Endocrine therapy options currently include ovarian suppression along with three main classes of drugs: the selective estrogen receptor modulators (tamoxifen and toremifene), an estrogen receptor antagonist (fulvestrant), and the aromatase inhibitors (letrozole, anastrozole, and exemestane). Learn how the specific choice of therapy depends upon the stage of disease, prior therapy, and the menopausal status of the patient. By the session’s end, you’ll have gained a thorough understanding of endocrine therapy, the backbone of hormone receptor positive breast cancer therapy.

**Content Area:** Clinical Practice

**Content Level:** Intermediate

**Speaker:**
Carolyn Lavender, RN, MSN, ARNP, AOCNP®
Medical Science Liaison
Prostrakan
St Pete Beach, FL
lavenderbeach@tampabay.rr.com

**Full Disclosure:**
Prostrakan Employee. Intends to discuss unapproved/investigational use of a commercial product/device during this educational activity.

**Speaker:**
Michelle Mintz, RN, ARNP-BC, OCN®
Florida Cancer Specialists
St. Petersburg, FL
michelle_mintz@hotmail.com

**Full Disclosure:**
Nothing to Disclose

**Objectives:**
At the end of this session, participants will be able to:
1. Understand the emerging treatment options, including endocrine therapy, for breast cancer.
2. Describe the implications of these treatment options for nursing practice.

**Content Outline:**
I. Introduction of speakers and topic
II. History and overview of endocrine therapy
   A. History
   B. ER positivity
   C. Ovarian suppression
   D. Pre-menopausal vs. post-menopausal therapy
III. Endocrine therapy treatment
   A. SERMS and SERD
      1. Mechanism of action
      2. Clinical data
      3. Adverse events
      4. Nursing implications
   B. AI’s
      1. Mechanism of action
      2. Clinical data
      3. Adverse events
      4. Nursing implications
IV. Future therapies
   A. Combination therapies
   B. Future new therapies
V. Case study premenopausal
VI. Case study post-menopausal
VII. Summary and Q & A

**Bibliography:**
AstraZeneca. (2012). Arimidex [package insert], Wilmington, DE.


Kim, J., Coss, C.C., et al. (2012). Role and pharmacologic significance of cytochrome P-450 2D6 in oxidative metabolism of toremifene and tamoxifen. *International Journal of Cancer.*


Positively Position your Hormone Sensitive Breast Cancer Patients for Success: Understanding Endocrine Therapy Options

Michelle Mintz, ARNP-BC
Carolyn Lavender, MSN, AOCNP, ARNP

Endocrine Therapy: Evolving Patient Options

- Endocrine Therapy continues to evolve due to:
  - Increasing knowledge of the complex biology of cancer
  - Increasing molecular understanding that “breast cancer” is a family of related diseases
  - Growing list of available agents and agents to combine with
  - Targeted therapies with mTOR inhibitors and beyond

Genomics Is Integral to Breast Cancer Treatment

- Molecular classification of breast cancer into clinically relevant subtypes such as luminal (A or B), basal-like, and Her2+
- Classifying into subtypes helps researchers tailor therapies to the subtype
- Oncotype DX® is a multigene expression test that predicts the likelihood of chemotherapy benefit and recurrence in invasive cancers
- OncoPanel™ 240 helps define genomic biomarkers during preclinical development of medications

Current Approaches

- Selective Estrogen Receptor Molecules (SERMs)
  - Tamoxifen (metastatic or adjuvant)
  - Toremifene (metastatic)
- Aromatase Inhibitors (AIs)
- Selective Estrogen Receptor Downregulator (SERD)
  - Fulvestrant
- Combination therapy or additive therapy
- HER2/endocrine therapy
- NCCN guidelines: sequence agents until progressive disease or refractory

Available Endocrine Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Agent(s)</th>
<th>Approval</th>
<th>Pre-menopausal</th>
<th>Post-menopausal</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERM</td>
<td>Compete with estrogen for binding to ER in breast</td>
<td>Tamoxifen</td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toremifene (Fareston®)</td>
<td></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Aromatase</td>
<td>Inhibit production of estrogen</td>
<td>Non-steroidal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitors</td>
<td></td>
<td>Anastrazole (Aromasin®)</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Letrozole (Femara®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exemestane (Aromasin®)</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SERD</td>
<td>Downregulate ER</td>
<td>Fulvestrant (Faslodex®)</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progestins/Androgens</td>
<td>Reduction of ER and PR and suppression of aromatase</td>
<td>Megestrol acetate (Megace®)</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgens</td>
<td></td>
<td>Ethinyl estradiol</td>
<td>✔</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen</td>
<td>Overstimulate ER</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Endocrine Treatment Options: Selective Estrogen Receptor Modulators (SERMs)
**SERMs for The Treatment of Breast Cancer**

- Tamoxifen
- Toremifene (Fareston®)

**SERMs in Clinical Use**

- Adjuvant therapy for pre-menopausal women with ER+ breast cancer (5 years)
- Post menopausal women with DCIS (would change to AI if intolerant)
- Metastatic breast cancer (patients who have transitioned through AIs or intolerant to AIs or for palliation)


---

**5 Years of Adjuvant Tamoxifen Has Been Standard of Care**

- 5 years adjuvant tamoxifen vs no tamoxifen showed a 33% reduction in recurrent breast cancer
- Protective effect carries out to 15 years
- Substantially reduces recurrence and mortality
  - 13% absolute reduction in recurrence at 15 years (33 vs 46%, RR 0.61, 95 CI 0.57-0.65)
  - 15% absolute reduction in mortality at 15 years (24 vs 33%, RR 0.70, 95 CI 0.64-0.75)
- Confers little net effect on other cause mortality

(Early Breast Cancer Trials: Collaborative Group, 2011)

---

**Length of Tamoxifen Treatment: ATLAS Trial**

- Global study involving 36 countries, 1996-2005
- Of total eligible population, 53% ER+; 10% ER--; 37% ER unknown
- Yearly follow up forms sent by central organizers noted recurrence, incidence of secondary cancer, hospital admissions or death
- Disease management beyond TAM therapy at physician’s discretion

**ATLAS Trial Results**

- Main effects on recurrence and in particular on breast cancer mortality become apparent only during the second decade after diagnosis
- Breast cancer mortality RR
  - Years 5-9 0.97 (0.79-1.18; p=0.74)
  - After year 10 0.71 (0.58-0.88; p=0.0016)
- No evidence of a rebound increase in recurrence rate when tamoxifen treatment ended

(Davies et al., 2013)

---

**ATLAS Trial: Non-breast cancer mortality**

- No increase in non-breast cancer mortality
- Increased RR for PE (RR 1.87, p=0.01)
  - But no increased mortality risk (0.2% vs 0.2%)
- Increased RR for endometrial cancer (3.1% vs 1.6%)
  - But no significant increased mortality risk (0.4% vs 0.2%)
- Although significant increases were seen in thrombotic events and endometrial cancer - these did not translate into increased mortality rates

(Davies et al., 2013)
ATLAS Trial Summary

Patients randomized to continue tamoxifen to 10 years show:

- Lower recurrence rates (617 vs 711, p=0.002)
- Reduced overall mortality (639 vs 722 deaths, p=0.01)
- Reduced breast cancer mortality (331 vs 397, p=0.01)
- Reduced breast cancer mortality (12.2 vs 15%) and recurrence rates (21.4 vs 25.1%) during years 5-14
- No increase in non-breast cancer mortality
- Increased RR for (but no increased mortality from) PE (RR 1.87, p=0.01)
- Increased RR for endometrial cancer (3.1% vs 1.6%) but no significant increased mortality risk (0.4 vs 0.2%)

(Davies et al., 2013)

aTTOM (Adjuvant Tamoxifen – To Offer More?) Trial

- ER+ or ER unknown
- N=6,053 women randomized to 10 vs 5 years tamoxifen

- Presented in abstract form, ASCO 2013

(Day R, et al. 2013)

What do the ATLAS and aTTOM Results Mean?

- ATLAS and aTTOM trial results are consistent
- The small increased risk of side effects from continued tamoxifen therapy is outweighed by the benefits
- Pre-menopausal ER+ patients should be offered up to 10 years tamoxifen treatment
- Continued ATLAS and aTTOM trial follow-up will eventually clarify the effects of tamoxifen on breast cancer outcomes 10-20 years after diagnosis

(aTTOM Trial Results

- Compared with 5 years of tamoxifen, 10 years of tamoxifen was associated with:
  - a significant 15% reduction in the recurrence risk [580 vs 672; RR 0.85, 95% CI [0.76, 0.95]; p = 0.003]
  - a significant 25% reduction in the risk of breast cancer mortality starting at year 10 [392 vs 443; RR 0.75, 95% CI [0.63, 0.90]; p = 0.007]
  - No difference in overall mortality
  - The benefits may have been underestimated – 60% ER unknown;15% ER negative

(Day R, et al. 2013)

Toremifene and Tamoxifen Show Comparable Efficacy in Phase III Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>North American</td>
<td>60</td>
<td>60</td>
<td>40</td>
<td>40</td>
<td>60</td>
<td>60</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Eastern European</td>
<td>221</td>
<td>149</td>
<td>107</td>
<td>107</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic</td>
<td>215</td>
<td>221</td>
<td>157</td>
<td>157</td>
<td>201</td>
<td>214</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Clinical Response Rate (CR+PR)
  - Toremifene: 21.3%, 19.1%, 20.4%, 20.8%, 31.3%, 37.3%
  - Tamoxifen: 19.1%, 20.8%, 20.4%, 21.3%, 37.3%, 31.3%

- 95% CI difference in RR
  - Toremifene vs. Tamoxifen:
    - Study 1: -5.8 to 10.2
    - Study 2: -9.5 to 8.6
    - Study 3: -15.1 to 3.1

- Time to Progression (months)
  - Median: 5.6, 5.8, 4.9, 5.0, 7.3, 10.2

- Adverse Events:
  - Pulmonary Embolism
    - Toremifene: 4 (2%), 2 (1%)
    - Tamoxifen: 2 (1%)
  - Thrombophlebitis
    - Toremifene: 1 (<1%)
    - Tamoxifen: 1 (<1%)
  - Thrombosis
    - Toremifene: 1 (<1%)
    - Tamoxifen: 1 (<1%)
  - CVA/TIA
    - Toremifene: 1 (<1%)
    - Tamoxifen: 1 (<1%)
  - Cardiac Failure
    - Toremifene: 2 (1%)
    - Tamoxifen: 1 (<1%)
  - Myocardial Infarction
    - Toremifene: 2 (1%)
    - Tamoxifen: 1 (<1%)
  - Arrhythmia
    - Toremifene: 4 (2%)
    - Tamoxifen: 1 (<1%)
  - Angina Pectoris
    - Toremifene: 1 (<1%)
    - Tamoxifen: 1 (<1%)
  - Cataracts
    - Toremifene: 22 (10%)
    - Tamoxifen: 16 (7.5%)
  - Elevated SGOT
    - Toremifene: 11 (5%)
    - Tamoxifen: 4 (2%)
  - Elevated Alkaline Phosphatase
    - Toremifene: 11 (5%)
    - Tamoxifen: 4 (2%)

Toremifene and Tamoxifen Show Comparable Safety in Phase III Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
<th>Toremifene</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>North American</td>
<td>60</td>
<td>60</td>
<td>40</td>
<td>40</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Eastern European</td>
<td>221</td>
<td>149</td>
<td>107</td>
<td>107</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic</td>
<td>215</td>
<td>221</td>
<td>157</td>
<td>157</td>
<td>201</td>
<td>214</td>
</tr>
</tbody>
</table>

- Median (months)
  - Clinical Response Rate: 19.1%, 20.8%, 21.3%, 37.3%, 31.3%, 20.4%

- HR (95% CI)
  - Median (months):
    - Toremifene: 3.3, 3.4, 2.5, 2.3, 3.0, 3.6
    - Tamoxifen: 3.4, 2.5, 2.3, 3.0, 3.6, 3.3

- 95% CI in difference in RR
  - Toremifene vs. Tamoxifen:
    - Study 1: -5.8 to 10.2
    - Study 2: -9.5 to 8.6
    - Study 3: -15.1 to 3.1

- Median (months)
  - Time to Progression: 5.6, 5.8, 4.9, 5.0, 7.3, 10.2

- HR (95% CI)
  - Median (months):
    - Toremifene: 1.01 (0.81 to 1.26)
    - Tamoxifen: 1.02 (0.79 to 1.31)

- Median (months)
  - Survival: 33.8, 34.0, 25.4, 23.4, 33.0, 38.7

- HR (95% CI)
  - Median (months):
    - Toremifene: 1.01 (0.64 to 1.60)
    - Tamoxifen: 0.80 (0.54 to 1.20)

References:
- Hayes et al., 1995; Gershanovich et al., 1997; Pyrhonnen et al., 1997

Toremifene and Tamoxifen Study: North American, Eastern European, Nordic study groups

Abbreviations: CR, complete response; PR, partial response; CI, confidence interval; RR, response rate; HR, hazard ratio

Note: (Fareston [package insert])
Metabolism of SERMS by Cytochrome P450 Enzymes

- Tamoxifen is considered a pro-drug as it requires the CYP2D6 pathway for conversion to its active metabolite, 4-hydroxy-N-desmethyl tamoxifen, or endoxifen.
- Toremifene’s biological activity comes from its parent form, and does not require CYP450 conversion for activity. Toremifene is not considered a pro-drug.

Select Inhibitors of CYP2D6

<table>
<thead>
<tr>
<th>Inhibitor Strength</th>
<th>SSRI and Other Antidepressants</th>
<th>Other Prescription Drugs</th>
<th>Over-the-counter Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>STRONG</td>
<td>Paroxetine (Paxil®)</td>
<td>Duloxetine (Cymbalta®)</td>
<td>Tramadol (Ultram®)</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine (Prozac®)</td>
<td>Amlopin (Sensipril®)</td>
<td>Ciprofloxacin (Cipro®)</td>
</tr>
<tr>
<td></td>
<td>Bupropion (Wellbutrin®)</td>
<td>Duloxetine (Cymbalta®)</td>
<td>Diphenhydramine (Benadryl®)</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Escitalopram (Lexapro®)</td>
<td>Sertraline (Zoloft®)</td>
<td>Carbamazepine (Tegretol®)</td>
</tr>
<tr>
<td></td>
<td>Cinacalcet (Tasigna®)</td>
<td>Raloxifene (Evista®)</td>
<td>Fluvastatin (Lescol®)</td>
</tr>
<tr>
<td></td>
<td>Antidepressant (Cordarone®)</td>
<td>Ritonavir (Norvir®)</td>
<td>Diphenhydramine (Benadryl®)</td>
</tr>
<tr>
<td></td>
<td>Terbinafine (Lamisil®)</td>
<td>Ranitidine (Zantac®)</td>
<td>Carbamazepine (Tegretol®)</td>
</tr>
<tr>
<td></td>
<td>Over-the-counter Medications</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Guideline Recommendations Regarding Coprescription of CYP2D6 Inhibitors and Tamoxifen

<table>
<thead>
<tr>
<th>Group</th>
<th>Date</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCCN</td>
<td>2012</td>
<td>Coadministration of strong inhibitors of CYP2D6 should be used with caution</td>
</tr>
<tr>
<td>ASCO</td>
<td>2010</td>
<td>Potent CYP2D6 inhibitors be avoided in women receiving tamoxifen</td>
</tr>
</tbody>
</table>

Adverse Events with SERMs

- Increased risk of Uterine cancer
- Venous thromboembolic events
- Menstrual irregularities
- Hot flashes
- Sexual dysfunction

Toremifene and CYP2D6

- Toremifene primarily metabolized by CYP3A4
- Metabolism of toremifene is not affected by potent CYP2D6 inhibitors

ACOG (The American Congress of Obstetricians and Gynecologists) Recommendations for Uterine/Endometrial Cancer

- Educate women about the signs and symptoms of cancer (vaginal discharge, abnormal vaginal bleeding)
- Routine annual gynecological exams
- Limit tamoxifen to 5 years
- If atypical hyperplasia develops reassess continued use
- Role for more invasive pre-treatment screen
Venous Thrombolytic Events

<table>
<thead>
<tr>
<th>Wells’ Criteria for DVT</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Cancer</td>
<td>+1</td>
</tr>
<tr>
<td>Bedridden recently &gt; 3 days or major surgery within 4 weeks</td>
<td>+1</td>
</tr>
<tr>
<td>Calf swelling &gt; 3 cm compared to other leg</td>
<td>+1</td>
</tr>
<tr>
<td>Collateral (nonvaricose superficial veins) present</td>
<td>+1</td>
</tr>
<tr>
<td>Extremity +4 weeks</td>
<td>+1</td>
</tr>
<tr>
<td>Lower extremity swelling along the deep venous system</td>
<td>+1</td>
</tr>
<tr>
<td>Pain, pressure, or increased pulsation of the involved extremity</td>
<td>+1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative diagnosis to DVT as likely or more likely</td>
<td>-2</td>
</tr>
</tbody>
</table>

Total Score
- High Probability of DVT: >3
- Moderate Probability of DVT: 1-2
- Low Probability of DVT: 0

(Wells et al, 2006)


Nursing Implications: VTEs
- Assess risk factors (smoking, obesity, sedentary lifestyle, Dehydration, frequent flying, family history of Coagulation disorder)
- Stress importance of symptom reporting
- Management with LMWH/ Wafarin
- Assess for possible PE if DVT develops

Managing Hot Flashes
- Diary – number, intensity, any known triggers
- Trial – lifestyle changes (dressing in layers, cotton clothing, fans)
- Reduction of risk factors – alcohol, smoking, caffeine

If hot flashes continue, refer for...patient does not want medication...SSRI/SNRI antidepressants
- Celexa 20 mg daily or Venlafaxine 37.5-75 mg daily (must taper to discontinuation)
- Oxycodone – 2.5 mg once or twice daily (can be titrated for 2 mg twice daily)
- Gabapentin 100 mg 3 times daily (taper to target daily dose, must taper to discontinuation)
- Clonidine 0.05 mg twice daily – 4-week trial

Endocrine Treatment Options: Aromatase Inhibitors

Aromatase Inhibitors
- In ER+ tumors, estrogen is like “fuel” to help tumors proliferate
- Instead of blocking the formation of estrogen, Aromatase Inhibitors (AIs) work by inhibiting the enzyme used to synthesize estrogen from androgens
- Reduce estrogen production >95%
- Used in women with no ovarian function

Management of Sexual Side Effects
- Counseling (sex and couples therapy)
- Pelvic physical therapists
- Psychotherapy
- Lifestyle changes
- Lubricants and moisturizers (NON estrogen)
- Improving body image
- Devices
AIs

<table>
<thead>
<tr>
<th>Brand</th>
<th>Anastrozole</th>
<th>Letrozole</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Non-Steroidal</td>
<td>Non-Steroidal</td>
<td>Steroidal forms</td>
</tr>
</tbody>
</table>

Trial leading to approval
- ATAC trial: N=9,366
- BIG 1-98 trial: N=8,010
- MAP.3 trial: N=4,560

Indications:
- All in post-menopausal ER+ Breast Cancer
  - Adjuvant therapy
  - and advanced dz after progression on Tamoxifen

Adverse Events With AIs
- Hot flashes
- Arthralgia’s and musculoskeletal complaints
- Decreased incidence of endometrial cancer and thromboembolic events than with tamoxifen
- Small but significant increase in risk of osteoporosis and fractures

Nursing Implications: AIs
- Be certain patient has no ovarian function
- Assist patient with financial coverage
- Educate regarding bone health: Adequate calcium, vitamin D, wt-bearing exercise, no smoking, possible screening or medication

NCCN Guidelines and AI Adjuvant Endocrine Therapy
- NCCN recommends postmenopausal women receive AI x 5 yr (cat 1) or Tamoxifen x 2-3 yr followed by AI to complete 5 yr
  - If unable to take AI, Tamoxifen for 5 year or consider up to 10 yr
- All 3 selective AIs have similar efficacy and toxicity
- Optimal duration of AIs in adjuvant therapy unknown

Endocrine Therapy Options: Selective Estrogen Receptor Downregulator (SERD)
**Fulvestrant**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Dosing</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postmenopausal women after progression on AI</td>
<td>Intramuscularly once per month</td>
<td>Injection site reactions, Nausea, Bone Pain, Arthralgia, Headache, Fatigue, Back pain, GI, Elevated liver enzymes</td>
</tr>
</tbody>
</table>

**Nursing Implications:** Fulvestrant

- Counsel patients on risk of thrombolic events, notify if SOB, swelling, pain in lower extremities
- Consider Z-track technique for injection, alternate site
- Educate regarding hot flashes, joint pain and sexual side effects
- Encourage exercise, healthy diet and weight maintenance

**Resistance to Endocrine Therapy**

- Complex interconnecting signaling pathways regulate cellular response to estrogen
  - May contribute to various mechanisms of resistance
- Resistance may be described as
  - Intrinsic or de novo: tumor does not respond to a drug from the onset of therapy
  - Acquired: tumor that initially responded to therapy resumes growing (50% of patients)
- Interconnectivity of signaling pathways offers opportunities and challenges for combining therapies

**mTOR Inhibitors in Breast Cancer**

- mTOR Inhibitors: Single agent appears to have limited clinical activity, limited to metastatic breast cancer at this time.
  - Everolimus: Approved in post menopausal, HR+, HER2- advanced disease with Exemestane after failure with letrozole or anastrozole
  - Temsirolimus: Not approved in breast cancer at this time, in clinical trials.

**TAMRAD: Tamoxifen +/- Everolimus in Advanced Breast Cancer**

- Postmenopausal women with HR-positive, HER2-negative advanced breast cancer
- Previously treated to AI in adjuvant or advanced setting (N = 111)
- Stratification:
  - Primary or secondary hormone resistance
  - Primary endpoint: Clinical benefit rate at 6 months
  - Secondary endpoints: TTP, OS, ORR, safety, biomarker

**TAMRAD: Results**

<table>
<thead>
<tr>
<th>Tamoxifen +</th>
<th>Tamoxifen Alone</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Everolimus (n = 54)</td>
<td>Tamoxifen Alone (n = 239)</td>
<td>Clinical Benefit Rate</td>
</tr>
<tr>
<td>Tamoxifen 20 mg/day + Everolimus 10 mg/day (n = 54)</td>
<td></td>
<td>Time to Progression</td>
</tr>
</tbody>
</table>

(Bachelot et al., 2012)
**BOLERO-2: Exemestane ± Everolimus in Nonsteroidal AI–Refractory Advanced Breast Cancer**

- Everolimus 10 mg/day + Exemestane 25 mg/day (n = 485)
- Placebo + Exemestane 25 mg/day (n = 239)

- **Refractory to therapy:**
  - Recurrence during or within 12 mos of end of adjuvant treatment
  - Progression during or within 1 mo after end of treatment for advanced disease

- **Stratification:**
  - Sensitivity to previous hormonal therapy
  - Presence of visceral disease
  - No crossover allowed
  - Primary endpoint: PFS
  - Secondary endpoints: OS, ORR, CBR, safety, QoL, bone markers

- **Postmenopausal women with HR-positive, HER2-negative advanced breast cancer refractory to letrozole or anastrozole (n = 724)**

- (Baselga, et al., 2012)

**Everolimus: Nursing Implications**

- **Overall 23% patients in combination group experienced serious AE’s, 11% attributed to treatment**
- **Stomatitis:** Known marker of mTOR inhibition, occurs early, can evolve rapidly. Nurses should monitor and may need to hold/stop therapy if severe. Nurses crucial for education/communication
  - Good oral hygiene
  - Avoid spicy, acidic, hard, hot foods/beverages
  - Baking soda rinses, topical analgesics or a steroid mouthwash for prevention

- **Noninfectious pneumonitis**
  - Reported in 11% to 14% of patients treated with everolimus\[1\]
  - Onset typically occurs within 2-6 mos of initiating therapy
  - Symptoms typically cough, SOB, Chest pain, wheezing

- **Infections**
  - Immunosuppressive properties
  - Opportunistic infection: pneumonia and other bacterial and fungal infections
  - Reported in up to 37% of the patients studied in everolimus clinical trials
  - Patients should avoid live vaccines and close contact with those who have received live vaccines. Potential for viral reactivation: hepatitis B, other infections.

- **Future Directions**
  - Targeting endocrine resistance
  - Combination therapies such as an AI + Fulvestrant
  - Use of estrogens for therapy
  - CDK4/6 inhibitors +/- endocrine therapies
  - Genomic sequencing to better target therapies

**Summary**

- Nurses are integral in educating patients on the rationale and management of endocrine therapy
- SERMS, AIs and fulvestrant represent multiple endocrine options for postmenopausal women with HR+ breast cancer
- Endocrine agents have manageable side effects but still require nurse monitoring
- AIs have become the standard of care for initial treatment of postmenopausal women with HR+ advanced breast cancer
- However, many patients with advanced breast cancer fail to respond initially and all patients eventually progress due to resistance
- New treatments may overcome endocrine resistance and delay need for chemotherapy
  - Combined targeting of both ER and growth factor receptor or intracellular signaling pathways may be promising treatment approach

- (Affinitor [package insert]; Green, 2013)
- (Everolimus: Nursing Implications)
- (Future Directions)
- (Summary)
### Available Endocrine Agents

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Agent(s)</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>SERM</td>
<td>Compete with estrogen for binding to ER in breast</td>
<td>Tamoxifen (Nolvadex) Toremifene (Fareston®)</td>
<td>✓ ✓</td>
</tr>
<tr>
<td>Aromatase Inhibitors</td>
<td>Inhibit production of estrogen</td>
<td>Non-steroidal</td>
<td>Anastrazole (Ivestarin®) Letrozole (Femara®) Exemestane (Aromasin®)</td>
</tr>
<tr>
<td>SERD</td>
<td>Downregulate ER</td>
<td>Fulvestrant (Faslodex®)</td>
<td>✓</td>
</tr>
<tr>
<td>Progestins/Androgens</td>
<td>Reduction of ER and PR and suppression of adrenals</td>
<td>Megestrol acetate (Megebrin®)</td>
<td>✓</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Overstimulate ER</td>
<td>Ethinyl estradiol</td>
<td>✓</td>
</tr>
</tbody>
</table>

(Rugo, 2007)
Metabolism of SERMS by Cytochrome P450 Enzymes

- Tamoxifen is considered a pro-drug as it requires the CYP2D6 pathway for conversion to its active metabolite, 4-hydroxy-N-desmethyl tamoxifen, or endoxifen.

- Toremifene’s biological activity comes from its parent form, and does not require CYP450 conversion for activity. Toremifene is not considered a pro-drug.

(Sideras et al., 2010; Goetz et al., 2007)
Managing Hot Flashes

- **Diary** – number, intensity, any known triggers
  - Two-week trial of
    1. Lifestyle changes (dressing in layers, cotton clothing, fans)
    2. Reduction of risk factors – alcohol, smoking caffeine
  - Can offer 4-week trial of paced respiration/relaxation
  - SSRI/SNRI antidepressants
    - Celexa 20 mg daily or Venlaxafine 37.5–75 mg daily
      (must taper to discontinues)
  - Oxybutynin – 2.5 mg once or twice daily
    (can be titrated to 5 mg twice daily)
  - Gabapentin 100 mg 3 times daily
    Takes 4 wks to reach target dose
    (must taper to discontinues)
  - Clonidine 0.05 mg twice daily

- **Discussion and counseling with Oncologist**
  - Possible change in hormone suppression therapy

If hot flashes continue, add or replace with either:

- Can offer 4-week trial of paced respiration/relaxation
  - SSRI/SNRI antidepressants
    - Celexa 20 mg daily or Venlaxafine 37.5–75 mg daily
      (must taper to discontinues)
  - Oxybutynin – 2.5 mg once or twice daily
    (can be titrated to 5 mg twice daily)
  - Gabapentin 100 mg 3 times daily
    Takes 4 wks to reach target dose
    (must taper to discontinues)
  - Clonidine 0.05 mg twice daily

Refer for hypnosis if patient does not want medication.
# AIs

<table>
<thead>
<tr>
<th>AI:</th>
<th>Anastrozole (Arimidex)</th>
<th>Letrozole (Femara)</th>
<th>Exemestane (Aromasin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Non-Steroidal</td>
<td>Non-Steroidal</td>
<td>Steroidal-about forms permanent bond May have less benefits on bone/lipids</td>
</tr>
<tr>
<td>Trial leading to approval</td>
<td>ATAC trial: N=9,366</td>
<td>BIG 1-98 trial: N= 8,010</td>
<td>MAP.3 trial: N=4,560</td>
</tr>
<tr>
<td>Indications:</td>
<td>Adjuvant therapy and advanced dz as initial therapy or after progression on Tamoxifen</td>
<td>Adjuvant therapy and advanced dz as 1st and 2nd line therapy</td>
<td>Adjuvant therapy after 2-3 y Tamoxifen and advanced dz after progression on Tamoxifen</td>
</tr>
</tbody>
</table>

(Fields, 2004; Arimidex [package insert]; Femara [package insert]; Aromasin [package insert])