Targeted therapies for breast cancer

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Objectives

• Recognize “targets” available to treat breast cancer.

• Identify current targeted therapies for breast cancer as well as potential ones.

• Integration of targeted therapy into personalized breast cancer care.

Targeted therapy paradigm: CML

• CML is a clonal bone marrow stem cell disorder associated with a characteristic chromosomal translocation called the Philadelphia chromosome.

BCR-ABL protein (tyrosine kinase) activates a cascade of proteins speeding up cell division and inhibiting DNA repair.
Targeted therapy paradigm: CML

What about breast cancer??
**Targeted therapy breast cancer**


**HR + breast cancer: endocrine therapy**

- Selective Estrogen Receptor Modulators-
  - Tamoxifen - competes for binding to ER.

- Aromatase Inhibitors
  - Steroidal: Exemestane-1999
  - MOA: deprivation of estrogen

- Selective Estrogen Receptor Downregulators
  - Fulvestrant-2002; 2010 500mg dose
  - MOA: competition for estrogen binding to ER and degradation of ER

- Progestins-Megace, Androgens
HR + breast cancer: endocrine trials

**ATLAS trial:**
- 5-10 y vs 10 y
- 12k women
- 5-14 risk recurrence: 25.1 vs 21.4%

**TEXT/SOFT trial:**
- exemestane + OS vs tamoxifen adjuvant
- DFS 92.8 vs 88.8, no OS difference (High risk?)

**FIRST trial:**
- phase II
- fulvestrant 500 vs anastrozole, 1st line mBC
- median time to disease progression 23.4 vs 13 mos (34% risk reduction), OS at 4 years 54.1 vs 48.4 mos

**TailorRx:**
- score 10 or less, 5y distant recurrence 1%
  on adjuvant endocrine therapy alone

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HR + breast cancer: endocrine resistance

- Metastatic ER+ tumors harbor mutations in the ER than can drive ER independent transcription and proliferation.
- PI3K/AKT/mTOR aberrancies are proven important mechanisms of resistance to endocrine therapy.
- RAS/cyclin D pathway inhibition proved to be synergistic with ER blockade.

Toy W. ESR1 ligand-binding domain mutations in hormone-resistant breast cancer. Nat Genet. 2013

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HR + breast cancer: PI3/Akt/mTOR inhibition
PI3/Akt/mTOR inhibition: everolimus

BOLERO-2: A Trial of Everolimus in HR+ Breast Cancer

- 734 women with HR+, ER+, metastatic breast cancer, with progression on AI
- Everolimus 10mg/day
- Everolimus 25mg/day (N=187)
- Placebo - Everolimus (N=363)
- Tumor and Safety Endpoints

PFS 11 mos vs 3.2 mos central review p<.0001
Diarrhea 33%, Stomatitis-67%, infection 50%


PI3/Akt/mTOR inhibition: pictilisib

- FERGI study: Phase II, 168 postmenopausal women with ER+ AI-resistant mBC

PI3K mutational status was not predictive


HR+ breast cancer: CDK4/6 inhibition

- Inhibition of CDK 4/6 and ER is synergistic.
CDK4/6 inhibition: Palbociclib

- **PALOMA 1 trial:** Phase 2, 165 mER+ postmenopausal, frontline -Letrozole plus or minus palbociclib 125 mg a day, 3 weeks on 1 week off.

  - OS 37.5 mos vs 33.3 mos

CDK4/6 inhibition: Palbociclib

- PFS 9.2 vs 3.8 months
- Benefits regardless menopausal status
- Neutropenia 78% vs 3.5% (NF same 0.6%)

HER2 overexpressed BC: targets and therapies
HER2 overexpressed BC: lapatinib

HER2 overexpressed BC: TDM-1

mHER2 overexpressed BC: Pertuzumab
HER2 overexpressed BC: Neoadjuvant pertuzumab/NeoSphere

NeoSphere Trial
A multicenter, randomized, clinical trial in patients scheduled for neoadjuvant therapy
Primary endpoint: pCR in the breast (ypT0/is), additional pCR endpoint (FDA-preferred): pCR in the breast and nodes (ypT0/is ypN0)

HER2 overexpressed BC: Neoadjuvant pertuzumab

TRYPHAENA Trial
An additional Phase 2 neoadjuvant study
225 patients with locally advanced, operable, or inflammatory HER2+ breast cancer (T2-4d)
Designed primarily to assess cardiac safety; all arms included pertuzumab
All treatments administered in 3-week cycles

HER2 overexpressed BC: ongoing trials

Patient population: Status Before treatment
- Neoadjuvant HER2+ patients
- Patients with HER2+ BC
- Patients with HER2+ and inflammatory BC
- Patients with HER2+ and locally advanced BC
- Patients with HER2+ and metastatic BC
- Patients with HER2+ and stage IV BC

Treatments:
- Neoadjuvant HER2+ patients
- HER2+ breast cancer
- HER2+ and inflammatory BC
- HER2+ and locally advanced BC
- HER2+ and metastatic BC
- HER2+ and stage IV BC
**HER2 overexpressed BC: mTOR inhibition: everolimus trials**

- **Bolero 1**: -o benefit (? ER+, 7.2 median PFS)
- **Bolero 3**: 5 week benefit in PFS did not justify toxicity

**HER2 overexpressed BC: Neratinib**

- Pan-HER tyrosine kinase inhibitor
- **ExteNET trial**
  - Phase III
  - Neratinib vs placebo (12 months after adjuvant Chemo/trastuzumab)
    - So far no OS difference (additional f/u needed)
    - Grade 3 diarrhea 40%
Triple negative breast cancer: PARP inhibition

- Niraparib: neg Phase III trial in metastatic setting along with carbo/gemzar (true inhibitor?).
- Olaparib (already approved based on Phase II trial-based on ORR- in met ovarian cancer BRCA germline +)
- Veliparib and Niraparib

Other targets

- Androgen receptor blockade: bicalutamide
- Anti-angiogenesis: bevacizumab, TKIs
- HDAC inhibitors: vorinostat
- HSP90 inhibitors: ganetespib
- Anti-FGFR
Breast cancer targeted therapies

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Summary

- Advances in understanding signaling pathways has been crucial in the development of novel targeted therapies (everolimus, palbociclib, pertuzumab).
- CML paradigm proved that we can effectively find an actionable target and engineer a specific therapy but that alone in breast cancer seems not to be enough.
- "Precision medicine": analysis of the tumor in real time (in the context of genomic medicine) may become the key to succeed with targeted/combination therapy.

THANKS!