Estrogen-Receptor Degrader GDC-0810 Active in Metastatic Breast Cancer

BY ROBERT H. CARLSON

PHILADELPHIA—A Phase I first-in-human study of the selective estrogen receptor degrader (SERD) GDC-0810 showed it to be safe in treating women with estrogen receptor(ER)-positive locally advanced or metastatic breast cancer, and encouragingly, to have a hint of activity.

The report was presented here at the American Association for Cancer Research Annual Meeting (***Abstract CT231***) by Maura N. Dickler, MD, Associate Member of the Breast Medicine Service at Memorial Sloan Kettering Cancer Center and Weill Medical College of Cornell University.

She reported that at a median follow-up of eight months, two patients had a confirmed partial response, and 42 percent achieved stable disease for at least six months.

Modulation of estrogen activity and/or synthesis is the main therapeutic strategy in the treatment of ER-positive breast cancer, Dickler explained. But 20 to 50 percent of ER-positive patients previously exposed to endocrine therapy develop activating mutations of the ESR1 gene. These mutations affect the ER-alpha ligand-binding domain, and drive ER-dependent transcription and proliferation in the absence of estrogen, leading to resistance to endocrine therapies.

Dicker described GDC-0810 as a prospectively designed drug optimized for ER antagonism and degradation, nonsteroidal and orally bioavailable, which induces tumor regression in tamoxifen-sensitive and resistant ER-positive breast cancer xenograft models. Importantly, the drug is active in both wild-type and mutant ER tumors.

A Phase IIa study of GDC-0810 is now ongoing in postmenopausal women with ER-positive advanced or metastatic breast cancer previously treated with an aromatase inhibitor, including tumors with ESR1 mutations.

Study Details

The Phase I dose-escalation study—which was funded by Seragon, subsequently acquired by Genentech, for which Dickler is a consultant—included 41 postmenopausal women with ER-positive/HER2-negative locally advanced or metastatic breast cancer that had progressed after six or more months of endocrine therapy. The patients' median age was 61 (range of 33 to 78). Patients had no more than two prior chemotherapies for metastatic/advanced stage disease.

A key feature of the study, Dickler noted, was the use of [18F]-fluoroestradiol (FES)-PET scans to assess pharmacodynamic activity.

The ESR1 mutation was positive in nine patients (22%), wild type in 10 patients (24%), and the status was unknown in 22 patients (54%).

As with most Phase I studies, the goals were to build a toxicity profile and determine a dose for a Phase II trial. Patients received one of five total daily dose levels from 100 to 800 mg, and two regimens: once or twice daily, given orally with or without fasting. Increases in GDC-0810 exposure were dose-dependent.

Dickler reported that common treatment-related adverse events were grade 1/2 diarrhea in 63 percent of patients, fatigue in 46 percent, nausea in 44 percent, flatulence in 24 percent, vomiting in 22 percent, and anemia in 22 percent.

"Diarrhea was mostly grade 1 and intermittent in nature, and manageable with dose modifications, dietary adjustments, and treatment with loperamide as needed," Dickler said. She reported one dose-limiting toxicity of grade 3 diarrhea at 800 mg daily (fasting).

The single-agent recommended Phase II dose was determined to be 600 mg daily given with food.

Dickler said complete or near complete (greater than 90 percent) suppression of FES uptake was observed in 90 percent of patients with the FES-PET scans, including five patients with known ESR1 mutations. Evidence of reduced ER levels and Ki67 staining was also observed in on-study biopsies.

"New therapies that have activity against tumors resistant to currently available treatments are urgently needed."

At a median follow-up of eight months, 13 of 31 patients (42%) on study for at least six months achieved stable disease, while 10 patients remained active on study with follow-up of less than six months.

MAURA N. DICKLER, MD: "The Phase I dose-escalation portion of the study enrolled heavily pretreated patients, and the observed antitumor activity is promising for GDC-0810, which is demonstrating clinical benefit in these patients who have developed resistance to other endocrine therapies for ER-positive breast cancer."

"That is encouraging and within the range of other second- and third-line endocrine therapy studies," Dickler said, adding that of particular interest, two patients had a confirmed partial response, both of whom had tumors harboring ESR1 mutations.

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Binding versus Degrading

After Dickler's presentation, a question from the audience was answered by the study's senior author, José Baselga, MD, PhD, Physician-in-Chief at Memorial Sloan Kettering Cancer Center, and now AACR President.

He said that in future studies the researchers will take FES-PET scans at different time points in an attempt to dissect the effect of the drug binding to the estrogen receptor versus the estrogen receptor being degraded. They are also seeking a way to measure how rapidly the ER goes back up when the drug is stopped, which Baselga said would also show the degree of ER degradation.

GDC-0810

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Kent Osborne: 'Potentially Exciting New Endocrine Therapy'

In remarks as the study's Discussant, C. Kent Osborne, MD, Director of the Dan L. Duncan Cancer Center and Professor of Medicine and Molecular and Cellular Biology at Baylor College of Medicine, called GDC-0810 a promising new antiestrogen. The findings are potentially exciting, he said, because the FES-PET scans suggest that the ER target is hit, and responses in stable disease in patients with ER-mutant tumors and prior fulvestrant are also very encouraging.

Osborne also posed a fundamental question, though: Is the estrogen receptor still important in the time of resistance?

"Well, we think it is," he said, describing how he and colleagues have developed 12 different cell lines resistant to tamoxifen or estrogen deprivation: "There is variability from tumor to tumor as there would be from patient to patient, but a knocked-out estrogen receptor is less effective, though still effective, particularly in the tamoxifen-resistant cells."

He said there are also clinical data to suggest that ER still functions after estrogen deprivation, and that ERs are lost in only 20 to 25 percent of tumors that are resistant to adjuvant therapy—"And as most oncologists know from long experience, there are frequent responses to secondary, tertiary, and even quadrenary endocrine therapies when resistance develops to the first agent."

So what is needed is a pure antagonist with little or no estrogen-agonist activity. "But most important would be to get rid of the estrogen receptor itself with an estrogen receptor downregulator that's capable of reducing the estrogen receptor to very low levels, or causing it to become totally downregulated itself, or a combination of the two, which might be even better."

He said fulvestrant is not a pure antagonist and is only a partial degrader, which is not optimal. It has very few side effects, the fewest side effects of any endocrine therapy. But one of the problems with fulvestrant, and with all endocrine therapies, is determining the optimal dose.

GDC-0810 appears to be a pure antagonist, Osborne said, although he said he was disappointed that it appears to be only a partial ER degrader like fulvestrant—"So from that perspective, GDC-0810 does not seem to offer an advantage over fulvestrant."

But GDC-0810 does have preclinical activity in tamoxifen-resistant and estrogen deprivation-resistant tumors, he continued. "And most importantly, and most interestingly, it may be active in estrogen receptor-mutant tumors."

Osborne noted that since all study patients had had prior therapy with tamoxifen, aromatase inhibitors, and fulvestrant, it would have been helpful to know the dose of fulvestrant. It also would be helpful to know how many patients had visceral disease and the number of sites of the disease.

The recommended dose of 600 milligrams with a meal might not be optimally defined, he said.

And he pointed out that there was marked reduction in FES-PET uptake with no clear dose response. "If the doses above 200 milligrams totally wiped out the FES-PET, do you need 600 milligrams to totally occupy the receptor?" he said.

The most exciting aspect of this report was the two partial responses, he said. Both were in women with ER-negative tumors, and one of the patients also had received prior fulvestrant.

Side Effects

Osborne pointed out that side effects are difficult to accurately assess in a Phase I study of patients with metastatic disease because of the existing symptoms from their cancer. And patients are often taking other drugs that can cause side effects, so it's difficult to know whether the effects are from the drug or the study or neither.

Most of the side effects in this study were grade 1 or 2—"but even that can be very important in patients who receive endocrine drugs for years—up to 10 years now for adjuvant therapy for many patients."

> "Resistance to currently available therapies targeting estrogen and the estrogen receptor causes morbidity and mortality for women with metastatic ER-positive breast cancer."

The side effects he was most concerned about were the GI side effects, which were reported to be mostly grade 1 at the recommended dose—"but even those," Osborne said, "would be a little difficult for a patient on long-term therapy to tolerate, unless, as the speaker said, these disappear with time."

C. KENT OSBORNE, MD: "FES-PET scans suggest that the ER target is hit, and responses in stable disease in patients with ER-mutant tumors and prior fulvestrant are also very encouraging."

Another toxicity concern was the possibility of off-target effects at the recommended dose. "It's always difficult to determine the optimal dose of an endocrine agent," Osborne said. "Even for targeted agents in general it's challenging, as suggested by the difficulty in determining the optimal dose of fulvestrant."

He said that since there was no clear dose response with the FES-PET, he wondered if some of the side effects were due to the recommended dose being too high.

He said that for the future, a neoadjuvant or a window-of-opportunity study might be helpful to determine the drug's optimal dose, the degree of ER downregulation with sequential biopsies, the effect on Ki-67, and the effect on apoptosis.

Other Novel Endocrine Strategies

Osborne concluded by saying that there are other novel endocrine strategies that are looking promising in the preclinical area. One is to block phosphorylation of the ER and its co-activators to prevent ligand-independent activation. Another is to block or downregulate co-activators themselves, such as SRC-3, perhaps in combination with ER blockade. In addition, strategies that more completely downgrade the ER are also showing promise in preclinical models.

"I thought a few years ago that we had maxed out our endocrine therapy and we knew everything about the estrogen receptors and that there wouldn't be any more discoveries," Osborne said. "But as we learn more and more about how estrogen works in cells, that always reveals new strategies to block the activity, and I think that's what we're seeing here."

In his disclosure at the start of his talk, Osborne said he has been an advisor for both AstraZeneca and Genentech, makers of fulvestrant and GDC-0810, respectively. "So there is no conflict—or a double conflict," he said.