Use of Novel Combination Therapies in Treatment of Advanced HR+/HER2- Breast Cancer

STAGING: AJCC TNM Classification for Breast Cancer

Changing Landscape of ER-positive Metastatic Breast Cancer

Educational Objectives

• Evaluate the updated clinical guidelines for combination therapies in the treatment of HR+/HER2- advanced breast cancer patients
• Integrate clinical data regarding the use of CDK 4/6 inhibitors and mTOR inhibitors to treat HR+/HER2- advanced breast cancer, including appropriate patient subpopulations
• Mitigate toxicities associated with multi-drug treatment regimens to improve patient outcomes
• Recognize potential drug-drug interactions to plan effective and safe treatment regimens for each patient

Agenda

• Welcome, Introduction, and Pre-survey
• Current Guidelines for Combination Therapy with Endocrine Agents
• Alleviation of Side Effects Associated with Best Practice Combination Therapies
• Novel Agents and Emerging Clinical Data for HR+ Breast Cancer
• Q&A Session and Concluding Remarks
Use of Novel Combination Therapies in the Treatment of Advanced HR+/HER2- Breast Cancer

Current Guidelines for Combination Therapy with Endocrine Therapy

**FACT: Phase III Study of Anastrozole + Fulvestrant 250 vs Anastrozole Alone**

<table>
<thead>
<tr>
<th></th>
<th>FUL + ANA</th>
<th>ANA</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTP (mo)</td>
<td>10.8</td>
<td>10.2</td>
</tr>
<tr>
<td>HR</td>
<td>0.72</td>
<td>0.91</td>
</tr>
<tr>
<td>OS (mo) median</td>
<td>37.8</td>
<td>38.2</td>
</tr>
<tr>
<td>P value</td>
<td>0.91</td>
<td>0.91</td>
</tr>
</tbody>
</table>

n = 514
Pre/Post menopausal women with HR+ advanced breast cancer, untreated with HR for advanced disease

**CDK 4/6 Inhibitors Approved by the FDA**

- Palbociclib (PD 0332991)
- Ribociclib (LEE011)
- Abemaciclib (LY2835219)

**SWOG S0226 Phase III Trial of Anastrozole + Fulvestrant 250 vs Anastrozole Alone**

<table>
<thead>
<tr>
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<th>ANA</th>
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</thead>
<tbody>
<tr>
<td>PFS (mo)</td>
<td>15.0</td>
<td>13.5</td>
</tr>
<tr>
<td>HR</td>
<td>0.80</td>
<td>0.087</td>
</tr>
<tr>
<td>OS (mo) median</td>
<td>47.7</td>
<td>41.3</td>
</tr>
<tr>
<td>P value</td>
<td>0.007</td>
<td>0.049</td>
</tr>
</tbody>
</table>

n = 707
Post menopausal women with HR+ advanced breast cancer, untreated with HR for advanced disease
*Crossover to fulvestrant 500 mg allowed after progression

**PALOMA 1: Progression-Free Survival**

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (n=64)</th>
<th>LET (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Events (%)</td>
<td>41 (64)</td>
<td>59 (60)</td>
</tr>
<tr>
<td>Median TTP (mos)</td>
<td>35.2</td>
<td>16.2</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>11.7-66.8</td>
<td>7.7-25.8</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>0.496</td>
<td>0.446</td>
</tr>
<tr>
<td>P value</td>
<td>0.0007</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

**PALOMA 1: Final Overall Survival**

<table>
<thead>
<tr>
<th></th>
<th>PAL + LET (n=60)</th>
<th>LET (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with events, n (%)</td>
<td>60 (71)</td>
<td>56 (69)</td>
</tr>
<tr>
<td>Median OS (mos)</td>
<td>37.5</td>
<td>34.5</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>31.4-47.8</td>
<td>27.4-42.6</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.897</td>
<td>0.623</td>
</tr>
<tr>
<td>P value</td>
<td>0.281</td>
<td>0.609</td>
</tr>
</tbody>
</table>
Use of Novel Combination Therapies in the Treatment of Advanced HR+/HER2- Breast Cancer

**PALOMA-2 and MONALEESA-2**

**Design of Phase III Studies**

**PALOMA-2**
- Primary endpoint: PFS
- Secondary endpoints:
  - OS, CS, safety, biomarkers, PROs

**MONALEESA-2**
- Primary endpoint: PFS
- Secondary endpoints:
  - CS (only), ORR, CBR, safety

**PALOMA-2**
- Randomized: 2:1
- Stratified by the presence/absence of liver and/or lung metastases

**MONALEESA-2**
- Randomized: 1:1
- Stratified by:
  - Presence/absence of liver/lung metastases
  - Prior chemotherapy for advanced disease
  - Endocrine therapy partner (tamoxifen vs NSAIs)

**Primary endpoint**
- PFS (locally assessed per RECIST v1.1)

**Secondary endpoints**
- OS (key)
- Overall response rate
- Clinical benefit rate
- Safety
- Patient-reported outcomes

**MONARCH 3: Primary Endpoint (PFS) Met at Interim Analysis**

**MONALEESA-7**

**Phase III Placebo-controlled Study of Ribociclib and Tamoxifen/NSAI + Goserelin**
- Pre/postmenopausal women with HR+, HER2- ABC
- No prior endocrine therapy for advanced disease
- ≤ 1 line of chemotherapy for advanced disease
- n=672

**Ribociclib**
- (300 mg/day; 21-day on/7-day off) + tamoxifen/NSAI + goserelin

**Placebo**
- tamoxifen/NSAI + goserelin

**Primary endpoint**
- PFS (investigator assessment)

**Number of events, n (%)**
- Ribociclib + tamoxifen/NSAI: 131 (39.1)
- Placebo + tamoxifen/NSAI: 187 (55.5)

**Median PFS, months (95% CI)**
- Ribociclib + tamoxifen/NSAI: 23.8 (19.2–NR)
- Placebo + tamoxifen/NSAI: 13.0 (11.0–16.4)

**Hazard ratio (95% CI)**
- Ribociclib + tamoxifen/NSAI vs Placebo + tamoxifen/NSAI: 0.553 (0.441–0.694)

**One-sided P-value**
- 0.0000000983

**Primary Endpoint: PFS**

**Investigator-assessed Probability of progression-free survival (%)**

<table>
<thead>
<tr>
<th>PFS (investigator assessment)</th>
<th>Ribociclib + tamoxifen/NSAI (n=335)</th>
<th>Placebo + tamoxifen/NSAI (n=337)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n (%)</td>
<td>131 (39.1)</td>
<td>187 (55.5)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>23.8 (19.2–NR)</td>
<td>13.0 (11.0–16.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.553 (0.441–0.694)</td>
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</table>
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**PFS by Endocrine Therapy Partner**

**Investigator-assessed**

<table>
<thead>
<tr>
<th>PFS (Investigator assessment)</th>
<th>Ribociclib arm</th>
<th>Placebo arm</th>
<th>Ribociclib arm</th>
<th>Placebo arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events, n</td>
<td>39</td>
<td>56</td>
<td>92</td>
<td>132</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>22.1 (16.6–24.7)</td>
<td>11.0 (8.1–16.4)</td>
<td>27.5 (19.1–NR)</td>
<td>13.8 (12.6–17.4)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.585 (0.387–0.884)</td>
<td>0.569 (0.356–0.891)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Goserelin included in all combinations.

**Patient-reported Outcomes**

EORTC QLQ-C30 – Global Health Status

![Graph showing patient-reported outcomes](image)

**EFECT**

**Endocrine Therapy in Hormone-refractory MBC**

- Ribociclib + tamoxifen/NSAI (n=335)
- Placebo + tamoxifen/NSAI (n=337)
- Number of events, n (%) 102 (30.4) 115 (34.1)
- Median, months (95% CI) NR (22.2–NR) 21.2 (15.4–23.0)
- Hazard ratio (95% CI) 0.699 (0.533–0.916)

**Primary Endpoint: PFS (ITT Population)**

- Ribociclib + fulvestrant: 2.1 months (95% CI 1.3–2.9)
- Placebo + fulvestrant: 0.5 months (95% CI 0.1–1.0)

**MONARCH 2: Study Design**

- HR+/HER2- ABC
- Pre- or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or within 1 yr of adjuvant ET
  - Progressed on first-line ET
  - No chemos for MBC
  - No more than 1 ET for MBC
- ECOG PS ≤1

- **abemaciclib:** 150 mg BID (continuous schedule)
- **fulvestrant:** 500 mg (monthly)

**Primary endpoint:** Investigator-assessed PFS

**Secondary endpoint:** OS, Response, Clinical Benefit Rate, Safety

**Stratification factors:**
- Metastatic site
- ET resistance (primary vs secondary)

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**Primary Endpoint: PFS (ITT)**

- **Median PFS**
  - Abemaciclib + fulvestrant: 16.4 months
  - Placebo + fulvestrant: 9.3 months
  - HR (95% CI): 0.553 (0.449, 0.681)
  - *P* = <0.000001

**MONARCH 1**

- Investigator Assessed Response
  - Abemaciclib 200 mg twice daily
  - Treatment continued until unacceptable toxicity or PD

**Acquired Resistance to Endocrine Therapy in ER+ BC**

- Acquired resistance is defined as:
  - Recurrence at least 12 months after completion of adjuvant therapy
  - Disease progression 26 months after endocrine therapy initiated in the metastatic setting

**Everolimus in Hormone-refractory MBC**

- **Hazard Ratio (HR)**
  - TAM: 0.50 (3.05, 0.81)
  - TAM + RAD: 0.43 (0.27, 0.68)

**Primary Resistance to Endocrine Therapy in ER+ BC**

- Primary resistance is defined as:
  - Recurrence within adjuvant therapy
  - Disease progression < 6 months after treatment in the metastatic setting

**Fulvestrant ± Everolimus: PFS**

- **Hazard Ratio (HR)**
  - Fulvestrant ± Everolimus: Everolimus 4 mg, fulvestrant 14 mg weekly, placebo: 4 mg weekly, fulvestrant 5.5 mg weekly

**Everolimus**

- TAM 4.5 mo.
- TAM + RAD 8.6 mo.
- HR = 0.53 (95% CI: 0.35-0.81)
- Exploratory log-rank: *P* = 0.0026

**Placebo**

- TAM 4.5 mo.
- TAM + RAD 8.6 mo.
- HR = 0.36 (95% CI: 0.27-0.47)
- Log-rank P-value = 3.3 x 10^-16
- EVE + EXE: 10.6 Months
- PBO + EXE: 4.1 Months
- *P* = 3.3 x 10^-15


**Fulvestrant**

- EVE + EXE: 10.6 Months
- PBO + EXE: 4.1 Months
- *P* = 3.3 x 10^-15


**Activity Slides**

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Use of Novel Combination Therapies in the Treatment of Advanced HR+/HER2- Breast Cancer

• Disease refractory to AI
• Postmenopausal
• Max. 1 line of chemotherapy

ET = endocrine therapy; ER = Estrogen Receptor, ABC = advanced breast cancer, AI = Aromatase inhibitor; PR/CR = Partial/Complete response, SD = stable disease, d = days; PFS = Progression-free survival

Stratification factors:
- Sensitivity to prior ET is defined as:
  - Relapsed on or ≤12 months from adjuvant AI; or
  - Progressed on AI in the advanced setting; or
  - ≥24 months of adjuvant ET before recurrence or from adjuvant AI, or
  - ≥12 months of adjuvant ET before recurrence or from adjuvant AI, or

Primary endpoint: PFS (ITT Population)

TEAE (Safety Population)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Fulvestrant + Vistusertib (F+V(cont))</th>
<th>Placebo + Fulvestrant (P+FV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All G3 G4</td>
<td>All G3 G4</td>
</tr>
<tr>
<td>≥20% in either arm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amy</td>
<td>435 (86.6) 241 (54.6) 26 (5.9) 199 (89.2) 46 (20.6) 5 (2.2)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>381 (86.4) 59 (13.4) 0 55 (24.7) 1 (0.4) 0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>203 (46.0) 104 (23.6) 13 (2.9) 9 (4.0) 3 (1.3) 1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>199 (45.1) 12 (2.7) - 51 (22.9) 2 (0.9) -</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>176 (39.9) 12 (2.7) - 40 (16.9) 1 (0.4) -</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>155 (35.4) 11 (2.3) - 35 (15.7) 2 (0.9) -</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>128 (28.9) 31 (7.0) 1 (0.2) 8 (3.6) 2 (0.9) 0</td>
<td></td>
</tr>
<tr>
<td>Leukopenia</td>
<td>125 (28.3) 38 (8.6) 1 (0.2) 4 (1.8) 0 0</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>117 (26.5) 5 (1.1) 0 27 (12.1) 1 (0.4) 0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>114 (25.9) 4 (0.9) 0 23 (10.3) 4 (1.8) 0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>89 (20.2) 3 (0.7) - 34 (15.2) 1 (0.4) -</td>
<td></td>
</tr>
</tbody>
</table>

*Grade 3 diarrhea: neutropenia: 3 patients in F+V(cont) were neutropenic, and 1 patient in P+FV.
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MANTA Study Design

Primary Endpoint: PFS (ITT Population)

San Antonio Breast Cancer Symposium, December 5-9, 2017

PALOMA-2 and MONALEESA-2: Toxicity

<table>
<thead>
<tr>
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<tr>
<td></td>
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<tr>
<td>≥20% in either arm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>119 (26.3) 1 (0.2) 0 5 (2.3) 0 0</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>106 (23.4) 2 (0.4) 0 11 (4.6) 0 0</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>234 (51.4) 10 (2.2) 0 19 (8.0) 0 0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>199 (45.1) 12 (2.7) - 51 (22.9) 2 (0.9) -</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>176 (39.9) 12 (2.7) - 40 (16.9) 1 (0.4) -</td>
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<td></td>
</tr>
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*Grade 3 diarrhea: neutropenia: 3 patients in F+V(cont) were neutropenic, and 1 patient in P+FV.

SWISH Study

• Phase II single-arm trial evaluated prophylaxis with steroid mouthwash on everolimus-associated stomatitis
• Mouthwash: 10ml with dexamethasone 0.5mg/5mL (swish 2 days on, 5 days off)
• Phase II single-arm trial evaluated prophylaxis with steroid mouthwash on everolimus-associated stomatitis

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**SWISH: Effect of Steroid Mouthwash on Everolimus-associated Stomatitis**

- **A**: No stomatitis (57%)
- **B**: Rare stomatitis (10%)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Management</th>
<th>Everolimus Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Asymptomatic (radiographic findings only)</td>
<td>Initiate appropriate monitoring</td>
<td>No dose adjustment required</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, not interfering with ADLs</td>
<td>Rule out infection, consider treatment with corticosteroids</td>
<td>Consider interruption of therapy until symptoms improve to grade 1</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, interfering with ADLs; oxygen required</td>
<td>Rule out infection, consider treatment with corticosteroids</td>
<td>Reinstitute everolimus at a lower dose</td>
</tr>
<tr>
<td>4</td>
<td>Life threatening; ventilatory support indicated</td>
<td>12 (2.7)</td>
<td>Consider ventilating everolimus at a lower dose. If toxicity recurs at grade 3, consider discontinuation</td>
</tr>
</tbody>
</table>

Based on Everolimus Package Insert.

**Rare Everolimus-related Pulmonary Side Effects**

**Where Do We Stand Today?**

**BELLE 2: Addition of Buparlisib (Pan-PI3K Inhibitor) to Fulvestrant in Hormone-resistant MBC**

- Toxically significant (80%, grade ≥ 3 toxicities)
- PIK3CA mutations not predictive (in tissue)

**BELLE 3: Progression-free Survival per Investigator Assessment**

- PFS results by independent central review were consistent with local assessment:
  - HR 0.57, 95% CI: 0.44–0.74; one-sided P < 0.001

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**SANDPIPER**
Phase 3 Study of Taselisib in ER+ MBC

- ER+/HER2- locally advanced or metastatic BC
- Postmenopausal
- Recurrence or progression during or after aromatase inhibitor

**Primary Endpoint:** PFS in pts with mutant tumors

- Target HR: 0.59 (mPFS 4.5 → 7.6 mo)
- >95% power at two-sided 1% alpha level

**Stratify:**
1) Visceral disease
2) Endocrine sensitivity
3) Geographic region

**120 Pts without PIK3CA Mutant Tumors**

- Taselisib 4 mg QD + Fulvestrant
- Placebo QD + Fulvestrant

**2:1 randomization**

- Treat until PD or unacceptable toxicity
- No Crossover

**Survival Data**

- **480 Pts with PIK3CA Mutant Tumors**

Available at: www.ClinicalTrials.gov; NCT02340221.

**Ongoing Trials**

<table>
<thead>
<tr>
<th>Activity Slides</th>
</tr>
</thead>
</table>

**α-specific PI3K inhibitors**

- NCT01923168 (Neo-Orb)
- Phase II Letrozole +/- Alpelisib or Buparlisib

- NCT02437318 (SOLAR-1)
- Phase III fulvestrant +/- alpelisib

- NCT02077933
- Phase I alpelisib + everolimus +/- exemestane

- NCT02340221 (Sandpiper)
- Phase III Fulvestrant +/- Taselisib

**Ribociclib (LEE011)**

- Palbociclib (PD-0332991)

- Abemaciclib (LY2835219)

- PI3K
- AKT
- mTOR
- CCND1
- CDK4/6
- pRb
- E2F

**Other signals**

- (AMPK/ERK/p90RSK)

**PI3K Inhibitor**

- CDK4/6 Inhibition + α-PI3K Inhibition Combinations
- Could Reverse Resistance to Endocrine Therapy as well as CDK4/6 Therapy

**FGFR1 amplification is an independent predictor of overall survival in patients with ER+ breast cancer treated with tamoxifen**

- Elbauomy Elsheikh S et al.
- Karlsson E et al.
- Turner N et al.
  - Cancer Res. 2010;70:2085-2094.

**Targeting FGFR**

- Formisano and Arteaga

**Exemestane + Everolimus + Ribociclib**
Phase Ib/II Study of Postmenopausal Women with AI-resistant ER+ MBC

- NCT02327507 (Liseto)
  - Phase II Letrozole +/- Taselisib

**Letrozole + Alpelisib + Ribociclib**
Phase Ib Study of Postmenopausal Women with ER+ MBC

- NCT02427565
  - Phase II fulvestrant +/- alpelisib

**FGFR1 amplification is present in ~15% of ER+ breast cancers**

**Exemestane + Ribociclib Phase Ib/II Study of Postmenopausal Women with AI-resistant ER+ MBC**

**PD-1/L1 Immunotherapy in Breast Cancer**

- Immune checkpoint inhibitors are effective in a variety of solid tumors.
- In the metastatic setting:
  - 20% ORR in TNBC
  - 6-12% ORR in ER+ BC
- In ER+ mBC resistant to endocrine therapy, total mutational burden increases, but these tumors are still generally immunologically 'cold'.
- Immunotherapy combination strategies that increase immune recognition through enhanced antigen presentation and/or increased T cell homing may increase immunotherapy response.


**Immunotherapy Combination Strategies in ER+ MBC – CDK4/6 Inhibition**

- Inhibition of CDK4/6 in ER+ breast cancer → induction of senescence and enhanced recruitment of immune cells
- This may result in increased sensitivity checkpoint inhibitors

**ENCORE 301**

**Exemestane ± Entinostat in HR-positive MBC with Prior Treatment with NSAIs: Overall Survival**

- Proposed Schema

**ECOG 2112**

**A Randomized Phase III Trial of Endocrine Therapy plus Entinostat/Placebo in HR-Positive Metastatic Breast Cancer**

- Eligible:
  - Advanced breast cancer
  - ER/PR+, HER2-
  - Progression/no progression on prior non-steroidal AI

- Treatment until progression/intolerance: exemestane 25 mg daily po AND entinostat/placebo 5 mg po weekly.

**Mutational Landscape of ER+ MBC**

**Significant Genes with SNV and Indel Alterations**

**Presented at: SABCS – December 6-10, 2016.**

**Acquired HER2 Mutations in ER+ MBC**

**Presented at: SABCS – December 6-10, 2016.**
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**ESR1 Mutation Background**

Genomic Alterations in ER+ Tumors

ESR1 mutations occur in ~20% of AI-resistant, ER+ breast cancer

**ESR1 Mutation Analysis by Digital PCR in the Randomized Phase III SoFEA Study**


Presented by Turner N at the 2016 ASCO Annual Meeting.

**ESR1 Mutations in PALOMA-3**

ESR1 mutations were detected in 27% (100/362) of patients with plasma samples

- Amino acid changes P535H and V634E were not detected

- ESR1 mutations were polymodal in 38% (40/105) of mutation-positive patients

Presented by Turner N at the 2016 ASCO Annual Meeting.

**PFS by ESR1 Mutation Status**

PFS = progression-free survival


Presented by Turner N at the 2016 ASCO Annual Meeting.

**Patient Information Brochures from CDC and Cancer.Net**

- A copy has been provided with your syllabus
- Excellent tool to provide patients
- Can be shipped to your office (minimal charge for postage)
- Available online with additional resources at:
  - [https://www.cdc.gov/cancer/breast/](https://www.cdc.gov/cancer/breast/)
  - [https://www.cancer.net/cancer-types/breast-cancer](https://www.cancer.net/cancer-types/breast-cancer)

**Conclusions**

- These are exciting times, as more and more (effective) therapies become available for the most common type of breast cancer
- But, are targeted therapies a must at all times?
- If so, how are we going to sequence (or combine) all the approved and to-be-approved targeted therapies? At what cost (side effects and financial?)?

  - Who knows?? Need to individualize based on patient and tumor characteristics...Whatever strategy ends up making a difference in overall survival is the one likely to prevail.
  - Anything else, becomes physician/patient preference...