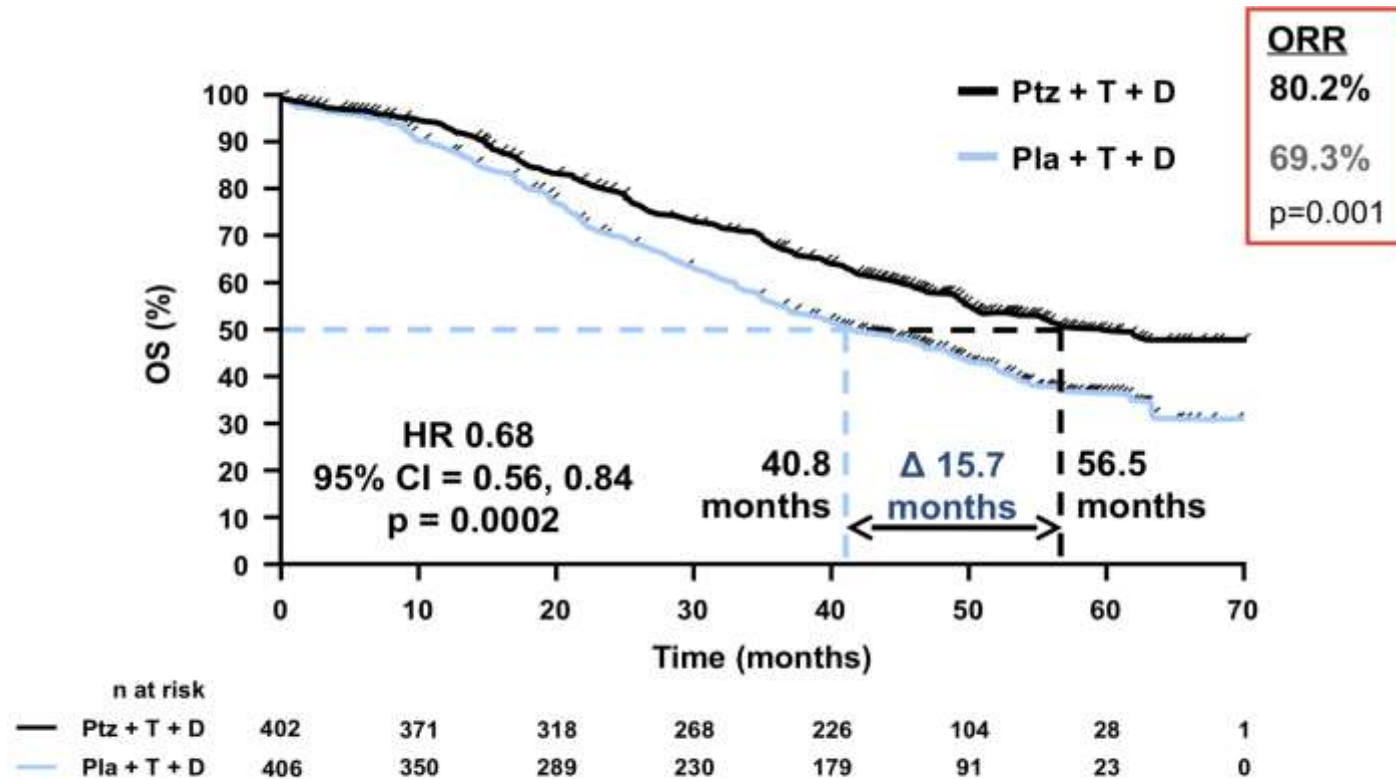


n at risk									
— Ptz + T + D	402	284	179	121	87	37	6	0	0
— Pla + T + D	406	223	110	75	51	21	6	0	0

ITT population. Stratified by geographic region and neo/adjuvant chemotherapy.

Swain et al, ESMO 2014

Pertuzumab improves survival



ITT population. Stratified by geographic region and neoadjuvant chemotherapy.
CI, confidence interval; Pla, placebo; Ptz, pertuzumab.

Swain et al, ESMO 2014¹

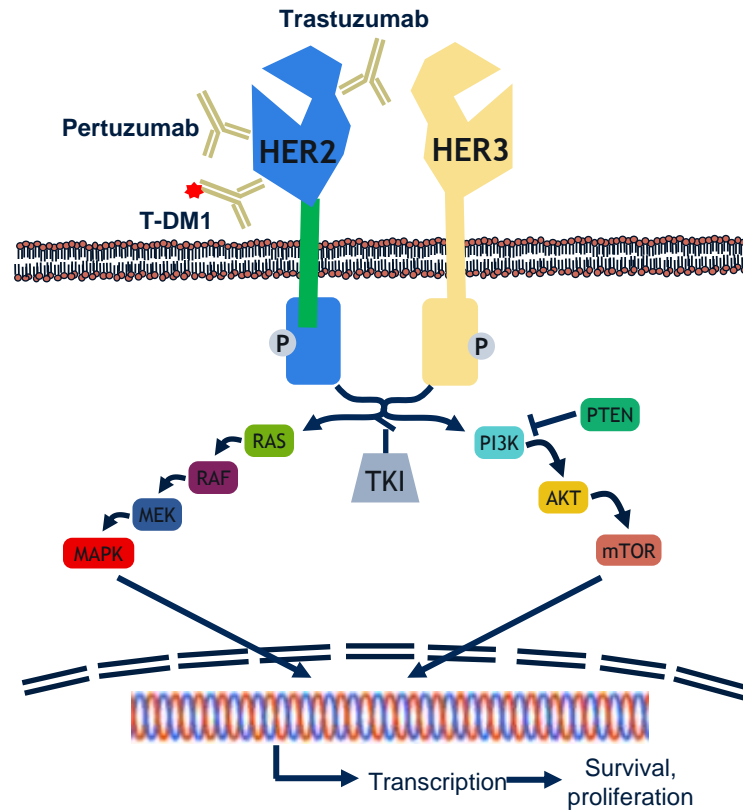
Hormonal therapy + anti-Her2 therapy

PERTAIN trial

- Phase 2, 258 women with ER positive, Her2 positive metastatic cancer
- Received trastuzumab (with/without taxane for 18 - 24 wks) + aromatase inhibitor vs trastuzumab (with/without a taxane for 18 - 24 wks)+ pertuzumab and aromatase inhibitor
- Addition of pertuzumab to trastuzumab + aromatase inhibitor resulted in longer progression free survival (19 months vs 16 months) and more lasting responses

Arpino et al. SABCS 2016

Targeting HER2 Receptors

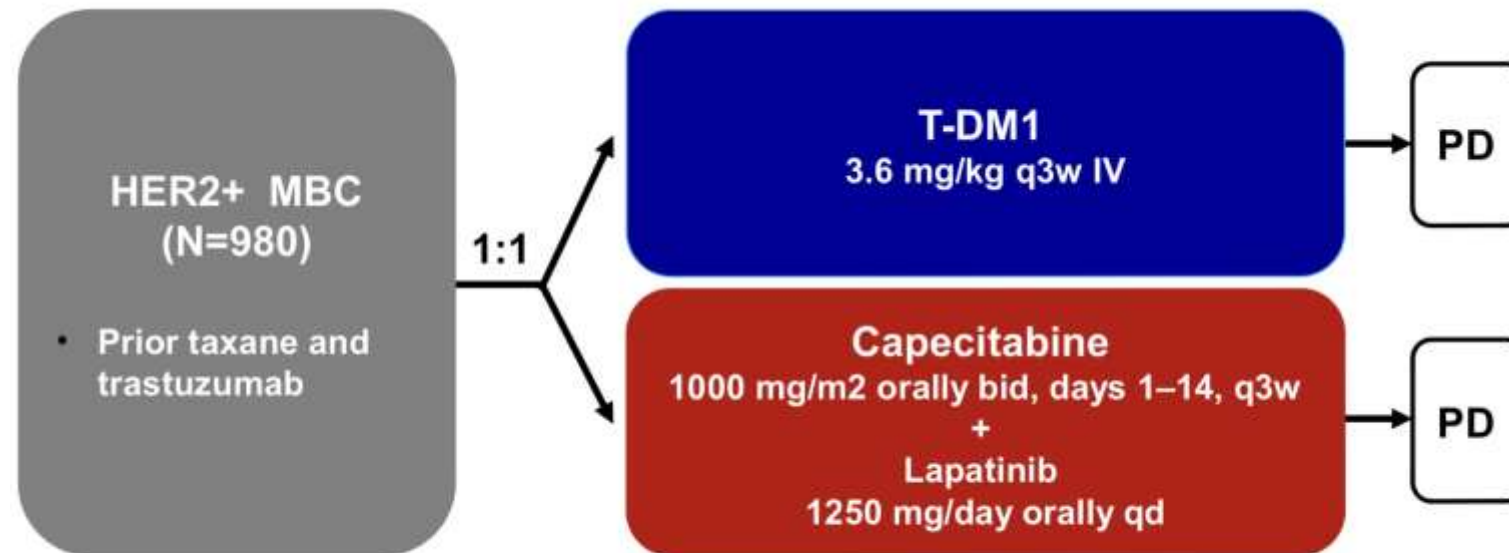


Olson EM, et al. J Clin Oncol. 2012;30:1712-1714.

T-DM1

- An antibody-drug conjugate linking trastuzumab with a chemotherapy called emtansine.
- T-DM attaches to Her2 protein on breast cancer cell - this tells the cancer cell to stop growing and signals immune system to destroy the cell.
- Then T-DM1 enters cancer cell, the Herceptin releases the emtansine, which attaches to microtubules inside the cell and stops the cancer cell from being able to grow and divide, leading to its death

EMILIA



Blackwell et al., 2012

EMILIA

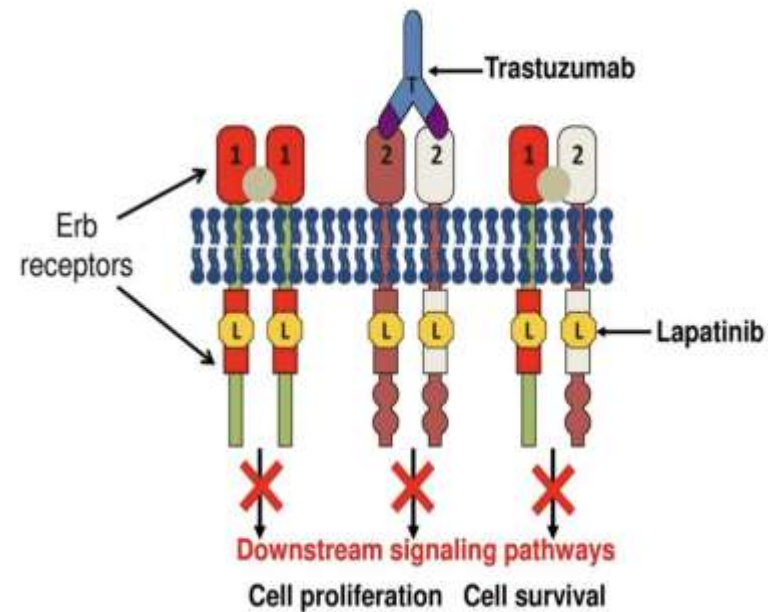
- Showed improvement in progression free survival, response, duration of response, and overall survival with T-DM1
- Median PFS was 9.6 months vs 6.4 months, median OS 31 months vs 25 months
- T-DM1 well tolerated
- Activity seen against brain metastases seen with T-DM1

TDM-1

- Side effects
 - Low platelets
 - Elevated liver function tests
 - Fatigue
 - Nausea
 - Diarrhea
 - Neuropathy

Lapatinib

- Small molecule tyrosine kinase inhibitor - oral
- Reversibly binds to and inhibits the intracellular portion of Her2
- Second anti-Her2 agent approved for management of Her2 - positive metastatic breast cancer



Lapatinib

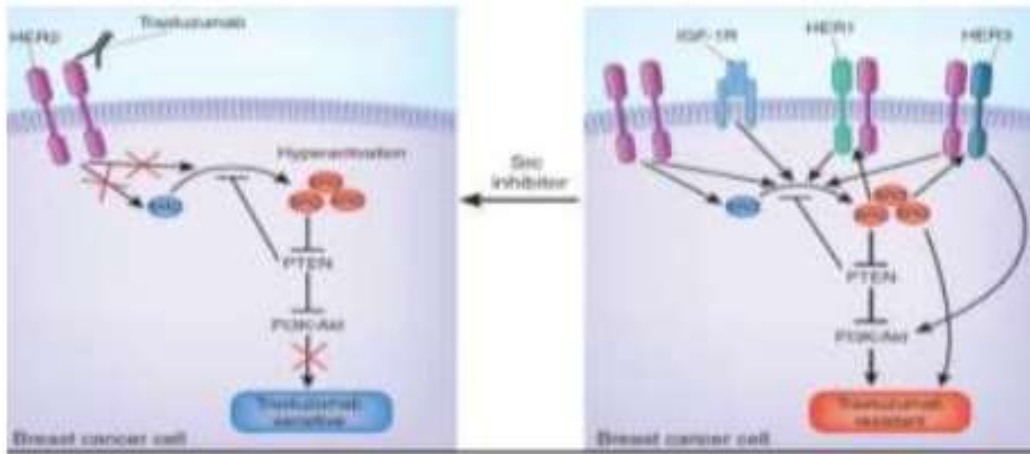
- Can be combined with chemotherapy (capecitabine), or trastuzumab
- Initial data suggested benefit with brain metastases
- Side effects:
 - Diarrhea (60% any grade)
 - Rash (27% any grade)
 - Hand-foot syndrome
 - Mouth sores
 - Nail bed changes
 - Liver test abnormalities

Trastuzumab + Chemotherapy

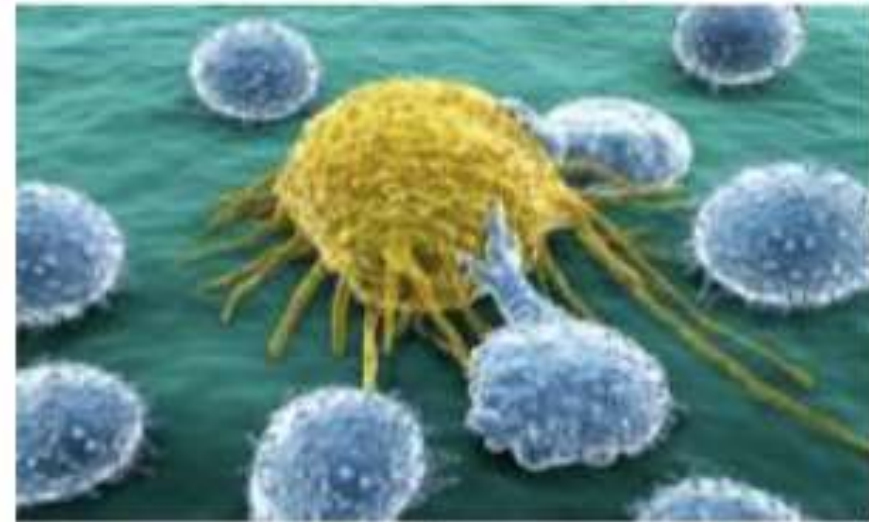
- Can be combined with many chemotherapies in subsequent-line settings with the exception of doxorubicin
- Several studies have suggested improvement in progression free survival with continuation of trastuzumab

Tumor Resistance

Changes in “cell signaling”

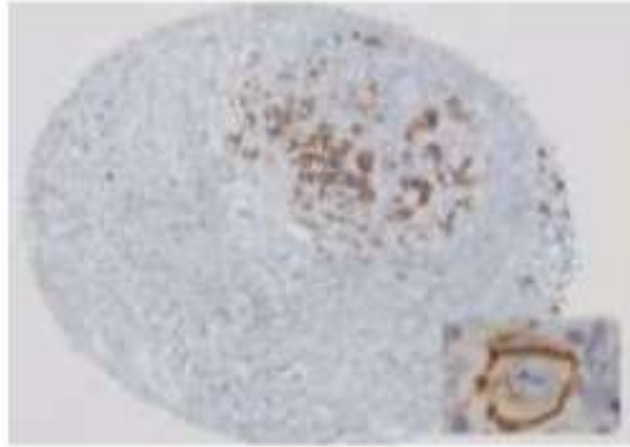
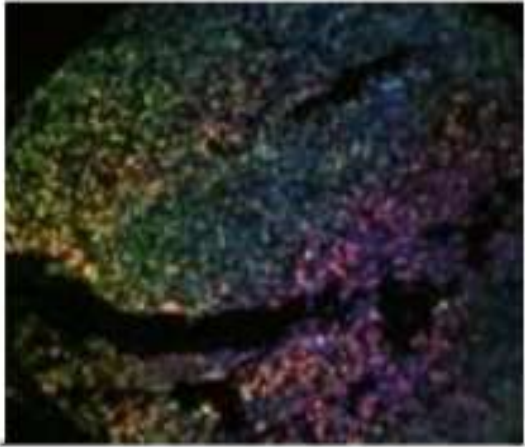


Turning off the immune system

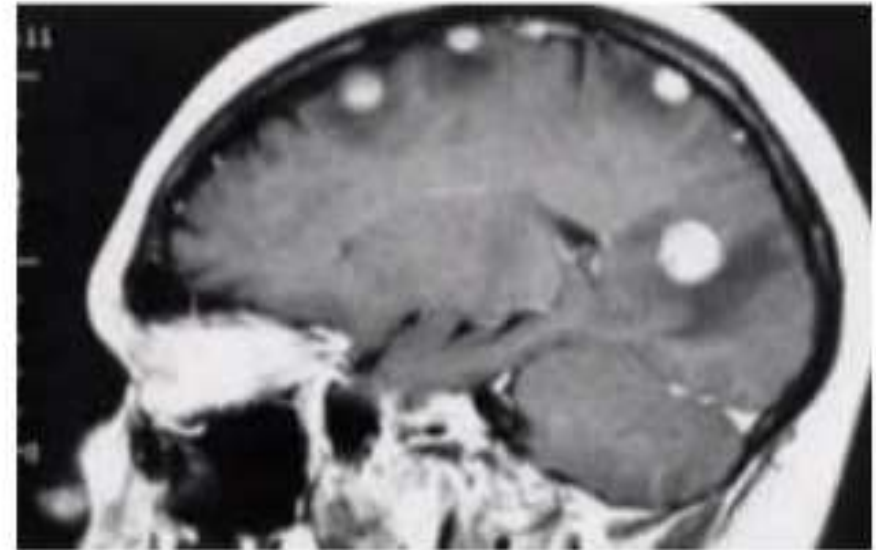


Tumor Resistance

Tumor heterogeneity

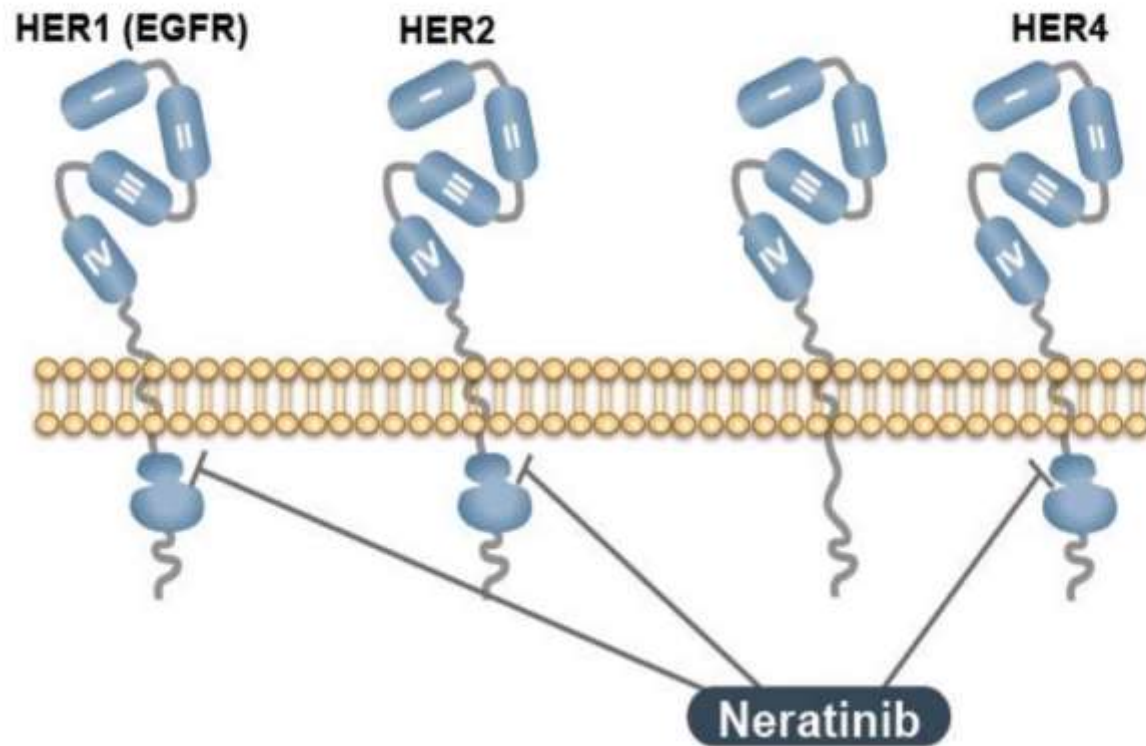


Growing in certain locations



Neratinib

Neratinib is an oral TKI that irreversibly inhibits HER1, HER2, and HER4



Neratinib Side Effects

- Diarrhea, nausea, abdominal pain, fatigue
- Vomiting, rash, decreased appetite
- Muscle spasms, liver enzyme elevations
- Nail disorder, dry skin

Drug Interactions

- Avoid use with proton pump inhibitors
- Separate Neratinib by at least 2 hours after or 10 hours before an H2 blocker
- Avoid concomitant use with CYP3A4 inhibitors or inducers

Brain Metastasis

- NEfERT-T trial (Aewada et al. JAMA Oncology Dec 2016)
 - 479 women randomized to receive paclitaxel + neratinib vs trastuzumab + neratinib
- Similar overall efficacy
- Neratinib-paclitaxel combo seemed to delay the onset and reduce the frequency of metastases in the brain

Brain Metastasis

NALA trial: A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2-directed regimens in the metastatic setting (NCT01808573)



Secondary CNS endpoint: Time to intervention for symptomatic metastatic CNS disease

NALA

- Improvement in progression free survival with Neratinib arm which was statistically significant
- Improved overall survival -trended in favor of neratinib arm but not statistically significant
- Neratinib arm showed improvement in time to intervention for brain metastases

Novel Treatments for Her2+ Breast Cancer

- Small molecules (TKIs)
 - Pyrotinib
 - Tucatinib
- Monoclonal antibodies
 - Margetuximab
- Antibody-drug conjugates
 - Trastuzumab deruxtecan
- Immunotherapy

Pyrotinib

- Irreversible pan-HER receptor tyrosine kinase inhibitor
- Phase II trial
 - Randomized to receive pyrotinib + capecitabine, vs lapatinib + capecitabine
- Pyrotinib arm had more side effects with diarrhea, hand-foot syndrome, diarrhea
- Pyrotinib arm had better response - 78.5% of patients vs 57.1% and median PFS of 18 months vs 7 months

Xu B et al. SABCS 2017

Tucatinib

- Oral selective Her2 tyrosine kinase inhibitor
- In approximately 60% of patients whose cancer has progressed on trastuzumab, tucatinib + capecitabine +trastuzumab causes significant tumor shrinkage
- Tucatinib has also been found to shrink the tumors in the brain in some patients
- It is also being studied in combination with T-DM1

Borges VF et al. JAMA Oncology 2018

HER2CLIMB

- Phase II trial looking to randomize 480 patients
 - Tucatinib + capecitabine, vs tucatanib + trastuzumab
- Locally advanced and metastatic Her2+ breast cancer, must have already received trastuzumab, pertuzumab, T-DM1
- Patients with and without brain metastases can enroll

Margetuximab

- Monoclonal antibody whose target is the same as trastuzumab
- Tail-end portion that activates immune cells is optimized
 - Binds more tightly
 - Increase antibody dependent cell mediated cytotoxicity
 - “Super trastuzumab”
 - Activates the immune system against the cancer cells

SOPHIA Trial

- Phase 3 trial, looking to confirm superiority of margetuximab over trastuzumab for Her2 positive metastatic breast cancer
- Enrolled 530 patients whose disease has progressed after two or more anti-HER agents to receive physician's choice of chemotherapy + either trastuzumab or margetuximab
 - In February, 2019 - This trial met endpoint of prolongation of progression-free survival
 - Patients in the margetuximab arm experienced a 24% risk reduction in progression free survival

Trastuzumab Deruxtecan (DS-8201)

- Antibody-drug conjugate
 - Topoisomerase inhibitor drug linked to a Her2 antibody
- In early Phase 1 trials, the drug was found to be safe and well tolerated
 - Low blood counts, nausea, some hair loss
- Tumor shrinkage was seen in up to 60% of heavily pre-treated patients, including both estrogen receptor positive and estrogen receptor negative subsets
- Enrollment in Phase 2 study (DESTINY-Breast01) is complete
- Phase 3 trials are under way comparing this drug head to head with investigator's choice of therapy, and with T-DM1
-
- Early trials under way combining it with immunotherapy

Immunotherapy - Checkpoint Inhibitors

- PD-1 is a checkpoint protein on immune cells called T-cells
 - Acts an “off switch” that keeps T-cells from attacking other cells in body
 - PD-1 does this when it attaches to PD-L1, a protein on normal and some cancer cells
 - When PD-1 binds to PD-L1 it tells the T-cell to leave the other cell alone
- Some cancer cells have large amounts of PDL-1 which helps them evade immune attack
- Antibodies that target PD-1 or PD-L1 can block this binding and boost immune response against cancer cells

Immunotherapy - Checkpoint Inhibitors

Her2 positive tumors have modest PD-L1 expression

- Moderate/high mutational load
- Combination of PD-L1 inhibitor and Her2 antibodies are effective in lab studies

TRIALS

- T-DM1 + anti-PD-1

- Trastuzumab + anti-PD-1

Pembrolizumab + Trastuzumab (PANACEA trial)

- 58 patients with metastatic Her2 positive breast cancer
- Showed some activity in 15% of patients, with a lasting clinical benefit in PD-L1 positive population
- Overall safe, however not without side effects
- Further studies should focus on PD-L1 positive tumors and less heavily pretreated patients

Loi at al. Lancet Oncology Feb 2019

Atezolizumab + T-DM1 (KATE2)

- Metastatic Her2 positive patients who progressed through trastuzumab and a taxane
- Atezolizumab + T-DM1 vs T-DM1 + placebo
- Addition of atezolizumab to T-DM1 did not demonstrate significant progression free survival or response benefit
- Suggestion that those patients with tumors with higher PDL-1 expression or high amounts of tumor infiltrating lymphocytes may have done better

Emens LA et al., SABCs 2018

CDK 4/6 inhibitors in Her2 positive disease

- Oral drugs - palbociclib, ribociclib, abemaciclib
- Target a pathway that plays a key role in the proliferation of both normal breast cells and breast cancer cells
- Approved by FDA and standard of care for ER positive Her2neu negative metastatic breast cancer both alone, and in conjunction with hormonal therapies
- Does it work in Her2neu positive disease?

Palbociclib + trastuzumab (PATRICIA trial)

- Patients enrolled had both estrogen negative and estrogen positive disease. All Her2 positive
- Combination of palbociclib and HER2-targeted therapy demonstrated clinical benefit
- Benefit appeared highest in those with estrogen receptor positive/luminal tumors
- Toxicity similar to that seen in other CDK4/6 inhibitor studies, though 60% of patients required dose reduction possibly owing to the more heavily pretreated nature of these patients

Ciruelos R et al. SABCS 2018

PI3 Kinase Inhibitors

- Alpelisib - A Phase 2 trial has shown tolerability and responses for patients who have progressed through T-DM1
- Taselisib
- Pictilisib

Trastuzumab and Hyaluronidase-oysk (Herceptin Hylecta)

- FDA approved this on 2/28/19
- Same monoclonal antibody as trastuzumab but added to an enzyme that helps deliver trastuzumab subcutaneously
- Subcutaneous injection that can be given in 2 to 5 minutes compared to 30 to 90 minutes for IV trastuzumab
- Approved for use in metastatic setting either in combination with paclitaxel or alone in patients who have received one or more prior chemotherapy regimens for metastatic disease

In Conclusion

- There has been significant progress in the treatment of Her2 metastatic breast cancer
- Tumor resistance remains an ongoing battle
- Exciting new drugs are on the horizon
- Clinical trial enrollment is important - ClinicalTrials.gov

THANK YOU!