CLINICAL UPDATE

Current Developments in the Management of Breast Cancer

The Evolving Use of SERDs in Estrogen Receptor–Positive, HER2-Negative Metastatic Breast Cancer

Rinath M. Jeselsohn, MD
Assistant Professor
Breast Oncology Center
Division of Molecular and Cellular Oncology
Department of Medical Oncology
Dana Farber Cancer Institute
Boston, Massachusetts

H&O What is the mechanism of action of selective estrogen receptor degraders (SERDs)?

RJ SERDs are direct estrogen receptor antagonists that lead to destabilization and degradation of the estrogen receptor.

H&O What is the current role of SERDs in the management of breast cancer?

RJ Currently, fulvestrant is the only SERD approved by the US Food and Drug Administration (FDA). Fulvestrant is approved in the first- and second-line settings for hormone receptor–positive metastatic breast cancer as a single agent and in combination with several other therapies: an aromatase inhibitor; CDK4/6 inhibitors; and the phosphoinositide 3-kinase (PI3K) inhibitor alpelisib (Piqray, Novartis). Fulvestrant was initially approved in 2002, based on data from 2 studies that showed activity among patients who developed resistance to initial endocrine therapy. The early indication was for the treatment of metastatic disease in patients who had developed progressive disease during prior endocrine therapy. Subsequently, the phase 3 FALCON study showed that fulvestrant can improve progression-free survival compared with an aromatase inhibitor as a first-line treatment for metastatic disease in patients who were naive to endocrine therapy; the improvement was particularly evident in patients with nonvisceral disease. The S0226 study showed improvement in progression-free survival and, later, in overall survival when fulvestrant was combined with an aromatase inhibitor compared with an aromatase inhibitor alone in patients with advanced hormone receptor–positive breast cancer who were naive to endocrine treatment. Based on these studies, fulvestrant was approved as first-line treatment for patients with metastatic disease.

Over the past several years, the FDA approved fulvestrant in combination with CDK4/6 inhibitors (palbociclib [Ibrance, Pfizer], ribociclib [Kisqali, Novartis], and abemaciclib [Verzenio, Lilly]). Additionally, the SOLAR-1 study showed that fulvestrant in combination with the PI3K inhibitor alpelisib improved progression-free survival compared with fulvestrant alone in patients with a *PIK3CA* mutation who developed progressive disease during prior treatment with endocrine therapy.

H&O What is the treatment strategy for hormone receptor–positive breast cancer?

RJ In general, first-line treatment consists of either endocrine therapy in combination with a CDK4/6 inhibitor or endocrine therapy alone followed by a second endocrine therapy in combination with a CDK4/6 inhibitor. Subsequent treatment options include the combination of endocrine treatment with everolimus or, in patients with a *PIK3CA* mutation, the combination of fulvestrant and alpelisib. After patients develop resistance to endocrine therapy combination regimens, options include chemotherapy agents, such as capecitabine, paclitaxel, and eribulin mesylate (Halaven, Eisai). For patients who have a *BRCA1/2* mutation, a poly (ADP-ribose) polymerase inhibitor is another option.

H&O What are the unmet needs in estrogen

receptor–positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer?

RJ One of the most important unmet needs is treatment options for patients who develop resistance to endocrine treatments and the other targeted treatment options in metastatic disease. For most patients at this point of the disease, chemotherapy agents are the only treatment option. There is a need for more treatments—likely combinations of targeted therapies and possibly immunotherapies—that are well tolerated and can lead to durable clinical benefit.

The rationale behind these newer agents was to develop SERDS that are administered orally and have better absorption, with improved pharmacokinetics, to enable superior blockade of the estrogen receptor.

H&O How do the SERDs in development differ from fulvestrant?

RJ The SERDs in development are administered orally. Fulvestrant is administered as an intramuscular injection. Fulvestrant is a very active SERD in preclinical models, but because this agent has relatively poor bioavailability, we are not seeing the full potential of a SERD in the clinic. The rationale behind these newer agents was to develop SERDs that are administered orally and have better absorption, with improved pharmacokinetics, to enable superior blockade of the estrogen receptor. This characteristic will be particularly important in the setting of the *ESR1* mutations, which are activating mutations that confer resistance to aromatase inhibitors and relative resistance to fulvestrant. The latter is caused by decreased affinity to fulvestrant, as shown in structural and biophysical studies of the *ESR1* mutations. In the context of the *ESR1* mutations, the estrogen receptor is altered, but remains an important driver of tumor progression and an important treatment target.

H&O Are there any clinical trial data for the oral SERDs in development?

RJ There are multiple oral SERDs in clinical development, including amcenestrant, giredestrant, camizestrant, LY3484356, ZN-c5, and rintodestrant. Other new oral drugs targeting the estrogen receptor include elacestrant, a selective estrogen receptor modulator with SERD activity; ARV-471, a PROTAC estrogen receptor degrader; and H3B-6545, a selective estrogen covalent antagonist.

A phase 1 study of elacestrant was recently published in the *Journal of Clinical Oncology*. Elacestrant was well tolerated overall, and the most common adverse events were grade 1 to 2 nausea and increased triglycerides. There was a signal of clinical benefit, including benefit in patients with *ESR1* mutations. The phase 3 EMERALD study is comparing elacestrant vs an aromatase inhibitor or fulvestrant in patients with advanced hormone receptor–positive breast cancer who have progressed during prior treatment with a CDK4/6 inhibitor in combination with an aromatase inhibitor or fulvestrant.

Another selective estrogen receptor modulator with SERD activity is bazedoxifene. At my institution, we have conducted a phase 1b/2 study evaluating the combination of bazedoxifene and palbociclib. Results were presented at the 2018 San Antonio Breast Cancer Symposium. Bazedoxifene was well tolerated, and there was a signal of clinical benefit for this combination in a relatively heavily pretreated patient population.

The phase 1/2 AMEERA-1 trial is evaluating amcenestrant as a single agent and in combination with palbociclib in postmenopausal women with estrogen receptor–positive/HER2-negative advanced breast cancer who were heavily pretreated. At the 2020 San Antonio Breast Cancer Symposium, results were presented for patients treated with amcenestrant monotherapy. Among 59 evaluable patients drawn from the dose-escalation phase (part A) and the dose-expansion phase (part B), the clinical benefit rate was 33.9%. An analysis presented at the 2021 American Society of Clinical Oncology (ASCO) annual meeting provided data for the combination regimen of amcenestrant plus palbociclib. The clinical benefit rate was 74.3% among 35 evaluable patients enrolled in the dose-escalation phase (part C) and the dose-expansion phase (part D). There was evidence of antitumor activity. Amcenestrant was well tolerated, with limited adverse events. Amcenestrant is the only oral SERD with no treatment-related grade 3 or higher adverse events reported in registrational studies. The AMEERA-5 study is an ongoing randomized, double-blind phase 3 study comparing the efficacy and safety of amcenestrant plus palbociclib vs letrozole plus palbociclib in patients with advanced, estrogen receptor–positive breast cancer who have not received

prior systemic treatment for advanced disease.

Results of the phase 1a/b EMBER trial of LY3484356 were reported at the 2021 ASCO annual meeting. There were no dose-limiting toxicities, and the most common adverse events were low-grade nausea, diarrhea, and fatigue.

Results of a phase 1a/b study of giredestrant were presented at the 2021 ASCO meeting. There were no dose-limiting toxicities associated with this drug. Low-grade sinus bradycardia that did not require treatment interruptions or dose modifications was reported in 8% of patients.

Results from a phase 1/2 study of H3B-6545 were also presented at the 2021 ASCO meeting. The most common adverse events with this agent included nausea, diarrhea, and fatigue. In addition, sinus bradycardia and QTc prolongation were seen.

H&O Do oral SERDs have the potential for use in early disease?

RJ As is the case in the development of many other drugs in oncology, the first clinical trials are evaluating oral SERDs in the metastatic setting. There are ongoing window-of-opportunity studies evaluating oral SERDs in early-stage disease. However, these studies are designed to evaluate the pharmacodynamics and molecular changes associated with oral SERDs, and not the clinical benefit. Eventually, as we learn more about the safety and activity of the oral SERDs in the metastatic setting, these drugs will be evaluated in adjuvant studies.

It is important to remember that results in metastatic disease do not always translate to early-stage disease. This concept was recently illustrated by results from the PALLAS study, which did not show benefit from 2 years of adjuvant palbociclib despite the remarkable activity of this agent in metastatic disease. This finding highlights differences between early-stage vs metastatic hormone receptor–positive breast cancer.

Currently, fulvestrant is not approved in early-stage disease, and there are no data showing that SERDs are superior to aromatase inhibitors in early-stage, treatment-naive patients. Recently, the large phase 3 ALTERNATE trial compared 6 months of an aromatase inhibitor vs fulvestrant vs a combination of fulvestrant and an aromatase inhibitor in the neoadjuvant setting. The study found that fulvestrant alone or in combination with an aromatase inhibitor was not superior to the aromatase inhibitor alone. However, this was a neoadjuvant study, and not an adjuvant study designed to evaluate long-term outcomes as the primary endpoint. In addition, the oral SERDs may have superior activity compared with fulvestrant in early-stage disease, and may be better tolerated than aromatase inhibitors and improve treatment adherence.

H&O Do you anticipate that an oral SERD will become the endocrine backbone of choice?

RJ I anticipate that an oral SERD will likely become an endocrine treatment option. In certain settings, such as patients with *ESR1* mutations or other mechanisms of ligand-independent estrogen receptor activity, oral SERDs will likely be the backbone of choice.

H&O For an oral SERD to become the endocrine treatment of choice, what attributes will it need?

RJ In order for an oral SERD to become the endocrine treatment of choice in early-stage disease, it will need to be more effective and/or better tolerated than aromatase inhibitors. In the setting of metastatic disease, it will need to show superior activity and no increase in side effects compared with an aromatase inhibitor and fulvestrant when used in combination with other targeted treatments.

Disclosure

Dr Jeselsohn is a consultant for Carrick Therapeutics and Luminex, and has received research funding from Pfizer and Lilly.

Suggested Readings

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