



Pyrotinib: a new promising targeted agent for human epidermal growth factor receptor 2-positive breast cancer

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Approximately 20% of all new breast cancer cases are characterized by the positivity for the human epidermal growth factor receptor 2 (HER2) in terms of gene amplification or overexpression of its protein (1). Despite being characterized by an aggressive behavior and poorer prognosis, the advent of anti-HER2 targeted therapies has dramatically improved the survival of patients affected by this disease subtype over the last two decades (2). Nowadays, in the advanced setting, patients with HER2-positive breast cancer are those who are administered with more lines of treatment and with the expected longer survival outcomes as compared to patients affected by other subtypes (3,4). To further improve the outcomes of patients with HER2-positive metastatic breast cancer and possibly increase the chances of cure even in the presence of advanced disease, developing new effective targeted treatment options remains a priority (5).

The current standard of care in the first-line setting of HER2-positive metastatic breast cancer is represented by chemotherapy with a taxane as single agent in combination with dual anti-HER2 blockade including the monoclonal antibodies pertuzumab plus trastuzumab (6,7). This regimen has shown an extraordinary and unprecedented overall survival (OS) gain in this setting (8). Following treatment with trastuzumab plus a taxane, the antibody drug-conjugate trastuzumab emtansine (T-DM1) represents the current recommended approach (9), although more limited evidence on its performance exists in patients

previously exposed also to pertuzumab (10). Based on current guidelines, the tyrosine kinase inhibitor (TKI) lapatinib in combination with capecitabine represents one of the available third-line treatment options (6,7).

In recent years, several other TKIs have been developed for patients with HER2-positive metastatic breast cancer (*Table 1*) (11-22).

Among the different TKIs, in addition to lapatinib, also neratinib and tucatinib have been recently approved by the Food and Drug Administration (FDA) thus becoming two new available targeted treatment options for patients with HER2-positive metastatic breast cancer (*Figure 1*).

The NALA trial compared a combination of neratinib plus capecitabine versus lapatinib plus capecitabine in patients affected by HER2-positive metastatic breast cancer previously treated with at least two lines of therapy (11). The study showed a significant improvement in progression-free survival (PFS) favoring neratinib [mean PFS 8.8 *vs.* 6.6 months; hazard ratio (HR) 0.76, 95% confidence interval (CI): 0.63–0.93, P=0.0059] without difference in OS (mean 24.0 *vs.* 22.2 months; HR 0.88, 95% CI: 0.72–1.07, P=0.2086) (11).

Important results have more recently become available from the HER2CLIMB trial that investigated the addition of tucatinib to capecitabine and trastuzumab. A significant improvement in both PFS (median 7.8 *vs.* 5.6 months; HR 0.54, 95% CI: 0.42–0.71, P<0.001) and OS (21.9 *vs.* 17.4 months; HR 0.66, 95% CI: 0.50–0.88, P=0.005) was

Table 1 Results from the main randomized trials investigating different tyrosine kinase inhibitors as single agent or combined with chemotherapy or other anti-HER2 targeted therapies in patients with HER2-positive metastatic breast cancer

Study	TKI	Phase	Population	Primary endpoints	Line of treatment	Interventions	ORR, N (%)	PFS/TTP, HR, 95% CI	OS, HR, 95% CI
Cameron 2010	Lapatinib (reversible epidermal growth factor receptor EGFR/ERBB1/HER1 and HER2)	III	408	TTP	<2 prior chemotherapy in the metastatic setting	Lapatinib + capecitabine; Capecitabine alone	22%*; 14%*	8.4 months*; 4.4 months* 0.49 (0.34–0.71)	75.0 weeks; 64.7 weeks; 0.87 (0.71–1.08)
Di Leo 2008	Lapatinib (reversible epidermal growth factor receptor EGFR/ERBB1/HER1 and HER2)	III	579	TTP	First-line treatment	Lapatinib plus paclitaxel; Placebo plus paclitaxel	35.10%; 25.30%	29 weeks; 22.9 weeks 0.87 (0.72–1.05)	99.1 weeks; 87 weeks; 0.86 (0.7–1.1)
Blackwell 2010	Lapatinib (reversible epidermal growth factor receptor EGFR/ERBB1/HER1 and HER2)	III	296	PFS	Progression on prior trastuzumab-containing regimens	Lapatinib alone; Lapatinib + trastuzumab	6.90%; 10.30%	8.1 weeks; 12.0 weeks 0.73 (0.57–0.93)	39.0 weeks; 51.6 weeks; 0.75 (0.53–1.07)
Gelmon 2015	Lapatinib (reversible epidermal growth factor receptor EGFR/ERBB1/HER1 and HER2)	III	652	PFS	First-line treatment	Lapatinib + taxane; Trastuzumab + taxane	54%; 55%	9.0 months; 11.3 months 1.37 (1.13–1.65)	Not observed; Not observed
Harbeck 2016	Afatinib (irreversible pan-ERBB tyrosine kinase inhibitor)	III	508	PFS	<2 prior chemotherapy in the metastatic setting	Afatinib + vinorelbine; Trastuzumab + vinorelbine	46%; 47%	5.5 months; 5.6 months 1.10 (0.86–1.41)	19.6 months; 28.6 months; 1.76 (1.20–2.59)
Cortés 2015	Afatinib (irreversible pan-ERBB tyrosine kinase inhibitor)	II	121	Benefit at 12 weeks (absence CNS or extra CNS disease progression)	Recurrence or progression during or after treatment with trastuzumab, lapatinib or both	Afatinib; Afatinib + vinorelbine; Investigator's choice	0%; 8%; 5–14%	11.9 weeks; 1.18 (0.72–1.93); 12.3 weeks; 0.94 (0.57–1.54); 18.4 weeks	57.7 weeks; 1.27 (0.72–2.21); 37.3 weeks; 1.60 (0.93–2.76); 52.1 weeks
Awada 2016	Neratinib (irreversible pan-ERBB tyrosine kinase inhibitor)	II	479	PFS	First line treatment	Neratinib + paclitaxel; Trastuzumab + paclitaxel	74.80%; 77.60%	12.9 months; 12.9 months 1.02 (0.81–1.27)	Not estimable; Not estimable
Saura 2019	Neratinib (irreversible pan-ERBB tyrosine kinase inhibitor); Lapatinib (reversible epidermal growth factor receptor EGFR/ERBB1/HER1 and HER2)	III	662	PFS, OS	≥2 prior anti-HER2 therapies	Neratinib+ capecitabine; Lapatinib + capecitabine	32.80%; 26.70%	8.8 months; 6.6 months 0.76 (0.63–0.93)	24.0 months; 22.2 months; HR 0.88 (0.72–1.07)
Murthy 2020	Tucatinib (highly selective inhibitor of the HER2 tyrosine kinase)	III	612	PFS	≤2 prior chemotherapy in the metastatic setting	Tucatinib + capecitabine + trastuzumab; Placebo + capecitabine + trastuzumab	40.60%; 22.80%	7.8 months; 5.6 months 0.54 (0.42–0.71)	21.9 months; 17.4 months; HR 0.66 (0.50–0.88)
Yan 2020	Pyrotinib (irreversible pan-ErbB tyrosine kinase EGFR/HER1, HER2, and HER4 inhibitor)	III	279	PFS	≤2 prior chemotherapy in the metastatic setting	Pyrotinib + capecitabine; Placebo + capecitabine	68.60%; 16.00%	11.1 months; 4.1 months 0.18 (0.13–0.26)	Not reached; Not reached
Xu 2020	Pyrotinib (irreversible pan-ErbB tyrosine kinase EGFR/HER1, HER2, and HER4 inhibitor)	III	267	PFS	≤2 prior chemotherapy in the metastatic setting	Pyrotinib + capecitabine; Lapatinib + capecitabine	67.20%; 51.50%	12.5 months; 6.8 months 0.39 (0.27–0.56)	Not mature yet; Not mature yet

*, data from the first publication (Geyer CE et al., *N Engl J Med* 2006). TKI, tyrosine kinase inhibitor; TTP, time to progression; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; CNS, central nervous system; HR, hazard ratio; CI, confidence interval.

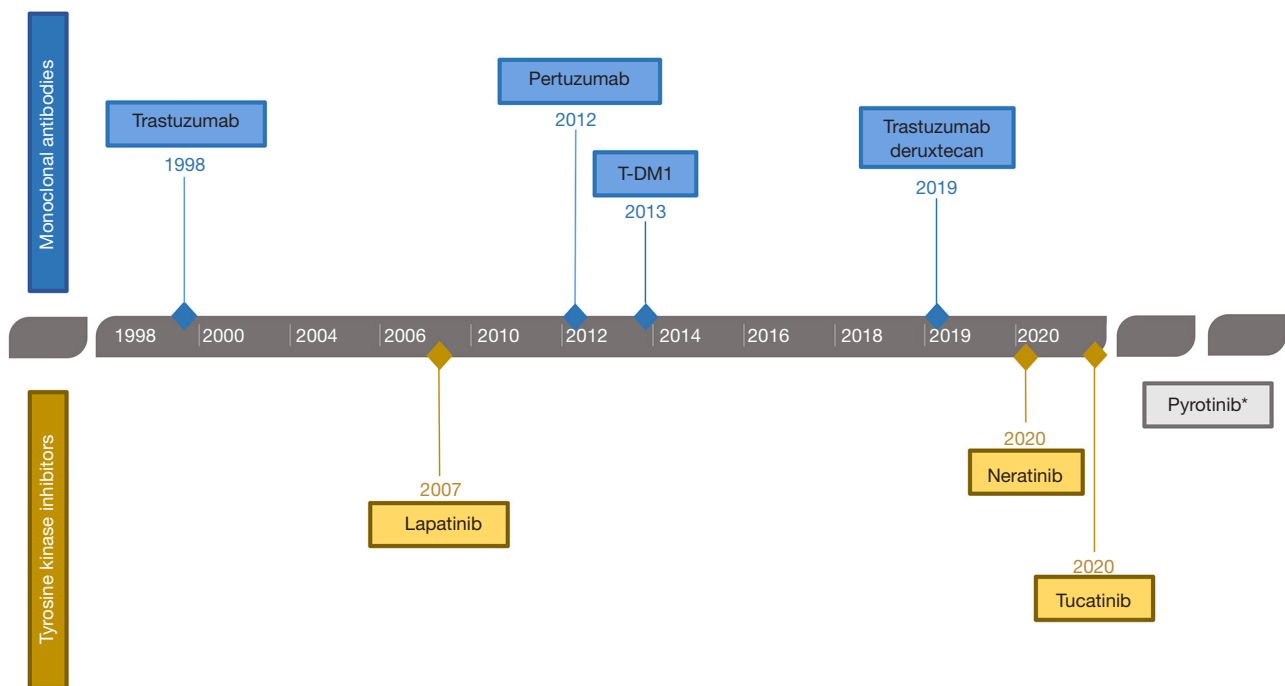


Figure 1 Approval by the Food and Drug Administration of anti-HER2 target therapies for patients with advanced breast cancer. *, only approved in China.

observed with the addition of the TKI (13). Moreover, this regimen proved to be highly effective also for patients with brain metastasis (23). Notably, in this trial all patients were previously treated with trastuzumab, pertuzumab, and T-DM1 (13).

In the current issue of *Translational Breast Cancer Research*, Yan and colleagues reports the results of the PHENIX phase III trial (24). In this study, the efficacy of a new TKI, pyrotinib (an irreversible pan-HER inhibitor targeting EGFR, HER2 and HER4), was investigated in patients with HER2-positive metastatic breast cancer previously treated with up to two prior lines of therapy (that included also trastuzumab plus a taxane). This is a double-blinded, placebo-controlled phase III study conducted in China that enrolled 279 patients who were randomized (2:1) to receive 21-day cycle of either oral pyrotinib or placebo (400 mg, qd) combined with capecitabine (1,000 mg/mq, bid on days 1–14). Patients progressing on placebo plus capecitabine could receive subsequent pyrotinib monotherapy. The primary endpoint was PFS; secondary endpoints included OS, disease control rate (DCR), clinical benefit rate (CBR), duration of response (DoR) and safety.

Approximately 54% of patients had hormone receptor-

positive disease and 78% had visceral involvement. A total of 11% of patients in both arms had brain metastases. All patients received prior trastuzumab in the early and/or advanced setting, but only 63% were exposed to this monoclonal antibody for metastatic disease. Notably, in terms of prior lines of therapy received for advanced disease, 34% of patients were treated in the first-line setting.

In the pyrotinib and control groups, respectively, median PFS was 11.1 and 4.1 months (HR 0.18, 95% CI: 0.13–0.26, $P < 0.001$). The objective response rate (ORR) rate was 68.6% and 16.0% in the pyrotinib and control groups, respectively ($P < 0.001$). Notably, 12 patients achieved a complete response in the pyrotinib group, while none in the control group. Both DCR (from 64.9% to 91.9%, $P < 0.001$) and CBR (from 22.3% to 76.8%, $P < 0.001$) were also significantly improved by the addition of pyrotinib. OS could not be assessed due to the limited number of events observed (41 deaths were registered: 23 in the pyrotinib group and 18 in the control group).

As regards to patients with visceral disease, improvement in PFS were observed in both patients with or without brain metastases that received pyrotinib (6.9 vs. 4.2 months and 11.1 vs. 4.1 months, respectively). New brain metastases

were developed in 1.2% of patients in the pyrotinib group and 3.6% of those in the control group.

A total of 71 patients received pyrotinib monotherapy after progressing on placebo plus capecitabine: promising activity was also observed in this setting with median PFS of 5.5 months, ORR of 38%, DCR of 80.3% and CBR of 42.3%.

In terms of safety profile, patients in the pyrotinib plus capecitabine arm experienced higher rates of treatment-related adverse events (TRAEs) of any grade than those on placebo plus capecitabine arm (99.5% *vs.* 95.7%). The most common observed side effects were diarrhea (98.4% *vs.* 68.1%), hand and foot syndrome (59.5% *vs.* 29.8%), nausea (48.6% *vs.* 18.1%) and vomiting (48.6% *vs.* 16.0%). A total of 55.1% of patients in the pyrotinib arm and 25.5% in the control arm developed Grade 3 and 4 TRAEs. Diarrhea was the most frequent Grade 3 TRAE (30.8% and 12.8%, respectively) followed by hand and foot syndrome (15.7% and 5.3%, respectively).

The PHENIX trial has provided important data on the potential use of a new TKI for the treatment of patients with HER2-positive metastatic breast cancer. Two important considerations should be made when placing the results of the trial in the current anti-HER2 treatment era. The comparator arm was chemotherapy alone without targeted anti-HER2 therapy and the patients included were not heavily pretreated being exposed only to prior trastuzumab plus taxane-based chemotherapy.

Regarding the first issue, a new trial addressing this concern has been recently presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Conference. In the PHOEBE trial, patients affected by metastatic HER2-positive breast cancer previously exposed to no more than 2 lines of therapy including also trastuzumab and taxane-based chemotherapy were randomly assigned to receive either pyrotinib (400 mg/day) or lapatinib (1,250 mg/day), both given with capecitabine (1,000 mg/m²). The primary endpoint was PFS. Median PFS in the pyrotinib plus capecitabine arm was 12.5 *vs.* 6.8 months in the lapatinib plus capecitabine arm (HR 0.39, 95% CI: 0.27–0.56, *P*<0.001). OS data were not mature yet; however, a trend for improved OS favoring the pyrotinib arm was observed. In terms of safety profile, Grade 3 diarrhea was experienced by 30.6% of patients in the pyrotinib arm as compared to 8.3% in the lapatinib arm (22).

Regarding the second issue, both the PHENIX and PHOEBE trials included a patient population that is currently not candidate yet to an anti-HER2 TKI according

to current guidelines. The performance of pyrotinib following pertuzumab-based therapy and T-DM1 remains unknown. In addition, with the availability of other important TKIs, such as tucatinib and neratinib, it would be important to investigate the efficacy of pyrotinib also in a more pretreated patient population to give a potential additional effective option in later lines.

Considering that HER2-positive metastatic breast cancer remains an incurable disease and resistance to the different available treatments occurs at some point, developing further effective agents for these patients remains a priority. In the last year, several steps forward have been made with the FDA approval of two TKIs and of the new antibody drug-conjugate trastuzumab-deruxtecan (*Figure 1*). Other promising strategies are currently being studied. Among them, promising results have been obtained with margetuximab, a new Fc-engineered anti-HER2 monoclonal antibody (25). In addition, several new combination strategies of anti-HER2 targeted agents are currently being developed, including with CDK4/6 inhibitors (26), phosphoinositide 3-kinase (PI3K) inhibitors (27) as well as immunotherapy (28).

In conclusion, the continuous successful advances in anti-HER2 targeted therapies has significantly improved the prognosis of patients with HER2-positive metastatic breast cancer. More treatment lines are now available for these patients. Pyrotinib represents another promising option that is already approved for clinical use in China. More data are needed to better understand where this strategy can be placed in the current treatment algorithm for patients with HER2-positive metastatic breast cancer.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tbcr-20-34>). ML reports that he acted as consultant for Roche and Novartis, and received honoraria from Theramex, Takeda, Roche, Lilly, Pfizer and Novartis outside the submitted work. The other authors have no conflicts of interest to declare.

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to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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