An Approach to Metastatic Breast Cancer

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GP Oncologist BCCA
Disclosures

- Dr. Elizabeth Kenward – None
- Dr. Lee Ann Martin - None
Team Approach
Goals of Treatment

- Prolongation of Life
  - Average life expectancy of 24 months*
    - Her2+ or ER +: 4 to 5 years
    - Triple negative: <1 year

- Alleviation of Symptoms
- Maintenance or Improvement in QOL
- Avoidance of unnecessary toxicity
Risk Assessment

- Receptor Status
  - Repeat biopsy if possible due to high rates of discordance when compared to primary disease
  - Change in HER2 status could allow the addition of targeted agents to chemotherapy protocols

- Did the patient receive prior treatment? If so what was the interval between initial treatment and relapse?
  - ≥ 12months

- Number of metastatic sites

- Symptom Burden/Performance Status

- Visceral Involvement
  - CBC, liver function tests, sCa\(^{2+}\)
  - CT chest/abdomen, bone scan +/- brain imaging (if symptomatic)
  - PET scan in high suspicion of relapse but negative imaging

- Biochemical Markers
  - Ca 15-3, CEA

Case Study: MK

- 33 year old female, premenopausal, G2P2
- Presents to her GP with post-partum back pain, night sweats and decreased appetite
- Limited activity due to fatigue/pain
- No family history of oncologic diagnoses
- CXR, plain films of the lumbar spine unremarkable
- AUS normal
- bHCG normal, CBC shows pancytopenia
Case Study: MK

- What relevant historical information is provided? What is missing?

- What physical exam findings, laboratory investigations and radiographic assessments should be considered now?
Case Study: MK

- CRP elevated > 200, LDH elevated 734, LFTs normal
- Sent to ER for urgent imaging.
- CT scan shows multiple lytic lesions in the axial skeleton, pathologic fracture at T8/T12, lesion in the left femur
- 3 masses noted in the left breast with enlarged axillary lymph nodes. Largest 12mm.

Next steps?
Case Study: MK

- Biopsy confirms ER+/PR+ Her2Neu - disease
- CT scan of the pelvis and femur shows 1.9 cm lucent lesion within the intertrochanteric region of the left femur.
- Bone scan negative confirms metastatic disease but except the left femur.
- Surgical consult obtained. Lesion likely benign. Intervention deferred.
- RT consultation obtained. Pain control with medication effective. RT deferred.
- pRBC transfusion co-ordinated at MDC
Hormone Positive Disease

- What is the first line of therapy in ER/PR positive disease?
- What other factors may influence this?
  - Disease burden
  - Interval prior to relapse
  - Prior treatment strategies
  - Menopausal status
  - HER2 Status
- What is our patient’s expected median survival?
- What are our goals of care?
- What other best supportive care practices must we consider?
Generalized Classification of Breast Cancer For Treatment Algorithms

- Hormone Receptor Positive, HER2 negative
  - Endocrine Therapy

- Hormone Receptor Positive/Negative, HER2 positive
  - Targeted Therapy combined with Chemotherapy

- Triple Negative Disease
  - Chemotherapy
Factors Influencing Treatment Decisions

- Disease/symptom burden
- Visceral involvement
- Prior treatment and interval to relapse
- Menopausal status
- HER2 status
Metastatic Disease

Hormone Positive

Endocrine Therapy

Multiple Relapse on Endocrine Therapy 3rd Line

Rapidly progressive Heavy visceral or symptom burden

Chemotherapy +/- Targeted Therapy

Hormone Negative Or Hormone Positive with HER2+ *

*may use lapatinib and AI if chemotherapy ineligible
First Line Endocrine Therapy

Who qualifies?

- De novo presentation or endocrine therapy naïve
- A relapse ≥ 12 months from adjuvant hormone therapy
- Low symptom and visceral burden of disease
- ER+/HER2- disease
- ER+/HER2+ disease but chemotherapy ineligible
First Line Endocrine Therapy

Menopausal status:
Prior bilateral oopherectomy
No prior menses in 12 months off treatment
On chemotherapy or endocrine therapy: post menopausal estradiol level
Premenopausal Women

- BRAVTAM
- BRAVLHRHT
- Combination of LHRH agonist with AI requires CAP approval
  - Tamoxifen intolerance (depression)
  - 2nd line at the time of progression
Estrogen Modulation

[Diagram showing the processes of estrogen modulation including aromatase inhibitors (AI), Trastuzumab, growth factor, and various pathways involving ERα, E2, and mTOR inhibitors like everolimus and tamoxifen and their metabolites.]
Evidence in Pre-Menopausal Women

- **BRAVLHRHT**
  - Combination (SERM + Ovarian suppression) > Ovarian suppression alone
    - Meta Analysis of 4 RCT (n=506)**
    - ORR PFS and OS benefit
  - There are no direct studies comparing combination treatment to tamoxifen

- **BRAVTAM**
  - SERM = Ovarian Ablation/Suppression alone
    - RCT, tamoxifen vs ablation, n=40*
    - No statistical difference in PFS (184 vs 126 days) or OS (2.35 vs 2.46 years)

- **LHRH agonism and NSAI**
  - 3 small non randomized Phase II Trials***
  - TTP was similar to post menopausal date of 9.5 months
  - Greater bone loss in combination

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LHRH Agonism

Ovarian production of estrogen may be incomplete

- Monthly injections preferred
- Monthly Estradiol levels should be monitored
  - FSH greater than 40mIU/mL
  - Estradiol less than 30pg/mL

Recognize special issues associated with this including loss of fertility
Post Menopausal Women

**FUNDED**
- NSAIs: BRAVLET, BRAVANAS
- BRAVTAM

**NOT FUNDED**
- Fulvestrant
- sAI plus Palbociclib
Evidence in Post Menopausal Women

- **BRAVLET, BRAVANAS**: Steroidal Reversible Aromatase Inhibitors
  - Are not to be used in sequence due to similar chemistry and MOA
  - Can be interchanged due to intolerability
  - Less vaginal bleeding and thromboembolic events

- **BRAVTAM**
  - Used when relapse occurs in the setting of an adjuvant AI
  - RCT have generally resulted in improved PFS with no OS advantage when tamoxifen compared to NSAI* and SAI**

<table>
<thead>
<tr>
<th></th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>21 vs 17%</td>
<td>30 vs 20%</td>
<td>46 vs 31%</td>
</tr>
<tr>
<td>PFS</td>
<td>11.1 vs 5.6m</td>
<td>10 vs 6.25m</td>
<td>9.9 vs 5.8m</td>
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<tr>
<td>OS</td>
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<table>
<thead>
<tr>
<th>Tamoxifen</th>
<th>Aromatase Inhibitors</th>
<th>Fulvestrant</th>
<th>CDK 4/6 Inhibitor</th>
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</thead>
<tbody>
<tr>
<td>Hypertension/IHD</td>
<td>HTN/IHD Edema</td>
<td>Injection Site Pain</td>
<td>Alopecia</td>
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<tr>
<td>Thromboembolism 2-5%</td>
<td>Thromboembolism</td>
<td></td>
<td>Bone Marrow Suppression</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Febrile Neutropenia</td>
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<td></td>
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<td>Pulmonary Emboli</td>
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<tr>
<td>Fatigue/Hot Flashes</td>
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<td>Fatigue/Hot Flashes</td>
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<td>Weight gain/loss</td>
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<td>Weight Gain</td>
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<tr>
<td>Depression</td>
<td>Depression</td>
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<tr>
<td>Vaginal Dryness</td>
<td>Vaginal Dryness</td>
<td>Vaginal Dryness</td>
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<tr>
<td>Mild nausea</td>
<td>Mild nausea</td>
<td>Mild nausea</td>
<td>Nausea</td>
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<tr>
<td>Vaginal Bleeding</td>
<td>Fractures/Osteoporosis</td>
<td></td>
<td></td>
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<tr>
<td>Endometrial Ca &lt;1%</td>
<td></td>
<td></td>
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<tr>
<td>Hypercalcemia</td>
<td>Elevated LFTs</td>
<td>Elevated LFTs</td>
<td></td>
</tr>
<tr>
<td>Decreased HDL/LDL (query ER agonism)</td>
<td>Increased Chol/LDL (Data scarce)</td>
<td>Cough/SOB</td>
<td>Diarrhea/Stomatitis</td>
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<tr>
<td>Increased TG/Chol</td>
<td>Headache</td>
<td></td>
<td>Peripheral Neuropathy</td>
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<tr>
<td>Cataracts</td>
<td></td>
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<tr>
<td>Arthralgia</td>
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<td>Arthralgia</td>
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<tr>
<td>Toxicity</td>
<td>Management</td>
<td></td>
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<tr>
<td>----------------------------------------------</td>
<td>---------------------------------------------------------------------------</td>
<td></td>
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</tbody>
</table>
| Hot Flashes -involvement of serotonin receptors | Venlafaxine 75mg PO OD  
Gabapentin 300mg PO OD-TID                                               |
| Vaginal Dryness/Dyspareunia                   | Replens (water based lubricant)  
Avoidance of topical estrogen                                               |
| Arthralgias/Myalgias                          | Rotate NSAI  
NSAIDs  
Reduction with time  
Check Vitamin D Levels                                                      |
| Cardiovascular Disease/Lipid Profile          | Monitor q4-6months  
Treat as needed                                                            |
| Memory Loss                                  | CB Strategies  
Blister pack medications                                                    |
| Depression                                   | Monitor for symptoms  
If on Tamoxifen switch to AI  
Counseling support/Anti-depressant  
*avoid Paxil, Prozac, Wellbutrin while on tamoxifen                          |
| Vaginal Bleeding                             | Biopsy/US                                                                 |
| Thromboembolic Event                         | Dalteparin 200mg/kg IU SC OD for 1 month, then  
150mg/kg IU SC daily                                                        |
| Osteoporosis                                 | Bone density assessment at baseline then q1-3 years  
Vit D and Calcium Supplementation or Increase  
Dietary Intake                                                               |
FULVESTRANT

- ER antagonist that blocks dimerization, inhibits nuclear uptake and prevents DNA binding
Fulvestrant

- **Fulvestrant alone vs nonsteroidal AI**
  - FIRST Trial
    - Phase II RCT n=205
    - Fulvestrant 500mg vs anastrozole alone
    - PFS 23 vs 13 months, OS 54 vs 48 months
  - FALCON Trial
    - Phase III
    - Pending Results

- **Combination Fulvestrant with nonsteroidal AI**
  - 2 RCT with opposing results.
  - Similar toxicity profile
    - FACT Trial: no impact on TTP or OS
    - SWOG 0226 Trial: significant reduction in TTP, trend to OS benefit
    - (note patient population diff. 50% of patients had no prior endocrine therapy)

FIRST: Fulvestrant 500 mg vs. Anastrozole as First-Line

HR = 0.66 (95% CI: 0.47-0.92)

\[ P = .01 \]

Number of patients at risk:

- Fulvestrant 500 mg: 102, 74, 65, 52, 45, 34, 20, 6, 0
- Anastrozole 1 mg: 103, 69, 55, 39, 30, 21, 8, 2, 0

CI = confidence interval; HR = hazard ratio; TTP = time to progression

PALBOCICLIB
G1 = growth
S = DNA replication
G2 = growth 2
M = mitosis
G0 = quiescence (not growing, just surviving)
ADDITION OF CDK 4/6 INHIBITION

- **Palbociclib**
  - Oral CDK 4/6 inhibitor
  - Increased alopecia, neutropenia, fatigue, nausea
- **PALOMA 1**
  - Phase II (n=165) Letrozole 2.5mg daily + palbociclib 125mg daily Day 1-21 on 28 day cycle vs Letrozole alone
  - Less than half had received adjuvant treatment
  - PFS 20 vs 10 months, OS *trend* 37.5 vs 33 month
- **PALOMA-2**
  - Preliminary results on Phase III trial
  - suggest similar improved PFS (24.8 vs 14.5m)
  - higher neutropenia (79 vs 6.3), fatigue (37 vs 28), nausea (35 vs 26)
PALOMA-1

Progression-Free Survival (ITT)

- **PAL + LET (N=84)**
  - Number of Events (%): 41 (49)
  - Median PFS, months (95% CI): 20.2 (13.8, 27.5)
  - Hazard Ratio (95% CI): 0.488 (0.319, 0.748)
  - p-value: 0.0004

- **LET (N=81)**
  - Number of Events (%): 59 (73)
  - Median PFS, months (95% CI): 10.2 (5.7, 12.6)

Number of patients at risk:
- **PAL + LET**: 84, 67, 60, 47, 36, 28, 21, 13, 8, 5, 1
- **LET**: 81, 48, 36, 28, 19, 14, 6, 3, 3, 1
Overall Survival (ITT)
At Time of Final PFS Analysis

Overall Survival Probability (%)

Number of Events (%)
30 (38)
31 (38)

Median OS, months
37.5 (28.4, NR)
33.3 (26.4, NR)

Hazard Ratio
0.813 (0.492, 1.345)

p-value
0.2105

Number of patients at risk
PAL + LET 84 80 78 73 68 65 47 35 22 17 7 2
LET 81 76 74 67 64 59 37 23 14 12 5 1

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Case Study: MK

- Does not fit criteria for first line endocrine maneuvers
- What is the best first line treatment in her case?
- What co-morbidities will impact treatment selection?
- Are there other supportive care measures to consider at this time?
Chemotherapy in Hormone Positive Disease

- Who do we consider?
  - ECOG 0-2
  - Symptomatic burden of disease
  - > 3 months anticipated survival
- How do we select our treatment regimens?
  - Prior treatment
  - Co-Morbid Disease
  - Patient Preference
- How long do we treat?
# Treatment Regimens

## Single Agent Combination

<table>
<thead>
<tr>
<th>Single Agent</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAVA7</td>
<td>BRAVAC, BRAVCAF</td>
</tr>
<tr>
<td>BRAVDOC, BRAVABR</td>
<td>BRAVGEMD/T (if prior anthracycline or cardiac disease)</td>
</tr>
<tr>
<td>BRAVTAX, BRAVTW</td>
<td>BRAVDCAP</td>
</tr>
<tr>
<td>BRAVCAP</td>
<td></td>
</tr>
<tr>
<td>BRAVGEM</td>
<td>BRAVGEMP</td>
</tr>
<tr>
<td>BRAVNAV</td>
<td>BRAVGEMD/T, BRAVCAP</td>
</tr>
</tbody>
</table>

**Anthracyclines:** De novo Stage IV disease, cumulative cardiac toxicity
Equal efficacy to taxanes.

**Taxanes:** Effective in pretreated population, cumulative peripheral neuropathy
Docetaxol > Paclitaxel (TTP: 5.7 vs 3.6/OS: 15.4 vs 12.7)
Nab-paclitaxel equivalent to paclitaxel

**Capecitabine:** Effective in pretreated population, PPE toxicity
Effective in the ER+, bone predominant patient.
More effective than BRAVCAMF (equivalent PFS, OS 20 vs 17 months)
# Specific Toxicities

<table>
<thead>
<tr>
<th>Single Agent Drug Class</th>
<th>Specific Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracycline</strong></td>
<td>Cardiac</td>
</tr>
<tr>
<td></td>
<td>Can be used in mild to moderate hepatic impairment</td>
</tr>
<tr>
<td><strong>Taxane</strong></td>
<td>Neuropathy/Myalgia (worse with paclitaxel)</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia (premedication)</td>
</tr>
<tr>
<td></td>
<td>Myelosuppression (worse with docetaxol)</td>
</tr>
<tr>
<td></td>
<td>Consider hepatic disease (can use paclitaxel)</td>
</tr>
<tr>
<td><strong>Capecitabine</strong></td>
<td>PPE</td>
</tr>
<tr>
<td></td>
<td>Daily medication</td>
</tr>
</tbody>
</table>

* Can give nab-paclitaxel which has a lower incidence to hypersensitivity reactions
Case Study: MK

- Received 4 cycles of weekly paclitaxel
  - Less hematologic suppression with paclitaxel
  - Reduced neuropathy/myalgias with weekly regimen

- How do we monitor her response? When should we consider discontinuing cytotoxic therapy?
Monitoring

- Response to treatment should be assessed after 2-3 cycles.
- Optimal duration of therapy can vary by protocol.
- May consider return to endocrine therapy after 6-8 cycles of cytotoxic treatment with good response.
How do we assess for failure?

- Clinical Progression
- Biochemical Progression
- Radiographic Progression
How do we monitor treatment?

- **Monthly history and physical**
  - Symptom palliation
  - Palpable disease reduction (lymph nodes, CW nodules)
  - Increasing toxicity
  - Declining performance status

- **Tumour Markers**
  - Assess trends!
  - Elevated markers occur in 20% of patients in the first 1-2 months of treatment
  - Vary with liver function, Vit B12 deficiency

- **Imaging**
  - CT/Bone scan q3-4m (decrease imaging frequency if stable)
  - MUGA/ECHO q12weeks for trastuzumab/pertuzumab
    - Can have up to 10-15% discrepancy when comparing between two modalities
    - No defined schedule for assessment in the metastatic setting
Clinical Signs

- Constitutional signs
- Neurologic Dysfunction
- Pain
- SOB
- Jaundice
- Palpable growth on exam
- Ascites
Biochemical Signs

- REPEATED Tumour Marker Elevations
- Hypercalcemia
- Elevated Alk Phos, LDH, AST, ALT, bilirubin
- Bone Marrow Suppression
Radiographic Signs

- **RECIST CRITERIA**
  - ≥ 20% increase (at least 5mm) in the sum of the longest diameters of the target lesions
  - New metastatic foci
  - If non-measurable disease, a marked increase in the overall tumour burden (ie. Pleural effusion from trace to large)
Case Study: MK

- Clinical Response:
  - Reduction in pain
  - Increased activity (jogging) and reduction in fatigue

- Biochemical Response
  - Tumour Marker Improvement Ca 15-3 667 dropped to 168
  - No longer reliant on blood transfusions, stability of hematology panel

- Radiographic Response
  - CT scan showing increased sclerosis of bone lesions, reduced lymphadenopathy
  - Bone scan shows scintigraphic healing flare
Now that MK has stabilized what other supportive care measures can be addressed?
What other supportive care measures must we consider?

- Residual bone pain/Oligometastases
- Ongoing transfusion needs
- Bone health
- Psychosocial support
- Palliative care introduction
When do we involve our Radiation Oncology Colleagues?

- Brain Metastases
- Symptomatic endobronchial lesions
- Ulcerating ST/chest wall disease
- SVC obstruction
- Escalating Pain with impeding fracture or lack of response to traditional analgesia
- Spinal Cord Compression
When do we involve our Surgical Colleagues?

- Surgical stabilization of an osseous lesion in the vertebrae or long bone

- Solitary metastases at an accessible site:
  - Lung
  - Liver
  - Brain
Bone Health

- What are the indications for using bone-modifying agents to reduce the risk of skeletal-related events (SREs) in patients with metastatic breast cancer? When is the best time to initiate treatment with bone-modifying agents?

- **First line:** oral clodronate, intravenous (IV) pamidronate 90 mg
- **Second line:** zoledronic acid 4 mg every 3 to 4 weeks
- There is insufficient evidence relating to efficacy to support one bone-modifying agent over another.
- **Show a reduction in SRE (fracture, palliative RT, SCC)***
- **Must have CT/XRAY confirmed bone disease with supportive bone scan**

Bone Health

- What are the renal safety concerns of bone-modifying agent therapy?
  - *In patients with a calculated serum creatinine clearance of more than 60 mL/min, no change in dosage, infusion time, or interval of pamidronate or zoledronic acid administration is required.*
  - Serum creatinine be monitored before each dose of pamidronate or zoledronic acid
  - *Serum calcium, electrolytes, phosphate, magnesium, and hematocrit/hemoglobin should also be monitored regularly.*
  - Monitor for hypocalcemia in patients with impaired creatinine clearance or low vitamin D levels.
What are the osteonecrosis of the jaw (ONJ) safety concerns of bone-modifying agent therapy?

- **ONJ is an uncommon but potentially serious condition associated with the use of bone-modifying agents.**
- **All patients with cancer receive a dental examination and necessary preventive dentistry prior to initiating therapy with inhibitors of osteoclast function.**
- **Although most cases of ONJ have occurred in patients treated with IV bisphosphonates and bone-modifying agents who underwent an invasive dental procedure, cases have occurred spontaneously and have been reported in patients treated with other bone-modifying agents, including oral bisphosphonates and direct osteoclast inhibitors.**
Osteonecrosis of the Jaw
Bone Health

- 1000-2000 IU Vitamin D and 1000-1500mg Calcium
  - By diet or vitamin supplementation
- Duration of therapy:
  - 2-3 years: Not well defined
Best Supportive Care: Psychosocial Support

- Discuss GOALS of treatment before your first treatment. (Include family as much as you can)
- Encourage regular family practice visits.
- Connect patients to local support groups/counseling services
- Assess support network
- Assess for pathologic coping strategies
  - ETOH, drugs, smoking
Best Supportive Care

- Patient M is a young mother who needs early am appointments to allow drop off for her daughters at school
- Her husband required a second appointment to discuss goals of care, counseling support
- She is a part of our local breast cancer support group
- Her daughters recently ran in the Run for the Cure and made a presentation to their class
- She is young and encouraging her to discuss Advanced Directives of Care is difficult
When addressing chemotherapy toxicities we must realize the impact of these symptoms on our ability to treat patients

- Fatigue: Hgb, dosing, schedule
- Nausea: premedication, constipation, analgesia, paracentesis for ascites
- Pain: radiation (pain palliation, SCC) and analgesia
- SOBOE: r/o PE/CHF, if pleural effusion plan ahead and book thoracentesis/Pleurex catheter
Second Line Therapy

- Return to your treatment algorithm

- Is this low burden/asymptomatic disease?

- Is this high volume/symptomatic/aggressive disease?
Case Study: MK

- Due to good response to treatment MK was transitioned to LHRH agonism/Tamoxifen after 4 cycles
Second Line Therapy

- **Who qualifies?**
  - Relapse after first line therapy in a metastatic setting
  - Stability achieved on first line cytotoxic treatment
  - ≤12 months since prior adjuvant hormone therapy

- **What are our options?**
  - BRAVTAM
  - BRAVEXE if duration of response to prior AI >4-6m
    - ORR 2-26% (prior NSAI)
    - Addition of Everolimus to Exemestane
Exemestane/Tamoxifen

- BRAVTAM
- BRAVEXE
  - Based on a 2011 Systematic review of nine studies
  - ORR 2-26 % with a CBR 12-55%
  - After treatment with anastrozole or letrozole

Insert reference here
Fulvestrant in Second Line

- Current data suggests a similar ORR and OS compared to AI

- No benefit to adding to exemestane as shown in the SoFEA trial.

Chia S. et al. Double blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in Postmenopausal women with hormone receptor positive advanced breast cancer: Results from EFECT. J Clin Oncol 26:1664-1670, 2008

Di Leo A et al. Results of the CONFIRM phase III trial comparing fulvestrant 250mg with fulvestrant 500mg in postmenopausal women with estrogen receptor Positive advanced breast cancer. J Clin Oncol 28:4594-4600, 2010

Johnston SR. et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal Patients with hormone receptor positive locally advanced or metastatic breast cancer (SoFEA): A composite, multicenter, phase 3 randomized trial. Lancet Oncol 14:989-998, 2013
EFECT Study

- Phase III RCT
- Exemestane vs Fulvestrant 250mg
- PFS and tolerance equivalent
EFECT Study

![Graph showing the proportion of patients progression-free over time to progression (days). The graph compares Fulvestrant and Exemestane treatments.]

**Proportion of Patients Progression-Free**

**Time to Progression (days)**

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<th>0</th>
<th>50</th>
<th>100</th>
<th>150</th>
<th>200</th>
<th>250</th>
<th>300</th>
<th>350</th>
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<th>450</th>
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<th>550</th>
<th>600</th>
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<th>700</th>
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</thead>
<tbody>
<tr>
<td>Fulvestrant at risk</td>
<td>351</td>
<td>301</td>
<td>191</td>
<td>127</td>
<td>89</td>
<td>67</td>
<td>46</td>
<td>29</td>
<td>23</td>
<td>13</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>0</td>
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<tr>
<td>Exemestane at risk</td>
<td>342</td>
<td>305</td>
<td>184</td>
<td>130</td>
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<td>8</td>
<td>8</td>
<td>6</td>
<td>2</td>
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</tbody>
</table>
CONFIRM Trial

- High dose fulvestrant vs low dose after standard loading schedule of 500mg Days 1/15/29
- PFS of 1 month
- OS of 4.1 months
- No increase risk of toxicity
CONFIRM Trial

Hazard ratio (95% CI): 0.80 (0.68 to 0.94)

\[ P = 0.006 \]

Proportion of Patients Progression Free

Time (months)

No. of patients at risk
- Fulvestrant 500 mg: 362, 216, 163, 113, 90, 54, 37, 19, 12, 7, 3, 2, 0
- Fulvestrant 250 mg: 374, 199, 144, 85, 60, 35, 25, 12, 4, 3, 1, 1, 0
Addition of Everolimus

- Exemestane and everolimus may be offered to postmenopausal women with HR positive MBC who experience progression during treatment on nonsteroidal AIs.

- Based on data from BOLERO-2 showing PFS but no OS advantage

- Should be given to those with relapse after <12 months of NSAI therapy

- TAMRAD was an open label phase II trial showing preliminary OS, PFS benefit when everolimus was added to tamoxifen. No phase III data.

BOLERO-2

- Phase III RCT n=724
  - Women who had progressed on anastrozole
- PFS: 7 vs 3 months
- OS: no difference
- ORR: 9.5 vs 0.4%
- Toxicity:
  - Stomatitis (8%), pneumonitis (3%), LFT abnormalities (3%), hyperglycemia
  - May require dose reductions and interruptions
BOLERO-2 Primary Endpoint: PFS Local Assessment

HR = 0.43 (95% CI: 0.35–0.54)
Log rank $P$ value = $1.4 \times 10^{-15}$

EVE + EXE: 6.9 months
PBO + EXE: 2.8 months

**PALOMA 3**

- Addition of palbociclib to fulvestrant after progression on nonsteroidal AIs <12 months

- More than doubling of PFS (9.5 vs 4.6 months) with immature OS data

- Increased Neutropenia (65 vs 1%)
  - Hematology panel assessment q2weeks for the first two cycles.

Case Study: MK

- Within 4 weeks of second line hormone therapy the patient was experiencing new escalating hip discomfort, biochemical progression and liver enzyme elevation.

- Imaging confirmed new hepatic disease, progressive osseous burden.
Case Study: MK

- The patient was started on dose reduced oral capecitabine at 750mg/m²

- Impacts to patient
  - Oral treatment
  - No alopecia
  - No neuropathy, myalgias
  - Pain resolution
Case Study: MK

Update:
- Recent trip to Disneyland with her family
- Hip pain settled without RT
- Weight stabilized

- Ca 15-3 334
- Resolution of liver enzyme elevation

- Recent CT scan shows stability of disease
HER2 Positive Disease

- What is our first line therapy in this setting?
- What specific challenges can we expect?
- What special monitoring must be considered?
- What median survival can our patients expect?
- How do our treatments improve mOS and QOL measures
What if MK had HER2 positive disease on biopsy?
HER 2 Directed Agents

• Trastuzumab
  • mAB for extra-cellular domain of HER2

• Pertuzumab
  • mAB for extra-cellular dimerization domain of HER2
  • Prevents HER2 from binding other EGFR receptors

• Kadcyla (TDM1)/Ado trastuzumab emtansine
  • Trastuzumab and an anti-microtubule DM1

• Lapatinib
  • TKI against EGFR1 and HER2
HER2 + Disease: First Line

- The standard of care in first line, regardless of hormone receptor status in Her2 + disease is targeted therapy and chemotherapy with a taxane.

- Addition of HER2 targeted therapy to AIs improved PFS with no OS advantage. Chemotherapy plus HER2 targeted therapy showed OS and PFS improvements.

<table>
<thead>
<tr>
<th>Healthy/Young</th>
<th>Frail/Elderly</th>
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<tbody>
<tr>
<td>BRAVTRAP, BRAVPTRAD,</td>
<td>BRAVTRVIN</td>
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<tr>
<td>BRAVCAP</td>
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- Cytotoxic treatments may be held after 6-8 cycles with continued herceptin BRAVTR until progression.


# Chemotherapy Options

<table>
<thead>
<tr>
<th>Single Agent</th>
<th>Combined Therapy</th>
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<tbody>
<tr>
<td>BRAVTR</td>
<td>BRAVTRAD</td>
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<tr>
<td>BRAVPTRAD</td>
<td>BRAVCAP</td>
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<tr>
<td>BRAVTPCARB</td>
<td>BRAVLCAP</td>
</tr>
<tr>
<td>BRAVKAD (TDM-1)</td>
<td>BRAVTRVIN</td>
</tr>
<tr>
<td>BRAVKAD (TDM-1)</td>
<td>BRAVLCAP</td>
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Based on data from the EMELIA Trial showing PFS/OS advantage of 4 months/6 months, respectively, BRAVKAD is used commonly in the 2nd line setting before BRAVLCAP. Less toxicity (neutropenia but increased risk of bleeding).
When do we use endocrine therapy in HER2+ Disease

- In patients too frail for chemotherapy
  - AI alone
  - AI and lapatinib (requires CAP approval)
What if MK developed brain metastases?
BRAIN METASTASES

- 40-60% of mHER2+ patients will develop brain metastases
  - Young <65yr /Controlled Disease/Good PS

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<thead>
<tr>
<th>Oligometastases</th>
<th>Multiple Metastases</th>
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<tbody>
<tr>
<td>Surgical Excision +/- Stereotactic Radiation</td>
<td>Stereotactic Radiation +/- Whole Brain Radiation</td>
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<tr>
<td>Whole Brain Radiation</td>
<td>Whole Brain Radiation</td>
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</tbody>
</table>

- Older Frail Patient
  - Whole Brain Radiation

- Use of steroids in patients with vasogenic edema
  - Dexamethasone 2-8mg PO BID, to taper 2-4 weeks after completion of radiotherapy
Chemotherapy in Brain Metastases

- Chemotherapy choices which cross the blood brain barrier
  - BRAVTRCAP, BRAVLCAP, anthracyclines/cisplatin
  - Recent LANDSCAPE Trial
Questions?