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EDITORIAL

Reversing Hormone Resistance: Have We Found the Golden Key?

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Hormone receptors are present in the majority of both early- and late-stage breast cancers, with expression found in approximately 65% to 70% of metastatic tumors. Despite the availability of a number of effective hormone therapies, resistance develops in a subset of early-stage tumors and in almost all tumors in the advanced setting. In addition, a subset of hormone receptor–positive tumors are primarily resistant to hormone therapies. The search for mechanisms to reverse resistance has focused on inhibiting pathways that are known to be upregulated in the setting of progressive disease.[1-3] Improvements in response and progression-free survival (PFS) that were seen with the addition of human epidermal growth factor receptor 2 (HER2)–targeted therapy to first-line aromatase inhibitors in patients with HER2-positive, hormone receptor–positive metastatic breast cancer represented the first clear indication that targeting growth factor receptor pathways could be an effective approach to reversing resistance,[4,5] and added additional validity to preclinical models that predicted this effect.[3] However, only approximately 8% to 10% of breast cancers are both HER2- and hormone receptor–positive, so the search for other approaches remains a critical research and clinical question.

Phosphatidyl inositol 3-kinase (PI3K) is the most frequently altered pathway in breast cancer, with both mutations and amplifications of the encoding genes.[6] This pathway mediates a number of critical cellular processes including cell growth, proliferation, and survival. Mammalian target of rapamycin (mTOR) is a signal transduction kinase in the PI3K pathway that exists in two multiprotein complexes, mTOR complexes 1 and 2 (mTORC1 and mTORC2; Fig 1). mTORC1 consists of mTOR that is associated with raptor (regulatory-associated protein of mTOR) and is downstream of AKT. In contrast, mTORC2 is associated with rictor (rapamycin-insensitive companion of mTOR) and phosphorylates AKT. Activation of PI3K phosphorylates AKT, which in turn phosphorylates mTORC1, which then phosphorylates its effectors, including eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and S6 kinase 1 (S6K1). 4E-BP1 plays an important role in enhancing cell proliferation, survival, and angiogenesis, and S6K1 is a key regulator of cell growth that phosphorylates ribosomal protein S6 as well as other important targets.

Activation of the PI3K pathway has been associated with resistance to hormone therapy in preclinical studies, and S6K1 directly phosphorylates the activation domain of estrogen receptors.[7-9] A variety of studies have shown an interaction between inhibition of mTOR and restoration of hormone sensitivity, particularly when inhibitors are given in combination with hormone agents.[10-12] These data, along with availability of mTOR inhibitors in the clinic, increased interest in the potential of MTOR inhibition to improve response to hormonal therapies. On the basis of encouraging results from a phase II trial, 1,112 patients with hormone therapy–naïve, metastatic breast cancer were randomly assigned to letrozole or letrozole combined with the mTOR inhibitor temsirolimus.[13] The study was closed for futility by the data monitoring committee when it became clear that the experimental arm was highly unlikely to demonstrate improvement in PFS, the primary end point, and subsequent

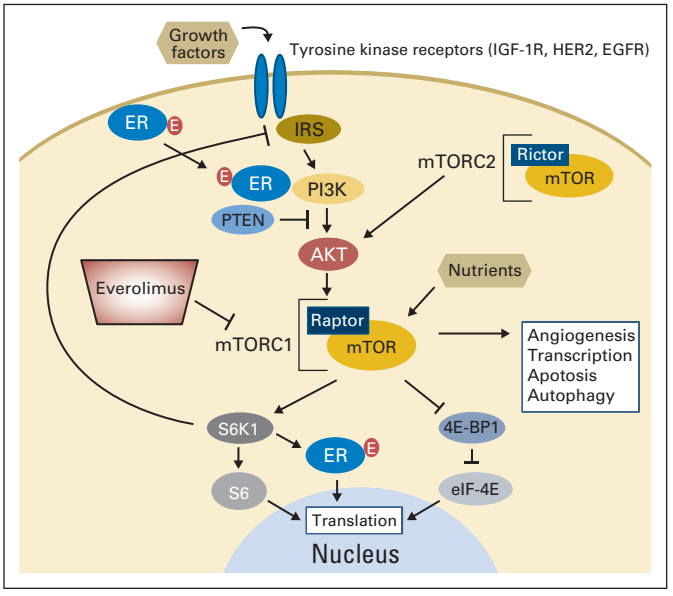

Fig 1. Schematic of the phosphatidyl inositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway. Reciprocal cross-talk exists between the estrogen receptor (ER) and growth factor receptor (GFR) signaling pathways. ER can induce transcription of genes important to GFR pathways, and PI3K can phosphorylate ER to modulate this transcriptional activity. 4E-BP1, 4E-binding protein-1; E, estrogen; EGFR, epidermal growth factor receptor; eIF-4E, eukaryotic initiation factor-4E; FKBP-12, FK506-binding protein-12; HER2, human epidermal growth factor receptor 2; IGF-1R, insulin-like growth factor-1 receptor; IRS, insulin receptor substrate; mTORC1, mTOR complex 1; mTORC2, mTOR complex 2; PTEN, phosphatase and tensin homolog deleted on chromosome 10; S6, 40S ribosomal protein; S6K1, S6 kinase 1.

analysis showed no difference in response. Grade 3 toxicity was increased in the experimental arm. An unplanned subset analysis suggested benefit in the 50% of patients with exposure to previous chemotherapy, and a planned analysis suggested benefit in younger patients who are more likely to have highly proliferative and hormone-resistant disease. Toxicity was modest, with less than 3% of patients reporting grade 3 to 4 mucositis. Potential reasons for these disappointing results include an inadequate dose or schedule (temsirolimus was dosed at 30 mg a day for 5 days in a row every 14 days, and toxicity was unexpectedly low) or possible dilution of benefit in the 55% of patients without previous exposure to adjuvant hormone therapy and presumably reduced activation of resistance pathways.

Everolimus is a rapamycin analog that inhibits mTORC1 kinase through high affinity binding to FK506-binding protein-12. In addition, preclinical data suggest that prolonged exposure to rapamycin may result in inhibition of mTORC2.[14,15] In a previous neoadjuvant trial, the combination of letrozole and everolimus improved clinical response and reduced tumor cell proliferation as measured by Ki67 compared with letrozole alone.[16] Mutational analyses documented PI3K mutations in 35% of patients, with a suggestion of improved reduction in Ki67 in those with mutations in exon 9. The phase III Breast Cancer Trial of Oral Everolimus 2 (BOLERO-2) randomly assigned 724 women with hormone receptor–positive metastatic breast cancer who previously progressed on nonsteroidal aromatase inhibitors to receive exemestane and a placebo or everolimus.[17] Patients who received everolimus had a significantly longer PFS (median, 6.9 months *v* 2.8 months by investigator assessment; $P < .001$), as well as an improved overall response rate. As expected, the addition of everolimus increased toxicity and particularly stomatitis (grade 3, 8% *v* 1%). Pneumonitis, although increased, was uncommon (grade 3, 3% *v* 0%). Survival data are still immature, although more deaths were seen in the placebo arm (22.6% *v* 17.3%) in a recent update with a median follow-up of 12.5 months.[18]

In the article that accompanies this editorial, Bachelot et al[19] report the results of the Tamoxifen Plus Everolimus (TAMRAD) trial, a randomized phase II trial that tested the combination of tamoxifen with everolimus compared with tamoxifen alone in patients previously treated with aromatase inhibitors. Although this study included only 111 patients, the results are striking and even more so in the context of the recently published BOLERO-2 data. Both trials hypothesized that restricting enrollment to patients with progression in the setting of previous hormone therapy would enrich for tumors driven by the PI3K/AKT/mTOR pathways, an approach that was apparently successful. Indeed, clinical data suggest that genetic alterations in the PI3K pathway may arise late in tumor development,[20,21] and a gene expression signature of PI3K activation was enriched in luminal B breast cancers, which tend to be less hormone responsive.[22] The primary end point in TAMRAD was clinical benefit rate at 6 months, which was significantly improved in patients treated with tamoxifen and everolimus compared with those who received tamoxifen alone (61% *v* 42%). An exploratory analysis of both time to progression and overall survival demonstrated improved outcome with the addition of everolimus. Interestingly, 84% of patients enrolled onto the BOLERO-2 trial were described as having hormone-sensitive disease, which was defined as disease that had demonstrated evidence of previous response to hormone therapy; however, subset analysis failed to demonstrate any difference in efficacy on the basis of this criteria. This is in contrast to the subset analysis in the TAMRAD trial, which suggested that the primary benefit of adding everolimus was seen in patients with hormone-sensitive disease rather than in those with primary hormone resistance. It is likely that the subsets were too small in TAMRAD to be reliable, or that BOLERO-2 was not informative in primary hormone resistance. Toxicity was similar between the two trials.

How should we use this information in clinical practice? First, it is clear that the addition of targeted agents to standard therapy often, if not always, increases toxicity of therapy as well as cost, and risk should be weighed against expected benefit in an individual patient. If well tolerated, a more than doubling of PFS certainly seems to be worthwhile. Both BOLERO-2 and TAMRAD enrolled patients whose tumors had previously progressed on noncorticosteroidal aromatase inhibitors, and whose tumors had not progressed on the hormone therapy used in each trial—exemestane or tamoxifen, respectively. A recent preclinical study[23] showed that the antitumor effects of PI3K inhibition could be reversed with exogenous estrogen, suggesting that treatment with PI3K pathway–targeted therapy alone in hormone receptor–positive disease might not be effective. Taken together, these data suggest that everolimus should be used in the clinic in combination with a secondary hormone agent in patients with hormone receptor–positive, advanced disease that progresses during or recurs after aromatase inhibitor therapy. Efficacy and toxicity did not seem to be age dependent in BOLERO-2, and TAMRAD is too small to evaluate these subsets. However, patients with significant comorbidities, or rapidly progressive disease that is associated with organ dysfunction, are probably not optimal candidates for this combination therapy. In addition, caution should be used in patients with primary hormone resistance, although there is no convincing evidence as yet to indicate that these patients should be excluded. An understanding of toxicity management, including appropriate dose reductions and delays when needed, will be critical components of safe and effective clinical use.

Future research is focusing on targeting patients with known mutations of the PI3K pathway with novel inhibitors and evaluating rational combinations of targeted biologic agents. Recent data from 217 patients with a variety of solid tumors treated in the phase I setting with PI3K/AKT/mTOR inhibitors showed higher responses in the subset who were found to have PI3K mutations compared with those with wild-type cancers.[24] Inhibition of mTORC1 may reduce negative feedback on growth factor receptors, including the insulin-like growth factor-1 receptor and HER3, which could potentially negate the impact of mTOR inhibition on tumor cells.[25] The mTOR inhibitor ridaforolimus combined with the insulin-like growth factor-1 receptor inhibitor dalotuzumab is being studied in a phase II study on the basis of encouraging phase I data,[26] and the HER3 antibody MM-121 is also being studied in a phase II study in combination with exemestane. A number of other approaches to reverse hormone resistance are currently being evaluated, as well as additional inhibitors of the PI3K pathway. Everolimus is also being tested in HER2-positive disease in two ongoing phase III trials after demonstrated responses in combination with chemotherapy and trastuzumab in trastuzumab-resistant disease.[27]

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