Susan G. Komen
Breast Cancer Issues Conference

**beyond** ER:
<New Targeted Strategies>

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"One in Eight"
Diana Young, TBCF '96

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the "name game"
...Its becoming more complex....

Clinical Breast Cancer Subsets
**Historic Breast Cancer Biomarker Panel**

<related targeted therapeutics>

**ER/PR (+) [70%]**
- Tamoxifen
- Aromatase Inhibitors
- Faslodex

**HER 2 (+) [20%]**
- Herceptin
- Perjeta
- Kadcyla
- Neratinib
- Lapatinib

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**The Evolving Landscape**

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**What is a growth pathway??**

ie: the estrogen receptor
Simply a one way street?

…or, more like a complex interstate system

…and a single cell is as complex as the particle of dust known as “Whoville”
Breast Cancer Subtypes

...the better we can define....

1. Hormone receptor positive
   luminal A/B
2. HER2 positive
3. Triple Negative
   PD-L1 positive
4. BRCA positive

Therapeutic “buckets”
...the better we can target....

1. Hormone therapies
2. HER2 directed therapies
3. Chemotherapy
4. CDK 4/6 inhibitors
5. mTOR inhibitors
6. Immunotherapy
7. PARP inhibitors
8. Evolving:
   a. PI3 Kinase inhibitors
   b. AKT inhibitors
   c. Androgen receptor blockade

Evolving Biomarkers

We NEED clarity and additional, informative biomarkers:

1. Prognostic information
2. Predictive therapeutic efficacy

*PD-L1
*PI3 Kinase
*AKT/mTOR
*Androgen receptor
**beyond ER:**
New/Evolving Targeted Strategies

<agenda>

- **Hormone Partners:**
  - CD4/6 inhibitors
  - mTOR-PI3K inhibitors

- **HER2 (+):**
  - APHINITY
  - ExteNET
  - KATHERINE

- IMpassion Trial (TNBC) and Immunotherapy
- PARP Inhibitors
- Androgen Receptor

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**CDK 4/6 Inhibition**

The CDK 4/6 apparatus permits the cell to proceed through
the cycle of cell division.

*What if:*

a. a **CDK 4/6 inhibitor** is developed

and

b. is paired with **hormone therapy** to offer a **dual**
  hormone-therapy + CDK 4/6 pathway blockade??

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**CDK4/6 Inhibitors = G1 Arrest**
**Dual Pathway Blockade**
Hormone Therapy + CDK 4/6 Inhibitor

- PALOMA (Ibrance/palbociclib)
- MONALEESA (Kisqali/ribociclib)
- MONARCH (Verzinio/abemaciclib)

Across trials the prolongation in progression-free survival (PFS) improved from ~10-15 months to **20-25 months** by adding a CDK 4/6 inhibitor to standard hormone therapy in the first line setting.

Oral, well tolerated (monitor wbc)

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**CDK 4/6 Inhibition**

Metastatic Trials = FDA APPROVED

- PALOMA (Ibrance/palbociclib)
- MONALEESA (Kisqali/ribociclib)
- MONARCH (Verzinio/abemaciclib)

Now, being explored in **HIGHER-risk** early stage breast cancer trials paired with standard hormone therapy

- standard hormone therapy (5+ years)
  +/−
- CDK 4/6 inhibitor for 2 years

*also, preoperative trials under investigation*
PI3Kinase/AKT/mTOR Pathway

An additional “target-able” strategy

Cell Signaling-Cross Talk:
PI3Kinase-AKT-mTOR Pathway

Dual Blockade?

A Model of Endocrine Resistance
**mTOR Aberrations**

"mammalian target of rapamycin"

Breast cancer cells can find other paths that can allow them to start to grow again.

The mTOR pathway is one path that can allow cancer to grow

UP TO 70%

"mTOR pathway" of breast cancer cases have changes, or mutations, on the mTOR pathway.

AI + mTOR inhibition = Dual Blockade

**Afinitor + Exemestane Works by Fighting in 2 Ways Instead of 1**

Blocking the mTOR pathway can slow the growth and spread of cancer cells.

**Everolimus (Afinitor): mTOR Inhibitor**

**BOLERO-2 Trial**

*The New England Journal of Medicine*
Everolimus + Exemestane Doubles CBR in HR (+) MBC

The Importance of the PI3K Pathway in Breast Cancer

The PI3K pathway is frequently altered in HR + breast cancer and has been implicated in endocrine resistance.

~40% of HR+ breast cancer harbor a PIK3CA mutation, leading to hyperactivation of the PI3K pathway.

PI3K signaling has been shown to promote estrogen independent growth of ER + breast cancer cells.
**SOLAR-1: Faslodex +/- Alpelisib**

\(<\text{study of an oral PI3Kinase Inhibitor}>\)

**SOLAR-1: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Trial (NCT02437318)**

- **Primary Endpoint:**
  - PFS in the PIK3CA mutant cohort

**Improvement in PFS in PIK3CA Mutant Cohort**

5.7 mo → 11 mo

**Sequencing Strategies**

HR (+) Stage IV Breast Cancer

- **Absolute algorithms evolving:**
  - [one strategy]
  - **1\(^{st}\) Line:** HT + CDK 4/6 Inhibitor
  - **2\(^{nd}\) Line:** Exemestane + Everolimus (mTOR Inhibitor)
  - **3\(^{rd}\) Line:** HT + PI3K Inhibitor [not yet approved]

*always consider a novel clinical trial concept, if eligible*

The goal is to **MAXIMIZE** effect/duration of hormone-based sequential therapies before resorting to chemotherapy.
**HER2 Updates**

**APHINITY:** Adding Pertuzumab/Perjeta to Herceptin x 1 yr

**ExteNET:** Sequencing Neratinib/Nerlynx x 1 yr after Herceptin/Perjeta

**KATHERINE:** Switching from Herceptin/Perjeta → Kadcyla following pre-operative therapy and <pCR

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**What is HER2?**

~20% of breast cancers

More aggressive YET "Target-able"

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**Adjuvant Herceptin**

![Graph showing disease-free survival rates for AC vs AC-TH with Herceptin](image)
Does the “HER Story” End at 2?

**Ligands**

- TGF-α
- Epiregulin
- Betacellulin
- HB-EGF
- Amphiregulin
- Neuregulins-3, -4

**Ligand-binding domain**

- Her2
- Erb-B1
- Erb-B2
- Erb-B3
- Erb-B4

**Tyrosine kinase domain**

- HER2
- EGFR
- ANU

*HER2 dimerizes with other members of the HER family.*


**...more complex than just HER2...**

**HER2 Pathway**

- HER2
- HER3
- HER4
- ERBB2
- ERBB3
- ERBB4

- Proliferation
- Migration
- Apoptosis

**Proportions of Patients Who Recurred Across Historical HER2+ Adjuvant Clinical Trials**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>% of patients with 10-year recurrence with the standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>HERA</td>
<td>26%</td>
</tr>
<tr>
<td>Joint Analysis</td>
<td>31%</td>
</tr>
<tr>
<td>N9640 (N203)</td>
<td>26%</td>
</tr>
<tr>
<td>BCIRG-006</td>
<td>26%</td>
</tr>
<tr>
<td>BCIRG-008</td>
<td>26%</td>
</tr>
<tr>
<td>AC 1501 Y and trastuzumab (N2075)</td>
<td>25%</td>
</tr>
</tbody>
</table>

**Describes improvement in the early stage treatment setting for HER2+ eBC**

≈1 in 4 patients who received a year of adjuvant treatment with the standard of care still experienced recurrence within 19 years*.

*Recurrence was based on patient experience at a disease-free survival (DFS) event, which included recurrence or death. 

† Rates of recurrence at 3 years were 19% in HER2, 13% in the Joint Analysis, 13% in BCIRG-006 with trastuzumab, and 12% in BCIRG-006 with AC followed by T and trastuzumab. 

‡ 3-year and 5-year event-free rates were derived from Kaplan-Meier analyses. 

AC = adjuvant chemotherapy alone; BCIRG = Breast Cancer International Research Group; TC = doxorubicin and cyclophosphamide; T = doxorubicin and cyclophosphamide in the nodalsetting alone (N203), or matched to the standard of care (N9640, N2075, N2040), or matched to the standard of care in the metastatic setting (N2061). 

Please see additional important Safety Information throughout and the accompanying.
Possible points of HER-blockade

Unmet Need....

1. ~25% risk of recurrence despite standard/historic therapy including chemotherapy + Herceptin x 1 year

2. Mechanisms of "escape" HER2 activation

..........can we improve upon outcomes??

HER2:HER3 Dimers May Provide An Escape Mechanism From Trastuzumab
**Herceptin + Perjeta**

Dual HER 2-3 Antibody Blockade

**Pertuzumab/Perjeta**

- Blocks alternate HER 2 → 3 pathway activation

- Preoperative trial data improved pathologic complete response (pCR) rates from ~30% → 60+%
...yet, dual HER2-3 Antibodies (Herceptin/Perjeta) do NOT result in COMPLETE HER-signaling Blockade

NERLYNX/Neratinib Provides More Comprehensive Irreversible Intracellular HER-Signaling Inhibition by Binding to HER 1,2,4

Sustained inhibition of signaling leads to increased tumor cell death**
**ExteNET: Phase 3, Global, Randomized, Double-Blind, Placebo-Controlled Trial**

Primary end point: invasive disease-free survival (iDFS)

Secondary end points: DFS, DCIS, time to distant recurrence, distant DFS, CNS metastases, OS, safety

Study population: 2840 women with early-stage HER2+ breast cancer; locally confirmed HER2 status; all patients had prior trastuzumab-based therapy within 2 years

**Treatment period**
- Trastuzumab-based adjuvant therapy
- Randomized 1:1
- NERLYNX 1 year
- n=1420
- NERLYNX 1 year, 240 mg, 1x daily
- n=1420

Primary analysis:
- iDFS at 2 years

Exploratory analysis:
- iDFS at 5 years

**ExteNET: 5-Year iDFS Analysis**

- 2.5% absolute benefit
- HR = 0.73; 95% CI: 0.57, 0.92
- vs placebo, P = .008

**What if a HER2 (+) tumor does NOT achieve a pCR following pre-op therapy?**

- More of the “same”?
  - continue Herceptin + Perjeta x 1 year?
  - OR

- Switch to an alternate targeted treatment strategy?
What is **Kadcyla**?

Trastuzumab Emtansine

- First antibody-drug conjugate approved in a solid tumor
- Trastuzumab connected via linker to small dose of emtansine (DM-1), a microtubule inhibitor 400-fold more potent than paclitaxel
- High affinity antibody and powerful payload
- Mechanisms of action:
  - Targeted delivery of chemotherapy
  - Anti-HER2 activity
- Limited toxicity
- Limited toxicity because of low systemic DM-1 levels
- Rare dose-limiting toxicities
- Mild fatigue
**Rationale for KATHERINE Study Design**

- HER2-positive early breast cancer patients with residual invasive disease following neoadjuvant chemotherapy combined with HER2-targeted therapy have an increased risk of recurrence and death.
- T-DH1 is active in HER2-positive metastatic breast cancer following prior exposure to trastuzumab and HER2-targeted therapy.
- A phase 2 study demonstrated that administration of T-DH1 following an anthracycline-containing regimen was feasible in patients with EBC.
- KATHERINE investigated whether substituting adjunctive T-DH1 for trastuzumab would improve outcomes for patients with residual invasive cancer following neoadjuvant therapy.

**KATHERINE Study Design**

- (T1-4N0-3M0 at presentation & T4bN1-2O0-excluded)
- Cancers confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of:
  - Minimum of 2 cycles of chemotherapy
  - Minimum of 3 weeks of abx
  - Anthracyclines and alkylating agents allowed
  - All chemotherapy prior to surgery
  - Minimum of 5 weeks of trastuzumab
  - Second HER2-targeted agent allowed
  - Residual invasive tumor in breast or axillary nodes
  - Randomization within 12 weeks of surgery

**KATHERINE: iDFS**

**Invasive Disease-Free Survival**

- Graph showing invasive disease-free survival rates among patients with and without T-DH1 treatment.
...even small volume residual disease benefits...

**IDFS Subgroup Analysis (2)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>T4N0</th>
<th>T1N0</th>
<th>T1N1</th>
<th>T2N0</th>
<th>T2N1</th>
<th>T3N0</th>
<th>T3N1</th>
<th>T4N1</th>
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<tbody>
<tr>
<td>pCR</td>
<td>0.8</td>
<td>0.6</td>
<td>0.7</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>pCR x 1 yr</td>
<td>0.8</td>
<td>0.6</td>
<td>0.7</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>&lt; pCR</td>
<td>0.2</td>
<td>0.4</td>
<td>0.3</td>
<td>0.4</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

**The Standard of Care Has Changed:**

T-DM1 should be recommended to the vast majority of patients with residual disease after a taxane-based neoadjuvant regimen

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wHERe do we go from here? <the evolving HER2 landscape>

**Early stage**

Preop chemo/HP → surgery

pCR: HP x 1 yr → Consider Nerlynx

< pCR: Kadcyla x 14 cycles → Consider Nerlynx

**Advanced stage**

Chemo/HP → Maintenance HP → [PD] → Kadcyla → *

*additional drugs in development

HP = Herceptin/Perjeta
IMpassion Trial  
Schmid et al

Triple Negative Breast Cancer (TNBC)  
- more aggressive  
- no discovered “targets”  

&  

Immunotherapy  
- historically, unclear role in breast cancer

Disrupting PD-1/PD-L1 interaction permits the immune system to "see" and attack the tumor

PD-L1/PD-1 blocking inhibits T cell killing of tumor cell  
Blinding PD-L1 or PD-1 allows T cell killing of tumor cell
What is PARP?

- an intracellular enzyme poly ADP ribose polymerase (PARP)
- plays a role in repairing damaged DNA
  - BRCA1, BRCA2 are proteins that are also important in the repair of DNA damage
- Drugs that inhibit PARP inhibit repair of DNA damage leading to the death of the cells
- BRCA (+) tumors are more susceptible to PARP inhibition cell death

...and why should it be INHIBITED?

- an intracellular enzyme poly ADP ribose polymerase (PARP)
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**PARP Inhibition**

**OlympiAD Trial**

Olaparib vs Chemo in BRCA (+) MBC

- PFS Improvement: 4.2 mo → 7.0 mo
- Favoring Olaparib/Lynparza vs Chemo
EMBRACA Trial
Talazoparib vs Chemo in BRCA (+) MBC

Study Design: EMBRACA

Primary endpoint:
Progression-free survival by RECIST by blinded central review

Key secondary endpoints:
- Treatment tolerability
- Overall survival
- OS by arm

PFS Improvement: 5.6 mo → 8.6 mo
Favoring Talazoparib/Talzenna vs Chemo

PARPi: lingering questions??

- patient selection
  - BRCA (+); TNBC
- stage of disease
  - MBC → EBC [neo and adjuvant]
- monotherapy or combination
  - platinum chemotherapy
- long term side effects
- ongoing clinical trials
The Unspoken Receptor: AR

Androgen Receptor
- Nuclear receptor activated by binding testosterone or dihydrotestosterone
- Closely related to PR
- Expressed in 75% of breast cancer and 10-20% of TNBC
- TNBC that express AR are molecularly similar to prostate cancer and could potentially be treated similarly
- Bicalutamide: anti-androgen used to treat prostate cancer
- 17 CMAG: semi-synthetic antibiotic derivative, has shown promise in clinical trials
Enzalutamide: androgen agonist used to treat prostate cancer; is in Phase III for TNBC

The AR Overlay in Breast Cancer

- ~70% of all breast cancers are positive for the AR
- 60-70% of ER+ express AR
- 50-60% of HER2+ express AR
- 20-30% of TNBC express AR

Enzalutamide activity in AR+ TNBC Model
AR: Evolving Target in TNBC

- AR biomarker development/validation
- Enzalutamide biomarker signature in other cohorts
- AR mutation analysis in BC
- Preferred agent or mechanism
- Pathways
  - PI3K inhibitors
  - mTOR inhibitors
  - CDK4/6 inhibitors
- Pharmacogenomics
- Mechanisms of resistance
- Role in adjuvant setting for AR+ TNBC

So.....it’s complicated!!

<much more so than it appears>

....yet, we are making progress!

<lots, recently>

the current mantra

1) Identify dominant/mutated pathways
2) Develop reliable, prognostic biomarkers
3) Develop targeted, effective therapeutics

As we tailor our “naming” and individualize management with targeted strategies, we will observe improved outcomes with lesser toxicity
Compass Oncology Trials
< a sampling >

17188: Neoadjuvant High Risk HR (+)/HER2(-):
Chemo +/- Pembrolizumab [immunotherapy]

18042: Neoadjuvant Talazoparib [PARPi] in BRCA (+) TNBC

17082: MonarchE: Adjuvant Abemaciclib [CDK 4/6i] in higher risk HR(+)/HER2(-)

< clinical trial lists are always changing >

Thanks
< to all of you >

Dr. Jejan Juric
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< for data/slide sharing >