Research Highlight

A balancing act for breast cancer? Everolimus for hormone receptor positive patients

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Recent results from a Phase III randomized trial comparing everolimus [a mammalian target of rapamycin (mTOR) inhibitor] plus exemestane versus placebo plus exemestane provide encouraging evidence of a new option for treatment of advanced, hormone receptor positive (HR+) breast cancer (1). Oral endocrine therapy (ET) is the first line therapeutic strategy of choice for most women with metastatic HR+, Her2 negative breast cancer (2). ET options include aromatase inhibitors (AI) such as exemestane, letrozole, and anastrozole, and selective estrogen receptor modifiers such as tamoxifen and fulvestrant. However, some tumors do not respond to ET, and many others become refractory to ET over time. Activation of the mTOR pathway has been associated with ET resistance in preclinical studies, leading investigators to explore mTOR inhibition as a treatment strategy in endocrine-refractory HR+ breast cancer (3-7). In this quickly changing therapeutic environment, understanding the comparative effectiveness of single and combination targeted therapies for breast cancer is essential (8).

The BOLERO-2 study, a multisite, international trial conducted by Baselga *et al.*, recruited breast cancer patients who were postmenopausal, with advanced, estrogen receptor-positive (ER+) and HER2-negative disease that was refractory to endocrine therapy (1). ET refractory disease was defined as recurrence during adjuvant therapy or within 12 months of completion of adjuvant therapy or progression during or within 1 month of treatment for advanced disease with a non-steroidal aromatase inhibitor. Early progression-free survival data strongly suggest an advantage for combination therapy-6.9 months for everolimus/exemestane compared to 2.8 months for placebo/exemestane, producing a hazard ratio for progression or death of 0.43 (95% Confidence Interval, 0.35-0.54; P<0.001) (1). This finding is remarkable given the limited therapeutic options available to women with advanced, HR+ disease whose tumors have become refractory to ET. However, substantial side effects and differential discontinuation of therapy were observed in the everolimus/exemestane arm, leading to some concerns about safety and tolerability of this combined therapeutic regimen. The authors' findings are consistent with other trials combining everolimus with ET for breast cancer, and preclinical data suggesting that everolimus and letrozole work synergistically to inhibit angiogenesis and tumor cell growth, while minimizing the potential for ET non-response (3,4,6,9). Because BOLERO-2 data are not yet fully mature, it remains to be seen whether combination therapy improves overall survival.

Patients in the BOLERO-2 trial were quite sick, admittedly by design; at recruitment, 56% had visceral disease, and over half had been previously exposed to at least three lines of therapy (1). Serious adverse events were recorded in 23% of patients in the everolimus/exemestane arm (11% attributed to therapy), compared to 12% in the exemestane/placebo arm (of which 1% were attributed to therapy), leading to higher discontinuation rates in the everolimus/exemestane arm. Disproportionately high rates of stomatitis, anemia, dyspnea, hyperglycemia, fatigue, and pneumonitis were observed in the everolimus/

exemestane arm, consistent with other studies (6). Unfortunately, the authors did not report statistical tests for significant differences in adverse events between the study arms, but they did acknowledge that adverse events were substantially higher in the combination therapy arm and that the majority of patients who discontinued everolimus did so because of lack of tolerability. Perhaps more concerning, seven deaths in the everolimus/exemestane arm were directly attributable to study-related adverse events and included deaths from sepsis, tumor hemorrhage, cerebrovascular incident, renal failure, suicide, and pneumonia. The authors concluded that "careful monitoring of patients and increase physician awareness of the safety profile of everolimus are warranted" (1). But the question remains: Given the tolerability concerns, does everolimus in combination with exemestane offer greater benefit (or reduced harms) compared to other available targeted therapies for ET refractory patients, such as traditional cytotoxic chemotherapy?

To answer these questions, a decision analytic model may be useful. In a decision model, by explicitly taking account of the comparative risk of harms and the corresponding utility of those harms (whether they result in morbidity or mortality), researchers can quantify and compare potential harms against potential benefits. Moreover, costs can be built into the equation - not just costs of everolimus (which are substantial) and AIs or other anti-estrogen therapies, but also costs of managing adverse events, costs of subsequent hospitalizations and emergency department visits, and costs of follow-up care. In light of the recent controversy surrounding novel therapies such as bevacizumab which may confer modest progression free survival benefits in combination with standard breast cancer therapies at significantly increased cost, such analyses are likely to become increasingly relevant in clinical practice. Although the BOLERO-2 trial suggests that progression-free survival may be improved with the addition of everolimus to exemestane *in a clinical trial setting*, it is well recognized that clinical trial populations are different from real-world populations in that clinical trial populations tend to be younger, healthier, wealthier, more educated and more health literate. In the real-world setting, patients may prefer to forego the significant risk of serious side effects in order to maintain quality of life, particularly when combination therapy may gain them a few additional months of less than ideal health (in the event that an adverse event occurs, which is likely in approximately 1 in 4 patients) but ultimately, is unlikely to save their lives. The early BOLERO-2 data indicate no difference in "time to deterioration of quality of life" as measured by European Organization for Research and Treatment of Cancer quality of life questionnaires (1). The authors are to be commended for including quality of life measures in their assessment of outcomes. However, providing access to the absolute quality of life data and collecting additional validated quality of life measures would make a more convincing case that there is no decrement in quality of life associated with the combination of everolimus/exemestane. Given the high incidence of adverse events in the combined therapy arm, it is possible that with longer follow-up quality of life between the two arms would diverge. Tolerability and quality of life associated with new cancer therapeutic regimens are essential components of informed decision making around cancer treatment. Survival benefits are only part of the complex equation that patients and physicians must implicitly consider in making decisions about cancer treatment. Building and parameterizing a comprehensive decision analytic model based on the BOLERO-2 trials results and other data will help patients and their physicians better understand the balance among all potential costs, harms, and benefits associated with this exciting and innovative mTOR therapy.

In addition to using decision models to understand the multiple dimensions of clinical and financial harms and benefits of everolimus, it will be important to better understand predictors of ET resistance in general and potential population heterogeneity in mTOR inhibitor effectiveness. In the adjuvant setting, evidence has indicated that as many as 50% of women who initiate ET discontinue the regimen prematurely (before 5 years) or do not take therapy as clinically prescribed, the reasons for which are unclear (10-14). Non-adherence, in theory, may diminish the active properties of AIs and anti-estrogen therapies. The extent of ET non-adherence in the metastatic setting and the contribution of non-adherence to real-world effectiveness of ET remain unexplored at this point. We also do not yet know whether and how population heterogeneity modulates the effectiveness of mTOR inhibitors. Clearly this complicated pathway has become increasingly identified as a significant player in oncogenic processes (5,7,15). However, there are no biomarkers clinically available to predict which patients will respond to mTOR inhibitors (7). At the same time, there appears to be some evidence that upstream mutations may decrease the effectiveness of mTOR

inhibitors (16,17). Given the potential therapeutic value of mTOR inhibitors but also non-trivial side-effects, it would be of great importance to identify biomarkers associated with heterogeneity in treatment response.

In conclusion, the BOLERO-2 preliminary data provide an exemplary picture of translational research at its best. In a very short period of time, everolimus as an active agent for the treatment of HR+ breast cancer has been catapulted from in vitro studies to human trials. The BOLERO-2 study also represents an exciting example of the potential benefit of combination therapy targeted to overcome specific resistance pathways in HR+ breast cancer. However, given the proliferation of therapies demonstrating progression free survival benefits in this disease setting, and the implausibility of testing each new therapeutic combination versus all its clinically reasonable comparators in randomized controlled trials, we must continue to develop not only novel therapies, but correspondingly more sophisticated methods for evaluating real world effectiveness and weighing risks and benefits for individual patients.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2012.03.02). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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