

Expanding therapeutic frontiers in metastatic HER2-positive breast cancer

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Extraordinary therapeutic advances have been made in the management of HER2-positive metastatic breast cancer (MBC) over the past 2 decades. The approval of pertuzumab, ado-trastuzumab emtansine, lapatinib, neratinib, trastuzumab deruxtecan, and tucatinib have demonstrated the continued successful outcomes and importance of targeting HER2. Unfortunately, despite these therapeutic advances, nearly all patients with metastatic HER2-positive breast cancer eventually will progress on anti-HER2 therapy due to *de novo* or acquired resistance. Unraveling resistance mechanisms to anti-HER2 therapies as well as unveiling compensatory pathways and tumor heterogeneity is essential for the development of novel therapeutic strategies.

Pyrotinib: mechanism of action & phase I data

Pyrotinib is an oral, irreversible pan-ERb receptor tyrosine kinase inhibitor with activity against epidermal growth factor receptor (EGFR)/HER1, HER2, and HER4. By covalently binding with ATP binding sites of intracellular regions, the drug inhibits the formation of homologous/ heterodimer and auto-phosphorylation of HER family, thus blocking the activation of RAS/RAF/MEK/MAPK, PI3K/AKT signaling pathways and tumor cell cycle in G1 phase and restricting tumor development (1). Data in the preclinical setting suggest that pyrotinib can irreversibly inhibit multiple ErbB receptors and effectively inhibit the proliferation of HER2-overexpressing cells both *in vivo* and *in vitro*. The phase I study determined the MTD of pyrotinib was 400 mg daily. The study also suggested that

pyrotinib is safe and effective in patients with HER2positive MBC, with an overall response rate (ORR) of 50.0% and a median-progression free survival (PFS) of 35.4 weeks in the dosage range of 80 to 400 mg daily. The phase I study also investigated biomarkers such as PIK3CA and TP53 mutations in circulating tumor DNA (ctDNA) led to worse efficacy with pyrotinib monotherapy (2).

Pyrotinib: efficacy in phase II and phase III studies

The efficacy of pyrotinib in combination with capecitabine in patients with HER2-positive MBC has been investigated in both phase II and phase III clinical trials. The efficacy in patients previously treated with taxanes, anthracyclines and/or trastuzumab was demonstrated in a randomized, open-label, active comparator-controlled, multicenter phase II trial. The primary endpoint was objective response rate which was significant greater with pyrotinib plus capecitabine compared to lapatinib plus capecitabine, as assessed by the investigator (79% vs. 57%; P=0.01) Independent imaging assessment reported similar findings (71% vs. 49%; P=0.0117). Other efficacy endpoints reported included duration of response and PFS. Duration of response was 16.7 months with pyrotinib plus capecitabine and 8.4 months with lapatinib plus capecitabine (hazard ratio 0.404). In terms of PFS, pyrotinib plus capecitabine significantly prolonged median PFS versus lapatinib plus capecitabine (18.1 vs. 7.0 months; adjusted HR 0.363; 95% CI, 0.228-0.579; P<0.0001) (3). At the 2020 American Society of Clinical Oncology annual meeting, interim

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results of the phase III PHOEBE study were presented. The PHOEBE trial enrolled patients who had already received treatment with trastuzumab and taxanes, with or without anthracyclines, and up to two lines of chemotherapy for metastatic disease (median, 1). Participants were randomly assigned to receive pyrotinib 400 mg/day (n=134) or lapatinib 1,250 mg/day (n=132), both given alongside capecitabine 1,000 mg/m² twice a day on days 1–14 of every 21-day cycle.

At a median follow-up of 9.9 months, the primary endpoint of PFS by independent review was significantly improved with pyrotinib versus lapatinib, at a median of 12.5 and 6.8 months, respectively, giving a hazard ratio of 0.39 in favor of pyrotinib.

Pyrotinib was favored across all subgroups, although the PFS benefit did not reach statistical significance for some subgroups, such as patients with trastuzumab resistance (defined as relapse within 6 months of adjuvant use and/or within 3 months in the metastatic setting) and those with non-visceral metastases.

The objective response rate was higher in the pyrotinib than lapatinib treatment arm, at 67.2% versus 51.5% (complete responses in 5.2% vs. 0.8%), as was the clinical benefit rate, at 73.1% versus 59.1%. The median durations of response were 11.1 and 7.0 months, respectively, and a corresponding 70.0% and 48.5% of responses were ongoing at data cutoff.

Overall survival (OS) data had not reached maturity (4). In August 2018, pyrotinib was approved in combination with capecitabine for the treatment of HER2-positive MBC in patients previously treated with anthracycline or taxane in China.

PHENIX study

In this issue of *Translational Breast Cancer Research*, Yan and colleagues evaluated the use of pyrotinib (400 mg orally once daily) in combination with capecitabine (1,000 mg/m² BID on days 1–14) for 21 day cycle compared to placebo/ capecitabine in MBC patients with pretreated trastuzumab/ taxane. Patients who progressed on placebo plus capecitabine received subsequent pyrotinib monotherapy. The primary endpoint was PFS per independent review; 185 patients were randomly assigned to the pyrotinib arm versus 94 in the placebo arm. The median PFS was 11.1 months (95% CI, 9.7–16.5) vs. 4.1 months (95% CI, 2.8–4.2) in the pyrotinib vs. placebo groups with a reported hazard ration, 0.18 (95% CI, 0.13–0.26); P<0.001. Seventy-one patients in

the placebo group subsequently received pyrotinib, showing a response rate of 38% (95% CI, 26.7–49.3%) and median PFS of 5.5 months (95% CI, 4.1–6.9). In terms of toxicity, the most frequent grade 3 or 4 treatment related adverse events were diarrhea and hand-foot syndrome (5).

PHENIX study applications in real world

This study demonstrates the efficacy of a novel oral treatment regimen for the management of HER2 positive breast cancer after failure of trastuzumab/taxane. Application of the data in a global perspective would be limited, as the study population was not previously treated with combination pertuzumab/trastuzumab plus taxane in the 1st line setting or treated in the second line setting with ado-trastuzumab or more recently US approved combination consisting of tucatinib/capecitabine/ trastuzumab. These regimens are considered preferred and standard of care in the US. However, because of cost and availability of pertuzumab, ado-trastuzumab, and other oral HER2 directed tyrosine kinase inhibitors (tucatinib, neratinib, lapatinib) these agents are not options for all patients in China. In addition to drug access issues, the COVID-19 pandemic has increased interest in toward a complete oral regimen. Therefore, other treatment options are needed after failure of trastuzumab/taxane or in the clinical situation where trastuzumab would be contraindicated because of cardiac issues and limited access to other trastuzumab directed therapies. The study design in the PHENIX supports treatment paradigms in China and other real world case scenarios where there is limited use of pertuzumab and ado-trastuzumab. In addition, data in China suggest that utilization of trastuzumab is also limited because of cost. This is an important detail, as optimal comparator arm would have been the combination of capecitabine plus trastuzumab or other HER2 directed therapy compared to capecitabine plus pyrotinib. The PHENIX study reported impressive improved PFS among all subsets of patients, including those with CNS metastases and visceral metastasis. In addition, pyrotinib demonstrated monotherapy activity after progression of capecitabine, with an impressive PFS and ORR. This monotherapy activity, although seen in a small subset of patients, suggests the potency of pyrotinib and benefit in a monotherapy setting. This is novel, given other oral HER2 directed agents have demonstrated limited efficacy as monotherapy. In terms of toxicity, diarrhea management is critical. Pyrotinib increases diarrhea in combination with capecitabine and was also

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observed as monotherapy (all grades 88.7%, grade 3 and 4 22.5%).

Conclusions

The PHENIX study provides efficacious and tolerable oral regimen in a real world setting in which costly HER2 directed agents are not available, limited access, contraindicated, or preference of an oral regimen secondary to COVID-19. The combination demonstrated efficacy across all subset of patients, including those with CNS involvement. Currently there are three to four options combining HER2 directed tyrosine kinase inhibitor with capecitabine, depending on drug approvals. Headto-head data in the PHOEBE trial suggest pyrotinib/ capecitabine has improved PFS compared to the lapatinib arm. However, we are lacking head-to-head data with neratinib and tucatinib. Therefore, it would be difficult at this time to have a preferred HER2 TKI combined with capecitabine. In addition, to efficacy and safety data, other considerations in selection of an anticancer regimen would be cost. Economic evaluation of these novel capecitabine combinations should also be a consideration in selection of treatment options for patients. In summary, the PHENIX data contributes to the other emerging data of the potent activity seen with pyrotinib in HER2 positive MBC and offers additional treatment options to patients diagnosed with HER2-positive breast cancer.

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