Targeted Therapy in an Era of Genomic Medicine

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Why Do Women Die of Breast Cancer?

• Bad biology
• Avoidable deaths
Important subsets of breast cancers defined by molecular markers and by clinical treatment options

Lesson: Breast cancer is a family of diseases, not one disease.
Inhibition of Estrogen-Dependent Growth

Estrogen biosynthesis

Antiestrogens

Aromatase inhibitors

Inhibition of cell proliferation
Estrogen receptor (ER) is the target of endocrine treatment and is expressed in ~70% of breast cancers

- Endocrine treatment is an effective targeted therapy for ER+ patients
- However, a significant fraction of patients develop resistance

Recurrence

- 13% recurrence
- 33% recurrence

BC mortality

- 10% BC mortality
- 24% BC mortality
Patients with Disease Progression on One Hormone Therapy May Respond to Another Hormone Therapy

- An optimal sequence of hormone therapies has not been defined

Resistance to Hormonal Therapy: Cross-Talk
Crosstalk between ER and mTOR Signaling

- mTORC1 activates ER in a ligand-independent fashion\(^1\)
- Estradiol suppresses apoptosis induced by PI3K/mTOR blockade\(^2\)
- Hyperactivation of the PI3K/mTOR pathway is observed in endocrine-resistant breast cancer cells\(^3\)
- mTOR is a rational target to enhance the efficacy of hormonal therapy

BOLERO-2 Primary Endpoint: PFS Central Assessment

HR = 0.36 (95% CI: 0.27–0.47)
Log rank P value = 3.3 x 10^{-15}

EVE + EXE: 10.6 Months
PBO + EXE: 4.1 Months

Presented by J. Baseiga at the 2011 European Multidisciplinary Cancer Congress (ECCO/ESMO), September 26, 2011. Abstract: 9LBA.
CDK 4/6 Inhibition: Mechanism of Action
PD 0332991 + Letrozole
Progression Free Survival

HR = 0.37 (CI 0.21- 0.63)
p < 0.001

PD + LET: 26.1 months
LET: 7.5 months
Oncotype DX 21 Gene Recurrence Score (RS) Assay

16 Cancer and 5 Reference Genes From 3 Studies

RS = + 0.47 x HER2 Group Score - 0.34 x ER Group Score + 1.04 x Proliferation Group Score + 0.10 x Invasion Group Score + 0.05 x CD68 - 0.08 x GSTM1 - 0.07 x BAG1

Category | RS (0 – 100)
--- | ---
Low risk | RS < 18
Int risk | RS ≥ 18 and < 31
High risk | RS ≥ 31
B-20: Absolute % Increase in DRFS at 10 Years

- Benefit of Chemo Depends on RS

- Low RS < 18
  - n = 353

- Intermediate RS 18-30
  - n = 134

- High RS ≥ 31
  - n = 164

% Increase in DRFS at 10 Yrs (mean ± SE)
The HER Family of Receptors

Ligands
- TGF-α
- EGF
- Epiregulin
- Betacellulin
- HB-EGF
- Amphiregulin

Tyrosine kinase domain

No ligand-binding activity*

Erb-B1 HER1

Erb-B2 HER2

Erb-B3 HER3

Erb-B4 HER4

Heregulin (neuregulin-1)
Epiregulin
HB-EGF
Neuregulins 3, 4

*HER2 dimerizes with other members of the HER family.

Fluorescence In Situ Hybridization Test Measures HER2 Gene Amplification

- FISH tests are designed to detect amplification of the HER2 gene.
Joint Analysis: Long-Term Follow-Up

Perez, E et al. J Clin Oncol 2014
Post-Trastuzumab Therapeutic Options:

1. Block kinase
   - lapatinib
   - neratinib
2. Prevent dimerization
   - pertuzumab
3. MAb-toxin delivery
   - T-DM1
4. Downstream blockade
   - PI3K, mTOR
HERs Hook Up
Pertuzumab Prevents Hook-Ups

Herman ten Kate: The Chaperone
Targeted Therapies for HER2+ Breast Cancer: Trastuzumab, Lapatinib, and T-DM1

- **Trastuzumab**
- **Lapatinib**

**T-DM1**

- Antibody: Trastuzumab
- Cytotoxic: Emtansine
- Stable linker: MCC

- Inhibition of microtubule polymerization
- Emtansine release
- Internalization
- Lysosome

Breast Cancer: Subtypes Reflect Genomic Complexity

Genome-wide Circos plots of somatic rearrangements

Table 1 | Analysis of the top somatically aberrated genes influencing expression

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Single Nucleus Genome Sequencing
Triple-Negative Breast Cancer

Nature 512; 155-160, 2014
TNBC Heat Map derived from Single Nucleus Genome Sequencing

374 clonal mutations
154 subclonal mutations

Three subpopulations:
A1: 66
A2: 52

23.44% damage protein function

Nature 512; 155-160, 2014
Breast Cancer as Whack-a-Mole

Rapid emergence of compensatory mechanisms of resistance
Chaos Reigns
25 Patients with HER2 Somatic Mutations

- Each blue circle represents a patient.
- From 8 publications with a total of 1,499 patients.
- 20% of patients have mutations at amino acids 309 or 310.
- 68% of patients have mutations at amino acids 755-781.
HER2 Somatic mutations

• Occur in $\leq 2\%$ of breast cancers
• Activating mutations
• IHC and FISH negative
• Sensitive to small molecules but not trastuzumab in preclinical models
Phase II Clinical Trial of Neratinib for HER2 Mutation Positive Breast Cancer

**Study Therapy**
Neratinib 240 mg P.O. daily
days 1-28 each cycle*

**HER2 gene amplification negative**
Stage IV Breast Cancer

**Tumor DNA Sequencing for HER2 Mutation**

**Mutation Absent**
Not Eligible for Study Therapy

**Mutation Present**
Study Therapy
Neratinib 240 mg P.O. daily
days 1-28 each cycle*

Restage every 2 cycles
Continue therapy until disease progression,
or unacceptable adverse events.

**Participating Institutions**
1. Washington University School of Medicine
2. Dana-Farber Cancer Institute
3. Memorial Sloan-Kettering Cancer Center
4. Univ. of North Carolina
5. Stanford University

San Antonio Breast Cancer Symposium – December 4-8, 2012
The Mutational Landscape of Breast Cancer

• 100 breast cancers genomes analyzed
• Driver mutations found in at least 40 different cancer genes
• 73 different combinations of driver mutated cancer genes
• 28 cancers had a single driver mutation, but some had as many as 6 driver mutations

Combinations are Hard

- Toxicity increases significantly with each added drug
- New toxicities occur
- Cost of regimen increases dramatically
  --$8-10K/drug/month
The Orphan Disease Era

- A myriad of rare diseases
- Many genomic drivers
- IT-driven
- Complex biology
- Uncertain therapeutics
- Phase III trials difficult
Cancers Live in Neighborhoods

Can We Enlist the Neighborhood Watch?
T Cell Attacking a Cancer Cell

Why Doesn’t the Immune System do it’s Job?
The Immune System
At the cellular level

Turning up The Activating Blocking the Inhibiting
Augmenting Antibody Activity with Anti-CD137 MAb

A. Tumor cell

B. Tumor cell
   NK cell

C. Tumor cell
   NK cell

D. Tumor cell
   NK cell
Anti-CD137 agonistic mAb enhances anti-breast cancer activity of trastuzumab in vivo while retaining HER2 specificity against HER2-overexpressing breast cancer cell lines and a primary breast tumor.
Conclusions

• Segmenting breast cancer has led to real advances via targeted therapies
• Resistance continues to be a problem
• Improved understanding of resistance → new therapeutic approaches
• Genomic analyses may help
• Novel immunotherapeutic approaches
Thank You