Goals of this presentation

• Discuss supposed mechanism of trastuzumab resistance
• Definition, frequency, prediction/biomarkers

Seems easy... Blurred... Tests?

• Clinical implementation
• Strategies to overcome "resistance"

Strategies to "overcome" resistance
Definition of resistance

• Primary, de novo resistance
  • Not achieving response (relapse/progression)

• Secondary, acquired resistance
  • Stop achieving response (progression)

Defining resistance is not simple because of:
  complexity of trastuzumab actions;
  chance for responses after reintroduction of trastuzumab despite previous progression!
Proposed/supposed trastuzumab action:

Targeting of **immune cells** that binds to trastuzumab Fc domains effects **antibody dependant cell-mediated cytotoxicity (ADCC)**

**Inhibition of HER2 shedding** (extracellular domain-ECD)

**Internalization and degradation of HER2**

*Wilken and Mhle NIH-PA 2011*
Obstacles for trastuzumab binding to HER2

p95 truncated form:
No binding site for trastuzumab

Antibody to detect p95 exists
Only 2 studies to confirm its significance
(Scaltriti, 2002: Molina, 2002)

MUC4:
Binding site covered/masked

Presence of upregulation of HER2 downstream signalling pathways

PTEN LOSS < 10 %

PTEN loss 26% (IHC 0%)
No difference in DFS
All pts with HER2 3+ BC benefited from adjuvant trastuzumab
(~1200 EBC pts, median FU 6 yrs)
Perez, JCO 2013

PI3KCA

Cancer find a way to sustain its growth

Presence of signalling through an alternate receptor and/or pathway
Failure to trigger immune-mediated mechanisms to destroy tumours cells

pSTAT3

- Signal transducer and transcription 3 protein (pSTAT3)...

- ...is persistently phosphorylated in response to numerous oncogenic signaling pathways in 30-40% BC..

- ...inhibiting native anti-tumor immunity...

- ...activates pathways resulting in cell proliferation and anti-apoptotic mechanism

• IMPAKT 7-9 May 2015
  Sonnenblick A et al
Frequency of resistance

- **EBC ~20-25%**
  
  - Standard treatment is (still) unchanged worldwide
    
    AC-taxane +trastuzumab+/-hormonal therapy+/-RT

- **MBC ~70%**
  
  - First line treatment in Serbia:
    
    taxanes + trastuzumab
Clinical significance

• Test for resistance to Herceptin prediction?

• NONE (EBC,LABC,MBC)

• Strategies for “overcoming “resistance

• Combining anti-HER drugs clearly prolongs time to progression...
Clarity to choice for first line therapy

Comments on first line treatment choice in HER2 3+ MBC

CLEOPATRA:
adding clarity to frontline HER2-Positive MBC Strategy

CLEOPATRA
trastuzumab + pertuzumab + docetaxel vs. trastuzumab + docetaxel (16m +!)

“In the future, in any country of the world, when you have a patient with HER2 3+ MBC, the proposal for treatment should include dual targeting with pertuzumab and trastuzumab plus chemotherapy,”

G. Curigliano, MD, PhD
Resistance to trastuzumab in every day clinical practice

• Can not be predicted before it appears as a disease progression (caveat: specific metastatic sites -BRAIN!)

• Does not means that trastuzumab should always be withhold...

• ..rather *combined* with other anti-HER2 agents