Updates in the Treatment of Breast Cancer
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Disclosures
Novartis Oncology
speaker’s bureau, advisory board
Genetech Oncology
advisory board

Objectives
- Differentiate between available CDK4/6 inhibitors used in the treatment of hormone positive (HR+) metastatic breast cancer (MBC) based on clinical efficacy and tolerability
- Explore the changing landscape of Her2 positive (Her2+) early stage breast cancer (ESBC) treatment
- Discuss the utility of selected biomarkers to guide treatment decisions in MBC
- Appraise emerging strategies for the treatment of triple negative metastatic breast cancer (TNMBC)

HR(+) MBC - Background
- < 10% patients initially present with MBC
- Heterogeneous behavior
  - Median survival ~ 4 - 5 years
- Goals of therapy
  - Clinical trials preferred
  - Endocrine therapy “-static”
- PFS interval will shorten with each new regimen

Pagani O et al. JNCI. 2010; 102(7):1

Cyclin-Dependent Kinase (CDK) 4 and 6 Pathway

NCCN Clinical Practice Guidelines for Breast Cancer 2018
Systemic first-line treatment of recurrent or Stage IV ER+/HER2- disease with no prior endocrine therapy within 1 year

CDK4/6 Inhibitor
CCND1 (Cyclin D1)
RB1
Cell Cycle Suspended (G, phase)
Cell Cycle Progression (S phase)
E2F
E2F
ER
and/or PR+
HER2-
Chemotherapy (category 2b)
Casematropic
Selective ER modulator (category 3)
Selective ER downregulator (category 3b)
CDK4/6 inhibitor + AI (category 1)
Vascular crisis
Chemotherapy (category 2b)
CDK 4/6 Inhibitors for HR+, Her2(-) Postmenopausal MBC

- **Palbociclib (Ibrance™)**
  - First-line, combination with aromatase inhibitor (AI)
  - Second-line, + Fulvestrant
- **Ribociclib (Kisqali™)**
  - First-line, + AI
  - First-line or Second-line, + Fulvestrant
  - Pre/perimenopausal or postmenopausal
- **Abemaciclib (Verzenio™)**
  - First-line, + AI
  - Second-line, + Fulvestrant
  - Monotherapy, following previous endocrine and chemo

### Phase III Trials: Efficacy of First-line CDK 4/6 Inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>Palbociclib + AI</th>
<th>Ribociclib + AI</th>
<th>Abemaciclib + Let/Ana</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment groups</strong></td>
<td>Palbociclib + Letrozole (n = 444) vs. Letrozole (n = 222)</td>
<td>Ribociclib + Letrozole (n = 334) vs. Letrozole (n = 334)</td>
<td>Abemaciclib + Letrozole (n = 328) vs. Letrozole (n = 165)</td>
</tr>
<tr>
<td><strong>Study drug dosing</strong></td>
<td>125 mg daily, (3 weeks on, 1 off)</td>
<td>600 mg daily, (3 weeks on, 1 off)</td>
<td>150 mg BID continuous dosing</td>
</tr>
<tr>
<td><strong>PFS (months)</strong></td>
<td>24.8 vs. 14.5 (HR 0.58, p&lt;0.001)</td>
<td>25.3 vs. 16 (HR 0.57, p&lt;0.0001)</td>
<td>28.2 vs. 16.7 (HR 0.54, p&lt;0.0001)</td>
</tr>
<tr>
<td><strong>ORR %</strong></td>
<td>42 vs. 35</td>
<td>41 vs. 26</td>
<td>48 vs. 35</td>
</tr>
</tbody>
</table>

### Phase III Trials, First-line: Safety of CDK 4/6 Inhibitors

<table>
<thead>
<tr>
<th>Selected adverse events (all grades) %</th>
<th>Palbociclib + AI</th>
<th>Ribociclib + AI</th>
<th>Abemaciclib + AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>80</td>
<td>75</td>
<td>41</td>
</tr>
<tr>
<td>Neutrophil count reduction</td>
<td>1.8</td>
<td>1.5</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Elevated LFT's</td>
<td>10</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>35</td>
<td>62</td>
<td>39</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26</td>
<td>35</td>
<td>81</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>Alopecia</td>
<td>32</td>
<td>23</td>
<td>27</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>2.5</td>
<td>2.7</td>
<td>8</td>
</tr>
<tr>
<td>QTc prolongation</td>
<td>0.7</td>
<td>4.3</td>
<td>0.3</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td>5.7</td>
<td>2.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

So What's the Difference?

<table>
<thead>
<tr>
<th>Palbociclib</th>
<th>Ribociclib</th>
<th>Abemaciclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA indication</td>
<td>1st, 2nd line</td>
<td>1st, 2nd line</td>
</tr>
<tr>
<td>Dosing</td>
<td>Daily x 3 wks</td>
<td>Daily x 3 wks</td>
</tr>
<tr>
<td>Cost of starting dose</td>
<td>$15,000 / month</td>
<td>$13,000 / month</td>
</tr>
<tr>
<td>Reduced cost for dose reduction</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Interactions with other medications</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>CYP3A4</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Required monitoring</td>
<td>QRS, LFT's</td>
<td>QTc, LFT's, EKG</td>
</tr>
<tr>
<td>Other</td>
<td>Take with food</td>
<td>Take with food</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>“niche”</td>
<td>“niche”</td>
</tr>
</tbody>
</table>

Summary – CDK 4/6

- All 3 agents approved for first line
- 2nd line indication when not used up-front
- Compelling PFS = 2 years
- No OS data
- Post-progression data needed
- Well tolerated
- Required monitoring
- “Niche” for for different agents
Objectives

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- Appraise emerging strategies for the treatment of triple negative metastatic breast cancer (TNMBC)

Pertuzumab and Trastuzumab Bind to Distinct Extracellular Regions


- Pertuzumab
- Trastuzumab

Pertuzumab

- Inhibits HER2 dimerization with other HER family receptors
- Activates ADCC
- Inhibits multiple HER-mediated signaling pathways
- Prevents HER2 domain cleavage

Trastuzumab

- Activates ADCC
- Inhibits HER-mediated signaling pathways

Her2(+) Early Stage Breast Cancer: What We Know

1. Locally advanced disease = neoadjuvant chemo
2. Adding pertuzumab to a trastuzumab + chemotherapy backbone increases pCR
   - NeoSphere
   - TRYPHAENA
3. Anthracycline or non-anthracycline based regimens have similar pCR rates
4. pCR correlates to DFS

Unanswered Questions

- Adjuvant pertuzumab?
  - Adjuvant pertuzumab if neoadjuvant pertuzumab-based chemo given?
- Extended Her2 targeted therapy?
  - pCR endpoint with OS correlate?

Phase III Trial of Adjuvant Pertuzumab + Chemotherapy: APHINITY

- ESBC
  - Adjuvant, Her2(+), Node(+) or Node(-) > 1 cm
  - Within 8 wks of surgery
- Primary endpoint
  - invasive DFS in months (mo) by independent review
- Stratification
  - Nodal status
  - Adjuvant chemo regimen
  - ER/PR
  - Geography

APHINITY – Efficacy Results

- Intention-to-Treat Population
- Node (-) 98.4
- Node (+) 96.2
- Stratified hazard ratio, 0.81 (95% CI, 0.66–1.00)
- P=0.045
Pertuzumab-induced Diarrhea

<table>
<thead>
<tr>
<th>Neosphere® (PTD)</th>
<th>TRYPHAENA® (TCH + P)</th>
<th>APHINITY (all chemo + Pertuz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea % (all grades)</td>
<td>46</td>
<td>72</td>
</tr>
<tr>
<td>Diarrhea % (grade 3)</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

- Clinical practice
- Refractory
- Future developments
  - Crofelemer 125 mg BID prophylactically (NCT 02910219)
  - Rifaxamin case reports

Scalp Cooling to Prevent Chemotherapy-induced Alopecia

- Anthracycline, Taxane alopecia
- CTCAE v4.0 grading for alopecia
- Concerns:
  - scalp metastases
  - safety
- Canadian/European experience
- Scalp cooling caps in USA
  - Rent for duration of therapy:
    - $300-500/month
  - Store in a cooler with dry ice
  - Many different manufacturers

Scalp Cooling Devices

- DigniCap™ system
  - FDA approved 2015
  - $325 / treatment in 2017
- Paxman™ system
  - FDA approved 2017
  - $2200 lifetime max
- Previous clinical trial
  - ≤ Grade 1 alopecia: cooling group 66.3% vs 0% control group (P < .001)
- SCALP trial

Neratinib

- Previous attempts to improve upon outcomes
- Oral TKI
- pan-HER inhibitor
- Dose is 240 mg once daily for 1 year
  - 40 mg caps x 6

Phase III Trial of Adjuvant Neratinib: ExteNET

- Adjuvant, HER2+ stage I-IIIC, completed previous neo/ad chemo and 1 year trastuzumab
- Within 1 yr of completing trastuzumab

**Primary endpoint**
- Invasive DFS

**Stratification**
- Nodal status
- Adjuvant chemotherapy regimen
- Hormone receptor status

Neratinib 240 mg PO once daily x 1 year
n = 1420

Endocrine therapy for ER/PR(+) patients permitted

Placibo 240 mg PO once daily x 1 year
n = 1420
ExteNET – 5-yr Results

Neratinib-induced diarrhea

<table>
<thead>
<tr>
<th>ExtNET → Neratinib Placebo</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea % (all grades)</td>
<td>72</td>
<td>36</td>
</tr>
<tr>
<td>Diarrhea % (grade 3)</td>
<td>40</td>
<td>2</td>
</tr>
</tbody>
</table>

Prophylactic Loperamide:  
First 2 weeks:  Loperamide 4 mg orally TID  
Next 6 weeks:  Loperamide 4 mg orally BID  
After the first 8 weeks:  Loperamide 4 mg orally PRN

Unanswered Questions

- Adjuvant pertuzumab benefit? Yes
- Adjuvant pertuzumab if neoadjuvant pertuzumab-based chemo given? Consider for high risk
- Extended Her2 targeted therapy? Yes
- pCR endpoint with OS correlate? Data maturing

Summary – Her2(+) ESBC

- Neoadjuvant chemo+ trastuzumab & pertuzumab remain the SOC for locally advanced, Her2(+) ESBC  
- High risk patients who did not receive neoadjuvant pertuzumab, or who have residual disease following surgery – consider adjuvant pertuzumab  
- Scalp cooling may prevent alopecia for patients receiving taxane based chemotherapy  
- Consider extending Her2-directed therapy with neratinib for selected (HR+) patients

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Pharmacogenomics: MBC Biomarkers

- Many tests commercially available for blood/tissue:  
  - TEMPUS™  
  - Guardant 360™  
  - Foundation Medicine™  
  - Others  
- ER/PR – endocrine therapy  
- HER2+ / ERBB2 – targeted therapy  
- BRCAT, BRCAT  
- AP  
- ESRR  
- EGFR – lapatinib (7)  
- AKT – pancreatin (7)  
- PI3K – lapatinib, everolimus (7)  
- PTEN  
- PALB2 – DNA damage (7)  
- ATM – DNA damage (7)  
- p53  
- PD, PD-L1 – checkpoint inhibitor (7)  
- CEA, CA 15-3, CA 27-29

Hurvitz S et al. SABCS 2017 annual meeting, Dec 6, 2017; San Antonio, TX. Poster #P1-14-01.
Olaparib (LYNPARZA™)

- BRCA mutations
- Potent, oral, PARP inhibitor
- FDA indication:
  - Germline BRCA-mutated metastatic breast
- BID with or without food
- Fatigue, anemia, neutropenia, N/V (mod-high), AML/MDS
- Major CYP3A4 substrate
- Potency: Talazoparib > Niraparib > Rucaparib > Olaparib

Mechanisms of DNA Repair

OliveiAD - PFS

Phase III Trial of Olaparib: OliviAD

MBC
- Germline BRCA mutation
- Her2⁻/ any ER/PR⁻
- Previous anthracycline and taxane
- Previous endocrine therapy for MBC if ER/PR⁻

Primary endpoint
- PFS

Secondary endpoints
- Overall survival
- Safety
- Objective response rate

Results
- CBR at 16 weeks: 38% (evaluable patients)
- CBR at 24 weeks: 29%
- Overall survival: 16.5 months

Robson M et al. NEJM 2017; Aug 10;377(6): 523-533

OliveiAD - OS

Androgen Receptor (AR⁺) - MBC

- Androgen receptor expression common in TNBC
- Less aggressive phenotype (“LAR“)
- Bicalutamide, Abiraterone trials
- Enzalutamide potent androgen blocker
- Enzalutamide drug interactions
  - Induces 2C9, 2C19, 3A4
  - Fatigue, GI distress, decreased appetite
- Medication access challenges

Phase II Trial of Enzalutamide

Locally advanced or MBC
- TNBC, AR⁺
- No limit on number of priors for MBC

Primary endpoint
- Clinical benefit rate (CBR) at 16 weeks
- Evaluable population – AR ≥ 10% (n = 78)

Results
- CBR at 16 weeks: 100%
- OS: 18.3 months

Robson M et al. NEJM 2017; Aug 10;377(6): 523-533

Robson M et al. NEJM 2017; Aug 10;377(6): 523-533
ESR1 gene mutation

- **ESR1** – estrogen receptor alpha
- **ESR2** - estrogen receptor beta
- Frequency – 12 - 20%1, as high as 54%
- Especially prevalent in patients who progressed on AI’s
- Confers resistance to AI’s1,2
- Mutation shortens PFS, OS2


Fulvestrant in ESR1 Mutation

- **SoFEA**
  - Wild-type ESR1 – no difference between arms
  - Mutant ESR1 (39%):
    - Fulvestrant (n=45): PFS - 5.7 months
    - Exemestane (n=18): PFS - 2.5 months (HR 0.52, p = 0.02)
- **PALOMA-3**
  - Wild-type ESR1
    - Fulvestrant + Palbo: PFS - 9.5 months
  - Mutant ESR1 (25%)
    - Fulvestrant + Palbo (n=63): PFS - 9.4 months
- Fulvestrant may confer benefit in ESR1 mutation
- CDK4/6 inhibitor may confer benefit regardless if ESR1 mutant

Summary – Selected Biomarkers for MBC

- Pharmacogenomic testing of tumor DNA to reveal actionable targets is evolving
  - Olaparib provides a nice PFS benefit in germline BRCA1/2 mutated MBC
  - Enzalutamide may provide a salvage treatment option in AR(+) MBC
  - Fulvestrant should be the preferred endocrine therapy backbone in MBC patients who harbor an ESR1 mutation

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Triple Negative MBC - Background

- Subtype lacking ER/PR receptor and Her2 overexpression
- Emerging sub classifications show much heterogeneity
- Disproportionately affects premenopausal African / Hispanic ancestry
- High proliferation, poorly differentiated, higher mutational load
- Aggressive – 15% of breast cancer cases but 25% of deaths
- More frequent mets to brain and viscera
- Decreased OS - 1 year from time of metastases
- Chemoresistant (platinum?) initial – multidrug resistant
- 10-20% of TNMBC harbor a BRCA mutation as well
  - Overlap here from previous section (olaparib, enzalutamide)

Phase III Trial of Carboplatin vs. Docetaxel in TNMBC: TNT

- **TNT** MBC / LABC
- TNBC or germline +BRCA mutation (any ER/PR/Her2)
- No previous platinum
- No previous chart for MBC

Primary endpoint

- **ORR**

Results

- **ORR:** Carbo 31%, Docetaxel 36%
- **PFS:** Carbo 3.1 mo, Docetaxel 4.5
- **ORR** germline +BRCA:
  - Carbo 68%, Docetaxel 33%

- Carboplatin AUC 6 Q21 days x 4-6 cycles n = 188
  - Or until disease progression or sooner, crossover allowed
- Docetaxel 100 mg/m2 Q21 days x 4-6 cycles n = 188

**Immunotherapy: Checkpoint Inhibitors in TNMBC**

- Many TNMBCs contain tumor-infiltrating lymphocytes (TILs) indicative of a robust host immune response.
- Presence of TILs is a prognostic indicator:
- Clear association with TILs and improved survival in early stage TNBC.
- Increased attention led to the study of immune-checkpoint blockade in TNMBC.
- Atezolizumab, Avetumab, and Pembrolizumab.

**Checkpoint Inhibitors**

**Mechanism of Action**


**Checkpoint Inhibitors: Monotherapy in TNMBC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Population</th>
<th>n</th>
<th>Primary endpoint</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>1a</td>
<td>PD-L1 (+) and (-)</td>
<td>115</td>
<td>Safety</td>
<td>10% (13% PD-L1+)</td>
</tr>
<tr>
<td>Avetumab</td>
<td>1b</td>
<td>PD-L1 (+) and (-)</td>
<td>28</td>
<td>Safety</td>
<td>8.6% (14% PD-L1+)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2</td>
<td>PD-L1 (+) and (-)</td>
<td>170</td>
<td>Safety &amp; efficacy</td>
<td>6.5% (6.2% PD-L1+)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2</td>
<td>PD-L1 (-)</td>
<td>20</td>
<td>Safety</td>
<td>27%</td>
</tr>
<tr>
<td>Pembrolizumab vs. CPC (KEYNOTE 10)</td>
<td>3</td>
<td>Stratified by PD-L1 tumor status (large cohort)</td>
<td>830</td>
<td>PFS, OS</td>
<td></td>
</tr>
</tbody>
</table>

**Checkpoint Inhibitors: Monotherapy in TNMBC**

**Checkpoint Inhibitors + Chemotherapy in TNMBC**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Population</th>
<th>n</th>
<th>Primary endpoint</th>
<th>ORR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>1b</td>
<td>PD-L1 (+) and (-)</td>
<td>32</td>
<td>Safety</td>
<td>18% (14% 1st line)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>1b/2</td>
<td>PD-L1 (+) and (-)</td>
<td>39</td>
<td>Safety &amp; efficacy</td>
<td>33% (41% 1st line)</td>
</tr>
<tr>
<td>Pembrolizumab vs. nab-paclitaxel (IMPASSION 130)</td>
<td>3</td>
<td>PD-L1 (+) and (-)</td>
<td>900</td>
<td>PFS, OS</td>
<td></td>
</tr>
</tbody>
</table>

**Sacituzumab govitecan**

- Antibody-drug conjugate
- SN-38 + humanized IgG
- SN-38 - Topoisomerase I inhibitor - double-stranded DNA breaks
- Niratocan - activity in MBC
- SN-38 - 100 to 1000 fold higher potency than irinotecan
- Targets TROP-2 glycoprotein receptor
- Found on > 90% triple (-) tumors
- Can selectively deliver SN-38 to tumors with limited toxicity.

**Phase I/II Trial of Sacituzumab govitecan**

**TNMBC**

- ≥ 1 prior chemo for MBC although median was 5 prior therapies

**Primary endpoints**

- ORR
- Secondary endpoints – PFS, OS, safety

**Results**

- ORR - 36%
- 70% patients had ≤ tumor burden
- PFS - 6 months
- OS - 16.6 months
- Safety – grade 3 neutropenia 39% (FN 7%), grade 3 diarrhea 13%

**Current status**

- FDA breakthrough designation, phase III trial vs. CPC, patients with at least 2 prior.
Ipatasertib

- PI3K/AKT signaling pathway
  - Often activated in breast cancer
  - Subgroup of TNMBC’s have pathway activation
  - PTEN deficiency ≈ 50% TNMBC’s

Ipatasertib

- Highly selective oral ATP-competitive, small-molecule AKT inhibitor
  - Phase I safety: GI, asthenia, fatigue, rash

Phase II Trial of Ipatasertib + Paclitaxel in TNMBC: LOTUS

TNMBC

- No previous chemo for MBC
  - Stratified:
    - PTEN status
    - Neo/adjuvant chemo Y/N
    - Chem-free interval > 12 mo

Primary endpoint

- PFS

Key secondary endpoint

- PFS in PI3K/AKT altered tumors

Results

- PFS 1.8 vs 4.9 months (p=0.037)
- PFS in PI3K/AKT altered tumors:
  - 9 vs 4.9 months (p=0.041)

Ipatasertib 400 mg once daily, days 1-21 + Paclitaxel 80 mg/m2 days 1, 8, 15 Q28 days
n = 62

Placebo 400 mg once daily, days 1-21 + Paclitaxel 80 mg/m2 days 1, 8, 15 Q28 days n = 62


Summary – Emerging Strategies for TNMBC

- Limited treatment options, no preferred options
- Pharmacogenomic testing may identify a target
- Clinical trials strongly encouraged
- Immunotherapy trials ongoing although early results not overwhelming
- Sacituzumab govitecan and ipatasertib are two investigational agents of interest

Thank You

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The Stefanie Spielman Comprehensive Breast Center,
The James Cancer Hospital & The Ohio State University Medical Center