Personalizing Breast Cancer Therapy: Promise and Challenges

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Professor, Divisions of Cancer Medicine and Surgery
## Disclosures

<table>
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<th>Nature of Relevant Financial Relationship (include all of those that apply)</th>
<th>Commercial Interest Provide Name of Company/Companies</th>
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<td>Grant or research support</td>
<td>Novartis, AstraZeneca, Taiho, Genentech, Calithera, Debiopharma, Bayer</td>
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Risk Markers
- Cancer Prevention
- Cancer Genetics
- Cancer Epidemiology
- Pathology

Prognosis Markers
- Clinical Oncology
- Pathology
- Radiology
- Molecular Diagnostics
- Cancer Genetics
- Immunology

Predictive Markers
- Pathology
- Molecular Diagnostics
- Cancer Genetics
- Investigational Therapeutics
- Immunology
- Outcomes Research
- Comparative Effectiveness

Response Markers
- Chemotherapy
- Targeted Therapy
- Immunotherapy/Vaccines
- Surgery
- Radiation

Meric-Bernstam, *JCO*, 2013
Outline

• Cancer Risk
• Cancer Prognosis
• Predictors of Response/Resistance
• Neoadjuvant Therapy as a Research Platform
• Genomic Mechanisms of Acquired Resistance and Genomic Evolution
• Liquid Biopsies
Germline Genetics: Breast Cancer Risk

Mutations in high-penetrance genes (*BRCA1/2, TP53, CDH1, LKB1, and PTEN*)
Moderate-penetrance genes (e.g., *CHEK2, ATM, and PALB2*)
Common low-penetrance genetic variants
Frequency of likely Pathogenic Somatic and Germline Variants

A

Number of patients with a deleterious somatic variant

B

Proportion of patients with germline vs. somatic pathogenic variant.

C

*P = 0.05

D

Previously known

Previously unknown

Outline

• Cancer Risk
• **Cancer Prognosis**
  • Predictors of Response/Resistance
  • Neoadjuvant Therapy as a Research Platform
  • Genomic Mechanisms of Acquired Resistance and Genomic Evolution
• Liquid Biopsies
TP53 Mutation is Associated with Worse Outcomes

Median 41 vs 95 months; P < 0.001
Median 22 vs 42 months; P < 0.001
Median 25 vs 43 months; P < 0.001
Median 26 vs 51 months; P < 0.001

Basho ASCO 2015
### Univariate and Multivariate Analysis for Recurrence Free Survival from Primary Cancer Diagnosis

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Outline

• Cancer Risk
• Cancer Prognosis
• Predictors of Response
• Genomic Predictors of Intrinsic Resistance
• Genomic Mechanisms of Acquired Resistance
• Liquid Biopsies
# Targetable Genomic Alterations in Breast Cancer

<table>
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<tr>
<th>Gene</th>
<th>Alteration</th>
<th>Frequency (%)</th>
<th>Candidate drug</th>
<th>Level of evidence for the target</th>
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**DNA repair (cont.)**

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Abbreviations: HDAC, histone deacetylases; NA, not available.
Genotype selected and relevant clinical trials submitted in FY 12-15

- genotype unselected
- genomic alteration(s) preferred
- genotype selected

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Genotype/Biomarker-Selected Basket Trials in ICT

- **Akt**: AZD5363, MSC2363318A
  - Buparlisib, MSC2363318A, Talazoparib
  - CRD2036, GDC-0032, MSC2363318A
  - BGJ398, TAS-120, Debio1347
- **PTEN**: TAS-120
- **PIK3R1/2**: BGJ398, TAS-120
- **PIK3CA**: CB-839, Selumetinib
- **FGFR1/2/3**: Dabrafenib+Trametinib, Trametinib, Sorafenib, Vemurafenib, BVD-523
- **FGFR4**: CB-839, Selumetinib
- **FGFs**: CB-839, Selumetinib
- **KRAS**: CB-839, Selumetinib
- **BRAF**: Dabrafenib+Trametinib, Trametinib, Sorafenib, Vemurafenib, BVD-523
- **N-MYC**: GSK525762
- **NUTM1**: GSK525762
- **EGFR**: Erlotinib, KBP-5209, Neratinib
- **HER3**: KBP-5209, Neratinib
- **HER2**: KBP-5209, Neratinib, Pertuzumab/Trastuzumab
- **HER2**: Crizotinib+Dasatinib, ABT-348
- **CDKN2A**: Crizotinib+Dasatinib, ABT-348
- **DDR2**: Crizotinib+Dasatinib
- **MET**: Crizotinib+Dasatinib, INC280
- **SMO**: Vismodegib, LY2940680
- **PTCH**: Vismodegib, LY2940680
- **PD-L1**: MK-3475
- **TP53**: MLN9708+Vorinostat, Pazopanib+Vorinostat
- **KIT**: Imatinib
- **IDH1**: IDH305, AG-221
- **DHH/HHH**: LY2940680
- **MLL**: EPZ-5676
- **RNF43**: LGK974
- **RSPO**: LGK974
- **MRCA1**: Talazoparib
- **ATM/ATR**: Talazoparib
- **FANCs**: Talazoparib
- **EMSY**: Talazoparib
- **NBS1**: Talazoparib
- **PALB2**: Talazoparib
- **RAD50/C**: Talazoparib
- **BRCA1/2**: Talazoparib
- **MAP2K1/3**: Olaparib, Talazoparib
- **NTRK1/2/3**: BVD-523
- **ROS1**: LOXO-101, RXDX-101
- **ALK**: Ceritinib, Crizotinib,RXDX-101
- **NOTCH1**: Ceritinib, Crizotinib, RXDX-101, X-396
- **OMP-52M51**: OMP-52M51

~80 alterations; 44 drugs, 47 trials
HER2 Mutations as a Novel Target

- **25 HER2 mutations among 1,499 patients**

### In vitro Kinase Activity of 3 HER2 Mutations

- WT: Monomer 2.3-fold, Dimer 10-fold
- D769: Monomer 20-fold, Dimer 22-fold
- V777L: Monomer 33-fold, Dimer 3.3-fold
- V842I: Monomer 7.5-fold

Fold increase is relative to WT HER2 monomer specific activity.

### HER2 mutations Increase Xenograft Growth

#### Phase II Clinical Trial of Neratinib for HER2 Mutation Positive Breast Cancer

- HER2 gene amplification negative
- Stage IV Breast Cancer
- Tumor DNA Sequencing for HER2 Mutation
- Mutation Absent
- Mutation Present
- Not Eligible for Study Therapy
- 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.

* 4-week Cycle

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HER2 mutations as a Target

SUMMIT trial: Neratinib for HER2 mutant, HER2 nonamplified BC
ORR at 8 weeks: 32%; Clinical benefit rate: 42%

Neratinib + fulvestrant

SUMMIT trial: Neratinib for HER2 mutant, HER2 nonamplified BC
ORR at 8 weeks: 32%; Clinical benefit rate: 42%
**Akt1 as a Target**

Best percentage change in tumor size in patients with E17K-mutated ER+ breast cancer treated with AZD5363

Plots are based on patients with available RECIST data at baseline and at least one follow-up assessment.

*Patient from the Japanese study*
NTRK1 fusion Soft tissue Sarcoma

- 42 yo female with undifferentiated sarcoma progressed through epirubicin, ifosfamide, sorafenib, and doxorubicin
- 100mg BID
- Rapid resolution of dyspnea and hypoxemia
- Confirmed partial response
- Currently on study; 8+ months

Study baseline    Study cycle 9 day 1

Hong et al, EORTC 2015
Secretory Breast Carcinoma and NTRK fusions

 Secretary cancer rare and potentially better prognosis
Targeting PI3K/Akt/mTOR
Greater PFS Benefit With EVE in Patients With Minimal Alterations in PIK3CA/PTEN/CCND1 or FGFR1/2

Presented By Gabriel Hortobagyi at 2013 ASCO Annual Meeting

HR (95% CI): 0.27 (0.18 - 0.41)
Effect of Everolimus on PFS in HER2 + Breast Cancer

**PIK3CA** wild type (WT) versus mutant (MT)

**PTEN** normal versus low/loss

**PI3K pathway activity** normal versus hyperactive

André et al. JCO 2016
Rationale for Neoadjuvant Systemic Therapy Trials

Tumor response as an *in vivo* assay to determine systemic therapy efficacy

- Test new therapy regimens
- Identify biomarkers
  - Predictors of response
  - Pharmacodynamic markers of response

- Modify therapy for non-responders
- Stratify for further therapy based on residual cancer burden and molecular characteristics?
pCR is a Surrogate for Event-Free Survival in All Subtypes
pCR Rate According to *PIK3CA* Mutation Status in the GeparSixto Study

- **All**: N = 512
  - PIK3CA wt: 41.6%
  - PIK3CA mut: 22.4%
  - P = .003

- **HER2+**: N = 271
  - PIK3CA wt: 37.1%
  - PIK3CA mut: 17.0%
  - P = .009

- **HER2+ / HR+**: N = 241
  - PIK3CA wt: 29.9%
  - PIK3CA mut: 6.3%
  - P = .006

- **HER2+ / HR-**: N = 149
  - PIK3CA wt: 48.1%
  - PIK3CA mut: 40.0%
  - P = .567

Loibl S et al. SABCS 2013. Abstract S4-06.
Multivariable Analysis for Prediction of pCR in HER2+ Breast Cancer in GeparSixto

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P-value</th>
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<tr>
<td><strong>Hormone receptor status</strong></td>
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<tr>
<td>Negative</td>
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<td>Positive</td>
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<td><strong>PIK3CA</strong></td>
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<td>Mutant</td>
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</table>

Adjusted for therapy, age, tumor and nodal status, histotype and grading

Role for combinations with PI3K inhibitors
Potential role for PIK3CA for stratification/therapy selection (TDM1?)

Loibl S et al. SABCS 2013. Abstract S4-06.
ARTEMIS: A Randomized TNBC Enrolling trial to confirm Molecular profiling Improves Survival

Patients randomized 2:1 to know molecular testing results vs. not know results (gene profiling, AR, vimentin)
Chemo-insensitive (prediction & interim imaging)

- BRCA1/2 +
  - PARPi combos
- Vimentin + (mesenchymal)
  - mTORi + chemo
  - FAKi + chemo
- AR+
  - ARi + chemo
- Other (Enriched for Basal-like)
  - EGFRi + chemo
  - PD-L1i + chemo

Comparison to control ‘predictor unknown’ group

Improved rate of pCR/RCB-I?

- Single arm phase II trials
- pCR improvement: 5% → 20%
- N=37
- Two stage design; close if pCR/RCB-I not seen in ≥1 of 14 patients

<table>
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<tr>
<th>Trial</th>
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<tr>
<td>PDL-1i</td>
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<tr>
<td>EGFRi</td>
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<tr>
<td>ARi</td>
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<tr>
<td>mTORi</td>
<td>everolimus</td>
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<td>PARPi</td>
<td>TBD</td>
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<td>FAKi</td>
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</table>
Targeting PD-L1 in TNBC

- Adriamycin
- Cyclophosphamide
  q3wk x 4
  - enroll

- nab-Paclitaxel
  q3wk
  Atezolizumab
  - blood

- Surgery
  - surgical specimen

- Atezolizumab to complete 6 mo of treatment
  - blood

PIs: Litton and Mittendorf
Neoadjuvant Therapy gives Unique Insights into Genomic Evolution

- Loss of HER2 in patients treated with HER2 targeted neoadjuvant therapy
- Molecular evolution with treatment and progression
Genomic Characterization of Residual Disease

TNBC after adjuvant chemotherapy is heterogeneous and has multiple alterations that are targetable with existing drugs in development.

~90% of all patients had an aberration in at least one of these pathways.

Development of PDXs for Study of Genotype-Phenotype Correlation

McAuliffe and Evans, Meric-Bernstam *Plos One*, 2015
Survival Outcomes in Patients whose Tumors Develop a Patient-Derived Breast Cancer Xenograft vs Not

Figure 2: Kaplan-Meier curves of DRFS by BCX or noBCX

McAuliffe and Evans et al *Plos One*, 2015
<table>
<thead>
<tr>
<th>Source</th>
<th>ER (%)</th>
<th>PR (%)</th>
<th>HER2</th>
<th>NeoCT</th>
<th>Alive</th>
<th>Distant Relapse</th>
<th>Follow-up (months)</th>
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</table>
[Image of a table with various data entries and diagrams of Buparlisib, MLN0128, and Trametinib]
PARP Inhibitor Sensitivity

A

B

BRCA1

ATM

PTEN

C
Somatic Genomic Alterations in Metastatic Breast Cancer

- Mutations in \textit{PIK3CA}, \textit{TP53}, \textit{ARID1A}, \textit{PTEN}, \textit{AKT1}, \textit{NF1}, \textit{FBXW7} and \textit{FGFR3}


Meric-Bernstam Mol Can Ther 2014
Concordance of Genomic Alterations in Primary vs Metastatic Tumors

- 33 matched primary and recurrent tumors
- Somatic mutations
  - 97 of 112 (86.6%) somatic mutations were concordant
- Copy number alterations
  - 136 of 159 (85.5%) were concordant
  - 37 (23.3%) were concordant, but below the reporting threshold in one of the matched samples
- 23 (14.5%) discordant
Alterations potentially targetable with established or investigational therapeutics were considered “actionable”

40 of 43 (93%) patients had actionable alterations that could inform targeted treatment options.

There were both losses and gains of actionable alterations.
Acquisition of a Constitutively Active ESR1 Mutation
Unusual Responder Program

Complete or Partial Response

Unexpected Rapid Progression

Mixed Response

Progression after Response
Liquid Biopsies

Applications of liquid biopsy

Early detection and monitoring

- Brain tumor DNA blocked by blood-brain barrier
- Breast cancer
- Pancreatic cancer
- Colon cancer

Many tumors release DNA fragments that circulate in the bloodstream

Detection of resistance mutations

- Targeted therapy
- Response to therapy
- Selective pressure
- Resistance mutation #1
- Resistance mutation #2

Analysis of ctDNA

ctDNA of resistance mutations collected in blood sample

Bettegowda C et al. Sci Transl Med 2014
Early Recurrence Detection

- Serial monitoring of ctDNA 20 patients diagnosed with primary breast cancer
- ctDNA monitoring discriminated between patients with (93%) and without (100%) eventual clinically detected recurrence
- ctDNA-based detection preceded clinical detection of metastasis in 86% of patients with an average lead time of 11 months (range 0-37 months)
- Patients with long-term disease-free survival had undetectable ctDNA postoperatively
- ctDNA quantity was predictive of poor survival

Olsson E, EMBO Mol Med, 2015
Liquid Biopsy Opportunities

- Early detection
- Monitoring of response in neoadjuvant therapy
- Determination of pathologic complete response after neoadjuvant therapy
- Monitoring response in metastatic breast cancer
- Monitoring for acquired resistance mechanisms
Novel Breast Targets

- Antibody drug conjugates
- DNA Damage repair
  - PARP, Wee1, ATR
- Cell signaling
  - PI3K/mTOR, PI3Kbeta, FGFR, MEK, Mnk
- Cell metabolism
- Epigenetics
- Other novel targets (eg. MDM2, XPO1)
Summary

• Genomics is increasingly available

• None of the somatic genomic markers are yet linked to approved therapy in breast cancer

• Novel targets in development

• Expect major advances with integrated multianalyte analysis
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• Mike Davies- melanoma
• John de Groot- neurooncology
• Ravi Vinod sarcoma
• John Heymach- lung
• Faye Johnson
• and William William- head and neck
• Shannon Westin /Rob Coleman- gyn onc

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