Susan G. Komen for the Cure
Virtual Metastatic Breast Cancer Conference 2020

Metastatic Breast Cancer Research: Past, Present, and Future

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Conflicts

- **Circulating Tumor Cells**
  - **CellSearch**
    - Laboratory and Clinical research funding from Veridex/Janssen Diagnostics/Menarini Silicon BioSystems
    - Patent regarding circulating tumor cells licensed to MSB
  
- **Other**
  - **Stock Options:** OncImmune, InBiomotion
  - **Consultant:** Agendia, Cellworks, Cepheid, CVS Caremark
  - **Sponsored Clin Research:** Merrimack Pharmaceuticals, Eli Lilly, Menarini/Silicon BioSystems, Puma Biotechnology, Pfizer, Astra Zeneca
  - Collaborated with GHI, manufacturer of 21-gene RS
    (no financial support or conflict)
The problem with quotes on the internet is that they are often not true.

—Abraham Lincoln
Early Stage Breast Cancer

First: the Good News-
Breast Cancer Mortality in the U.S. Has **Decreased** Substantially Over the Last 30 Years
Increase in Breast Cancer Incidence but Decrease in Mortality
1975-2012

For white women, proportionally decreased by ~ 40%

For Black women, proportionally decreased by ~ 20%

OVERALL: Breast Cancer Mortality Decreased by 36%
First: the Good News-

Breast Cancer Mortality in the U.S. Has Decreased Substantially Over the Last 30 Years

Why?

• Screening

• Better and More Well Tolerated Therapies
Increase in Breast Cancer Incidence but Decrease in Mortality

1975-2012

OVERALL: Breast Cancer Mortality Decreased by 36%
Early Stage Breast Cancer

Second: Mixed News-

Although We Would Have Lost Many More Patients to Breast Cancer Without the Advances,

~40,000 U.S. Women Will Die of Br Ca in 2020
Deaths Averted by Advances in Breast Cancer Screening and Therapy 1990-2012

Anticipated Breast Cancer Deaths in US at unabated 1989 rate

Actual Number of Breast Cancer Deaths recorded in each year

Early Stage Breast Cancer

Second: Mixed News-
Although We Would Have Lost Many More Patients to Breast Cancer Without the Advances,

~40,000 U.S. Women Will Die of Br Ca in 2020

Who Are These Patients?
• All Types of Breast Cancers
• Disproportionally those with **ER Positive** Disease Who Will Experience **Late Recurrences**
Distant Recurrence by Nodal Status & T Size

Patients Without Recurrence @ 5 Yrs; Years 5-20

No. at risk (and, in each 5-year period, no. of events and a

| T1N4-9   | 3832 (391, 33%) | (68, 2.2%) |
| T1N1-3  | 14342 (734, 19%) | (162, 1.1%) |
| T1N0   | 19402 (509, 0.8%) | (218, 1.1%) |
Why Do These Patients Keep Suffering Recurrences?

• They are not taking their drugs
  – Adherence/Toxicity

• They still have cells but the current therapy isn’t working
  – Prediction/Resistance

• They still have cells but the current therapy isn’t working
  – Prognosis/Dormancy
Does Everyone Need to Take Extended ET?

- Potential determinants of late risk other than nodal status, tumor size and grade

- Biology of primary tumor (multi-gene expression assays, etc)

- Identification of dormant disease with recurrence potential:
  - Disseminated or circulating tumor cells (DTC, CTC)
  - Circulating cell free tumor DNA (cftDNA)
  - Circulating protein or metabolites?

NONE OF THESE HAS BEEN CLINICALLY VALIDATED AND SHOULD NOT BE MONITORED OR USED TO MAKE THE DECISION REGARDING EXTENDED ET!!
New Advances in Metastatic Disease

• **Goal of Therapy (2020)**
  – Very few if any patients with established metastatic disease are cured
  – But, the length of time patients live with their disease is much longer than 35 years ago
    • Median was ~ 18 months
    • Now ~ 35 months
  – Why?
    • Better understanding of the biology of Breast Cancer
    • Ability to target the biology
New Advances in Metastatic Disease

• **Goal of Therapy (2020)**
  – Therefore, main goal of therapy is “Palliation”
    • Keeping you feeling as good as you can for as long as you can
  – In addition, longer survival
  – Taken together: *living longer, living well.*

• **How?**
  – Pick therapies most likely to work with the fewest side effects
  – Assess whether:
    • You are tolerating the therapy
    • It is working
  – Change if
    • Not tolerating
    • Not working
Breast Cancer Biology

- Estrogen Receptor
  - MTOR activation
  - CDK4/6 activation
  - PIK3CA mutations

- HER2

- BRCA1/2 mutations

- Programmed Death Ligand 1 (PD-L1)
<table>
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<tr>
<th>Condition</th>
<th>Type drug</th>
<th>Generic</th>
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<td>LHRH agonists</td>
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<td>Arom Inhibitor</td>
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<td>Letrozole</td>
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<td>Ambemaciclib</td>
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<td>MTOR inhibitor</td>
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<td>ADC</td>
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<td>PARP Inhib</td>
<td>Olabari</td>
<td>Lynparza</td>
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<td>Talazoparib</td>
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<td>Cancer</td>
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Estrogen Receptor (ER)

- **Too much ER – “Endocrine” (or anti-estrogen) therapies:**
  - Selective ER Modulator (SERM)  Tamoxifen (Nolvadex)
  - Suppression of ovarian function  Zoladex, Leupron
  - Aromatase inhibitors  Arimidex, Femara, Aromasin
  - Selective ER DownRegulator (SERD)  Faslodex

- **Mutated ER**
  - SERD (Oral) in trials

- **Add to Endocrine therapies**
  - MTOR inhibitor  Afinitor
  - CDK 4/6 inhibitor  Ibrance, Kisqaly, Versinio
  - PIK3CA inhibitor  Piqray
HER2

• Too much HER2 – anti-HER2 therapies:
  – Antibodies directly against HER2
    • Subcutaneous Herceptin
    – Herceptin+drug conjugates (Trojan Horse)
  – Tyrosine Kinase Inhibitors
  Herceptin, Perjeta, (Margetuxumab)
  Hylecta
  Kadcyla (Herceptin plus emtansine),
  Enhertu (Herceptin plus deruxtecan)
  Tykerb, Nerlynx, Tukysa

• Mutated HER2
  Nerlynx
Antibody-Drug Conjugates

• Chemotherapy “payload” is linked to antibody
• Antibody binds to a target on the cancer cell
• Entire Complex internalized
• Link broken
• Chemotherapy kills cell
• Chemotherapy leaks out but at much lower concentrations in blood – less toxicity than if infused as free chemotherapy
“Triple Negative”

• **BRCA1/2 mutated OR “mutated like”**

• **Inhibitors of PARP**
  - Lynparza, Talzenna
  - Veliparib (not approved)

• **PD-L1 over-expressed (ImmunoRx)**
  - Immune Checkpoint inhibitors
    - Tecentriq, Keytruda

• **Antibody-Drug Conjugate**
  - Trodelvy
Proposed Mechanism of PARP1 Inhibition in “BRCA-like” (germ line and/or somatic) Breast Cancer

DNA Damage

DNA Repair Occurs

Cell Viable

DNA Repair Inhibited

Cell Dies = Response

Cancer Cell

BrCa1 PARP1

Non-Ca Cells (WBC, GI, etc)

BrCa1 PARP1

DNA Repair Occurs

Cell Viable

DNA Repair Occurs

Cell Viable = low toxicity
Innovations in Immune Therapies Against Cancer

The immune system is designed to get rid of invading germs from outside our bodies.

Bacteria

BUT the immune system cannot go after our own cells, even when they become malignant!

They have a cloak of invisibility!!

Cancer Cell
Innovations in Immune Therapies Against Cancer

Scientists have figured out how to break through the “cloak of invisibility”!!

At least 7 new drugs that break the cloak of invisibility and allow the immune system to go after the cancer cells:

These work for:
- Melanoma
- Colon Cancer
- Lung Cancer
- Others (NOBEL PRIZE: 2018)
- And now: selected Triple Negative Breast Cancers!
Research in Metastatic Breast Cancer

• Diagnostics
  – “Next Generation Sequencing”- looking for needles in big haystack that might be targets for therapy
  – “Circulating” Tumor biomarkers in blood
    • Circulating tumor cells
    • Circulating cell free tumor DNA
  – Novel Imaging approaches
Research in Metastatic Breast Cancer

• Summary
  – Lots better than 35 years ago
  – New stuff almost every month
  – Still not good enough

  – RESEARCH RESEARCH RESEARCH

• Participate in clinical trials if they make sense to you
• Raise more money (Komen for the Cure!!)