ESR1 mutations: A Mechanism for Acquired Endocrine Resistance

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• Introduction
• New insights for ESR1 mutations in MBC
• New diagnostic strategies
• Therapeutic strategies
• Summary
Endocrine Therapy: The 1st Target Tx

Dr. Schinziner & Sir. Beatson GT

1870
1st description of surgical oophorectomy

1940’s
Full range of ablative hormonal therapy developed

1950’s
Era of Additive hormonal therapy

1970’s
Development of Tamoxifen

1980’s
ER/PR detection and resurgence in interest in endocrine Rx

Dr. Arthur Walpole/Dr. Dora Richardson

IHC Detection

1990’s
Demonstration of the therapeutic efficacy of Tamoxifen

Genomic & Functional Structure of Estrogen Receptors

Trends in Endocrinology and Metabolism, September 2015
Signaling through ER
Molecular Mechanisms of **Endocrine Resistance**

EBC: ~25% Resistance
MBC: ~30% initial regression
TCGA data

- **N=962** breast cancer samples
- **Frequency > 5%** in Luminal types: PIK3CA, TP53, MAP3K1, MAP2K4, GATA3, MLL3, CDH1, and PTEN

- **ESR1 genes**: mutations 0.5%, amplifications 2.6%

**ESR-1 Genomic Alterations in MBC**

- **ESR1 amplifications**: 0-23%
  - mechanism for endocrine resistance and treatment failure

- **ESR1 Genomic rearrangements**: *ESR1-CCDC170, YAP1-ESR1*
  - transcriptional dysregulation
  - ↑motility, tumorigenecity, resistance to fulvestrant

- **ESR1 missense mutations**
Genomic Characterization of *ESR1* Variants by Breast cancer PDX

**PDXs study**

7 ER+ PDXs/Met

3*/7

**ESR1** amplification

**ESR1-YAP1**

**ESR1-Y537S**

**ESR1-E380Q**

Cell Reports 4, 1116–1130, September 26, 2013
Biologic Consequences
ER-LBD-activating *ESR1* mutations

- **MSKCC cohort**
  - 38 BC
  - 36 ER+ Met
  - 9*/36 2 Primary
  - 0*/2

- **2013 Nat Genet**
Endocrine resistant Biology

2013 Nat Genet
Emergence of Constitutively Active *ESR1* Mutations in Pretreated ABC

Clin Cancer Res; 20(7) April 1, 2014
LBD mutations and Endocrine Resistance

Tamoxifen

Fulvestrant

Cell Survival

Clin Cancer Res; 20(7) April 1, 2014
Scenarios for Clonal Selection of rare $ESR1$ Mutation

- Pre-existing rare mutation
- De novo acquired mutation

Detection modality & Timing
Treatment strategy

Detection of rare *ESR1* Mutation

- Very low mutational frequency
- Limited availability of tissue
- Monitoring by repeated test

More sensitive platform & **Liquid biopsy**

## Emerging detection Platforms

<table>
<thead>
<tr>
<th>ctDNA detection method</th>
<th>Detection limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanger sequencing</td>
<td>&gt;10%</td>
</tr>
<tr>
<td>Pyrosequencing</td>
<td>10%</td>
</tr>
<tr>
<td>Whole exome sequencing</td>
<td>5%</td>
</tr>
<tr>
<td>Whole genome sequencing</td>
<td>1%</td>
</tr>
<tr>
<td>Allele-specific PCR</td>
<td>0.1-1%</td>
</tr>
<tr>
<td>Digital PCR (BEAMing, ddPCR, etc.)</td>
<td>0.01%</td>
</tr>
<tr>
<td>Targeted NGS (CAPP-Seq, Safe-SeqS, etc.)</td>
<td>≤0.01%</td>
</tr>
</tbody>
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Diehn M. 2015 SABCS
Droplet Digital PCR

- Nanodroplet PCR reactions are independent, single amplification events.
- Many thousands of discrete measurements.

Graph showing data points and axes labeled: Concentration, copies/µL vs. Sample.
Application of Sensitive Detection Platforms

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment A</th>
<th>Treatment B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue biopsy</td>
<td>Accessibility ✓</td>
<td>✓ Heterogeneity</td>
</tr>
<tr>
<td>Liquid biopsy</td>
<td>✓ Non-invasive</td>
<td>✓ Representative ✓</td>
</tr>
</tbody>
</table>

Mutation A
Mutation B

Non-invasive Genotyping of cancer
→ Prognosis/Section of Treatment/Disease monitoring (MRD)
New Treatment Strategies: HD Endocrine

**In vitro Study**

**CONFIRM Study**

: Fulvestrant 250mg vs 500mg

Clin Cancer Res; 20(7) April 1, 2014

J Clin Oncol. 2010 Oct 20;28(30):4594-600
New Treatment Strategies: **New SERD**

J. Med. Chem. 2015, 58, 4883–4887
Estrogen-Receptor Degrader **GDC-0810** Active in Metastatic Breast Cancer

- **GDC-0810 (ARN-0810):** ER antagonism and degradation, non-steroidal and **orally** bioavailable
- Active in TAM-sensitive, resistant & *ESR1*-wild, mutant

- Phase I dose-escalation study (n=41)
- *ESR1* mutation: positive (n=9, 22%), wild type (n=10, 24%), unknown (n=22, 54%)
- **Response:** SD (42%)

**Phase IIa study:** GDC-0810 in postmenopausal women with ER-positive advanced or metastatic breast cancer who have been previously treated with an aromatase inhibitor, **including tumors with *ESR1*** mutations.
New Treatment Strategies: **Summary**
Summary

• Endocrine resistance after treatment is a case for Darwinian tumor evolution.
• *ESR1*-LBD mutations confer endocrine resistance and ligand independent tumor growth.
• New technologies with better sensitivity: Safe-Seq, ddPCR
• Application of liquid biopsy
• New strategies: HD endocrine therapy, New SERD