Metastatic Breast Cancer

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Disclosures

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Epidemiology of Metastatic Breast Cancer

Approximately 40,000 deaths per year from breast cancer, but declining because of advances in HER2+ disease

Median survival 2-3 years, but highly variable

Prevalent population in U.S. ≈200,000 women

Any general oncologist by necessity is also a breast cancer specialist

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>~15-20% (↓ing)</td>
</tr>
<tr>
<td>Triple Neg</td>
<td>~ 15-20%</td>
</tr>
<tr>
<td>ER/PR+ and HER2-</td>
<td>~ 60-70%</td>
</tr>
</tbody>
</table>
Breast cancer tropisms differ by subtype
Bone more dominant in hormone receptor positive
Visceral and CNS in hormone receptor negative

Heterogeneity of Metastatic Breast Cancer

**Disease Characteristics**
- Disease-free interval
- Sites and volume of disease
- Tempo of disease
- Prior therapy
- ER and PR status
- HER-2 status

**Patient Characteristics**
- Performance status
- Comorbidity
- Host factors
  - Immune response
  - Drug metabolism
Growing Number of Therapies

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of Drugs Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>5</td>
</tr>
<tr>
<td>1970s</td>
<td>10</td>
</tr>
<tr>
<td>1980s</td>
<td>15</td>
</tr>
<tr>
<td>1990s</td>
<td>20</td>
</tr>
<tr>
<td>2000s</td>
<td>30</td>
</tr>
</tbody>
</table>

1950s: Cyclophosphamide, methotrexate
1960s: 5-fluorouracil
1970s: Doxorubicin, tamoxifen
1980s: Mitoxantrone, megestrol acetate, goserelin, leuprolide
1990s: Paclitaxel, docetaxel, vinorelbine, trastuzumab, capecitabine, gemcitabine, epirubicin, toremifene, anastrozole, letrozole, exemestane
2000s: nab-paclitaxel, lapatinib, ixabepilone, eribulin, denosumab, everolimus, palbociclib, fulvestrant, T-DM1, pertuzumab, ribociclib...

Metastatic Breast Cancer 2018

All therapy is palliative
Survival has increased
Survival depends mostly on tempo
• Biology of tumor is key
Goals of treatment
• Control of disease and symptoms
• Maximizing quality of life
• Minimize treatment toxicity

You can’t improve on being asymptomatic!
Systemic Therapy for Metastatic Breast Cancer

Treatment Based on Tumor Phenotype

Advanced Breast Cancer Requiring Therapy

- ER and/or PR Positive
  - Endocrine therapy +/- additional Rx
  - Refractory to Endocrine therapy
- ER and/or PR Negative
  - Chemotherapy

- HER2 Positive
  - Chemotherapy or ET + HER2 targeting
- HER2 Negative
  - Chemotherapy

Additional HER2-targeted drugs
ASCO/ESMO Clinical Practice Guidelines

Chemotherapy and Targeted Therapy for Women With HER2–Negative (or unknown) ABC.

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer.

Endocrine Therapy for Hormone Receptor Positive Metastatic Breast Cancer.

ESO-ESMO Consensus Conference Advanced Breast Cancer (ABC3)

ABC4 coming this fall!

ASCO Guidelines: General Principles

HR+ HER2-
- Endocrine (usually) preferable to chemotherapy in 1st line
- Targeted agents added to ET (CDK4/6, mTOR, PI3K inhibitors)

Any HER2- receiving chemotherapy
- Single agent chemotherapy preferable to combination
  - Exception: symptomatic, immediately life-threatening
- Longer duration ↑ outcome but must be balanced against ↑ toxicity.
  - No single optimal 1st or later chemotherapy
  - Factors: prior Rx, toxicity, performance status, comorbidity, patient preference.

HER2+
- HER2-directed Rx is mainstay
- First-line taxane + trastuzumab + pertuzumab, 2nd line T-DM1
- HR+ HER2+ may consider ET + HER2-Rx or ET alone in selected cases
Endocrine Therapy Options

- Premenopausal
  - Tamoxifen
  - Oophorectomy (OA)/LHRH agonist (OS)
  - OA/OS + the postmenopausal options

- Postmenopausal
  - Nonsteroidal aromatase inhibitor (AI*)
  - AI plus palbo-, abema- or ribociclib
  - Fulvestrant
  - Fulvestrant + palbo/abema/ribociclib
  - Fulvestrant + alpelisib (PIK3CAmt)
  - Steroidal AI
  - Steroidal AI + everolimus
  - Tamoxifen
  - Estradiol

*Nonsteroidal AI = letrozole, anastrozole; Steroidal AI = exemestane

Ovarian Suppression (or Ablation) in MBC

161 pts. with ER+ and MBC

Tamoxifen  Buserelin  Combination  Median f/u 7.3 years 76% of patients DOD

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>5-yr OS</th>
</tr>
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<tbody>
<tr>
<td>Tamoxifen</td>
<td>28%</td>
<td>5.6m</td>
<td>2.9y</td>
<td>18%</td>
</tr>
<tr>
<td>Buserelin</td>
<td>34%</td>
<td>6.3m</td>
<td>2.5y</td>
<td>14%</td>
</tr>
<tr>
<td>Combination</td>
<td>48%</td>
<td>9.7m</td>
<td>3.7y</td>
<td>34%</td>
</tr>
<tr>
<td>P-value</td>
<td>0.11</td>
<td>0.03</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Klijn JGM et al, JNCI 2000

OS/OA is itself therapeutic, and opens door for highly effective postmenopausal drugs. Standard of care.
AI vs Tamoxifen: 1st Line Postmenopausal

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>353</td>
<td>907</td>
<td>371</td>
</tr>
<tr>
<td>CR+PR</td>
<td>21% vs 17%</td>
<td>30% vs 20%</td>
<td>45% vs 30%</td>
</tr>
<tr>
<td>CR+PR+SD</td>
<td>59% vs 46%</td>
<td>49% vs 38%</td>
<td>--</td>
</tr>
<tr>
<td>TTP (mo)</td>
<td>11.1 vs 5.6</td>
<td>9.4 vs 6.0</td>
<td>9.9 vs 5.8</td>
</tr>
</tbody>
</table>

AI at least as good as tamoxifen
Anastrozole = Letrozole = Exemestane
Limited data including CDK4/6i or mTORi

Fulvestrant vs AI: 1st Line

**FALCON study: Phase III trial**

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant</th>
<th>Anastrozole</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+PR</td>
<td>46%</td>
<td>45%</td>
<td>NS</td>
</tr>
<tr>
<td>CBR</td>
<td>78%</td>
<td>74%</td>
<td>NS</td>
</tr>
<tr>
<td>PFS*</td>
<td>17m</td>
<td>14m</td>
<td>0.049</td>
</tr>
</tbody>
</table>

ET-naïve!
OS 5.5m improvement in phase II FIRST trial

Fulvestrant as single agent => AI in 1st line endocrine Rx

Considerations:
1. Prior adjuvant AI (if anything) should augment difference
2. CDK 4/6i trials usually AI 1st line, fulvestrant later
**2nd Line Endocrine Rx (after NSAI)**

SoFEA: Phase III trial fulvestrant vs exemestane (no difference)

If NSAI/CDK4/6i used 1st, either fulvestrant or exemestane next is ok

However, if you’re going to use exemestane…

BOLERO-2: Phase III trial exemestane + everolimus (mTOR inhibitor) in 2nd line

Everolimus added to exemestane improves PFS but not OS (AE- stomatitis, anemia, glc, pneumonitis)

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**Cyclin Dependent Kinase 4/6 Inhibitors**

Role in HR+ breast cancer
- Growth of HR+ BC depends on cyclin D1, a transcriptional target of ER
- Cyclin D1 activates CDK 4/6 causing G1-S phase transition and cell cycle entry

3 drugs approved for HR+ HER2- MBC with similar efficacy.
- Palbociclib (ANC major toxicity)
- Abemaciclib (GI major toxicity)
- Ribociclib (QTc = EKG monitoring)
**Palbociclib Trials in HR+ Disease**

**PALOMA-2:** Phase III letrozole + palbo in 1st line HR+/HER2-

- **PFS:** 25m vs 14m, p<0.001
- **(OS in PALOMA1 phase II: 37m vs 33m, ns)**
- **AE:** ANC (66% grade 3+, febrile 2%) *
- **FDA approved 2015:**
  - Letrozole + palbo in 1st line

**PALOMA-3:** Phase III fulvestrant + palbo in 2nd+ line HR+/HER2-

- **PFS:** 9m vs 4m, p<0.0001
- **(OS immature)**
- **Accelerated FDA approval 2016:**
  - Fulvestrant + palbo in pretreated (no prior palbo)
  
  **Key AE:** neutropenia, infections, anemia (needs monitoring ET doesn’t)

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**Ribociclib Trials in HR+ Disease**

**MONALEESA-2:** Phase III letrozole + ribo in 1st line

- **PFS:** NR vs 15m, p<0.001
- **Grade 3+ AE:** ANC (63%, febrile 2%), LFT 11%. QTc ↑ 3% *
- **FDA approved 2016:**
  - Letrozole + ribo in 1st line

**MONALEESA-3:** Phase III fulvestrant + ribo in 1-2nd+ line

Not yet reported

**FDA approval 2016:** Letrozole + ribo in 1st line

*How much will QTc matter?*

**HR 0.56 ribo, HR 0.55 palbo vs letrozole alone**
Abemaciclib Trials in HR+ HER2- Disease

MONARCH-1: Single agent abemaciclib in 2nd+ line

RR 15-20% (unusual in single agent CDK4/6i)
Toxicity differs: diarrhea grade 3+ > ANC ↓

MONARCH-2: Phase III fulvestrant + abema in 2st line

PFS: 16m vs 9m, HR 0.55, p<0.001

MONARCH-3: Phase III NSAI + abema 1st line
– PFS HR 0.54
(81% diarrhea, 41% neutropenia)

Not yet approved.
FDA review likely in 2018 alone and combined with fulvestrant

Dickler M et al, Clin Cancer Res 2017; Sledge G et al, JCO 2017;
di Leo A et al, ESMO 2017

Alpelisib Added to Fulvestrant in PreRx

Men or postmenopausal women, with HR+, HER2- ABC
- Recurrence/progression on prior endocrine AI
- Identified PIK3CA status (in archival or fresh tumor tissue)
- Metastatic disease or 2+1 predominantly lytic bone lesion
- ECOG performance status ≤1 (N=572)

PIK3CA-mutant cohort (n=341)
PIK3CA-non-mutant cohort (n=231)

ALP 300 mg QD PO + FUL 500 mg IM* am169
PBO + FUL 500 mg IM* am172
ALP 300 mg QD PO + FUL 500 mg IM* am115
PBO + FUL 500 mg IM* am116

PIK3CAmt
PIK3CAwt

Andre F, NEJM 2019
Alpelisib Added to Fulvestrant in PreRx

Reason to obtain DNA sequencing in metastatic breast cancer

Endocrine Rx Algorithm in HR+/HER2-

(If premenopausal - OA/OS)

- NSAI
  (+ palbo-, abema- or ribociclib)

Chemotherapy

Fulvestrant
  (? + -ciclib if naive)
  (? + alpelisib if PIK3CAmt)

Chemotherapy

Exemestane
  (+ everolimus)

Chemotherapy

Other options: Tamoxifen, megace, low dose estradiol, aminoglutethemide...
PARP Inhibition in Germline BRCA1/2 Carriers

**OlympiAD**
- HER2- MBC gBRCAmt ≤2 chemo for MBC (prior A, T. No plat-R)
- 2:1 randomization
- Chemo TPC
  - Capecitabine
  - Eribulin
  - Vinorelbine
- Olaparib 300 mg po bid
- Primary endpoint PFS
- Treat until progression

**EMBRACA**
- HER2- MBC gBRCAmt ≤2 chemo for MBC (prior A, T. No plat-R)
- 2:1 randomization
- Chemo TPC
  - Capecitabine
  - Eribulin
  - Vinorelbine
  - Gemcitabine
- Talazoparib 1mg po qd
- Primary endpoint PFS
- Treat until progression

**PARP Inhibition in PreRx Germline BRCA+**

- Both drugs are better and more tolerable than 2nd line chemo.
- Neither has much of an OS advantage.
- Comparison to 1st line Rx especially platinums unknown.

Robson et al, NEJM 2017; Litton et al, NEJM 2018
Chemotherapy in HER2- Breast Cancer

HR+ Disease

Endocrine Rx

Endocrine Refractory Disease

Triple Negative Disease

CHEMOTHERAPY

(Chemotherapy for ER+ and TN disease same. However + immunoRx only in TNBC)

MBC Chemotherapy: Wide Options

**Anthracycline**
- Doxorubicin
- Epirubicin
- Liposomal doxorubicin

**Taxanes**
- Paclitaxel
- Docetaxel
- Nab-paclitaxel

**Vinca alkaloids**
- Vinorelbine

**Other anti-tubule**
- Eribulin

**Antimetabolites**
- Methotrexate
- 5-FU
- Capecitabine
- Gemcitabine

**Alkylating agents**
- Cyclophosphamide
- Platinum agents

**Epothilones**
- Ixabepilone
Combination vs Single Agent Chemotherapy

<table>
<thead>
<tr>
<th>Combination</th>
<th>Single Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher RR</td>
<td>✔</td>
</tr>
<tr>
<td>Longer TTP (initial)</td>
<td>✔</td>
</tr>
<tr>
<td>Survival</td>
<td>✔</td>
</tr>
<tr>
<td>QOL</td>
<td>✔</td>
</tr>
<tr>
<td>Easier to customize</td>
<td>✔</td>
</tr>
<tr>
<td>Less “wasted” toxicity</td>
<td>✔</td>
</tr>
</tbody>
</table>

Single agent preferred unless response is important

Is There a Standard 1st Line Agent?

- Anthracyclines and taxanes 1st line agents; may be less appealing in relapse soon post adjuvant Rx
- No evidence that sequence of therapies affects OS or QOL
- Response more influenced by line of therapy than specific agent
- Treatment decisions often individualized to patient
- NCCN/ASCO guidelines generally avoid specific recommendations first-line agents
Immunotherapy in TNBC

- Eligibility criteria:
  - mTNBC
  - No prior Rx mTNBC, > 12 m DFI

- Stratification factors:
  - Prior taxane
  - Liver metastases
  - PD-L1 status

Atelo + nab-P arm:
Atezolizumab 840 mg IV D1, 15 q28d + Nab-paclitaxel 100 mg/m² IV D1, 8, 15 q28d

- RECIST v1.1
- Double-blind; no crossover permitted
- PD or toxicity

Plac + nab-P arm:
Placebo IV D1, 15 q28d + Nab-paclitaxel 100 mg/m² IV D1, 8, 15 q28d

IMpassion 130: Progression-Free Survival (ITT)

**Stratified HR = 0.80**
(95% CI: 0.69, 0.92)
*P = 0.0025*

**Overall population**
1.7 month ↑

**PDL1+**
2.5 month ↑
Stratified HR = 0.62
(95% CI: 0.49, 0.78)
*P < 0.0001*

Schmid et al, NEJM 2019
**IMpassion 130 Interim Overall Survival: PD-L1+**

Stratified HR = 0.62 (95% CI: 0.45, 0.86)

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P  (n = 185)</th>
<th>Plac + nab-P (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td>2-year OS</td>
<td>54% (42, 65)</td>
<td>37% (26, 47)</td>
</tr>
</tbody>
</table>

Schmid et al, NEJM 2019

Reason to obtain PDL1 on TNBC metastasis at initial relapse

FDA-approved 2019

40%+ using Ventana assay
**1st Line Chemotherapy Otherwise**

**CALGB 40502: Phase III trial of 3 antitubule drugs in 1st line**

- Paclitaxel 90 mg/m² weekly
- ABI-007 100 mg/m² weekly
- Ixabepilone 14 mg/m² weekly

**ALL WITH BEVACIZUMAB 10 MG/KG q 2 wk**

**NOT SUPERIOR**

Results of 40502:
- Paclitaxel > ixabepilone
- Paclitaxel least toxic

Meta-analysis first-line trials
- Taxane > anthracycline

**REASONABLE**: single agent weekly taxane (paclitaxel, nab-paclitaxel, docetaxel) unless recent adjuvant taxane. Platinums ok 1st line in triple negative.

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**Direct DNA Damaging Agents in TNBC**

**BRCA-associated cancer** is usually TNBC (basal-like)

**BRCA + and BRCA – TNBC** have many shared characteristics.

Is this therapeutically meaningful?

**Classic DNA-damaging agents** = platinums, ionizing radiation

<table>
<thead>
<tr>
<th>Normal BRCA1</th>
<th>Abnormal BRCA1</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNA damage</td>
<td>DNA damage</td>
</tr>
<tr>
<td>DNA damage kinases</td>
<td>DNA damage kinases</td>
</tr>
<tr>
<td>BRCA1 - Cell cycle arrest to repair DNA damage</td>
<td>Brc1 -</td>
</tr>
<tr>
<td>G1 S G2</td>
<td>G1 S G2</td>
</tr>
<tr>
<td>Mitosis - Prophase</td>
<td>Mitosis - Prophase</td>
</tr>
<tr>
<td>DNA damage checkpoint DNA repair</td>
<td>NO DNA damage checkpoint NO DNA repair</td>
</tr>
</tbody>
</table>

**RESISTANCE to DNA damaging agents** | **SENSITIVE to DNA damaging agents**
Platinums 1st Line in TNBC: TNT Trial

ER-, PgR-/unknown & HER2- or known BRCA1/2
Metastatic or recurrent locally advanced

- Carboplatin (C)
  AUC 6 q3w, 6 cycles
  On progression, crossover if appropriate

- Docetaxel (D)
  100mg/m² q3w, 6 cycles
  On progression, crossover if appropriate

TNT: Objective response

Randomised treatment - all patients (N=376)

Carboplatin: 59/188 (31.4%)
Docetaxel: 67/188 (35.6%)

C-D: -4.2%, p = 0.44

Germline BRCA 1/2 Mutation (n=43)

Carboplatin: 17/25 (68.0%)
Docetaxel: 6/18 (33.3%)

C-D: 34.7%, p = 0.03
2nd+ Chemotherapy Lines: Eribulin vs TPC

Eribulin novel antitubule drug (halichondrin A analog from sea sponge)

OS: 13.1 vs 10.6m

Eribulin may be better in TNBC

Very different toxicity profiles:
- Eribulin: neutropenia, alopecia, neuropathy
- Capecitabine: HFS, diarrhea

Capecitabine (older oral antimetabolite) = eribulin (novel antimetabolite)

OS 14.5m vs 15.9m
Toxicity is a Key Feature to Consider

- **alopecia**
  - Capecitabine
  - Vinorelbine
  - Carboplatin

- **GI symptoms**
  - Capecitabine
  - GI symptoms

- **neuropathy**
  - Capecitabine
  - Anthracyclines
  - Gemcitabine

- **myelosuppression**
  - Capecitabine
  - Anthracyclines
  - Taxanes
  - Gemcitabine

- **IVs**
  - Capecitabine

- **IVs**

Continued versus Interrupted Chemotherapy

- Ongoing chemotherapy better outcome
  - However more toxic

Park YH et al, JCO 2013
## Meta-Analysis Chemotherapy Duration: Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>HR ± 95% CI</th>
<th>% Weight</th>
<th>HR</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Coates 1987</td>
<td>13</td>
<td>0.79</td>
<td>0.62 to 1.01</td>
<td></td>
</tr>
<tr>
<td>Harris 1990</td>
<td>2</td>
<td>1.06</td>
<td>0.57 to 1.97</td>
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<tr>
<td>Muss 1991</td>
<td>5</td>
<td>1.11</td>
<td>0.74 to 1.67</td>
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</tr>
<tr>
<td>Ejertensen 1993</td>
<td>17</td>
<td>0.78</td>
<td>0.63 to 0.97</td>
<td></td>
</tr>
<tr>
<td>Gregory 1997</td>
<td>5</td>
<td>0.81</td>
<td>0.54 to 1.21</td>
<td></td>
</tr>
<tr>
<td>Falkson 1998</td>
<td>8</td>
<td>0.94</td>
<td>0.69 to 1.28</td>
<td></td>
</tr>
<tr>
<td>Bestit 2000</td>
<td>10</td>
<td>0.96</td>
<td>0.78 to 1.16</td>
<td></td>
</tr>
<tr>
<td>Nooij 2003</td>
<td>17</td>
<td>1.03</td>
<td>0.83 to 1.27</td>
<td></td>
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<tr>
<td>Gennari 2006</td>
<td>4</td>
<td>1.12</td>
<td>0.73 to 1.72</td>
<td></td>
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<tr>
<td>Majiordomo 2009</td>
<td>7</td>
<td>0.94</td>
<td>0.67 to 1.32</td>
<td></td>
</tr>
<tr>
<td>Alba 2010</td>
<td>5</td>
<td>0.86</td>
<td>0.58 to 1.27</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>100</td>
<td>0.91</td>
<td>0.84 to 0.99</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity, $P = .69$
Test for treatment effect, $P = .046$

## General Principles of Chemotherapy

All treatment is palliative

- TNBC and endocrine-resistant HR+
  - HER2 different principles
  - TNBC – initial Rx nab-paclitaxel if PDL1+ and giving immunotherapy
- Single agent > polychemotherapy
  - (unless symptomatic or rapidly progressive)
- First-line: Taxane (unless recently Rx adjuvantly)
  - Platinum in TNBC
- Later-line: Many choices
  - Eribulin, capecitabine, platinums
  - Anthracyclines (if did not receive adjuvantly – cannot give twice)
**HER2+ Disease: Major Clinical Advances**

1989

**Studies of the HER-2/neu Proto-oncogene in Human Breast and Ovarian Cancer**


1998

Trastuzumab approved stage IV

2002

First Preoperative Trials Reported Paving The Way For Use in Early Stage Disease

2005

Lapatinib approved stage IV

2007-

2008

Initial Trials of T-DM1, Neratinib

2005

3 large adjuvant trials reported

2005

Preoperative trials of Dual blockade

2007-

2008

2008

2010

2012

2013

T-DM1 approved for MBC

Pertuzumab approved for MBC

Pertuzumab approved added to neo(adj)

**Targeting HER2**

Humanized monoclonal Ab to HER2 extracellular domain

Humanized monoclonal Ab, blocks heterodimerization

Maytansine analogue DM1 (vinca-like antitubule) conjugated to trastuzumab

Small molecule kinase inhibitor

Irreversible HER-1, 2, 4 inhibitor

Ligand

Trastuzumab

Neratinib, etc

RAS

Akt

mTOR

MAPK

ERK

Maytansine

DM1

Proliferation, Survival, Invasion, Angiogenesis

Transcription Downstream Cellular Effects

Cytoplasm

Nucleus

Antibody

HER2

HER1,3,4

HER2

Trastuzumab

T-DM1

POK

AKT

mTOR

MAPK

ERK

DM1

POK

AKT

mTOR

MAPK

ERK

DM1
Trastuzumab Added To Chemotherapy

- **Chemo + H (paclitaxel or AC)**
  - **Chemo**
  - **PFS** 7.4m 4.6m

![Graph showing comparison between Trastuzumab added to chemotherapy and chemotherapy alone.](image)

Slamon DJ, et al. NEJM 2001

HER2-Targeting Added To Endocrine Therapy

- **Anastrozole vs Anastrozole + Trastuzumab**
  - Kaufman B et al, JCO 2009

- **Letrozole vs Letrozole + Lapatinib**
  - Johnston S et al, JCO 2009

![Graphs showing progression-free survival and alive without progression.](image)

Adds toxicity with modest changes in outcome. Most co-target but ok in individual patients to just use ET.
**HER2-Targeting: The First Generation**

Post-trastuzumab progression, ongoing HER2-targeting works

- Lapatinib
- TDM1
- Trastuzumab!

Multiple chemotherapy partners for HER2-targeting

- Platinums, vinorelbine, gemcitabine, capecitabine
- What is optimal?

ER+ HER2+ disease benefits from dual targeting

- AI + either trastuzumab or lapatinib
- Ok to omit HER2-targeting in strongly ER+, indolent, asymptomatic.

---

**Pertuzumab**

**CLEOPATRA: Phase III trial if addition of pertuzumab (1st line)**

N=800

End points

- PFS and OS
- quality of life
- biomarker analysis

Docetaxel + trastuzumab + placebo

Docetaxel + trastuzumab + pertuzumab

*Baselga J et al. NEJM 2012*
**CLEOPATRA: Overall Survival**

PFS 18.5 vs 12.4m, p<0.0001

- 15.7 months improvement in median OS in the final analysis (secondary endpoint)²

<table>
<thead>
<tr>
<th>Pertuzumab + Trastuzumab + Docetaxel</th>
<th>Placebo + Trastuzumab + Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>68.95% CI: 0.56-0.84</td>
<td>P=0.0002</td>
</tr>
</tbody>
</table>

**Trastuzumab-emtansine (T-DM1), HER2 Antibody-Drug Conjugate**

- Maytansine analogue DM1 (antitubule akin to vincas) conjugated to trastuzumab – similar to gemtuzumab (Myelotarg)

- Will it allow omission of separate cytotoxic?

- Average number of DM1 molecules/monoclonal antibody=3.5

![Diagram of T-DM1 conjugate](image)

- T-MCC-DM1
- HER2-mediated internalization
- Lysosomal degradation
- Active metabolite can’t cross plasma membrane (no bystander effect)
EMILIA: Phase III Trial T-DM1 versus XL

Pre-treated setting

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

HR=0.650, p<0.001
OS (secondary) 31m vs 25m, p<0.001

Toxicity better (and different) with T-DM1: grade 3+ 57% vs 41%
T-DM1 – thrombocytopenia, LFT↑
XL – N/V, hand-foot syndrome

Win-Win

Next Generation of HER2-Targeting

<table>
<thead>
<tr>
<th>Trial</th>
<th>Line</th>
<th>Regimens</th>
<th>PFS</th>
<th>OS</th>
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</thead>
<tbody>
<tr>
<td>CLEOPATRA</td>
<td>1</td>
<td>TH + Pert</td>
<td>19 v. 12m (HR 0.69*)</td>
<td>56 v. 41m (HR 0.68*)</td>
</tr>
<tr>
<td>MARIANNE®</td>
<td>1</td>
<td>TH v. TDM1 v. TDM1+P</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>NEFERTTI®</td>
<td>1</td>
<td>TH v. TN</td>
<td>17 v. 17m (ns)</td>
<td>?fewer CNS with TN?</td>
</tr>
<tr>
<td>BOLERO-1</td>
<td>1</td>
<td>TH + Eve</td>
<td>15 v. 14m</td>
<td>-</td>
</tr>
<tr>
<td>EMILIA</td>
<td>2</td>
<td>TDM1 v. XL</td>
<td>10 v. 6m (HR 0.65*)</td>
<td>31 vs 29m (HR 0.68*)</td>
</tr>
<tr>
<td>BOLERO-3</td>
<td>2</td>
<td>VH + Eve</td>
<td>7 v. 6m (HR 0.78*)</td>
<td>-</td>
</tr>
<tr>
<td>TH3RESA</td>
<td>3+</td>
<td>TDM1 v. MD choice</td>
<td>6 v. 3m (HR 0.53)</td>
<td>HR 0.55 (interim)</td>
</tr>
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* significant

T=taxane; N=neratinib; V=vinorelbine; E=everolimus
## Next Generation of HER2-Targeting

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*significant

T=taxane; N=neratinib; V=vinorelbine; E=everolimus

1st line: T+H+P wins (~$10,000/m)
2nd+ line: TDM1 wins (~$10,000/m)

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## Oncogene Addiction:

**HER2 is Still a Relevant Target After Progression on Trastuzumab**
Capecitabine + Trastuzumab: Time To Progression (after prior trastuzumab)

ORR 48% vs 27%, p=0.0011

Summary: Metastatic Options for HER2+

<table>
<thead>
<tr>
<th>Line of therapy</th>
<th>Regimen Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy-based</strong></td>
<td><strong>Endocrine therapy-based</strong></td>
</tr>
<tr>
<td>First</td>
<td>Taxane + trast + pert</td>
</tr>
<tr>
<td>Second</td>
<td>T-DM1</td>
</tr>
<tr>
<td>Third</td>
<td>Capecitabine + lapatinib</td>
</tr>
<tr>
<td>Later</td>
<td>Other drugs + trastuzumab</td>
</tr>
</tbody>
</table>

Median survival increasing
Multiple drug choices
How do we treat most thoughtfully?
Treatment Approach HER2+ MBC in 2018

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

Who Should Receive Endocrine Therapy Upfront?

ET + HER2-targeting ET alone

**Second Line:** TDM-1

**Third, Fourth, Fifth, Sixth Line:**
- Capecitabine + Lapatinib
- Capecitabine + Trastuzumab
- Vinorelbine + Trastuzumab
- Lapatinib + Trastuzumab
- Other chemotherapy + Trastuzumab
- Endocrine Therapy + Trastuzumab

Local Therapy for Metastatic / Recurrent Breast Cancer
Local Therapy of Metastatic Breast Cancer

Role of surgery or radiation

• Regional recurrence – e.g. chest wall lesion, regional LN – curative intent R
• Distant disease – e.g. isolated pulmonary nodule, hepatic met – **not standard, used for symptomatic relief**
• Local Rx of oligometastatic disease – controversial – **not standard**

Exception #1: symptomatic or locally threatening disease
Exception #2: brain metastases

• Survival advantage associated with local therapy
  • Surgery
  • Radiosurgery
  • Coordinated multidisciplinary management is key

When Else to Consider Local Therapy

Disease is truly localized

Local symptoms are present and low chance of palliation with systemic rx

Impending localized complication (spinal cord compression, fracture)
Breast Surgery in Metastatic Disease

Multiple retrospective, a few prospective studies – remains controversial

Patients who undergo breast surgery typically live longer than those who do not – but many uncontrolled variables

Underlying hypothesis is the breast serves as a site of ongoing tumor cell dissemination

Recently completed randomized trial in U.S.

RECOMMENDATION: option but not standard. Consider if local complications exist or oligometastatic.

Diagnosis of Brain Metastases

Presentation
• Headaches, seizures, neurologic deficit
• More found incidentally
• Routine screening not recommended
• 4x more common in HER2+ (often isolated) and TNBC (usually with progression elsewhere)

MRI best diagnostic test, CT next choice
• 50% multiple, 50% 1-3 lesions

11% false + if single lesion (Patchell RA et al, NEJM 1990)
• DDx: Primary brain tumors, infections, infarcts, MS, hemorrhage

Rx:
• 1-3 metastases: SRS or surgery then consideration of whole brain RT (may defer in good prognosis patients)
• multiple intraparenchymal = WBRT, then systemic Rx
• Leptomeningeal – poor px = consider craniospinal RT, IT Rx
Brain Metastasis: Heterogeneous Prognosis

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>GPA Scoring Criteria</th>
<th>Patient Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>KPS</td>
<td>0.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Subtype</td>
<td>Basal</td>
<td>60</td>
</tr>
<tr>
<td>Age, years</td>
<td>≥ 60</td>
<td>&lt; 60</td>
</tr>
<tr>
<td>Sum total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drugs with Reported CNS Activity

- CMF
- CAF
- Cisplatin
- Carboplatin
- Capecitabine
- Temozolomide
- Irinotecan
- High dose methotrexate

In HER2+: lapatinib (and newer small molecule TKI) maybe trastuzumab.

No systemic standard of care, Rx is individualized.
**Skeletal Morbidity from Bone Metastases in Advanced Cancer**

**Skeletal Related Events (SREs)**

<table>
<thead>
<tr>
<th>Pathologic Fracture</th>
<th>Radiotherapy to Bone</th>
<th>Surgery to Bone</th>
<th>Spinal Cord Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Pathologic Fracture Image" /></td>
<td><img src="image2" alt="Radiotherapy to Bone Image" /></td>
<td><img src="image3" alt="Surgery to Bone Image" /></td>
<td><img src="image4" alt="Spinal Cord Compression Image" /></td>
</tr>
</tbody>
</table>

**Hypercalcemia**

**Bone-targeted Agents**

- **Bisphosphonates**
  - Zoledronic acid
  - Clodronate
  - Pamidronate
  - Ibandronate

- **RANK Ligand inhibitor**
  - Denosumab

- **Radiopharmaceuticals**
  - Radium-223
  - Strontium-89
  - Samarium-153

*Little data, not standard*
Benefits of Bone Resorption Inhibitors in Advanced Breast Cancer

- 64% risk of skeletal complication with no bisphosphonate at 2 years
- Approx 33% risk reduction with pamidronate
- Further 20% risk reduction with zoledronate

Bone-modifying agents are added to remainder of MBC Rx in those with lytic bone mets

Treatment of MBC: Where Now?

Major progress in MBC management:
- Multiple HR- and HER2-targeted options
- Immunotherapy in some TNBC
- PARP inhibition mainstay in germline carriers.

Chemotherapy still primary or key for many – optimize!
- Consider entire menu of Rx, toxicity, and patient preference.

Involve Palliative Care / Symptom Management colleagues early.

Goals of therapy in MBC:

1. Disease control
2. Quality of life
Thank you!

Questions
Question 1

Which of the following regimens represent acceptable first-line treatment for a postmenopausal women with hormone receptor positive breast cancer?

A. Letrozole  
B. Anastrozole  
C. Exemestane  
D. Low dose estradiol  
E. Megesterol acetate  
F. Tamoxifen

Choices

1) A only  
2) A, B, and C  
3) All of the above  
4) A, B, C, F
The aromatase inhibitors (letrozole, anastrozole, and exemestane) represent appropriate first-line drugs. A CDK4/6 inhibitor (palbociclib, ribociclib, abemaciclib) can be added in first-line with the nonsteroidal AI (letrozole, anastrozole).

Fulvestrant, an ER downregulator, is at least as effective as AI in the first-line but has only been combined with CDK4/6 inhibitors in pretreated setting.

Tamoxifen is an acceptable alternative, generally in those who have already received AI and fulvestrant.

Neither low dose estradiol nor megestrol acetate are appropriate first-line treatments as each has more toxicity and is likely less effective than the other options.

Question 1: Explanation
Answer = 4

When chemotherapy is administered in the first- or second-line setting, combination therapy should usually be used.

A. True
B. False
False. Although combination chemotherapy is associated with higher response rates and longer time to progression than single agents, combination therapy does not improve survival when cross-over is allowed and has greater toxicity.

Combination therapy is appropriate for symptomatic disease or impending visceral crisis, when higher response rate is desired.

Either combination therapy or single agent treatment represents appropriate clinical care, and the approach can be individualized to the patient’s disease status and preferences.

**Question 3**

**In a patient progressing on antiHER2 therapy with trastuzumab, subsequent treatments should also include antiHER2 therapy.**

A. True

B. False
**Question 3: Explanation**

Unlike most cancer treatments, randomized controlled trials suggest benefit from continuing anti-HER2 therapy after disease progression on trastuzumab.

This has been seen in studies with regimens including trastuzumab, lapatinib, pertuzumab, and trastuzumab emtansine (T-DM1).