

Pyrotinib with chemotherapy may improve outcomes in patients with pretreated HER2-positive breast cancer

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Among patients with previously treated HER2-positive metastatic breast cancer, those who received pyrotinib plus capecitabine had longer overall survival than those who received lapatinib (Tykerb) plus capecitabine, according to updated results from the phase III [PHOEBE](#) trial presented at the [San Antonio Breast Cancer Symposium](#), held December 7–10, 2021.

"Patients with metastatic HER2-positive breast cancer are typically treated with the HER2-targeted therapies trastuzumab (Herceptin) and pertuzumab (Perjeta) in combination with a taxane, but resistance to this regimen inevitably develops," explained Binghe Xu, MD, Ph.D., a professor of medical oncology at the Chinese Academy of Medical Sciences.

Patients who progress on this standard therapy may then be treated with the HER2-targeted [tyrosine kinase inhibitor](#) (TKI) [lapatinib](#) in combination with the chemotherapeutic capecitabine or with alternative HER2-targeted therapies, such as trastuzumab emtansine. However, lapatinib and many other available HER2-targeted TKIs are reversible and do not sustain the inhibition of HER2 signaling. This may facilitate the development of treatment resistance, Xu noted. In addition, trastuzumab emtansine (T-DM1), which is the preferred regimen for second-line therapy after trastuzumab in many international guidelines, is not approved for metastatic disease in many countries.

"There is an urgent unmet need for additional HER2-targeted therapies for [patients](#) who progress on standard therapies in countries and regions where access to HER2-directed agents is scarce," said Xu.

Pyrotinib, which was tested in the PHOEBE trial, is an irreversible tyrosine kinase receptor inhibitor that targets HER2, as well as the related proteins HER4 and epidermal growth factor receptor (EGFR), also known as HER1. A prior [phase II clinical trial](#) found that pyrotinib

plus capecitabine led to clinical responses in previously treated patients with HER2-positive metastatic breast cancer. The phase III PHOEBE trial sought to understand the impact of pyrotinib compared with that of lapatinib in this patient population.

The PHOEBE trial enrolled 267 Chinese patients with HER2-positive metastatic breast cancer who had been previously treated with trastuzumab and taxanes and up to two previous lines of chemotherapy in the metastatic setting. Patients were randomly assigned to receive either pyrotinib plus capecitabine or lapatinib plus capecitabine. The median follow-up was 33.2 months in the pyrotinib arm and 31.8 months in the lapatinib arm. At data cutoff, 40.3 percent of patients in the pyrotinib arm and 52.3 percent in the lapatinib arm had died.

Xu reported that patients treated with pyrotinib plus capecitabine had a 31 percent lower risk of death than those treated with lapatinib and capecitabine, with overall survival not reached in the pyrotinib arm compared with an overall survival of 26.9 months in the lapatinib arm. Furthermore, patients in the pyrotinib arm had significantly longer [progression-free survival](#) than those in the lapatinib arm (12.5 months vs 5.6 months), with a 52 percent lower risk of disease progression, as [previously reported](#).

"Among the patients enrolled in the study, pyrotinib plus capecitabine had a manageable safety profile and led to a statistically and clinically significant improvement in progression-free and overall survival compared with that for lapatinib," concluded Xu. He noted that the results of the PHOEBE clinical trial led to the approval of pyrotinib in combination with capecitabine as second-line standard-of-care treatment for HER2-positive metastatic breast cancer in China. "The updated analysis of overall survival we present here reaffirms pyrotinib plus capecitabine as a viable treatment option in this patient population."

A limitation of the study was that the inclusion of patients from 29 different research centers precluded centralized testing of HER2 status, which was instead assessed separately by pathologists at each site using ASCO/CAP guidelines. An additional limitation was that neither pertuzumab nor T-DM1 were approved in China at the time of patient enrollment. Thus, the study was unable to assess the efficacy of the pyrotinib plus [capecitabine](#) regimen in patients previously treated with either of these therapies. "Nevertheless, our results do inform treatment decisions in patients for whom pertuzumab and T-DM1 are not available, not affordable, or contraindicated," said Xu.

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