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
New Patients With Metastatic Breast Cancer in U.S.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2+</td>
<td>~15-20%</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>

Metastatic Sites

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

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
- 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

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

Median f/u 7.3 years
76% of patients DOD

**OS/OA is itself therapeutic, and opens door for highly effective postmenopausal drugs. Standard of care.**

**Al 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-rel!  
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 NSA/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, edema, pneumonitis)

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
Accelerated FDA approval 2016:
Fulvestrant + palbo in pretreated (no prior palbo)
Key AE: neutropenia, infections, anemia (needs monitoring ET doesn’t)

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+ 20% > ANC ↓

MONARCH-2: Phase III fulvestrant + abema in 2nd 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
Alpelisib Added to Fulvestrant in PreRx

Reason to obtain DNA sequencing in metastatic breast cancer

Endocrine Rx Algorithm in HR+/HER2-

(Full premenopausal - OA/OS)

NSAI (+ palbo, abema- or ribociclib)

Chemotherapy

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

Chemotherapy

Exemestane (+ everolimus)

Exemestane (+ everolimus)

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

**OlympiAD**
- HER2- MBC gBRCA+ ≤2 chemo for MBC (prior A, T, No plat-R)
- 2:1 randomization
- N=300
- Primary endpoint PFS
- Chemo TPC
  - Capecitabine
  - Eribulin
  - Vinorelbine
- Olaparib 300 mg po bid

**EMBRACA**
- HER2- MBC gBRCA+ ≤2 chemo for MBC (prior A, T, No plat-R)
- 2:1 randomization
- N=300
- Primary endpoint PFS
- Chemo TPC
  - Capecitabine
  - Eribulin
  - Vinorelbine
  - Gemcitabine
- Talazoparib 1mg po qd

Primary endpoint PFS

PARP Inhibition in PreRx Germline BRCA+

**OlympiAD** (olaparib)
- HR 0.58 (0.43 - 0.80)

**EMBRACA** (talazoparib)
- HR 0.54 (0.41 - 0.71)

- 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.

Chemotherapy in HER2- Breast Cancer

- HR+ Disease
  - Endocrine Rx
    - Endocrine Refractory Disease
  - Chemotherapy (Chemotherapy for ER+ and TN disease same. However + immunoRx only in TNBC)
- Triple Negative Disease
**MBC Chemotherapy: Wide Options**

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

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

**Vinca alkaloids**
- Vinorelbine

**Other anti-tubule**
- Enbulin

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

**Alkylating agents**
- Cyclophosphamide
- Platinum agents

**Epothilones**
- Ixabepilone

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**Combination vs Single Agent Chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>Combination</th>
<th>Single Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher RR</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Longer TTP (initial)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Survival</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>QOL</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Easier to customize</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Less &quot;wasted&quot; toxicity</td>
<td>✓</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
- Prior taxane
- Liver metastases
- PD-L1 status

**IMpassion 130: Progression-Free Survival (ITT)**

**Overall population**

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

- PDL1+
  2.5 month ↑
  
- Overall population
  1.7 month ↑

**IMpassion 130 Interim Overall Survival: PD-L1+**

- Stratified HR = 0.62  
  (95% CI: 0.45, 0.86)  
  \( P < 0.0001 \)

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

- Stratified HR = 0.62 (95% CI: 0.45, 0.86)
- OS events, n = 64
- 2-year OS (95% CI), %: 54% (42, 65)

Reason to obtain PDL1 on TNBC metastasis at initial relapse

40%+ using Ventana assay

1st Line Chemotherapy Otherwise

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

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.

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

Normal BRCA1
- DNA damage
- DNA damage kinases

Abnormal BRCA1
- DNA damage
- DNA damage kinases

RESTITUTION to DNA damaging agents

REZATRICE to DNA damaging agents

FDA-approved 2019

Reason to obtain PDL1 on TNBC metastasis at initial relapse

40%+ using Ventana assay
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
Docetaxel (D)
100mg/m² q3w, 6 cycles
On progression, crossover if appropriate

TNT: Objective response

Randomised treatment - all patients (N=376)

% with OR at cycle 3 or 6 (95% CI)

Carboplatin

Docetaxel

Germline BRCA 1/2 Mutation (n=43)

Percentage with OR at cycle 3 or 6 (95% CI)

Carboplatin

Docetaxel

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

Kaufman P et al, JCO 2015

OS 14.5m vs 15.9m

Toxicity is a Key Feature to Consider

- alopecia
  - Capecitabine
  - Vinorelbine
  - Carboplatin

- neuropathy
  - Capecitabine
  - Anthracyclines
  - Gemcitabine

- GI symptoms
  - Taxanes
  - Gemcitabine

- myelosuppression
  - Taxanes
  - Capecitabine

- IVs
  - Capecitabine

Continued versus Interrupted Chemotherapy

Ongoing chemotherapy better outcome However more toxic
Meta-Analysis Chemotherapy Duration: Survival

<table>
<thead>
<tr>
<th>Study</th>
<th>HR ± 95% CI</th>
<th>% Weight</th>
<th>HR ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gancz 1987</td>
<td>1.1 ± 1.2</td>
<td>10%</td>
<td>1.1 ± 1.2</td>
</tr>
<tr>
<td>Harris 1990</td>
<td>1.06 ± 1.07</td>
<td>10%</td>
<td>1.06 ± 1.07</td>
</tr>
<tr>
<td>Mao 1991</td>
<td>1.11 ± 1.04</td>
<td>10%</td>
<td>1.11 ± 1.04</td>
</tr>
<tr>
<td>Guggenheim 1983</td>
<td>0.78 ± 0.87</td>
<td>10%</td>
<td>0.78 ± 0.87</td>
</tr>
<tr>
<td>Gregory 1987</td>
<td>0.60 ± 1.16</td>
<td>10%</td>
<td>0.60 ± 1.16</td>
</tr>
<tr>
<td>Flicker 1988</td>
<td>0.66 ± 1.38</td>
<td>10%</td>
<td>0.66 ± 1.38</td>
</tr>
<tr>
<td>Bassert 2000</td>
<td>1.0 ± 1.18</td>
<td>10%</td>
<td>1.0 ± 1.18</td>
</tr>
<tr>
<td>Novi 2003</td>
<td>1.03 ± 1.27</td>
<td>10%</td>
<td>1.03 ± 1.27</td>
</tr>
<tr>
<td>Overmert 2006</td>
<td>1.12 ± 1.72</td>
<td>10%</td>
<td>1.12 ± 1.72</td>
</tr>
<tr>
<td>Majumder 2009</td>
<td>0.84 ± 2.02</td>
<td>0%</td>
<td>0.84 ± 2.02</td>
</tr>
<tr>
<td>Aite 2010</td>
<td>0.66 ± 1.27</td>
<td>0%</td>
<td>0.66 ± 1.27</td>
</tr>
</tbody>
</table>

Overall: 0.95 ± 0.90

Test for heterogeneity, P 0.84; Test for treatment effect, P 0.40

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, platinum
  - Anthracyclines (if did not receive adjuvantly – cannot give twice)

HER2+ Disease: Major Clinical Advances

- Trastuzumab approved stage IV
- Lapatinib approved stage IV
- Pertuzumab approved for MBC
- Pertuzumab approved added to neo(AD)
- T-DME approved for MBC
**Targeting HER2**

Humanized monoclonal Ab to HER2 extracellular domain

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

Small molecule kinase inhibitor

Irreversible HER-1, 2, 4 inhibitor

**Trastuzumab Added To Chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>Chemo + H (paclitaxel or AC)</th>
<th>Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>7.4m</td>
<td>4.6m</td>
</tr>
</tbody>
</table>

**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

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)**

![Diagram](Diagram.png)

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

**CLEOPATRA: Overall Survival**

![Diagram](Diagram2.png)

**PFS 18.5 vs 12.4m, p<0.0001**

**Baselga J et al. NEJM 2012**

**Swain S et al. NEJM 2015**

13.7 months improvement in median OS in the final analysis

Secondary endpoint

**56.5 months**

**40.8 months**

**18.5 months**

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

- Maytansine analogue DM1 (antitubule akin to vinca) conjugated to trastuzumab – similar to gemtuzumab (Mylotarg)
- Will it allow omission of separate cytotoxic?

T-DM1, HER2 Antibody

T-MCC-DM1

HER2-mediated internalization

T-MCC-DM1

Lyosomal degradation

Active metabolite can't cross plasma membrane (no bystander effect)

EMILIA: Phase III Trial T-DM1 versus XL

<table>
<thead>
<tr>
<th>Pre-treated setting</th>
<th>Median (mos)</th>
<th>No. events</th>
<th>Cape + Lapa</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAP vs Lapa</td>
<td>6.4</td>
<td>304</td>
<td></td>
<td>9.6</td>
</tr>
<tr>
<td>HR=0.65, p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>201</td>
</tr>
<tr>
<td>OS (secondary): 31m vs 25m, p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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>Regimen</th>
<th>PFS</th>
<th>OS</th>
</tr>
</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>NERETTA</td>
<td>1</td>
<td>TH v. TN</td>
<td>17 v. 17m (ns)</td>
<td>Fewer CNS with TN?</td>
</tr>
<tr>
<td>BOLOER-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>BOLOER-3</td>
<td>2</td>
<td>VH + Eve</td>
<td>7 v. 6m (HR 0.78*)</td>
<td></td>
</tr>
<tr>
<td>THRESA</td>
<td>3+</td>
<td>TDM1 v. MD choice</td>
<td>6 v. 3m (HR 0.53) (interim)</td>
<td>0.55</td>
</tr>
</tbody>
</table>

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

Next Generation of HER2-Targeting

<table>
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<tr>
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<th>Line</th>
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<th>PFS</th>
<th>OS</th>
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</tr>
<tr>
<td>MARIANNE</td>
<td>1</td>
<td>TH v. TDM1 ± P</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>NEERTT‡</td>
<td>1</td>
<td>TH v. TN</td>
<td>17 v. 10 m (HR 0.71)</td>
<td>Newer CNS with TN?</td>
</tr>
<tr>
<td>BOLERO-1</td>
<td>1</td>
<td>TH ± Eri</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>EMILIA</td>
<td>2</td>
<td>TH v. TDM1 ± P</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>BOLERO-2</td>
<td>2</td>
<td>TH v. TDM1 ± Eri</td>
<td>7 v. 6 m (HR 0.78*)</td>
<td>-</td>
</tr>
<tr>
<td>TH3RESA</td>
<td>1</td>
<td>TDM1 ± MD choice</td>
<td>6 v. 3 m (HR 0.53)</td>
<td>HR 0.55 (interim)</td>
</tr>
</tbody>
</table>

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

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></td>
<td>Chemotherapy-based</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
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, N Engl J Med 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

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)

- Pathologic Fracture
- Radiotherapy to Bone
- Surgery to Bone
- Spinal Cord Compression

Hypercalcemia

Bone-targeted Agents

- Little data, not standard
- Bisphosphonates
  - Zoledronic acid
  - Clodronate
  - Pamidronate
  - Ibandronate
- RANK Ligand inhibitor
- Denosumab
- Radiopharmaceuticals
  - Radium-223
  - Strontium-89
  - Samarium-153

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
- Additional 20% risk reduction with denosumab

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

- Lipton et al., Cancer 2000; Rosen et al., Cancer 2003; Stopeck et al., JCO 2010 (adapted courtesy of Hope Rugo)
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
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

Answer = 4

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 megesterol acetate are appropriate first-line treatments as each has more toxicity and is likely less effective than the other options.
Question 2

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

A. True
B. False

Question 2: Explanation

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
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).