Treatment of Endocrine Resistance in ER+ Advanced Breast Cancer

Presented by
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Hormone Receptor-Positive (HR+) Breast Cancer

- Approximately 60% to 75% of invasive breast cancers are classified as HR +1,2,3
- ER signaling leads to
  - ↑ Cell proliferation
  - ↓ Time available for DNA repair
  - ↑ Risk of mutation
- ↑ ER expression correlates with improved response to endocrine therapy1

Abbreviations: ER, estrogen receptor; HR, hormone receptor.
Images reprinted from NHS Trust, Edinburgh, UK (www.breastpathology.info).
Abbreviations: AI, aromatase inhibitor; ERDs, estrogen receptor downregulator; HR⁺; hormone receptor positive; SERMS, selective estrogen receptor modulators.

* Marginal improvement over lower dose fulvestrant.

Endocrine Therapy for HR+ Advanced Breast Cancer

Growth factor receptor

Estrogen

Aromatase inhibitors (AIs)
- Nonsteroidal AIs
  - Anastrozole
  - Letrozole
- Steroidal AIs
  - Exemestane

Estrogen receptor downregulator (ERD)
- Fulvestrant

Selective estrogen receptor modulators (SERMs)
- Tamoxifen
- Toremifene

EFECT: Fulvestrant Is Similar to Exemestane in Postmenopausal Women With HR+ Advanced Breast Cancer Following Prior Nonsteroidal Aromatase Inhibitor Therapy

Phase 3 study; n=693
Postmenopausal women with HR+ advanced breast cancer
Progressed after nonsteroidal AI in adjuvant or first-line metastatic setting (~15% endocrine therapy-naive in advanced setting)

Fulvestrant 500 mg d 1
250 mg day 14, 28, mo

Exemestane 25 mg/d

Primary endpoint
TTP
Secondary endpoints
ORR, CBR, DOR, DoCB, OS

<table>
<thead>
<tr>
<th></th>
<th>Fulvestrant (n=351)</th>
<th>Exemestane (n=342)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up, all</td>
<td>13.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP (mo)</td>
<td>3.7</td>
<td>3.7</td>
<td>.653</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>7.4</td>
<td>6.7</td>
<td>.736</td>
</tr>
<tr>
<td>CBR (%)</td>
<td>32.2</td>
<td>31.5</td>
<td>.853</td>
</tr>
<tr>
<td>DoCB (mo)</td>
<td>9.3</td>
<td>8.3</td>
<td></td>
</tr>
<tr>
<td>DOR (mo)</td>
<td>7.5</td>
<td>5.5</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AI, aromatase inhibitor; CBR, clinical benefit rate; DoCB, duration of clinical benefit; DOR, duration of response; HR, hormone receptor; ORR, objective response rate; OS, overall survival; TTP, time to progression.

<table>
<thead>
<tr>
<th>Indolent/Indolent Disease</th>
<th>Bone-Only Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET Sensitive/Indolent Disease</td>
<td>EVE + EXE</td>
</tr>
<tr>
<td>Indolent/Asymptomatic ET Resistant</td>
<td>TAM</td>
</tr>
<tr>
<td>&gt;3 Lines Prior Therapy</td>
<td>F500</td>
</tr>
<tr>
<td>Indolent/Asymptomatic ET Resistant</td>
<td>TAM</td>
</tr>
<tr>
<td>&gt;3 Lines Prior Therapy</td>
<td>F250</td>
</tr>
<tr>
<td>Indolent/Asymptomatic ET Resistant</td>
<td>TAM</td>
</tr>
<tr>
<td>&gt;3 Lines Prior Therapy</td>
<td>EXE</td>
</tr>
<tr>
<td>Indolent/Asymptomatic ET Resistant</td>
<td>TAM</td>
</tr>
<tr>
<td>&gt;3 Lines Prior Therapy</td>
<td>CT</td>
</tr>
<tr>
<td>Indolent/Asymptomatic ET Resistant</td>
<td>TAM</td>
</tr>
<tr>
<td>&gt;3 Lines Prior Therapy</td>
<td>CT</td>
</tr>
<tr>
<td>Indolent/Asymptomatic ET Resistant</td>
<td>TAM</td>
</tr>
<tr>
<td>&gt;3 Lines Prior Therapy</td>
<td>CT</td>
</tr>
<tr>
<td>Elderly</td>
<td>TAM</td>
</tr>
<tr>
<td>Elderly</td>
<td>EVE (+/- dose escalation) + EXE</td>
</tr>
<tr>
<td>Elderly</td>
<td>F500</td>
</tr>
<tr>
<td>Elderly</td>
<td>F250</td>
</tr>
<tr>
<td>Elderly</td>
<td>EXE</td>
</tr>
</tbody>
</table>
Key Endocrine Resistance Mechanisms

Transmembrane tyrosine kinase

Second messengers

Key Resistance Mechanisms

- Trans Membrane Tyrosine Kinase Receptors
  - Epidermal Growth Factor Receptor (EGFR)
  - Insulin Growth Factor Receptor (IGFR)
  - Fibroblast Growth Factor (FGFR)

- Second Messengers (Intracellular)
  - PI3-K/AKT/mTOR pathway
The PI3K / AKT / mTOR Pathway

mTOR is activated by PI3K / AKT and LKB1 / AMPK pathways
mTOR mediates ER phosphorylation
Crosstalk Between ER and PI3K/AKT/mTOR Signaling: Rationale for Dual Inhibition

- mTORC1 activates ER in a ligand-independent fashion\(^1\)
- **Hyperactivation** of the PI3K/AKT/mTOR pathway is observed in endocrine-resistant breast cancer cells\(^3\)

mTOR is a rational target to enhance the efficacy of endocrine therapy

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Abbreviations: AKT, protein kinase B; EGFR, epidermal growth factor receptor; ER, endocrine receptor; ERE, endocrine response element; HER2, human epidermal growth factor receptor-2; IGF-1R, insulin-like growth factor-1 receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; PI3K, phosphatidylinositol-3-kinase; PTEN, phosphatase and tensin.

The mTOR Pathway is Active in Breast Cancer

- Genetic alterations result in activation of the PI3K/AKT/mTOR pathway in breast cancer
  - Loss of PTEN protein (~30% to 48%), PTEN mutation (<5%)\(^1\)\(^-\)\(^3\)
  - PIK3CA mutation (~21% to 33%)\(^4\)\(^-\)\(^8\)

- ~30% to 40% of breast cancer cells exhibit AKT activation\(^9\)\(^,\)\(^10\)

- Overexpression/mutation of receptor tyrosine-kinases (eg, HER2, EGFR) also activates the PI3K/AKT/mTOR pathway\(^11\)

EGFR, epidermal growth factor receptor

TAMRAD: Tamoxifen ± Everolimus in Aromatase Inhibitor-Refractory Advanced Breast Cancer

Phase 2 study; n=111
Postmenopausal women with ER+ HER2- advanced breast cancer
Previously treated with aromatase inhibitor therapy in adjuvant or metastatic setting

Primary endpoint:
CBR at 6 mo

Secondary endpoints:
TTP, OS, ORR, biomarkers, safety

Stratification:
Primary or secondary hormone resistance

Tamoxifen 20 mg/d + Everolimus 10 mg/d
Tamoxifen 20 mg/d + Placebo

Abbreviations: CBR, clinical benefit rate; ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; ORR, overall response rate; OS, overall survival; TTP, time to progression.

TAMRAD: Primary Endpoint, Clinical Benefit Rate

Clinical Benefit Rate, % of patients

- Tamoxifen: 42%
- Tamoxifen + Everolimus: 61%

$p=0.045$ (exploratory analysis)

Everolimus increased CBR 45% over tamoxifen alone (absolute difference 19%)

Abbreviations: CBR, clinical benefit rate.
TAMRAD: Time to Progression

HR = 0.54 (95% CI = 0.36, 0.81)
\( p = 0.002 \) (exploratory analysis)

Tamoxifen: 4.5 mo
Tamoxifen + Everolimus: 8.6 mo

Abbreviations: CI, confidence interval; HR, hazard ratio; TTP, time to progression.

**BOLERO-2: Exemestane ± Everolimus in Non-Steroidal Aromatase Inhibitor-Refractory Advanced Breast Cancer**

*Phase 3 study; n=724*

Postmenopausal women with ER+ HER2- advanced breast cancer refractory to letrozole or anastrozole

Recurrence during or within 12 mo after end of adjuvant treatment or progression during or within 1 mo after end of treatment for advanced disease

**Everolimus 10 mg/d + Exemestane 25 mg/d (n=485)**

**Placebo + Exemestane 25 mg/d (n=239)**

**Primary endpoint:** PFS

**Secondary endpoints:** OS, ORR, CBR, safety, QoL, bone markers

- Stratification
  1. Sensitivity to prior hormonal therapy
  2. Presence of visceral disease

- No crossover

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life.

### BOLERO-2: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Everolimus + Exemestane</th>
<th>Placebo + Exemestane (n=239), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>62 (34, 93)</td>
<td>61 (28, 90)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>74</td>
<td>78</td>
</tr>
<tr>
<td>Asian</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Performance status 0</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Metastatic site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>33</td>
<td>30</td>
</tr>
<tr>
<td>Lung</td>
<td>29</td>
<td>33</td>
</tr>
<tr>
<td>Bone</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>Visceral disease</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Measurable disease&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70</td>
<td>68</td>
</tr>
</tbody>
</table>

<sup>a</sup> All other patients had ≥1 bone lesion.

PFS Based on Local Assessment at 18-mo Follow-up in BOLERO-2 Confirms Earlier Reports

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.


HR = 0.45 (95% CI, 0.38-0.54)
Log-rank P < .0001

Kaplan-Meier medians
EVE+EXE: 7.8 months
PBO+EXE: 3.2 months
PFS Based on Central Review at 18-mo Follow-up in BOLERO-2 Confirms Earlier Reports and Local Assessment

HR = 0.38 (95% CI, 0.31-0.48)
Log-rank $P < .0001$

Kaplan-Meier medians
EVE+EXE: 11.0 months
PBO+EXE: 4.1 months

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
BOLERO-2 (18-mo f/up): PFS Benefits Were Comparable in Elderly vs Younger Patients

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; wk, weeks.

BOLERO-2 (18-mo f/up): PFS Benefits Were Comparable in Asian and Non-Asian Patients

Abbreviations: EVE, everolimus; EXE, exemestane; PBO, placebo; PFS, progression-free survival; wk, weeks.
BOLERO-2 (18-mo f/up): PFS Benefits Were Comparable in Patients With (A) Visceral Metastases, (B) Without Visceral Metastases, and (C) With Bone-Only Metastases

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.
**BOLERO-2 (18-mo f/up): PFS Benefits Were Comparable In Patients With Visceral Mets Regardless of ECOG PS**

- Among patients with visceral involvement at baseline and ECOG PS = 0, median PFS was 6.83 months for EVE+EXE treated patients and 2.76 months for PBO+EXE treated patients.

- Among patients with visceral involvement at baseline and ECOG PS ≥ 1, EVE+EXE extended the median PFS (6.77 months) compared with PBO+EXE (1.45 months).

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane</th>
<th>Placebo + Exemestane</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pts with visceral disease at baseline</strong></td>
<td><strong>Pts</strong></td>
<td><strong>Events</strong></td>
<td><strong>%</strong></td>
</tr>
<tr>
<td>Pts</td>
<td>271</td>
<td>188</td>
<td>69.4</td>
</tr>
<tr>
<td><strong>ECOG PS = 0</strong></td>
<td>167</td>
<td>114</td>
<td>68.3</td>
</tr>
<tr>
<td><strong>ECOG PS ≥ 1</strong></td>
<td>100</td>
<td>71</td>
<td>71</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; Mets, metastases; PFS, progression-free survival.

BOLERO-2 (18-mo f/up): Everolimus Improved PFS in Patients Progressing After Adjuvant Therapy$^a,b$

HR = 0.39 (95% CI, 0.25-0.62)

Kaplan-Meier medians
EVE+EXE: 11.50 mo
PBO+EXE: 4.07 mo

EVE+EXE improved PFS in pts who received adjuvant endocrine therapy ± chemotherapy

These data support the efficacy of EVE +EXE as first-line therapy in the advanced setting

Subgroup | EVE+EXE (N = 100) | PBO+EXE (N = 37)
--- | --- | ---
Any adjuvant therapy, %$^a$ | 100 | 37
Adjuvant endocrine therapy only, %$^a$ | 26 | 9
Adjuvant endocrine therapy + chemotherapy, %$^a$ | 74 | 28

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo; PFS, progression-free survival.

$^a$ Includes patients who also had prior neoadjuvant therapy.

$^b$ By local investigator assessment.

BOLERO-2 (18-mo f/up): Everolimus Improved PFS in Patients Who Received Prior Chemotherapy for Advanced BC

Progression-free survival

Local Assessment
HR = 0.38 (95% CI, 0.27-0.53)
Kaplan-Meier medians
EVE+EXE = 6.1 mo
PBO+EXE = 2.7 mo

Central Assessment
HR = 0.42 (95% CI, 0.27-0.65)
Kaplan-Meier medians
EVE+EXE = 7.1 mo
PBO+EXE = 2.8 mo

Conclusion
- Demonstrated the efficacy of EVE+EXE in patients who received chemotherapy for advanced BC before BOLERO-2 study entry or in patients who recurred during or after adjuvant endocrine therapy, consistent with the overall population

BC, breast cancer; CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.

Campone M, et al, ASCO 2013, abstract 557 (poster)
BOLERO-2 (18-mo f/up): Response Rates & Clinical Benefit Were Significantly Higher in the Everolimus Arm

- **Response**
  - Everolimus + Exemestane: 12.6%
  - Placebo + Exemestane: 1.7%
  - **P < 0.0001**

- **Clinical Benefit**
  - Everolimus + Exemestane: 51.3%
  - Placebo + Exemestane: 26.4%
  - **P < 0.0001**

BOLERO-2 (39-mo f/up): Overall Survival

- 410 deaths had occurred at 39-months’ median follow-up (data cut-off date: 03-Oct-2013)
  - 267 deaths (55%) in the EVE+EXE arm vs 143 deaths (60%) in the PBO+EXE arm
- Median OS with EVE+EXE was 31.0 months vs 26.6 months with PBO+EXE (HR = 0.89; 95% CI: 0.73, 1.10; \( P = .14 \), not statistically significant)
- No new safety signals were observed

<table>
<thead>
<tr>
<th>Cut-off Date</th>
<th>Interim PFS (7-mo follow-up)</th>
<th>Update PFS (12-mo follow-up)</th>
<th>Final PFS (18-mo update)</th>
<th>Final OS (39-mo update)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-Feb-2011</td>
<td></td>
<td>8-Jul-2011</td>
<td>15-Dec-2011</td>
<td>03-Oct-2013</td>
</tr>
<tr>
<td>OS events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(EVE vs PBO)</td>
<td>83</td>
<td>137</td>
<td>200</td>
<td>410</td>
</tr>
<tr>
<td>(10.6 vs 13.0%)</td>
<td>(17.3 vs 22.7%)</td>
<td>(25.4 vs 32.2%)</td>
<td>(55.1% vs 59.8%)</td>
<td></td>
</tr>
<tr>
<td>( \Delta ) OS events</td>
<td><strong>2.4%</strong></td>
<td><strong>5.4%</strong></td>
<td><strong>6.8%</strong></td>
<td><strong>4.7%</strong></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; mo, month; OS, overall survival; PBO, placebo; PFS, progression-free survival; vs, versus.

BOLERO-2 (39-mo f/up): Posttreatment Anticancer Therapies

<table>
<thead>
<tr>
<th>Therapy Type</th>
<th>Everolimus + Exemestane</th>
<th>Placebo + Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any posttreatment therapy</td>
<td>84</td>
<td>90</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>53</td>
<td>63</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Targeted therapy</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Radiation therapy</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Surgery</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane</th>
<th>Placebo + Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxane</td>
<td>28</td>
<td>36</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Platinum-based regimens</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
BOLERO-2 (39-mo f/up): Overall Survival

HR = 0.89 (95% CI, 0.73-1.10)
Log-rank $P = .1426$

Kaplan-Meier medians
EVE+EXE: 30.98 months
PBO+EXE: 26.55 months

Abbreviations: CI, confidence interval; EVE, everolimus; EXE, exemestane; HR, hazard ratio; PBO, placebo.
Everolimus decreases disease progression in bone in the overall population (N = 724)

Cumulative incidence of disease progression was determined using the competing risk method; exploratory $P = .036$ by Gray’s test.

Abbreviations: EVE, everolimus; EXE, exemestane; PBO, placebo.


* Cumulative incidence of disease progression was determined using the competing risk method; exploratory $P = .036$ by Gray’s test.
Clinically Notable AEs Associated With mTOR Inhibition

- Stomatitis
- Noninfectious pneumonitis
- Infections
- Hyperglycemia and hyperlipidemia
- Skin rash

Abbreviations: AE, adverse event; mTOR, mammalian target of rapamycin.
## Stomatitis: Incidence in BOLERO-2 (18 month follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n=482), %</th>
<th>Placebo + Exemestane (n=238), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>59</td>
<td>8</td>
</tr>
<tr>
<td>Rash</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>37</td>
<td>4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>31</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Noninfectious pneumonitis</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td>Infections and infestations(^a)</td>
<td>50</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^a\) Incidence based on system organ class (SOC); includes all infections.
Stomatitis: Clinical Presentation

- mTOR inhibitor-associated stomatitis\(^1,2\)
  - Distinct from chemotherapy-induced stomatitis
  - Aphthous-like ulcers characterized by discrete, ovoid, superficial, well-demarcated ulcerations with a grayish-white pseudomembrane
  - Ulcers typically develop acutely in the first cycle of therapy
  - Severity usually peaks within the first 2 weeks of therapy

Abbreviation: mTOR, mammalian target of rapamycin.

## Stomatitis: Clinical Management Strategy

<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>Minimal, normal diet</td>
<td>- Rinse several times daily with nonalcoholic mouthwash or 0.9% salt water.</td>
<td>- No change</td>
</tr>
</tbody>
</table>
| 2     | Symptomatic but can eat and swallow modified diet | - Topical analgesic mouth treatments (eg, benzocaine, butylaminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (eg, triamcinolone oral paste)* | - Temporary dose interruption until recovery to grade ≤1, then re-initiate at same dose  
- If recurs at grade 2, interrupt dose until recovery to grade <1, then re-initiate at a lower dose |
| 3     | Symptomatic and unable to adequately eat or hydrate orally | - Avoid agents containing alcohol, hydrogen peroxide, iodine, and antifungal agents unless an oral fungal infection is diagnosed, in which case oral topical antifungal agents are preferred  
- Treat with appropriate medical therapy  
- Same as grade 2 | - Hold dose until recovery to grade ≤1, then restart at reduced dose  
- Discontinue everolimus |
| 4     | Severe (symptoms are life threatening)        | - Treat with appropriate medical therapy  
- Same as grade 2 | - Discontinue everolimus |

*Antifungal agents should not be used unless an oral fungal infection is diagnosed, in which case oral topical antifungal agents are preferred.

If dose reduction required, the suggested dose is about 50% lower than the dose previously administered.

Two reductions of everolimus were permitted in the BOLERO-2 trial: an initial reduction to 5 mg daily and a subsequent reduction to 5 mg every other day.

1. Afinitor® Product Monograph. Novartis Pharmaceuticals Canada Inc.  
Stomatitis: Patient Education

- Patient awareness and early intervention are important\textsuperscript{1,2}
  - Consider evaluation for herpes virus or fungal infection\textsuperscript{1}
  - Educate patients about good oral hygiene\textsuperscript{1,2}
    - Note: Preventive treatment with sodium bicarbonate-based mouthwash has been shown to be ineffective\textsuperscript{4}
  - Advise patients to avoid foods that are spicy/acidic/salty\textsuperscript{3}
  - Advise patients to promptly report any signs or symptoms\textsuperscript{1}

<table>
<thead>
<tr>
<th>Good Oral Hygiene</th>
<th>Prompt Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rinse with baking soda (or equivalent product)</td>
<td>• &gt;3 lesions</td>
</tr>
<tr>
<td>• Floss after each meal</td>
<td>• Lesions lasting &gt;3 days</td>
</tr>
<tr>
<td>• Use mild toothpaste and soft-bristled toothbrush</td>
<td>• Lesions interfering with eating and drinking</td>
</tr>
<tr>
<td>• Avoid agents containing hydrogen peroxide, iodine, and thyme derivatives</td>
<td></td>
</tr>
</tbody>
</table>
## Noninfectious Pneumonitis: Incidence in BOLERO-2 (18 month follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n=482), %</th>
<th>Placebo + Exemestane (n=238), %</th>
</tr>
</thead>
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<tr>
<td></td>
<td>All Grades</td>
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</tr>
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<td><strong>Stomatitis</strong></td>
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</tr>
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<td>1</td>
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</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td>50</td>
<td>4</td>
</tr>
</tbody>
</table>

*Incidence based on system organ class (SOC); includes all infections.*

Noninfectious Pneumonitis: Clinical Presentation

• Noninfectious pneumonitis should be considered in patients presenting with nonspecific respiratory symptoms and in whom infectious, neoplastic, and other etiologies have been excluded\(^1\)

• Noninfectious, nonmalignant infiltration of the lungs\(^2,3\)
  – Class effect associated with rapamycin derivatives\(^2,3\)

• Presents with no symptoms or with nonspecific signs and symptoms\(^2\)
  – Cough, shortness of breath/dyspnea, nonspecific radiologic changes, pleural effusion, or hypoxia

• Symptomatic cases are usually mild to moderate in severity and reversible; however, a small proportion may be severe\(^3,4\)

---

Noninfectious Pneumonitis: Radiographic Appearance

- Obtain baseline radiographic image
- Radiographic appearance¹
  - Common appearances can include diffuse “ground-glass” or patchy opacification

During Everolimus Treatment²

After AE Management²

## Noninfectious Pneumonitis: Clinical Management Strategy

<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 change</td>
</tr>
<tr>
<td>2</td>
<td>Symptomatic, not interfering with ADL</td>
<td>▪ Consider consulting a pulmonologist</td>
<td>▪ Consider temporary interruption of therapy until symptoms improve to grade ≤1.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Rule out infections</td>
<td>▪ Reinitiate Everolimus at a lower dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Consider treatment with corticosteroids</td>
<td>▪ Discontinue treatment if failure to recover within 4 weeks</td>
</tr>
<tr>
<td>3</td>
<td>Symptomatic, interfering with ADL, O₂ required</td>
<td>▪ Consult a pulmonologist</td>
<td>▪ Hold dose until recovery to grade ≤1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Perform diagnostics to rule out infections</td>
<td>▪ If Everolimus is re-initiated, use a lower dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Consider treatment with corticosteroids</td>
<td>▪ If toxicity recurs at grade 3, consider discontinuation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ In the presence of impending respiratory distress, consider use of concomitant antibiotics or corticosteroids</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Life threatening, ventilator support indicated</td>
<td>▪ Discontinue Everolimus</td>
<td></td>
</tr>
</tbody>
</table>

- If dose reduction required, the suggested dose is about 50% lower than the dose previously administered. ¹
- Two reductions of everolimus were permitted in the BOLERO-2 trial: an initial reduction to 5 mg daily and a subsequent reduction to 5 mg every other day.³

Noninfectious Pneumonitis: Patient Education

- Advise patients to promptly report any new or worsening respiratory symptoms
  - Shortness of breath
- Cough
- Fever
**Infections: Incidence in BOLERO-2 (18 month follow-up)**

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n=482), %</th>
<th>Placebo + Exemestane (n=238), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
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<td><strong>Hyperglycemia</strong></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>

*Infections and infestations* include all infections. 

Infections: Clinical Considerations

- Everolimus has immunosuppressive properties and may predispose patients to infections, especially opportunistic infections such as aspergillosis and candidiasis.

- Localized and systemic infections, including pneumonia, other bacterial infections, and invasive fungal infections have been reported with everolimus.

- Infections can be severe (leading to respiratory failure) and occasionally fatal.
Infections: Guidance for Practical Management

- Obtain a thorough history of prior infections including fungal infections, hepatitis, HIV, other viral infections, tuberculosis, and other opportunistic infections

- Patients with fungal infections should be comprehensively treated before initiation of everolimus therapy

- Everolimus should not be given to patients with an invasive systemic fungal infection

- Avoid coadministration of everolimus with strong cytochrome P450 enzyme (CYP) 3A4 inhibitors

### Infections*: Clinical Management Strategy\(^1-4\) (cont’d)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Everolimus Dose Modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initiate appropriate medical therapy and monitor</td>
<td>No change if toxicity is tolerable</td>
</tr>
<tr>
<td></td>
<td>Institute adequate treatment of infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Appropriate antibiotic use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perform culture and be aware of atypical infections</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Initiate appropriate medical therapy and monitor</td>
<td>Maintain dose if patient able to tolerate</td>
</tr>
<tr>
<td></td>
<td>IV antibiotic, antifungal,** or antiviral therapy; institute additional interventions as indicated</td>
<td>If patient unable to tolerate, temporary dose interruption until recovery to Grade (\leq 1), then restart at same dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If recurs at Grade 2, hold dose until</td>
</tr>
<tr>
<td>3</td>
<td>Initiate appropriate medical therapy and monitor</td>
<td>Hold dose until recovery to Grade (\leq 1)</td>
</tr>
<tr>
<td></td>
<td>IV antibiotic, antifungal,** or antiviral therapy; institute additional interventions as indicated</td>
<td>If Everolimus is re-initiated restart at lower dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If toxicity recurs at Grade 3, consider</td>
</tr>
<tr>
<td>4</td>
<td>Treat with appropriate medical therapy</td>
<td>Discontinue Everolimus</td>
</tr>
</tbody>
</table>

- * Note: Excluding hepatitis
- **If diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy
- If dose reduction required, the suggested dose is about 50% lower than the dose previously administered.\(^1\)
- Two reductions of everolimus were permitted in the BOLERO-2 trial: an initial reduction to 5 mg daily and a subsequent reduction to 5 mg every other day.\(^4\)

Hepatitis Reactivation

- Use of immunosuppressants in patients with past medical history of hepatitis is a concern
  - This is particularly important in regions where hepatitis infections are more common
- HBV and HCV infections can reactivate or flare during immunosuppression
- PI3K/mTOR pathway activation has been associated with suppressed HBV viral replication; thus, mTOR inhibition may trigger HBV replication and the process of viral reactivation\(^1\)
- Everolimus has been associated with hepatitis reactivation, including in patients with HCC\(^2,3\)

Abbreviations: HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

Infections: Patient Education

- Inform patients that they may be more susceptible to infections while being treated with everolimus\(^1,2\)

- Advise patients to be aware of and to promptly report any signs and symptoms of infections\(^1,2\)
  - Cough
  - Shortness of breath
  - Fever

- Inform patients with hepatitis infections of the possibility of reactivation

Inhibition of PI3K/AKT/mTOR Signaling Affects Glucose Homeostasis and Fat Metabolism

Abbreviations: ATP, adenosine triphosphate; PI3K, phosphoinositol-3 kinase; mTOR, mammalian target of rapamycin.

# Hyperglycemia: Incidence in BOLERO-2 (18 month follow-up)

<table>
<thead>
<tr>
<th></th>
<th>Everolimus + Exemestane (n=482), %</th>
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</tr>
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<td>3</td>
</tr>
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<td>Hyperglycemia</td>
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<td>5</td>
</tr>
<tr>
<td>Infections and infestations(^a)</td>
<td>50</td>
<td>4</td>
</tr>
</tbody>
</table>

\(^a\) Incidence based on system organ class (SOC); includes all infections. Piccart M, et al. J Clin Oncol. 2012;30(suppl; abstr 559)(poster).
Hyperglycemia: Guidance for Practical Management

- Patients should be monitored for fasting serum glucose levels before initiating everolimus therapy and monthly thereafter\(^1,2,4\)
- Achieve optimal glycemic control before starting a patient on everolimus\(^1,2\)
- Manage according to standard consensus guidelines\(^3,4\)
  - Achievement and maintenance of normal glycemic goal (HbA1c <7%)
  - Initial therapy of lifestyle intervention, metformin, or both
  - Rapid addition of medications and transition to new medications when target glycemic goals are not achieved/sustained
  - Early addition of insulin therapy in patients not meeting target glycemic goals

Abbreviation: HbA1c, glycosylated hemoglobin.

Hyperglycemia and Hyperlipidemia: Patient Education

- Inform patients of the importance of regular monitoring of blood glucose and lipid levels
- Advise patients to promptly report excessive thirst or increased frequency of urination\(^1\)
- Advise patients to manage weight appropriately\(^2\)
- For patients already receiving lipid-lowering agents, advise them of the possible need for increased doses during concurrent treatment with everolimus\(^2\)

BOLEREO-2 Biomarker Analyses
BOLERO-2 Biomarker Analyses: Patients With No or Single Genetic Alteration in PIK3CA/PTEN/CCND1 or FGFR1/2 Derive Greater PFS Benefit With EVE

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Events, %</th>
<th>Median PFS, d</th>
<th>HR$^a$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EVE: WT</td>
<td>43</td>
<td>19 (44)</td>
<td>356</td>
<td>0.24 (0.11 - 0.54)</td>
</tr>
<tr>
<td>PBO: WT</td>
<td>18</td>
<td>14 (78)</td>
<td>203</td>
<td></td>
</tr>
<tr>
<td>EVE: Single</td>
<td>76</td>
<td>48 (63)</td>
<td>214</td>
<td>0.26 (0.16 - 0.43)</td>
</tr>
<tr>
<td>PBO: Single</td>
<td>35</td>
<td>31 (89)</td>
<td>77</td>
<td></td>
</tr>
<tr>
<td>EVE: Multiple</td>
<td>38</td>
<td>27 (71)</td>
<td>138</td>
<td>0.78 (0.39 - 1.54)</td>
</tr>
<tr>
<td>PBO: Multiple</td>
<td>17</td>
<td>14 (82)</td>
<td>128</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ HR adjusted with imbalanced covariates

### Subgroup Definition and Size

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Definition</th>
<th>Size, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>No alteration in PIK3CA AND PTEN AND FGFR1/2 AND CCND1</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76%</td>
</tr>
<tr>
<td>Single</td>
<td>Single alteration only in PIK3CA OR PTEN OR FGFR1/2 OR CCND1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>49%</td>
</tr>
<tr>
<td>Multiple</td>
<td>Two or more alterations in PIK3CA OR PTEN OR FGFR1/2 OR CCND1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24%</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EVE, everolimus; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; WT, wild type.
Hortobagyi G, et al. ASCO 2013, abstract LBA509 (oral)
BOLERO-2 (18 month follow-up): PFS Subgroup Analyses

Subgroups (N)

All (724)

Age

<65 (449)

≥65 (275)

Region

Asia (137)

Europe (275)

North America (274)

Other (38)

Sensitivity to prior hormonal therapy

Yes (610)

No (114)

Visceral metastasis

Yes (406)

No (318)

Last therapy

Aromatase inhibitor (532)

Antiestrogen (122)

Other (70)

Last therapy setting

Metastatic (586)

Adjuvant (138)

Prior chemotherapy

Adjuvant only (306)

Metastatic (186)

None (232)

Hazard Ratio

Favors EVE + EXE

Favors PBO + EXE

BOLERO-2 Biomarker Analyses: Greater PFS Benefit With EVE in Patients With Minimal Alterations in PIK3CA/PTEN/CCND1 or FGFR1/2

Abbreviations: CI, confidence interval; EVE, everolimus; HR, hazard ratio; PBO, placebo; PFS, progression-free survival; WT, wild type.

Hortobagyi G, et al. ASCO 2013, abstract LBA509 (oral)
BOLERO-2 (18-mo f/up): Summary

- Addition of everolimus to exemestane prolongs PFS in patients with HR\textsuperscript{+}, HER2\textsuperscript{−} breast cancer after a nonsteroidal aromatase inhibitor\textsuperscript{1}
  - Local Assessment: Median 7.8 vs 3.2 months (HR = 0.45, \(P < .0001\))
  - Central Assessment: Median 11.0 vs 4.1 months (HR = 0.38, \(P < .0001\))
  - Benefit is observed in all subgroups
- Adverse events were consistent with previous experience with everolimus\textsuperscript{1}
- Time to deterioration of QOL was significantly longer with the addition of everolimus to exemestane\textsuperscript{2}

Abbreviations: ER\textsuperscript{+}, estrogen receptor-positive; HER2\textsuperscript{−}, human epidermal growth factor receptor 2-negative; HR, hazard ratio; PFS, progression-free survival; QOL, quality of life; vs, versus.

BOLERO-2 (18-mo f/up): Conclusions

- Everolimus is the first agent to enhance the clinical benefit of endocrine therapy in patients with HR⁺, HER2⁻ advanced BC progressing after NSAI therapy.

- The addition of everolimus in advanced BC could represent a paradigm shift in the management of this patient population.

Abbreviations: BC, breast cancer; HER2⁻, human epidermal growth factor receptor 2-negative; HR⁺, hormone receptor-positive; NSAI, nonsteroidal aromatase inhibitor.

BOLERO-2 Publications and Presentations

Publications

Presentations
- Ito Y, et al. ASCO 2013, abstract 561 (poster)
- Perez A, et al. ASCO 2013, abstract 558 (poster)
- Piccart M, et al. ASCO 2012, abstract 559 (poster)
- Piccart M, et al. SABCS 2012, poster P6-04-02
- Piccart M, et al. EBCC 2014, abstract 1LBA (oral presentation)
Breast Cancer Treatment With Everolimus and Exemestane for ER + Women — Results of the 2nd Interim Analysis of the Non-interventional Trial, BRAWO

Peter A. Fasching,¹ Thomas Decker,² Andreas Schneeweis,³ Christoph Uleer,⁴ Frank Förster,⁵ Pauline Wimberger,⁶ Christian Kurbacher,⁷ Nadia Harbeck,⁸ Oliver Tomé,⁹ Bettina Müller,¹⁰ Christoph Mundhenke,¹¹ Sherko Kümmel,¹² Mathias Muth,¹³ Julia Kreuzeder,¹³ Wilhelm Bloch,¹⁴ Hans Tesch,¹⁵ Diana Lüftner,¹⁶ Christian Jackisch,¹⁷ Florian Schütz,³ Eva-Maria Grischke¹⁸

¹Department of Obstetrics and Gynecology, University Erlangen, Erlangen, Germany; ²Medical Centre Ravensburg, Ravensburg, Germany; ³Department of Obstetrics and Gynecology, University Heidelberg, Heidelberg, Germany; ⁴Medical Centre Hildesheim, Hildesheim, Germany; ⁵Poliklinik GmbH Chemnitz, Chemnitz, Germany; ⁶Department of Obstetrics and Gynecology, Technical University Dresden, Dresden, Germany; ⁷Gynecology and Obstetrics, Medical Center Bonn-Friedensplatz, Bonn, Germany; ⁸Department of Obstetrics and Gynecology, Hospitals Grosshadern and Maistrasse-Innenstadt, University of Munich, Munich, Germany; ⁹Women’s Hospital and School for Midwives, St. Vincentius Clinic, Karlsruhe, Germany; ¹⁰Obstetrics & Gynecology, The GRN Health Centers Rhein-Neckar, Weinheim, Germany; ¹¹Department of Obstetrics and Gynecology, University Hospital of Schleswig-Holstein, University of Kiel, Kiel, Germany; ¹²Interdisciplinary Breast Center, The Kliniken Essen-Mitte, University of Duisburg, Essen, Germany; ¹³Novartis Pharma GmbH, Nuremberg, Germany; ¹⁴Department of Sport Medicine, University Cologne, Cologne, Germany; ¹⁵Oncology Bethanien, Frankfurt/Main, Germany; ¹⁶Department of Hematology, Oncology, and Tumor Immunology, Charité University Medicine, Campus Benjamin Franklin, Berlin, Germany; ¹⁷Breast Centre at the Hospital Offenbach, Offenbach, Germany; ¹⁸Department of Obstetrics and Gynecology, University Tuebingen, Tuebingen, Germany
Introduction

- In the pivotal phase 3 BOLERO-2 trial, the combination of everolimus (EVE) with exemestane (EXE) more than doubled median progression-free survival (PFS) versus placebo (PBO) +EXE in postmenopausal women with hormone-receptor- positive (HR+) advanced breast cancer progressing after a nonsteroidal aromatase inhibitor
  - 7.8 months with EVE+EXE versus 3.2 months with PBO+EXE (hazard ratio [HR]= 0.45; \( P < .0001 \)) by local radiologic assessment
  - Results were confirmed by central radiologic assessment (11.0 months vs 4.1 months, respectively; HR = 0.38; \( P < .0001 \))
- BRAWO is a large, German, non-interventional study (NIS) with a planned enrollment of 3,000 patients with HR+ advanced breast cancer receiving EVE+EXE
Figure 1: BRAWO study design and objectives.

- Postmenopausal women
- HR+, HER2−, advanced breast cancer
- No symptomatic visceral metastasis
- Disease refractory to non-steroidal aromatase inhibitors
- Treatment with EVE+EXE according to the clinical routine and labeling text from the EVE SmPC

- Non-interventional study
- Patients observed for the duration of treatment with EVE+EXE
- Observation intervals after initiating EVE+EXE:
  - 2 weeks
  - 1 month
  - 3 months
  - Every 3 months thereafter
- Observation ends no later than 1 year after last patient enrolled

Approximately 3,000 patients at 400 sites

Start of enrollment: OCT 2012; End of enrollment: DEC 2015; End of documentation: DEC 2016

Primary Objective:
- Efficacy (PFS) and impact of physical activity on efficacy (PFS)

Secondary Objectives:
- Quality of life and impact of physical activity on quality of life
- Stomatitis management—prophylactic measures and treatment of stomatitis in clinical routine
- Sequence of therapies and utilization of EVE in clinical routine

Abbreviations: EVE, everolimus; EXE, exemestane; HER2, human epidermal growth factor receptor 2; HR, hormone receptor-positive; PFS, progression-free survival; SmPC, summary of product characteristics.
Study number: CRAD001JDE53
Reason for Discontinuation of Documentation and EVE+EXE (N = 500)

<table>
<thead>
<tr>
<th>Reason for Discontinuation</th>
<th>Patients, n (%) (N = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discontinuation of Documentation</strong>a</td>
<td></td>
</tr>
<tr>
<td>Consent withdraw</td>
<td>17 (3.4)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>Therapy with EVE+EXE discontinued</td>
<td>335 (67.0)</td>
</tr>
<tr>
<td>Death</td>
<td>38 (7.6)</td>
</tr>
<tr>
<td>Formal study end reachedb</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Missing (including ongoing patients)</td>
<td>94 (18.8)</td>
</tr>
<tr>
<td><strong>Discontinuation of Therapy With EVE+EXE</strong>a</td>
<td></td>
</tr>
<tr>
<td>Progression</td>
<td>204 (40.8)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>113 (22.6)</td>
</tr>
<tr>
<td>Poor compliance</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Patient’s wish</td>
<td>69 (13.8)</td>
</tr>
<tr>
<td>Missing (including ongoing patients)</td>
<td>110 (22.0)</td>
</tr>
</tbody>
</table>

*aThe data capture form asks for reason for discontinuation of documentation and reason for discontinuation of therapy as 2 separate questions. Therefore, various combinations of reasons are possible.

bFor 2 patients formal study end was documented by mistake. Formal study end has not been reached yet.
Results: EVE+EXE Treatment Characteristics

- Most patients received EVE+EXE as first-line (131 patients, 26.2%) or second-line (144 patients, 28.8%) treatment for advanced disease, followed by third-line treatment (94 patients, 18.8%) (Figure 2)
  - Most patients (445, 89.0%) switched to EVE+EXE because of disease progression under a previous therapy
- For patients receiving EVE+EXE in the advanced setting as
  - First- or second-line therapy, letrozole and anastrozole, were the most common last prior antineoplastic therapy
  - Third- or later line therapy, fulvestrant or chemotherapy, were increasingly documented as last prior therapy
Distribution of line of therapy for EVE +EXE (N = 500).

- **First line**
- **Second line**
- **Third line**
- **Fourth line**
- **Fifth line (and later)**

**Legend:**
- **FUL or CT** most common last anticancer therapy before EVE +EXE
- **NSAI** most common last anticancer therapy before EVE +EXE

**Abbreviations:** CT, chemotherapy; EVE, everolimus; EXE, exemestane; FUL, fulvestrant; NSAI, nonsteroidal aromatase inhibitor.
Results: Progression-Free Survival

- The median PFS observed with the first 500 patients was 8.0 months (95% CI, 6.7-9.1).
- The median PFS observed in the subset of patients who received EVE+EXE as first-line therapy for advanced disease (n = 131) was 10.1 months (95% CI, 6.7-17.6).
Progression-free survival (first 500 patients)

Median PFS = 8.0 months; 95% CI, 6.7-9.1 months

Abbreviation: CI, confidence interval; PFS, progression-free survival.
PFS in patients receiving EVE+EXE as first-line therapy for advanced disease (n = 131, subset of first 500 patients)

Median PFS = 10.1 months; 95% CI, 6.7-17.6 months

Patients at Risk, n 131 86 60 45 36 20 10

Abbreviation: CI, confidence interval; PFS, progression-free survival.
Results: Safety

- Adverse events (AEs) observed in BRAWO were consistent with that previously reported with EVE+EXE in patients with advanced breast cancer (Table 3)\(^1\)
- The most commonly reported AEs of any grade reported in ≥ 10% of patients were
  - Stomatitis (39.8%)
  - Fatigue (15.6%)
  - Diarrhea (13.2%)
  - Dyspnea (13.0%)
  - Nausea (12.0%)
  - Decreased appetite (10.4%)
48.1% of patients required EVE dose reduction during therapy
   - Patients starting at 10.0 mg received a median dose intensity of 93.5%, patients starting at 5.0 mg received a considerably lower median dose intensity of 50.0%

Most treatment interruptions were implemented because of adverse events
   - Median duration of treatment interruptions was 10.0 days
# Frequency of Everolimus Dose Modifications

<table>
<thead>
<tr>
<th>EVE Dose Modification</th>
<th>EVE 5-mg Start Dose (n = 66)</th>
<th>EVE 10-mg Start Dose (n = 431)</th>
<th>Total (n = 497)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median relative dose intensity, %</td>
<td>50.0</td>
<td>93.5</td>
<td>88.1</td>
</tr>
<tr>
<td>Treatment interruption, n (%)</td>
<td>5 (7.6)</td>
<td>166 (38.5)</td>
<td>171 (34.4)</td>
</tr>
<tr>
<td>Dose reduction (incl. to 0 mg), n (%)</td>
<td>14 (21.2)</td>
<td>225 (52.2)</td>
<td>239 (48.1)</td>
</tr>
<tr>
<td>Dose increase, n (%)</td>
<td>24 (36.4)</td>
<td>23 (5.3)a</td>
<td>47 (9.5)</td>
</tr>
</tbody>
</table>

*aThe majority of patients received the dose increase after a dose reduction.*
The majority of the patients (n = 429, 86.8%) received recommendations regarding stomatitis prevention from their physician (Table 5).

- Data on recommended prophylactic measures was missing for 6 patients.

Table 5. Stomatitis Prophylactic Measures Recommended to Patients

<table>
<thead>
<tr>
<th>Type of Recommended Prophylactic Measure</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild dental hygiene (eg, soft toothbrush)</td>
<td>362 (73.3)</td>
</tr>
<tr>
<td>Avoidance of hot, sour, or salty food</td>
<td>344 (69.6)</td>
</tr>
<tr>
<td>Rinsing with tea</td>
<td>281 (56.9)</td>
</tr>
<tr>
<td>Cooling (eg, sucking ice or frozen pineapple)</td>
<td>263 (53.2)</td>
</tr>
<tr>
<td>Avoidance of peroxide-/ alcohol-containing mouthwash solution</td>
<td>213 (43.1)</td>
</tr>
<tr>
<td>Rinsing with mouthwash solution</td>
<td>195 (39.5)</td>
</tr>
<tr>
<td>Rinsing with NaCl</td>
<td>57 (11.5)</td>
</tr>
<tr>
<td>Other</td>
<td>23 (4.7)</td>
</tr>
</tbody>
</table>

*Patients with available information.*
Results: Therapeutic Interventions for Stomatitis

- At least one therapeutic measure was documented for 232 (83.2%) of the 279 events with stomatitis.

Table 6. Stomatitis Therapeutic Interventions (First 500 Patients)

<table>
<thead>
<tr>
<th>Action Taken</th>
<th>Grade 1 (n = 143)</th>
<th>Grade 2 (n = 90)</th>
<th>Grade 3 (n = 17)</th>
<th>Unknown (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None specified</td>
<td>43 (30.1)</td>
<td>3 (3.3)</td>
<td>1 (5.9)</td>
<td>0</td>
</tr>
<tr>
<td>≥1 therapeutic measure</td>
<td>100 (63.9)</td>
<td>87 (96.7)</td>
<td>16 (94.1)</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Type of action (multiple specifications possible)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-drug mouthwash solution</td>
<td>78 (54.5)</td>
<td>46 (51.1)</td>
<td>7 (41.2)</td>
<td>22 (75.9)</td>
</tr>
<tr>
<td>Cooling (eg, sucking ice or frozen pineapple)</td>
<td>26 (18.2)</td>
<td>34 (37.8)</td>
<td>7 (41.2)</td>
<td>15 (51.7)</td>
</tr>
<tr>
<td>Drug Intervention</td>
<td>35 (24.5)</td>
<td>42 (46.7)</td>
<td>13 (76.5)</td>
<td>8 (27.6)</td>
</tr>
<tr>
<td>Topical drug</td>
<td>10 (7.0)</td>
<td>16 (17.8)</td>
<td>8 (47.1)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Systemic drug</td>
<td>26 (18.2)</td>
<td>30 (33.3)</td>
<td>10 (58.8)</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Temporary everolimus dose adjustment</td>
<td>6 (4.2)</td>
<td>16 (17.8)</td>
<td>3 (17.6)</td>
<td>4 (13.8)</td>
</tr>
<tr>
<td>Temporary everolimus dose interruption</td>
<td>12 (8.4)</td>
<td>37 (41.1)</td>
<td>10 (58.8)</td>
<td>2 (6.9)</td>
</tr>
</tbody>
</table>
Comparison with BOLERO-2, patients in the BRAW0 trial were older (66 vs 62 years, respectively) and a smaller percentage of patients had an ECOG PS of 0 (43.6% vs 60%, respectively)\(^1\)
- The percentages of patients with visceral metastases were comparable in BRAW0 and BOLERO-2 (53.7% vs 58%, respectively)\(^1\)
  - Note: BRAW0 does not include pleural and peritoneal involvement, unlike BOLERO 2, which included pleural and peritoneal involvement\(^2\)
- Median PFS in BRAW0 was consistent with BOLERO-2 in the overall population (8.0 months and 7.8 months, respectively)\(^1\) and in patients receiving EVE+EXE as first-line therapy in the advanced setting (10.1 months and 11.5 months, respectively)\(^3\)
Discussion

- The overall safety profile observed in the BRAWO study is comparable to that observed in BOLERO-2 and reported with EVE in other cancer indications.
- The percentage of patients with any grade stomatitis was lower in BRAWO (39.8%) compared with BOLERO-2 (59%).
  - 86.8% of patients received prophylactic stomatitis treatment in BRAWO.
Cyclin D-Cyclin Dependent Kinase 4/6-Rb Protein: A Key Pathway in Cell Progression

Abbreviations: CDK, cyclin dependent kinase; Cip/Kip, kinase inhibitor protein family; E2F, elongation factor 2; INK4, inhibitors of CDK4; P, phosphate; Rb, retionoblastoma protein; STAT, signal transducer and activator of transcription
Phase Ib/II Trial
Letrozole +/- Palbociclib

- 12 ER+/HER2-
  - No drug/drug interactions
  - AEs
    - ↓ Neutrophils
    - ↓ WBC
    - Fatigue
  - PR in 3/12
  - Stable 9/12
Phase II Trial of Palbociclib

- Multiple advanced solid tumours
- Activity seen in heavily preterated breast cancer patients
- ↑ ABC cohort to 37 (31 HR+)
Phase II Trial of Palbociclib

- Palbociclib 125 mg day 1-21/4 weeks
  - Well tolerated
  - Partial response rate 7% (3/37)
  - PFS = 3.8 mos
  - Grade 3-4 toxicity
    - ↓ WBC
    - ↓ Platelets
    - One febrile neutropenia
  - Dose modification for hematologic toxicity in 43% (16/37)
International Phase II Clinical Trial
ER+ HER2- ABC
Letrozole +/- Palbociclib

- Palbociclib 125 mg po day 1-21/28

- Unacceptable toxicity or disease progression
International Phase II Clinical Trial
ER+ HER2- ABC
Letrozole +/- Palbociclib

- Cohort 1: 66 patients; ER+ HER2-
- Cohort 2: 99 restricted to patients with gene amplification of cyclin D1 or loss of P16

- ↑ PFS for both
- Analyses combined
Best Overall Response in Intent-to-Treat Population

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib plus Letrozole (n=84)</th>
<th>Letrozole (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (%)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Partial Response (%)</td>
<td>42</td>
<td>32</td>
</tr>
<tr>
<td>Objective Response (%)</td>
<td>43</td>
<td>33</td>
</tr>
<tr>
<td>Clinical Benefit (%) (CR+PR+SD ≥ 24 weeks)</td>
<td>81</td>
<td>58</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; PR, partial response; SD, stable disease
Progression Free Survival in the Intent-to-Treat Population

Both cohorts

Progression-free survival (%)

HR 0.488 (95% CI 0.319–0.748; one-sided p=0.0004)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib plus letrozole</th>
<th>Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>0</td>
<td>84</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>48</td>
</tr>
<tr>
<td>8</td>
<td>60</td>
<td>36</td>
</tr>
<tr>
<td>12</td>
<td>47</td>
<td>28</td>
</tr>
<tr>
<td>16</td>
<td>36</td>
<td>19</td>
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<tr>
<td>20</td>
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<td>14</td>
</tr>
<tr>
<td>24</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td>28</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>32</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>36</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>40</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>
Overall Survival in the Intent-to-Treat Population

HR 0.813 (95% CI 0.492–1.345; two-sided p=0.42)

Number at risk
Palbociclib plus letrozole 84 80 78 73 68 65 47 35 22 17 7 2
Letrozole 81 76 74 67 64 59 37 23 14 12 5 1
### Sub-Group for Progression-Free Survival

ECOG, Eastern Cooperative Oncology Group.

*Two-sided p value*
# Overall and Selected Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Any Grade</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Palbociclib plus Letrozole (n=83)</td>
<td>Letrozole (n=77)</td>
</tr>
<tr>
<td>Overall AE (%)</td>
<td>98.7</td>
<td>84.4</td>
</tr>
<tr>
<td>Neutropenia (%)</td>
<td>74.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Leucopenia (%)</td>
<td>43.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Fatigue (%)</td>
<td>41.0</td>
<td>23.4</td>
</tr>
<tr>
<td>Anthralgia (%)</td>
<td>22.9</td>
<td>15.6</td>
</tr>
<tr>
<td>Backpain (%)</td>
<td>14.5</td>
<td>15.6</td>
</tr>
<tr>
<td>Pulmonary Embolism (%)</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
Potential place in therapy of palbociclib and letrozole in the treatment of postmenopausal women with HR+/HER2- ABC
Randomized trials of palbociclib in the treatment of HR+, HER2- breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT Number/ Expected Accrual</th>
<th>Treatment arms</th>
<th>Primary endpoint(s)</th>
<th>Secondary endpoints</th>
<th>Primary completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line ABC</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALOMA-2 Phase III</td>
<td>NCT01740427 n=650</td>
<td>palbociclib + letrozole versus placebo + letrozole</td>
<td>PFS</td>
<td>OS, OR, DR, DC, biomarker analysis</td>
<td>Oct 2015</td>
</tr>
<tr>
<td>PALOMA-4 Phase III</td>
<td>NCT02297438 n=330</td>
<td>palbociclib + letrozole versus placebo + letrozole</td>
<td>PFS</td>
<td>OS, OR, DR, biomarker analysis</td>
<td>Jul 2017</td>
</tr>
<tr>
<td><strong>First-line ABC or later</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PALOMA-3 Phase III</td>
<td>NCT01942135 n=417</td>
<td>palbociclib + fulvestrant versus placebo + fulvestrant</td>
<td>PFS</td>
<td>OS, OR, DR, CBR, biomarker analysis</td>
<td>Jul 2015</td>
</tr>
<tr>
<td>PEARL Phase III</td>
<td>NCT02028507 n=348</td>
<td>palbociclib + exemestane versus capecitabine</td>
<td>PFS</td>
<td>ORR, CBR, RD, OS, safety</td>
<td>Jan 2018</td>
</tr>
<tr>
<td><strong>Second line ABC or later</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TREnd Rd phase II</td>
<td>NA n= 30</td>
<td>palbociclib + ET versus palbociclib</td>
<td>CB</td>
<td>ORR, DR, TTP, PFS, OS, biomarker analysis</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PENEOLOPE-B Phase III</td>
<td>NCT01864746 n=800</td>
<td>palbociclib + ET versus placebo + ET</td>
<td>iDFS</td>
<td>iDFS, DDFS, OS, safety</td>
<td>Dec 2019</td>
</tr>
</tbody>
</table>
Randomized trials of palbociclib in the treatment of HR+, HER2- breast cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Treatment</th>
<th>Endpoints</th>
<th>Treatment</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PALLET</strong>&lt;br&gt;Rd phase II&lt;br&gt;Palbo + Let (seq) vs Let</td>
<td>NCT0229680 1 n=306</td>
<td>Palbociclib + letrozole versus letrozole then palbociclib + letrozole versus palbociclib then palbociclib + letrozole vs letrozole</td>
<td>Ki67, cCR</td>
<td>pCR, PEPI, safety, biomarker analysis</td>
<td>Jul 2017</td>
<td></td>
</tr>
<tr>
<td><strong>Rd phase II</strong>&lt;br&gt;Palbo vs. no treat</td>
<td>NCT0200873 4 n=105&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Palbociclib versus no treatment</td>
<td>APR</td>
<td>DLT, Ki67 level</td>
<td>Nov 2014</td>
<td></td>
</tr>
<tr>
<td><strong>Phase II</strong>&lt;br&gt;Palbo</td>
<td>NCT0170937 0 n=45</td>
<td>Palbociclib + letrozole</td>
<td>ORR</td>
<td>safety</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Phase II</strong>&lt;br&gt;Palbo + Anas or Gos</td>
<td>NCT0172377 4 n=29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Palbociclib + anastrozole or goserelin&lt;sup&gt;f&lt;/sup&gt;</td>
<td>CCCA</td>
<td>PEPI, CR and RR, Ki67 level</td>
<td>Jul 2015</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: APR, anti-proliferative response; CB, clinical benefit defined as complete response, partial response, stable disease ≥ 24 weeks; CBR, clinical benefit rate; CCCA, complete cell cycle arrest (Ki67 < 2.7%); cCR, clinical complete response; CR, complete response; DC, disease control; DDFS, distant disease free survival defined as the time period between randomization and diagnosis of first distant breast cancer recurrences; DLT, dose-limiting toxicities; DR, duration of response; EAP, expanded access program; ET, endocrine therapy ER+, estrogen receptor-positive; Gos, goserelin; HER2-, human epidermal growth factor receptor 2-negative; HR+, ER+ and/or PR+; iDFS, invasive disease-free survival; Ki67, nuclear protein associated with cellular proliferation; Let, letrozole; NA, not applicable; NR, not reported; NSAI, non-steroidal aromatase inhibitor; OR, objective response; ORR, objective response rate; OS, overall survival; Palbo, palbociclib; pCR, pathological complete response; PEPI, Preoperative Endocrine Prognostic Index score; PFS, progression-free survival; PR, progesterone receptor; Rd, randomized; RD, residual disease; RR, radiological response; TDR, treatment discontinuation rate; TTP, time to progression.
Current Regulatory Status of Palbociclib

- Palbociclib approved in US for use first line with letrozole
- Not available in Canada as yet
Mrs. K.M.

DOB: June 7, 1955

Late 2009

- Noted breast lump in right breast
- 2 cm lump

Dec/2010

- Ultrasound and guided biopsy
  - Invasive ductal carcinoma
- Coned views
  - Spiculated nodule at 3 o’clock
Patient Case K.M.

Mrs. K.M.

Mar/2011

- Extensive right partial breast resection
  - Right sentinel node biopsy

- IDC
  - 1.6 cm
  - Grade III
  - LVI positive
  - Deep margins involved
  - ER 90%
  - PgR 10%
  - HER2 negative
  - ½ nodes : ITC
Patient Case K.M.

Mrs. K.M.

Apr/2011
- Seen by KP

May/2011
- Oncotype DX score of 18
- dd ACT

Sept/2011
- Whole breast rads
  - 4256 rads/16 fx
  - Breast to tumour cavity 1600/8 fx
Patient Case K.M.

Mrs. K.M.

17/Nov/2011
- Tamoxifen
- Entered MA.32

Jan/2012
- Off MA.32 medication

Oct/2012
- Breast MRI showed:
  - Left breast mass 0.7 cm LOQ
  - Sternal lesions/liver/bone
Patient Case K.M.

Mrs. K.M.

Oct/2012
- Extensive liver metastasis

24/Oct/2012
- Pamidronate
- MD Anderson-2\textsuperscript{nd} opinion

16/Nov/2012
- Liver biopsy
  - ER 98%
  - PgR 5%
  - HER2 FISH negative
Patient Case K.M.

Mrs. K.M.

2,23/Nov/2012; 14/Dec/2012; 4/Jan/2013
- Docetaxel q 3 weeks

20/Dec/2012
- Restaging scans
  - Stable

13/Jan/2013-19/Feb/2013
- Prolonged admission for PICC line infection leading to sepsis
- Mechanical ventilation + vasopressors in ICU

6/Feb/2013
- Liver CT improved
Patient Case K.M.

Mrs. K.M.

8/Mar/2013
- Docetaxel
  - 60% dose

Aug/2014
- ↑ LFTs

8/Sep/2014
- ↑ liver metastasis
  - CT scan
  - ↑ LFTs
  - ↑ ascites
Mrs. K.M.

8/Sep/2014
● Started on exemestane and everolimus

22/Sep/2014
● ↑ bloating
● Tolerating drugs fine

30/Oct/2014
● LFTs improved
● Less bloating
● Liver scan
Patient Case K.M.

Mrs. K.M.

30/Oct/2014

- Ground glass opacity in lung
- Slight shortness of breath and cough
  - Still jogs!

- Liver CT
  - ↓ ascites
  - ? ↑ lesion in liver

- Pruritis
Patient Case K.M.

Mrs. K.M.

December 23, 2014
- CT scan abdomen
  - Shrinkage in all liver lesions
- CT scan chest
  - Still ground glass opacity
- Pruritus

January 2015
- Continues on exemestane and everolimus
Patient Case J.C

Mrs. J.C.
DOB: October 7, 1957
Financial advisor, married, no children

1999
- Lumpectomy + AND
- 4 cm, Grade III, ER positive, PgR negative, HER2 negative, 2/11+ve nodes

- CEFx6
- Amenorrheic

15/Mar/2000-26/Apr/2000
- 5000 rad/25 fx + 6 fx boost
Patient Case J.C.

Mid-May/2000
- Tamoxifen

Jul/2002
- Adopts child

Jun/2005
- Letrozole
- Vitamin D, calcium, bisphosphonate

Feb/2012
- DCed letrozole

March-May/2012
- Increased low back pain, not well controlled
Patient Case J.C.

25/Jun/2012
- Bone scan
- Increased uptakes in skull, spine, sacrum, pelvis, ribs, etc.

Jul/2012
- CT chest – OK
- CT abdomen – liver mets? – small?
- Rads to pelvis
- Fulvestrant
- Pamidronate

Sep/2012
- Progression at L1 – rads there
Nov/2012
● Orbit metastasis
● Rads to orbit

18/Dec/2012
● New liver mets
● Taxotere

26/Dec/2012-1/Jan/2012
● Febrile neutropenia

Mar/2013
● Response

May/2013
● Response
Patient Case J.C.

11/Jun/2013
- Exemestane + Everolimus
- ↑ lipid – Pravastatin 5 mg

Dec/2013
- Further ↓ liver mets

3/Jan/2014
- Orbital cellulitis – bacterial
- Hospitalized
- Antibiotics

Feb/2014
- Everolimus + exemestane
Patient Case J.C.

Mar/2014
- Further↓ liver mets
- Pravastatin 10 mg

Jun/2014
- ? ↑ liver mets

Jun/2014
- ↑ liver mets
- Capecitabine

Dec/2014
- Disease progression on capecitabine

Jan/2015
- Switched to vinorelbine
THANK YOU!