Orally Bioavailable SERD Shows Promise in Certain Breast Cancer Patients

BY CATLIN NALLEY

A first-in-human, Phase I study is exploring D-0502 in women with advanced or metastatic HR-positive and HER2-negative breast cancer. This orally bioavailable selective estrogen receptor degrader (SERD) is well-tolerated with no dose-limiting toxicities observed, according to data presented at the 2020 San Antonio Breast Cancer Symposium (Abstract PS11-26).

“Currently, fulvestrant is the only SERD approved for the treatment of advanced HR-positive breast cancer. It requires IM injection and has low bioavailability,” noted study author Cynthia Osborne, MD, with Texas Oncology-Baylor Charles A. Sammons Cancer Center. “This Phase I study is evaluating the drug D-0502, an oral bioavailable SERD. In preclinical models, it has demonstrated significant activity in a number of HR+ breast cancer models, including those with ESR1 mutations.”

The aim of this Phase I study is to characterize the safety and tolerability of D-0502 alone and in combination with palbociclib, as well as to identify a maximum tolerated dose (MTD) and/or recommended Phase II dose. Secondary objectives included the evaluation of PK properties and preliminary anti-tumor activities.

D-0502 was administered orally once daily in 28-day cycles. In the Phase Ia portion of the study, a standard 3+3 dose-escalation was used to identify the MTD of D-0502 as a single agent. The Phase Ib study, which is ongoing, includes two stages.

“In stage I, D-0502 was evaluated with palbociclib at a dose below the MTD first before escalating to the MTD. Stage I also included patients in China treated at a dose below and at the MTD as a single agent, as well as in combination with palbociclib,” the study authors outlined. “Stage II will further evaluate the MTD for both single agent and combination of D-0502 with palbociclib.”

The recommended dose for expansion was identified as 400 mg once daily x 28 days, according to Osborne, who noted that the MTD was not yet reached.

“The combination [of D-0502] with palbociclib did not result in a significant change in the PK profiles of either drug,” she noted during SABCS. “To date, D-0502 has been evaluated in 16 patients as a single agent in [Phase] Ia, and an additional 19 patients in expansion and combination with palbociclib in [Phase] Ib.”

Overall, D-0502—as a single agent and in combination with palbociclib—has been well-tolerated, with the majority of adverse events (AEs) occurring at grade 1 or 2, Osborne reported. “Gastrointestinal disorders, including nausea, vomiting, diarrhea, and fatigue, were the most common AEs,” she said. “No dose-limiting toxicities have been observed.”

A heavily pretreated patient population was included in the Phase Ia portion of the study, with a median of four prior therapies, according to Osborne. “Fifty percent had received prior chemotherapy, 75 percent had received a prior CDK4/6 inhibitor, and 38 percent had received a prior SERD.”

Osborne also presented preliminary efficacy results during SABCS. “In the Phase Ia portion, 75 percent obtained stable disease, with 31 percent of participants achieving disease control greater than 24 weeks,” she said. “Out of 19 participants in the Phase Ib portion, there has been one confirmed complete response, two confirmed partial responses, 84 percent achieved stable disease, and 68 percent maintained disease control for greater than 24 weeks. We find the preliminary efficacy results quite promising and warrant ongoing evaluation.”

When discussing the findings with Oncology Times, Osborne noted, “Early results from 36 patients show that, in general, [this approach] is well-tolerated. Low-grade GI disturbances and fatigue were among the most common adverse events noted with expected myelosuppression with the addition of palbociclib.

“Preliminary efficacy results are encouraging, with a high clinical benefit rate and confirmed PRs and CR,” she concluded. “Having a highly active oral SERD available for our patients would give them another potent drug in the HR-positive breast cancer armamentarium and more freedom from clinic visits.”

Catlin Nalley is a contributing writer.