Metastatic Breast Cancer: What is New?

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Where are we now compared to 10 years ago?

- Better understanding of breast cancer subtypes
- Many more treatments available across all subtypes
- More ability to tailor treatments to specific features of the cancer or the patient
- More attention paid to quality of life, symptom management, mental health, and more options to enhance these
- **Longer and better survival**
Drugs approved by the FDA for treatment of MBC since 1995

• **Hormonal therapy**
  - Anastrozole (Arimidex)
  - Letrozole (Femara)
  - Exemestane (Aromasin)
  - Fulvestrant (Faslodex)

• **Chemotherapy**
  - Capecitabine (Xeloda)
  - Docetaxel (Taxotere)
  - Gemcitabine (Gemzar)
  - Ixabepilone (Ixempra)
  - Eribulin (Halaven)
  - Nab-paclitaxel (Abraxane)

• **HER2 Therapy**
  - Trastuzumab (Herceptin)
  - Pertuzumab (Perjeta)
  - Lapatinib (Tykerb)
  - Trastuzumab emtansine (TDM1)

• **Other targeted therapy**
  - Everolimus (Affinitor)
  - Palbociclib (Ibrance)
  - Ribociclib (Kisqali)
  - Abemaciclib (Verzenio)
  - Olaparib (Lynparza)
  - Talazoparib (Talzenna)
  - Alpelisib (Piqray)
  - Atezolizumab (Tecentriq)
Supportive care drugs approved by the FDA since 1995

- **Bone protective agents**
  - Pamidronate (Aredia)
  - Zoledronic acid (Zometa)
  - Denosumab (Xgeva)

- **Growth factors**
  - Neulasta

- **Anti-nausea medications**
  - Emend
  - Aloxí
  - Kytril

- **Anti-depressants/other**
  - Effexor
  - Celexa
  - Lexapro
  - Cymbalta
What do we want the future to look like?

• More effective treatments, with fewer side effects

• Better ability to match the right treatment to the right patient

• Minimize/eliminate death from metastatic breast cancer

• Cure?
Why has progress been so slow?

• Breast cancer is complex

• There are multiple subtypes, and there are subtypes of subtypes

• Unfortunately, breast cancer is a “smart” cancer....it can adapt and change in response to outside influence, like drugs

• Metastatic cancer is even smarter, because it takes additional skills to spread beyond the breast and lymph nodes

• Cancer is not a “foreign invader”, to a large extent it is self, which makes treatment strategies particularly challenging
The Importance of Basic Research, Translational Research and Clinical Trials

**Basic Research**

• Basic research provides the backbone for scientific discovery

• Our understanding of breast cancer biology is dependent on vibrant basic research – from scientific standpoint, it is an investment that pay off time and time again

• Many critical questions have been addressed by basic research
  - What makes cancer cells grow?
  - How do they invade?
  - How do they spread?
The Importance of Basis Research, Translational Research and Clinical Trials

**Translational Research**

- Brings together basic science and clinical research
- Seeks to provide biologic explanations for clinical findings and clinical implications of biologic findings
- Can lead to new treatments
- Almost all clinical trials contain translational component – we don’t want to develop new treatments without understand why and how they work and in whom they work best
The Importance of Basis Research, Translational Research and Clinical Trials

Clinical Trials

• Clinical trials test new approaches – either entirely new drugs, new combinations, or new uses

• The treatments we use today are the result of information gained from patient volunteers in clinical trials – which is why breast cancer is ahead of many malignancies

• We have a much better understanding of underlying biology and drug mechanism going into a clinical trial than ever before

• No drug goes from the laboratory to the pharmacy shelf – clinical trials are a necessary intermediate step
Will participating in a clinical trial help me?

• True beneficiaries are the next generation of patients
• But patients can clearly benefit from trials and access treatments that might not be available in any other way
• Phase I trials test safety and efficacy
• Phase II trials test efficacy and safety
• Phase III trials, which are randomized, are trying to change the standard of care – they test the standard approach vs an approach that many people believe may be better
• Of course, the purpose of a trial is to improve outcomes, but there are no guarantees
Genes are not the entire answer, but they can shed light on how a cancer is different from normal tissue and what strategies might be effective.
Circulating tumor DNA (ctDNA)

- Metastatic biopsies can be challenging
- Cancer (and normal) cells shed ctDNA into blood
- ctDNA could identify markers of drug sensitivity or resistance in a cancer
Genomic analysis, either from tumor tissue or circulating tumor DNA, has been most useful in setting of ER+ disease.

Testing for PIK3CA mutations affects decisions about a commercially available agent, alpelisib. Furthermore, testing for ESR, Rb, and HER2 mutations may impact trial participation.

In setting of TNBC and HER2+ breast cancer, genomic testing has not been clinically useful to date but is of interest from research perspective.
Genetic testing vs tumor testing

• “genetic testing” usually refers to *germline* testing
  
  ▪ Blood or saliva test
  
  ▪ Looks for genes inherited through mother or father
  
  ▪ Can be passed on to children
  
  ▪ Spelling changes in these genes can raise the risk of cancer
Who should get genetic testing?

- Breast cancer diagnosed < age 45
- Triple-negative breast cancer age ≤ 60
  - Even if no family history of breast cancer
- Family history of breast and/or ovarian cancer
- Male relative with breast cancer
- Certain ethnic groups at higher risk of carrying BRCA 1 or BRCA 2 mutation
Who should get genetic testing?

Updated Recommendations:
The availability of “panel testing” and the approval of PARP inhibitors means that most patients with MBC should be considered for genetic testing.
Breast Cancer Subtypes

Talk to your doctor if you are not sure what type of breast cancer you have!

The proportions differ in the metastatic setting:
- TN: 25-30%
- HER2+: 10-15%
- ER+/HER2-: 55-65%

ER-positive
HER2-positive
Triple-negative
ER+ (HR+) Disease
Therapy for patients with advanced ER+ breast cancer

• Strong preference to begin treatment using endocrine (hormone) therapy

• Several standard choices ("lines") of endocrine therapy; generally can be very effective at controlling the cancer with minimal side effects
  • Non-steroidal AI (letrozole, anastrozole), steroidal AI ( exemestane), fulvestrant, tamoxifen

• We have new choices to improve efficacy of endocrine therapy and delay onset of resistance
How can we enhance efficacy of endocrine therapy?
Cyclin Dependent Kinase (CDK 4/6) inhibition

• A classic feature of breast cancer is uncontrolled growth

• In ER+ breast cancer, out-of-control growth may be due to a failure in the braking system: overactive CDK4/6
Many potential mechanisms of action

• Cell cycle inhibition:
  • puts the brakes on cell growth

• Synergistic activity
  • potentiates hormonal therapy

• Immune modulatory
  • potential to boost our immune response
## Summary: CDK4/6 in ER+/HER2- MBC

<table>
<thead>
<tr>
<th>Line</th>
<th>Study Name</th>
<th>Endocrine Agent</th>
<th>CDK4/6 inhibitor</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>PALOMA-1 Lancet 2015</td>
<td>Letrozole</td>
<td>Palbociclib</td>
<td>POSITIVE</td>
</tr>
<tr>
<td></td>
<td>PALOMA-2 NEJM 2016</td>
<td>Letrozole</td>
<td>Palbociclib</td>
<td>POSITIVE</td>
</tr>
<tr>
<td></td>
<td>MONALEESA-2 NEJM 2016</td>
<td>Letrozole</td>
<td>Ribociclib</td>
<td>POSITIVE</td>
</tr>
<tr>
<td></td>
<td>MONALEESA-7 SABCS 2017</td>
<td>Letrozole + OFS</td>
<td>Ribociclib</td>
<td>POSITIVE</td>
</tr>
<tr>
<td></td>
<td>MONALEESA-3 JCO 2018</td>
<td>Fulvestrant</td>
<td>Ribociclib</td>
<td>POSITIVE</td>
</tr>
<tr>
<td></td>
<td>MONARCH-3 JCO 2017</td>
<td>NSAI</td>
<td>Abemaciclib</td>
<td>POSITIVE</td>
</tr>
<tr>
<td>2nd</td>
<td>PALOMA3 NEJM 2015</td>
<td>Fulvestrant</td>
<td>Palbociclib</td>
<td>POSITIVE</td>
</tr>
<tr>
<td></td>
<td>MONARCH2 JCO 2017</td>
<td>Fulvestrant</td>
<td>Abemaciclib</td>
<td>POSITIVE</td>
</tr>
</tbody>
</table>
CDK4/6 inhibitors: Efficacy not affected by age (and toxicity is not substantially worse)
### CDK4/6 Inhibitors Selection and Toxicities

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Most Common Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palbociclib (Ibrance)</td>
<td>Low white blood cell count, fatigue, hair thinning</td>
</tr>
<tr>
<td>Ribociclib (Kisqali)</td>
<td>Low white blood cell count, elevated liver function tests, rare prolongation of heart conduction</td>
</tr>
<tr>
<td>Abemaciclib (Verzenio)</td>
<td>Diarrhea, fatigue</td>
</tr>
</tbody>
</table>

Activity of the three agents in clinical trials is remarkably consistent and similar

- Supports the important role of CDK4/6 inhibition for advanced ER+ breast cancer, used with first line endocrine therapy, or with subsequent lines
- No data to support one agent over another, one can select by side effect profile
Overall Survival: Fulvestrant +/- Ribociclib
Reduction in Relative Risk of Death with Ribociclib was 28%

**N=726**

- The $P$ value of 0.00455 crossed the prespecified boundary to claim superior efficacy ($P < 0.01129$)

**Landmark Analysis**

<table>
<thead>
<tr>
<th>KM Estimate</th>
<th>RIB + FUL</th>
<th>PBO + FUL</th>
</tr>
</thead>
<tbody>
<tr>
<td>36 months</td>
<td>67.0%</td>
<td>58.2%</td>
</tr>
<tr>
<td>42 months</td>
<td>57.8%</td>
<td>45.9%</td>
</tr>
</tbody>
</table>

**Events/N**
- RIB + FUL: 167/484
- PBO + FUL: 108/242

**OS, median (95% CI), mo**
- RIB + FUL: NR (42.5-NR)
- PBO + FUL: 40.0 (37.0-NR)

**HR (95% CI)**
- RIB + FUL: 0.724 (0.568-0.924)

**$P$ value**
- 0.00455
Overall Survival: Fulvestrant +/− Abemaciclib

**abemaciclib + fulvestrant:**

- Median OS: 46.7 months
- No. of events: 211

**placebo + fulvestrant:**

- Median OS: 37.3 months
- No. of events: 127

**9.4 month OS benefit**

HR (95% CI) = 0.757 (0.606 to 0.945)
P = 0.0137

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Many Questions about the Use of CDK4/6 Inhibitors

• Can we identify markers in a cancer that will predict if the cancer will respond to CDK4/6 therapy, or whether a cancer has become resistant?

• Should we continue CDK4/6 if a cancer gets worse? Is it resistant to endocrine therapy, CDK4/6 inhibitor, or both?

• What about combining CDK4/6 inhibitors with other agents, for example with immunotherapy medications?
PACE Trial: Palbociblib after CDK4/6 Inhibitor and Endocrine Therapy

Advanced HR+/HER2- Progression on AI + CDK4/6 inhibitor 0-1 prior chemo

cfDNA to determine RB status, ESR1 mutation, PIK3CA mutation

Designed and open at DFCI
PI: Erica Mayer
Targeting the PI3K pathway

In setting of endocrine resistance, dual targeting may be important.
**BOLERO-2: Successful mTOR Inhibition**

- **N = 724**
  - Postmenopausal ER+ HER2- MBC refractory to letrozole or anastrozole

- **Everolimus 10 mg/day + Exemestane 25 mg/day (N = 485)**

- **Placebo + Exemestane 25 mg/day (N = 239)**

  - **PFS**
  - **OS**
  - **ORR**
  - **Bone Markers**
  - **Safety**
  - **PK**

- **Stratification:**
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease

- **No cross-over**

Baselga et al, ESMO 2011
**BOLERO-2 Efficacy:**
Addition of Everolimus (EVE) to Exemestane (EXE)
More Than Doubled Median PFS

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**PFS Local***

<table>
<thead>
<tr>
<th>Event Type</th>
<th>HR (95% CI)</th>
<th>Log-rank P value</th>
<th>EVE + EXE</th>
<th>PBO + EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>0.45 (0.38–0.54)</td>
<td>&lt; 0.0001</td>
<td>7.82 months</td>
<td>3.19 months</td>
</tr>
</tbody>
</table>

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**PFS Central***

<table>
<thead>
<tr>
<th>Event Type</th>
<th>HR (95% CI)</th>
<th>Log-rank P value</th>
<th>EVE + EXE</th>
<th>PBO + EXE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>0.38 (0.31–0.48)</td>
<td>&lt; 0.0001</td>
<td>11.01 months</td>
<td>4.14 months</td>
</tr>
</tbody>
</table>

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**Final PFS Analysis at 18 mo:** 4 month improvement in PFS over AI alone

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What About Targeting PI3K?

- Laboratory work suggests PI3K inhibitor + endocrine therapy is additive

- Almost 40-45% of ER+ breast cancer has a PIK3CA mutation – does this predict a cancer will be sensitive?

- Selective PI3K inhibitors are in Phase III trials

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1. Miller et al. JCO 2010
2. Baselga et al. NEJM 2012; Bachelot et al. JCO 2012
3. Raynaud et al., MCT 2009
SOLAR-1: Progression free survival in PIK3CA-mutant cohort

<table>
<thead>
<tr>
<th></th>
<th>Alpelisib + Fulvestrant (n = 169)</th>
<th>Placebo + Fulvestrant (n = 172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mos (95% CI)</td>
<td>11.0 (7.5-14.5)</td>
<td>5.7 (3.7-7.4)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.65 (0.50-0.85); P = .00065</td>
<td></td>
</tr>
<tr>
<td>Events, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Progression</td>
<td>99 (58.6)</td>
<td>120 (69.8)</td>
</tr>
<tr>
<td>▪ Death</td>
<td>4 (2.4)</td>
<td>9 (5.2)</td>
</tr>
<tr>
<td>▪ Censored</td>
<td>66 (39.1)</td>
<td>43 (25.0)</td>
</tr>
</tbody>
</table>

- Similar PFS outcome for alpelisib + fulvestrant vs placebo + fulvestrant in retrospective analysis of PIK3CA mutation status via ctDNA testing
  - Median PFS: 10.9 vs 3.7 mos, respectively; HR: 0.55

- More patients with BL measurable disease experienced decreases in tumor burden with alpelisib + fulvestrant vs placebo + fulvestrant (75.9% vs 43.5%, respectively)
Selective Estrogen Receptor Downregulators (SERDs)

- SERDs degrade the estrogen receptor on the outside and the inside of the breast cancer cell
- ER degradation prevents the stimulation of many genes involved in cancer cell proliferation and survival

Several agents in development:
- RAD1901 – phase III
- Bazedoxifene – phase II
- GDC-9545 – phase I
Conclusions for ER+ Breast Cancer

• Incredibly exciting work in breast cancer research for ER+ breast cancer
  • New targets
  • Moving away from chemotherapy
  • Real progress in understanding (and overcoming) drug resistance

• Future progress depends on...
  • Continued clinical trial efforts
  • Strong basic and translational work
  • Funding from the government, foundations, industry, and philanthropy
HER2 gene amplification results in marked overexpression of HER2 proteins

There has been dramatic progress in treatment of HER2+ MBC over the past 20 years...and it continues!
Trastuzumab is a recombinant antibody that specifically binds to the HER2 protein.
Chemotherapy versus Trastuzumab + Chemotherapy in HER2+ MBC

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy (AC/paclitaxel)</th>
<th>Chemotherapy plus trastuzumab</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>32%</td>
<td>50%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PFS</td>
<td>4.6 months</td>
<td>7.4 months</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OS</td>
<td>20.3 months</td>
<td>25.4 months</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Slamon et al, NEJM 2001
Proposed Mechanism of Pertuzumab/Trastuzumab Synergy
First-Line Setting: CLEOPATRA:
Phase III Trial of Docetaxel + Trastuzumab + Placebo vs Pertuzumab

End points
- PFS and OS
- quality of life
- biomarker analysis

HER2-positive MBC
(53% no prior chemo
10% prior trastuzumab)

Docetaxel + trastuzumab + placebo
Docetaxel + trastuzumab + pertuzumab

N=800

Only 10% had prior trastuzumab in adjuvant setting
The 56.5-month median OS was unprecedented and established the role of pertuzumab in the first-line metastatic. Improvement in OS is larger than the PFS benefit.
T-DM1 Selectively Delivers DM1 to HER2-Positive Tumor Cells

- T-DM1 binds to the HER2 protein on cancer cells.
- Receptor-T-DM1 complex is internalized into HER2-positive cancer cell.
- Potent antimicrotubule agent is released once inside the HER2-positive tumor cell.
EMILIA: T-DM1 vs Capecitabine/Lapatinib in Second Line Setting

Second interim analysis confirmed a statistically significant benefit in overall survival with T-DM1

<table>
<thead>
<tr>
<th></th>
<th>Median (mos)</th>
<th>No. events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>6.4</td>
<td>304</td>
</tr>
<tr>
<td>T-DM1</td>
<td>9.6</td>
<td>265</td>
</tr>
</tbody>
</table>

Stratified HR=0.650 (95% CI, 0.55, 0.77)  

\[ P<0.0001 \]
Trastuzumab +/- Pertuzumab in Combination with Hormonal Therapy? (PFS)

### Table: Event-Free Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events, n (%)</th>
<th>Median, months</th>
<th>(95% CI)</th>
<th>Δ, months</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab + Trastuzumab + AI</td>
<td>74 (57.4)</td>
<td>18.39</td>
<td>(14.95, 27.66)</td>
<td>3.09</td>
<td>0.65 (0.48, 0.89)</td>
<td>0.0070</td>
</tr>
<tr>
<td>Trastuzumab + AI</td>
<td>92 (71.3)</td>
<td>15.80</td>
<td>(11.94, 18.56)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Analysis

- **N at risk**
  - 129 at 0 months
  - 123 at 1 month
  - 121 at 2 months
  - 114 at 3 months
  - 107 at 4 months
  - 102 at 5 months
  - 91 at 6 months
  - 81 at 7 months
  - 73 at 8 months
  - 67 at 9 months
  - 64 at 10 months
  - 54 at 11 months
  - 47 at 12 months
  - 42 at 13 months
  - 33 at 14 months
  - 28 at 15 months
  - 22 at 16 months
  - 18 at 17 months
  - 13 at 18 months
  - 8 at 19 months
  - 5 at 20 months
  - 3 at 21 months
  - 1 at 22 months

Analysis based upon Kaplan–Meier approach including stratification factors from IXRS. HR from a stratified Cox proportional hazards model including stratification factors from IXRS. Median time of follow-up: 31 months. CI, confidence interval; HR, hazard ratio.

Rimawi, SABCS 2016
Treatment Approach For Patient Presenting With HER2+ MBC in 2018

**First Line:**
- Taxane + Trastuzumab + Pertuzumab

**Second Line:**
- TDM-1

**Third, Fourth... Line**
- Capecitabine + Lap
- Capecitabine + Trast
- Vinorelbine + Trast
- Lapatinib + Trast
- Other chemo + Trast
- Endocrine Therapy + Trast +/- Pertuzumab

**Exception:**
*Patients with ER+/PR+ disease can be treated up front with hormonal therapy generally with anti-HER2 therapy*
## CNS Relapse in HERA

<table>
<thead>
<tr>
<th></th>
<th>1 Year Trastuzumab</th>
<th>Observation</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
<td>1703</td>
<td>1698</td>
<td>3401</td>
</tr>
<tr>
<td><strong>CNS as 1st Event</strong></td>
<td>37 (2%)</td>
<td>32 (2%)</td>
<td>69 (2%)</td>
</tr>
<tr>
<td><strong>Other Site as 1st Event</strong></td>
<td>326 (19%)</td>
<td>421 (25%)</td>
<td>747 (22%)</td>
</tr>
<tr>
<td><strong>Died with CNS Relapse</strong></td>
<td>98 (47%)</td>
<td>98 (57%)</td>
<td>196 (53%)</td>
</tr>
</tbody>
</table>

*Pestalozzi et al, Lancet Oncol 2013*
Many potential challenges

• Blood brain barrier?
• Tumor microenvironment?
• Genomic changes?
CNS Response to Large HER2-Directed Molecules

Pre-T-DM1

Post-T-DM1

High Dose Trastuzumab + Pertuzumab

Figure 4. Efficacy within the CNS per RANO-BM criteria (N=15)

CBR, clinical benefit rate; CNS, central nervous system; CR, complete response; ORR, objective response rate; PR, partial response; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; SD, stable disease.
Lapatinib + Capecitabine for HER2+ BCBM

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prior RT</th>
<th>CNS ORR</th>
<th>TTP/PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al, CCR 2009*</td>
<td>50</td>
<td>100%</td>
<td>20%</td>
<td>3.6 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Boccardo et al, ASCO 2008 (LEAP)</td>
<td>138</td>
<td>NR</td>
<td>18%</td>
<td>Median time on study 2.8 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Sutherland et al, Br J Ca 2010 (LEAP)</td>
<td>34</td>
<td>94%</td>
<td>21%</td>
<td>5.1 mo</td>
<td>NR</td>
</tr>
<tr>
<td>Metro et al, Ann Oncol 2011</td>
<td>22</td>
<td>86%</td>
<td>32%</td>
<td>5.1 mo</td>
<td>11 mo from start of LC</td>
</tr>
<tr>
<td>Lin et al, J Neuro-Oncol 2011*</td>
<td>13</td>
<td>100%</td>
<td>38%</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Bachelot et al, Lancet Oncol 2013*</td>
<td>45</td>
<td>0%</td>
<td>66%</td>
<td>5.5 mo</td>
<td>91% alive at 6 mo</td>
</tr>
</tbody>
</table>

As a single agent, CNS ORR to lapatinib is only ~ 6%
(Lin et al, CCR 2009)

In pre-treated patients, lapatinib-cape results in CNS ORR 18-38%

In the upfront setting (instead of RT), lap-cape results in CNS ORR 66%
Capecitabine and Neratinib: Volumetric Response

Best CNS Volumetric Response (n=31)*

CNS ORR = 49% (95% CI 32-66%)

18 responses

Led to compendium listing by NCCN

Freedman et al, ASCO 2017, JCO 2019
Tucatinib – Potent and Selective HER2 Inhibitor

- Selective small molecular tyrosine kinase inhibitor with nanomolar potency
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
  - Phase 1 single agent data had no rx-related g3 diarrhea in heavily pretreated patients
- Penetrates CNS very well

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cellular Selectivity Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HER2 IC₅₀ (nM)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>49</td>
</tr>
<tr>
<td>Neratinib</td>
<td>7</td>
</tr>
<tr>
<td>Tucatinib</td>
<td>8</td>
</tr>
</tbody>
</table>

Moulder et al. AACR-NCI-EORTC 2011; Koch et al. AACR 2011; Borges et al. AACR Special Conference on Advances in Breast Cancer Research 2013
Orthotopic PDX Models of Brain Metastases

*Note: Initial experiments done by intracranial injection—we have subsequently shown success using intra-carotid or intra-cardiac injection

Courtesy of Jean Zhao
PDXs maintain the pathological and molecular profiles of primary tumors

<table>
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<tr>
<th>BM-ID#</th>
<th>HER2</th>
<th>ER</th>
<th>PTEN</th>
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</table>
PDX models of brain metastases derived from HER2 breast cancer patients

In the brain

Primary Tx

Primary Tx
In the brain

Primary Tx
mammary gland

BT354

BT355

+  

+  

-

In general, brain mets have a substantially higher take rate in brain than mammary fat pad

J Ni, & S. Ramkissoon
(Zhao laboratory)
Evaluation of Rational Targeted Therapies

Single Agents with Minimal Activity
-- lapatinib
-- BKM 120
-- bromodomain inhibitor
-- RAD 001

Multiple Combinations Tested
With Minimal Activity Except
BKM + RAD 001

Ni et al, Nat Med 2016
Perhaps more than in any other area of HER2+ disease, progress will only be made as a result of close collaboration between laboratory and clinic
Triple Negative Breast Cancer

• The most feared subtype of metastatic disease
• We still need to make a great deal of progress
• But we finally have new drugs and far greater hope
Commonly Used Chemotherapy Regimens for Patients with Metastatic TNBC

- Paclitaxel (Taxol)
- Eribulin (Halaven)
- Carboplatin
- Cisplatin
- Gemcitabine (Gemzar)

- Capecitabine (Xeloda)
- Vinorelbine (Navelbine)
- Nab-Paclitaxel (Abraxane)
- Liposomal Doxorubicin (Doxil)
- Doxetaxel (Taxotere)
Choice of Chemotherapy in Metastatic TNBC

• Order of chemotherapy does not appear to influence survival

• Choose chemotherapy based on:
  • Activity level seen in clinical trials
  • Amount of active cancer/need for rapid response
  • Prior treatments
  • Route of administration (pills versus IV)
  • Side effect profile
  • BRCA 1/2 status
  • Other health problems
    • Blood counts, neuropathy, diabetes, heart problems, liver function
What is the function of BRCA1 or BRCA2?

• BRCA proteins participate in repair of cells can lose the normal copy of BRCA 1 or 2

• This leads to problems repairing DNA, which increases the chance of cancer

• Triple negative breast cancer is most common subtype in BRCA-associated breast cancer, particularly BRCA1

• When both copies of BRCA are lost, the cell depends on another pathway, which is dependent on PARP, to repair DNA (which happens very frequently)
Phase 3 **OlympiAD** Trial: Olaparib vs Chemotherapy in gBRCA-Associated Breast Cancer

- Patient with germline BRCA1 or BRCA2 mutation
- Metastatic breast cancer (MBC)
-Either ER+ or Triple Negative
- Up to 2 previous types of chemo for MBC

CHEMOTHERAPY*

OLAPARIB

*Choice of vinorelbine (Navelbine), capecitabine (Xeloda), or eribulin (Halaven)

302 patients enrolled and randomized

Robson et al, NEJM 2017
Phase 3 OlympiAD Trial: Olaparib vs Chemotherapy in gBRCA-Associated Breast Cancer

Fewer side effects overall in the olaparib group
Benefits seen in ER+ and TNBC patients
Benefits seen in BRCA1 and BRCA2 patients
Waiting to follow patients longer to understand effects on survival

Robson et al, NEJM 2017

FDA approval granted on Jan 12, 2018

% of Patients with >30% tumor shrinkage

Chemotherapy  Olaparib
Phase 3 EMBRACA Trial: Talazoparib vs Chemotherapy in gBRCA-Associated Breast Cancer

FDA approval on October 16, 2018

Better quality of life in the talazoparib group

Benefits seen in ER+ and TNBC patients

Benefits seen in BRCA1 and BRCA2 patients

Waiting to follow patients longer to understand effects on survival

Robson et al, NEJM 2017
Immunotherapy
Immunotherapy: Background

• Our immune systems evolved to recognize “foreign invaders”
  - Bacteria, viruses, etc

• Our immune systems also can recognize cancer cells, but...
  - More difficult because cancer cells are our own cells that have mutated/morphed
  - More difficult because cancers find ways to escape or hide
  - We want to avoid nonspecifically activating all of our immune cells, as this could cause autoimmune disease
Immunotherapy works in many cancers... What about breast cancer?

Impassion 130: Randomized Phase 3 Trial for First-Line Metastatic TNBC

Metastatic TNBC
No prior chemo for metastatic disease

~900 patients entered

Nab-Paclitaxel + Atezolizumab

Nab-Paclitaxel

Schmid et al, New Engl J Med 2018
Impassion 130: Randomized Phase 3 Trial for First-Line Metastatic TNBC

• Improvement in average length of survival for patients who received chemotherapy + immunotherapy
  • But only seen in patients with PDL1+ tumors

• Immune side effects were seen

• A good start, but still more progress to be made

Schmid et al, New Engl J Med 2018
Strategies to make first generation immunotherapy work better
Antibody-Drug Conjugates
Antibody Drug Conjugates

Tumor Cell

Normal cell
IMMU-132 (Sacituzumab Govitecan)

Most common side effects: low blood counts, diarrhea, fatigue

FDA Approval is likely in 2020

Bardia et al, SABCS 2017
# ADCs in Trials for Breast Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
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<tr>
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<tr>
<td>DS-1062</td>
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</table>
Other Targets

• AKT1, PTEN, PIK3CA
  • Ipatasertib, capivasertib, etc.

• Androgen receptor

• DNA repair
  • ATR inhibitors, etc

• MYC
  • Bromodomain inhibitors, CDK7 or CDK9 inhibitors, Aurora kinase inhibitors, CHK1 inhibitors
Increasing Attention on Quality of Life

PubMed search 10/3/19: quality of life and “metastatic breast cancer”
Patient reported outcomes

• Ultimately, patient assessment of symptoms far more important than external assessments

• PROs particularly important when treatments lead to improvements in progression free survival but no improvement in overall survival

• Unfortunately, we still do not know how to integrate disease assessments and PROs....there is no simple formula

• PROs, and patient-centered assessments, are gaining traction
Relationship with health care team

• Not critical when you are healthy

• Becomes more and more important as health care needs increase

• Important to establish relationships with health care team that encourage open communication and feel supportive