Session 7: Cancer Interception
Targeting Early Oncogenic Drivers

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Houston, Texas

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Cancer Interception Concept

Blackburn EH.
Cancer Prev Res 2011

Need for earlier interception!
Cancer Interception:

Main Points:

1. Need to improve uptake of proven preventive drugs in high-risk groups

2. We can prevent cancer by targeting premalignant lesions

3. We need to implement a comprehensive “Premalignant Genome Atlas” program
Identification of Molecular Oncogenic Drivers

• To date, most efforts to target oncogenic drivers have been focused on molecules discovered in established cancers

• Such drivers include:
  • Viruses and virally activated genes
  • Mutated or activated growth factor receptors
  • Mutated or activated signal transduction molecules
  • Mutated or lost tumor suppressor genes

• To move the field forward:
  • Need better characterization of early oncogenic drivers in premalignant lesions
Breast Cancer in the U.S.

- More than 250,000 new breast cancer diagnoses expected/year
- Estrogen receptor-positive (Luminal)
  - ~60-70% of all BC
  - Can target estrogen signaling w/ SERMS, AIs
- HER2 amplification (HER2)
  - ~15-20% of all BC
  - Can target HER2 w/ trastuzumab, lapatinib, pertuzumab, TDM1, and possibly vaccines
- Triple-negative BC (ER-neg/PR-neg/HER2-neg)
  - ~15-20% of all BC (many are Basal-like BCs)
  - 85% or more have P53 mutations
  - Includes some BRCA-mutant tumors
  - PARP inhibitors may treat BRCA-mutant tumors
  - No other targeted therapy for most TNBCs

Can we prevent **ALL** forms of breast cancer?
Preventing Breast Cancer: Targeting “Oncogenic Drivers” - ER

Targeting ER

Cox2 inhibitors
Retinoids
Rexinoids
Metformin
SERMs And AIs
P53 Modulators

\[ \text{Arachidonic Acid} \]
\[ \text{COX-1, COX-2} \]
\[ \text{Prostaglandin G2} \]
\[ \text{PI3K, Ras/Raf} \]
\[ \text{MAPKs, JNKs, p38, AKT} \]

\[ \text{insulin, IGFs} \]
\[ \text{ErbB ligands} \]
\[ \text{Trastuzumab} \]
\[ \text{Iressa} \]
\[ \text{Lapatinib} \]
\[ \text{Kinase inhibitors} \]
\[ \text{Statins} \]
\[ \text{Transcription factor inhibitors} \]

\[ \text{AMPK} \]
\[ \text{AMP} \]
\[ \text{p70S6K1, AKT} \]
\[ \text{NR, RXR} \]
\[ \text{XXRE} \]
\[ \text{ER} \]
\[ \text{ErbB} \]

\[ \text{Cancer} \]
\[ \text{Growth Control} \]
\[ \text{genes} \]
Prevention of ER+ Invasive Breast Cancers
SERM vs. Placebo, Exemestane vs. Placebo

Tamoxifen vs. placebo
- Italian
- NSABP P1
- IBIS1
- Marsden

Raloxifene vs. placebo
- MORE/CORE
- RUTH
- STAR

Lasofoxifene vs. placebo
- PEARL 25 mg
- PEARL 50 mg

SERMs Combined

Exemestane vs. placebo
Anastrozole vs. placebo

Cuzick AACR from:
2. Vogel V. JAMA 295:2727, 2006
5. LaCroix A. JNCI 102:1706, 2010
What Has Been the Uptake of Breast Cancer Anti-estrogen Preventive Therapy?

All Women

Women eligible for preventive therapy (15.5%)

Uptake of raloxifene = 0.21%

Uptake of tamoxifen = 0.03%

NSABP P-1 Results: Incidence of Invasive Breast Cancer by Previous Pathology

MDACC Breast Cancer High-Risk Cohort
PI: Abenaa Brewster
Uptake of Preventive Therapy at MD Anderson 2011-2013 (n=1,183)

Preventive Therapy in High Risk Breast Cancer Patients by Category

Chemoprevention Yes (%)
Tamoxifen Yes (%)
Raloxifen Yes (%)

BC Prevention Moonshot at MDACC to increase SERM use in patients with premalignant disease: in 3 months increased the use of SERMs to greater than 50%
Preventing Breast Cancer: Targeting “Oncogenic Drivers” - HER2

- MAPKs, JNKs, p38, AKT
- PI3K, Ras/Raf
- Arachidonic Acid
- Prostaglandin G2
- COX-1, COX-2
- Prostaglandin G2
- MAPKs, JNKs, p38, AKT
- PI3K, Ras/Raf
- Trastuzumab
- Iressa
- Lapatinib
- Kinase inhibitors
- Statins
- Transcription factor inhibitors
- Mevalonate
- AMPK
- Metformin
- Cox2 inhibitors
- Retinoids, Rexinoids
- AMPK
- p70S6K1, AKT
- IGF-R
- IGFR inhibitors
- insulin, IGFs
- ErbB ligands
- IGF-R
- IR
- ErbB2
- ErbB
- NR, RXR
- XXRE
- NR
- RXR
- P53
- P53
- ER, ER
- Growth Control genes
Targeting Molecular Oncogenic Drivers: Targeting HER2

Multiple studies testing anti-HER2 strategies:

Trastuzumab: mAb targeting HER2
  • NSABP B-43 Treatment of DCIS Using Trastuzumab Phase III DCIS Trial

Lapatinib: small molecule inhibitor of HER2/EGFR
  • Phase I and II trials conducted in patients with cancer
  • Phase II trial conducted as adjuvant therapy for patients with early breast cancer
  • 2 Phase II trials in HER2-positive DCIS patients conducted and showed biomarker modulation

Anti-HER2 vaccines:
  • Preclinical studies of HER2 vaccines
  • Multiple groups testing vaccines

Bottom line:
Targeting individuals with HER2-positive lesions
Targeting Molecular Oncogenic Drivers: Targeting HER2

Multiple studies testing anti-HER2 vaccines:\(^1\):

- **Brian Czerniecki:** Testing pulsed dendritic cells
  - Phase II study ongoing
- **Mittendorf / Peoples:** Testing HER2 peptide vaccines
  - Phase I and II trials conducted in patients with cancer
  - Phase II trial conducted as adjuvant therapy for patient with early breast cancer
  - Phase II trial testing in DCIS patients to open in 2016
- **Nora Disis:** Testing DNA vaccines
  - Preclinical studies of HER2 vaccine
  - Phase I/II and II studies in patients with cancer
  - Multi-antigen vaccine being tested in Phase I trial

Preventing Breast Cancer: Targeting “Oncogenic Drivers”

Preventing Basal or "Triple-negative" BC

- MAPKs, JNKs, p38, AKT
- PI3K, Ras/Raf
- Arachidonic Acid
- Prostaglandin G2 (PG2)
- *COX-1*, *COX-2*
- PGE2
- *ErbB* ligands
- Trastuzumab
- Iressa
- Lapatinib
- EGCG
- Kinase inhibitors
- Statins
- Mevalonate

- Retinoids
- Rexinoids
- Metformin
- SERMs
- PARP Inhibitors
- Bisphosphonates
- Cox2 inhibitors

- p70S6K1, AKT
- AMPK
- AMP
- NR, RXR
- XXRE
- ER, ER
- Growth Control Genes
- Cell death
- Preventing Breast Cancer
- Preventing Basal or "Triple-negative" BC
- Preparing for Breast Cancer
- Targeting "Oncogenic Drivers"
Genomic Analysis of 192 “triple-negative” breast cancers

Four TNBC groups:

1. Luminal / AR
   [anti-Androgens]
2. Mesenchymal
   [FGF, PDGF, IGF inhibitors]
3. Basal-like Immune Activated
   [Stat, IL6 & IL8 inhibitors]
4. Basal-like Immune Suppressed
   [Vaccines, immune regulators]

(similar but not same grouping as Dr. Pietenpol who found 6 groups)

Burstein et al. *Clin Ca Res* 2015
### Gene Mutations in ER-positive and ER-negative Invasive Breast Cancers in TCGA

#### Top Mutated Genes by Subtype

<table>
<thead>
<tr>
<th>Gene</th>
<th>ER+ Rank</th>
<th>ER+ (n=720) Mutated</th>
<th>ER+ Frequency</th>
<th>ER- Rank</th>
<th>ER- (n=86) Mutated</th>
<th>ER- Frequency</th>
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<td>PIK3CA</td>
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<td>304</td>
<td>42.2%</td>
<td>3</td>
<td>9</td>
<td>10.5%</td>
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<td>102</td>
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<td>68</td>
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<tr>
<td>TTN</td>
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<td>100</td>
<td>13.9%</td>
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<tr>
<td>GATA3</td>
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<td>99</td>
<td>13.8%</td>
<td>94</td>
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<td>CDH1</td>
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<td>MAP2K4</td>
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<td>RUNX1</td>
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<tr>
<td>PTEN</td>
<td>10</td>
<td>32</td>
<td>4.4%</td>
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**ER (+): 42% PI3KCA-mutated**

<table>
<thead>
<tr>
<th>Gene</th>
<th>ER+ Rank</th>
<th>ER+ (n=720) Mutated</th>
<th>ER+ Frequency</th>
<th>ER- Rank</th>
<th>ER- (n=86) Mutated</th>
<th>ER- Frequency</th>
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</tr>
<tr>
<td>SPTA1</td>
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<td>9</td>
<td>4</td>
<td>4.7%</td>
</tr>
<tr>
<td>KIAA1210</td>
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<td>9</td>
<td>1.3%</td>
<td>10</td>
<td>4</td>
<td>4.7%</td>
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</table>

**ER (-): 79% p53-mutated**
Preventing “Triple-negative” Breast Cancer

Drugs with preventive activity in preclinical studies:

• PARP inhibitors in BRCA1-null / P53-null mice ¹
• Rexinoids in P53-null² and SV40Tag mice³
• EGFR inhibitor in P53-null mice³
• mTOR inhibitors in P53-null and SV40Tag mice⁴
• Metformin: in HER2-positive mice⁵ and P53-null mice⁶

3. Wu et al. CEBP 11:467, 2002
4. Brown, unpublished data
Cancer Interception: How to move forward?
Cancer Development is Analogous to a Growing Tree

Premalignant Genome Progress: (in order of development)

1. CRC
2. Oral neoplasia
3. Lung cancer
4. Esophagus
5. Skin cancer
6. Pancreas cancer
7. Prostate cancer
8. Breast cancer
9. Ovarian cancer
10. Others? (hematologic, brain)

Need to identify early drivers

Provided by Ki Hong

Adapted from Gazdar, CCR, 2008
Conclusions:

• Cancer prevention is possible through preventive drug therapy (“cancer interception”)

• Targeting known oncogenic drivers such as HRs (ER, AR), TKR oncogenes (Her2, EGFR), signaling molecules (Cox2, mTOR), and tumor suppressor genes (BRCA1/2, P53) are promising strategies for cancer prevention

• Targeting pre-cancerous lesions may be most effective (individuals willing to accept some risk of side effects if they have a precancerous “lesion”)

• Future molecular characterization of precancerous lesions is needed to better define early oncogenic drivers (“Premalignant Genome Atlas” program)
Brown Research Group
Abhijit Mazumdar, Ivan Uray,
Petra Den Hollander
Zack Hartman, Graham Poage,
Neidi Bhatia, Svasti Haricharan,
Lakshmi Bollu, Z. Ma,
Jing Zhao, Jonathan Shepherd,
Yun Zhang, Jamal Hill,
Gordon Mills, Xiaochun Xu,
Banu Arun,

CCP / CPC
Eduardo Vilar-Sanchez,
Theresa Bevers, Diane Weber
Carrie Mays, Val Sepeda,
Elise Cook, Lonzetta Newman, APNs
Abenna Brewster, Priya Thomas,
Lana Vornik, Saba Ab, Tawana Castile

NCI, DCP
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Brandy Heckman, Leslie Ford

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Rob Freidman, Tona Gilmer

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BCRF Foundation Grant
SAB Komen Grant

Clinical Sites
MDACC
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Henry Kuerer
Beth Mittendorf

Georgetown
Claudine Isaacs
Shawna Willey

DFCI, Harvard U.
Judy Garber
Dirk Iglehart

MSKCC/Cornell
C. Hudis, A. Gulcap
Andy Dannenberg

Columbia
Dawn Herschman
Kathy Crew

UTHSC-SA
Alex Miller

Mayo Clinic
Paul Limburg
Sandia Pruthi
Questions ?
General Strategies to Reduce Cancer Risk

Diet & Nutrition
- Avoid Carcinogens

Exercise

Avoid Carcinogens
- Vaccines
- Surgery

Preventive Therapy