Therapeutic and economic value of everolimus plus exemestane for the treatment of postmenopausal women with hormone receptor positive, HER2/neu negative advanced breast cancer

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BACKGROUND AND OBJECTIVES
Up to 70% of women with hormone-sensitive advanced breast cancer (ABC) need further therapy lines following first-line hormonal therapy. Although treatment guidelines provide useful recommendations for treating patients with ABC they rarely compare different treatment options or provide guidance on how to optimize their value.

This research aimed to assess the therapeutic and economic value of everolimus 10mg plus exemestane 25mg daily (everolimus+exemestane) in comparison to fulvestrant (500mg intramuscularly on days 0, 14 and 28, and every 28 days thereafter) for the treatment of hormone receptor-positive, HER2/neu negative ABC postmenopausal women who failed first-line hormonal therapy.

METHODS
We used a discrete-time, state-transition model to estimate the expected lifetime health outcomes and costs of everolimus+exemestane and fulvestrant for ABC patients failing first-line hormonal therapy.

Cost-effectiveness of everolimus+exemestane as compared to fulvestrant was assessed in terms of the incremental cost per life year (LY) gained, from a Portuguese National Health Service (NHS) perspective. Next to main therapeutic drug costs, other healthcare costs included costs for medical visits, complementary diagnostic procedures, surgery, inpatient visits, additional therapy and end-of-life care. An annual 5% discount rate was applied to both costs and effectiveness.

Disease progression after initiation of treatment with everolimus+exemestane and fulvestrant was modelled using three mutually exclusive health states: alive without progression, alive with progression and dead.

The time-evolving percentage of everolimus+exemestane treated patients in either of the three health-states was determined using overall survival (OS) and progression-free survival (PFS) based partitioned survival analysis of BOLERO-2 individual patient level data [1,2].

Corresponding percentages for fulvestrant treated patients were obtained using hazard ratios (HR) for OS and PFS comparing everolimus+exemestane to fulvestrant, estimated using a mixed treatment comparison (MTC) [3]:

- A systematic review identified all relevant RCTs on hormonal and chemotherapeutic agents used as second line treatment in postmenopausal women with hormone-sensitive ABC.
- A Bayesian Generalized Linear Model framework for MTC was adopted to pool the evidence from the selected RCT and estimate the relative treatment effects (HRs) between all considered treatments in terms of OS and PFS.

RESULTS
Mixed Treatment Comparison – Of 235 references identified, 25 studies met the inclusion criteria defined and 19 entered the quantitative analysis (Figure 1) [3]. The treatment options reviewed were: aminoglutethimide (AGT), anastrozole (ANA), everolimus (EVE), exemestane (EXE), forsteranate (FOR), fulvestrant (FUL), letrozole (LET), megestrol acetate (MGA), premarin (PRE) and vorozole (VOR).

Overall, MTC results suggest superiority of everolimus+exemestane in terms of efficacy over other endocrine therapeutic options for the treatment of postmenopausal women with hormone-sensitive ABC after failing a previous line of treatment [3].

Specifically, in comparison to fulvestrant, everolimus+exemestane is estimated to significantly delay progression or death (HR PFS = 0.53; 95% CI: [0.37; 0.76]) and to increase life expectancy (HR OS = 0.82; 95% CI: [0.50; 1.36]) [3].

Cost-Effectiveness – Everolimus+exemestane is estimated to increase life expectancy by 6.8 months in comparison to fulvestrant (Figure 2), resulting in a 0.45 discounted life year gain.

Figure 2. Estimated parametric survival curves for OS and PFS in everolimus+exemestane and fulvestrant treated ABC patients, based on BOLERO-2 individual patient level data for everolimus+exemestane (---) and fulvestrant (---) [3].

Corresponding lifetime discounted incremental health care costs amount to 16,544€/patient starting treatment with everolimus+exemestane over fulvestrant. Of those, roughly 97% relate do drug therapy costs (16,107€) with the remaining 437€ attributable mainly to patients being alive for longer periods and consuming more health care resources.

This results in an incremental cost-effectiveness ratio (ICER) of 36,703€/LY gained with everolimus+exemestane. Probabilistic sensitivity analysis showed a greater than 60% probability of everolimus+exemestane being cost-effective against fulvestrant, at a willingness to pay of 50,000€/LY.

Table 2. Cost-effectiveness results of everolimus+exemestane in comparison to fulvestrant.

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<tr>
<th>Discounted Costs</th>
<th>EVE</th>
<th>EXE</th>
<th>FUL</th>
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<tr>
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CONCLUSION
We evidence how valuable information from clinical trials can be pooled and used to inform about the therapeutic and economic value of guideline recommended therapies for advanced breast cancer.


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