Clinical significance of overall survival and progression-free survival in advanced hormone receptor positive breast cancer

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Advanced hormone receptor positive breast cancer
• Hormone receptor (ER and/or PR) positive breast cancer is the most prevalent subtype in both early and advanced stage breast cancer.
• Though improvements in survival of metastatic breast cancer (MBC) have been demonstrated over time, and are likely related to the use of newer systemic agents, the gains have been relatively modest.¹
• More recently it has been the HER-2 positive subtype that has made further significant improvements in overall survival based on clinical trials of pertuzumab and TDM1 as first- and predominantly second-line therapy respectively in HER2+ MBC.²,³

Mechanisms of endocrine resistance
• Proposed mechanisms of endocrine resistance include activation of cross-talk pathways (e.g., EGFR, HER-2, IGFR, Src) and/or activation of downstream pathways (PI3K-Akt-mTOR; MAPK-MEK; and cell cycle activation).⁴
• The most frequently altered genomic aberration in ER+ (luminal) breast cancers are mutations in the phosphatidylinositol 3-kinase (PIK3CA) gene, with an observed frequency of 45% in luminal A breast cancers and 29% in luminal B breast cancers.⁵
• Preclinical studies have also demonstrated an interaction between the mTOR pathway and ER signalling, resulting in ligand-independent receptor activation.⁶

BOLERO-2: Primary endpoint—Progression-free survival
• BOLERO-2 is a large, randomized, phase III trial comparing exemestane + placebo to exemestane plus everolimus (an mTOR inhibitor) in 724 post-menopausal women with hormone receptor positive advanced breast cancer previously treated with a non-steroidal aromatase inhibitor (NSAI).⁷
• Stratification was based on ‘sensitivity’ to prior hormonal therapy (84% of the population) and presence of visceral disease (56% of the population).
• The minority of patients (16%-21% per arm) had received the NSAI in the adjuvant setting.
• The primary efficacy endpoint of BOLERO-2 was progression-free survival (PFS) by local assessment.
• With a median follow-up of 18 months (final analysis for PFS), there was a clear statistical and clinically significant improvement in PFS in favour of everolimus and exemestane (7.8 months) versus placebo and exemestane (3.2 months) with a hazard ratio of 0.45 (95% CI: 0.38–0.54) p<0.0001.
• The control arm in BOLERO-2 replicated the efficacy of the exemestane arms in the EFECT⁷ and SoFEA⁸ studies in terms of PFS, demonstrating consistency in the limited efficacy of exemestane alone following prior NSAI exposure (Table 1).
• There was a greater rate of serious adverse events (as defined in the protocol) in the everolimus and exemestane arm (23%) compared to the placebo and exemestane arm (12%).
• Despite the greater rate of grade 3 and 4 toxicities, the time to definitive

Table 1: Primary and secondary efficacy endpoints of hormonal clinical trials in ER+ MBC following prior exposure to NSAI. * Meta-analysis of EFECT and SoFEA efficacy data. E: exemestane

<table>
<thead>
<tr>
<th>Trial</th>
<th>Median PFS</th>
<th>p value</th>
<th>Median OS</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>EFECT⁷</td>
<td></td>
<td></td>
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<tr>
<td>exemestane (E)</td>
<td>3.7 months</td>
<td>p=0.653</td>
<td>22.6 months¹²*</td>
<td>p=0.72</td>
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<tr>
<td>fulvestrant</td>
<td>3.7 months</td>
<td></td>
<td>21.9 months</td>
<td></td>
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<tr>
<td>SoFEA⁸</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>exemestane (E)</td>
<td>3.4 months</td>
<td>p=0.56</td>
<td>22.6 months¹²*</td>
<td>p=0.72</td>
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<tr>
<td>fulvestrant</td>
<td>4.8 months</td>
<td></td>
<td>21.9 months</td>
<td></td>
</tr>
<tr>
<td>BOLERO-2⁹</td>
<td></td>
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<tr>
<td>placebo + E</td>
<td>3.2 months</td>
<td>p&lt;0.0001</td>
<td>26.55 months¹⁰</td>
<td>p=0.14</td>
</tr>
<tr>
<td>everolimus + E</td>
<td>7.8 months</td>
<td></td>
<td>30.98 months</td>
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deterioration of QOL (as measured by the EORTC QLQ C30 GHS) was longer in the everolimus + exemestane arm versus the placebo + exemestane arm (8.3 months versus 5.8 months, p=0.0084).9

BOLERO-2: Secondary endpoint—Overall survival

- Overall survival (OS) was a predefined secondary efficacy endpoint of the BOLERO-2 study.
- The protocol assumptions were that the expected median OS in the placebo + exemestane arm was 24 months. The addition of everolimus to exemestane was calculated to improve the OS to 32.4 months (an eight-month absolute improvement in OS)—which corresponds to a HR of 0.74.
- With a median follow-up of 39 months now, the final OS analysis was recently presented at the EBCC-9 meeting.10
- The overall survival difference in BOLERO-2 was not statistically significant. The median OS in the everolimus + exemestane arm was 30.98 months compared to 26.55 months in the placebo + exemestane arm [HR 0.89; 95% CI 0.73–1.10; p=0.14] (Table 1).
- This numerical difference in median OS between the two arms of 4.4 months is potentially in keeping with a maintenance of benefit seen in the median PFS difference gained with everolimus and exemestane over placebo and exemestane.
- There was demonstration of a longer median time from randomization to either first chemotherapy or death in the everolimus and exemestane arm (11.86 months; 95% CI 10.45–13.08) versus placebo and exemestane (5.98 months; 95% CI 5.09–7.39).
- No new safety signals were seen with longer follow-up on the study. The rate of reported grade 3/4 adverse events was 55% in the everolimus arm and 29% in the placebo arm.

Conclusions

- The improvement in PFS for the combination of everolimus and exemestane (median PFS of 7.8 months; hazard ratio of 0.45 [95% CI: 0.38–0.54] p<0.0001), as demonstrated in BOLERO-2, is both clinically and statistically significant.
- This has led to the combination of everolimus and exemestane as a standard of care option in Canada in ER+ post-menopausal MBC with prior exposure to NSAIs.
- Though a statistical difference in OS was not demonstrated in the final efficacy analysis of BOLERO-2, as this was a secondary endpoint, perhaps it was not only underpowered to detect a statistical difference, but also somewhat unrealistic to expect the magnitude of difference powered for in the statistical plan of BOLERO-2.
- Accounting for and addressing post-progression survival is important in attempting to correlate PFS and OS.11
- In clinical trials that have demonstrated a PFS benefit, lack of a statistical significance in OS may not simply imply lack of improvement in OS, especially when there are associated long median post-progression survivals.11
- While the ability to demonstrate improvements in overall survival in large phase III clinical trials in MBC have been challenging and limited, it should remain a gold standard goal.
- However, attention to powering the studies appropriately and adequately for OS as a primary endpoint (or co-endpoint) is pivotal.
- Quality maintained improvements in PFS of significant clinical magnitudes are an important clinical efficacy endpoint if we hope to continue to improve the quality and quantity of life for women battling MBC.

REFERENCES