Clinical Roundtable Monograph

Clinical Advances in Hematology & Oncology September 2020

Neratinib: An Option for HER2-Positive Metastatic Breast Cancer

Moderator

Joyce A. O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
Texas Oncology
US Oncology
Dallas, Texas

Discussants

Ruth O'Regan, MD
Professor
Hematology/Oncology Faculty
University of Wisconsin
School of Medicine and Public Health
Madison, Wisconsin

Claudine Isaacs, MD
Professor of Medicine and Oncology
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center
Washington, DC

Abstract: Metastatic human epidermal growth factor receptor 2 (HER2)-positive breast cancer is currently incurable. The primary goals of treatment are to prolong survival while optimizing quality of life. Several agents are now available in this setting, including neratinib, tucatinib, ado-trastuzumab emtansine, and trastuzumab deruxtecan. Neratinib in combination with capecitabine was recently approved for the treatment of adult patients with advanced or metastatic breast cancer who have received 2 or more prior anti-HER2–based regimens in the metastatic setting. Neratinib is an oral pan-HER inhibitor that binds covalently to the kinase site, providing irreversible binding. Phase 3 data showed that the combination of neratinib plus capecitabine improved progression-free survival vs lapatinib plus capecitabine. The duration of response was longer among patients in the neratinib arm. Neratinib plus capecitabine was also active against brain metastases associated with refractory, HER2-positive breast cancer, and this combination is listed in guidelines from the National Comprehensive Cancer Network for this indication. When combined with fulvestrant, neratinib demonstrated efficacy in patients with HER2-positive breast cancer, regardless of their hormone receptor status. Ongoing trials are evaluating the ability of neratinib to treat brain metastases, as well as the efficacy and safety of the triplet combination of neratinib, fulvestrant, and trastuzumab in this setting.

Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

Table of Contents

Treatment Goals in the Management of HER2-Positive Metastatic Breast Cancer

Ruth O'Regan MD

Professor
Hematology/Oncology Faculty
University of Wisconsin
School of Medicine and Public Health
Madison, Wisconsin

Approximately 15% to 20% of breast cancers diagnosed are human epidermal growth factor receptor 2 (HER2)-positive.[1] Approximately 10% of these patients present with de novo metastatic disease, and in the pivotal adjuvant trials, approximately a quarter of patients with early-stage HER2-positive breast cancer experienced a recurrence.[2,3] Poor response to therapy in the early-stage setting predicts for higher likelihood of relapse. There are other potential biomarkers that may be associated with resistance to HER2-directed agents, such as activation of the phosphoinositide 3-kinase pathway. In the CLEOPATRA trial (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer), which evaluated the addition of pertuzumab to trastuzumab and docetaxel, the median survival was almost 5 years,[4] demonstrating that patients can live a long time with metastatic HER2-positive breast cancer. Therefore, a key issue is to maintain quality of life while prolonging survival.

One of the goals of managing patients with metastatic HER2-positive disease in the first-line setting is to transition them from chemotherapy to HER2-directed agents—such as trastuzumab and pertuzumab—alone,

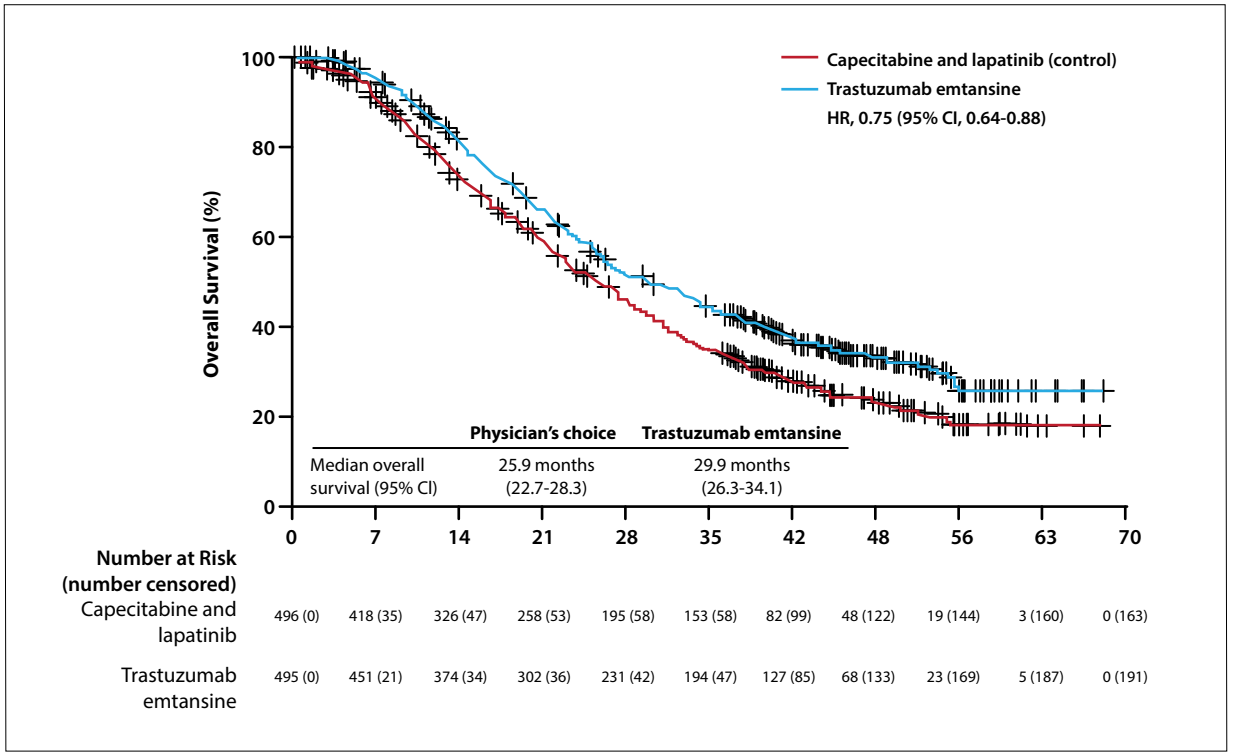


Figure 1. Overall survival in the EMILIA trial. EMILIA, A Study of Trastuzumab Emtansine Versus Capecitabine + Lapatinib in Participants With HER2-Positive Locally Advanced or Metastatic Breast Cancer; HR, hazard ratio. Adapted from Diéras V et al. *Lancet Oncol.* 2017;18(6):732-742.[9]

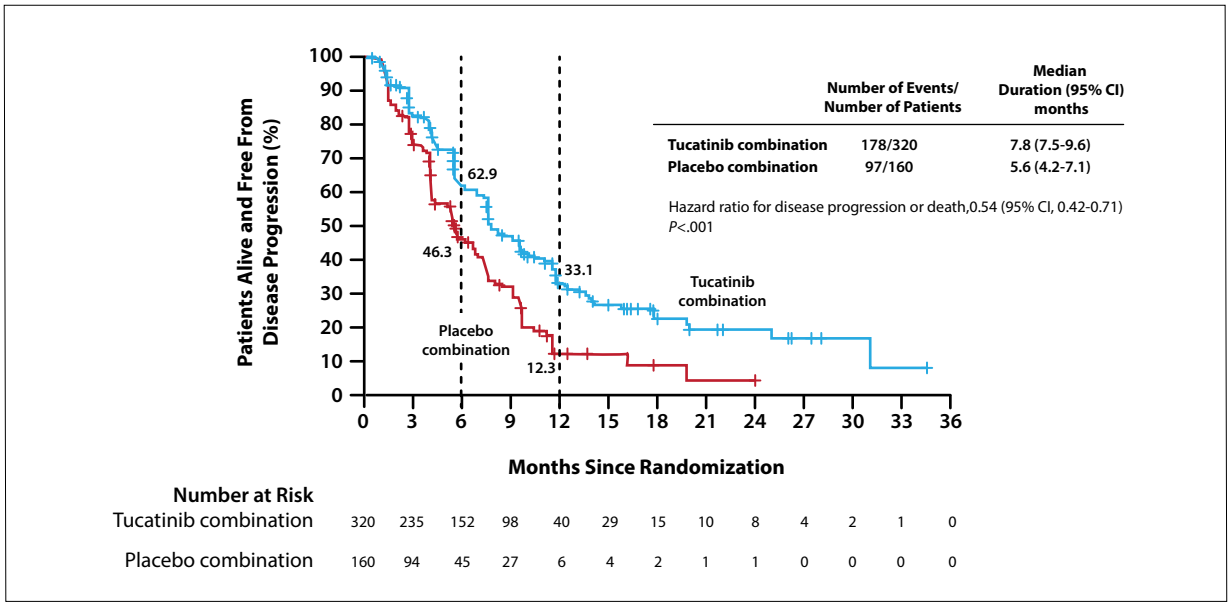


Figure 2. Progression-free survival in the HER2CLIMB trial. HER2CLIMB, A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer. Adapted from Murthy RK et al. *N Engl J Med.* 2020;382(7):597-609.[12]

thereby decreasing toxicity and maintaining quality of life. Brain metastases are a common concern with HER2-positive breast cancer, occurring in approximately one-third of patients throughout the spectrum of disease.[5] Brain metastases are associated with a worse prognosis.[6] The outcome is better, however, for patients with brain metastases who have HER2-positive disease vs triple-negative disease.[6] Given that patients with metastatic HER2-positive disease can live for a long time, it is critical to have therapies available that can control disease.

In guidelines for the management of breast cancer from the National Comprehensive Cancer Network (NCCN), the first-line recommendation is to use a taxane—either docetaxel or paclitaxel—with trastuzumab and pertuzumab.[7] The taxane is given for a finite number of cycles, usually 6 to 8. Patients with stable or improved scans can transition to trastuzumab and pertuzumab. At the time of disease progression, selection of the next therapy is based on the duration of treatment with pertuzumab and trastuzumab. In some patients, it may be beneficial to add back a taxane. Another option for second-line therapy is ado-trastuzumab emtansine (T-DM1). In the last year, several new agents have been approved by the US Food and Drug Administration (FDA) for use in the third-line setting, such as trastuzumab deruxtecan, tucatinib, and neratinib. Margetuximab is not yet approved, but early data are promising.[8] In the future, these third-line agents may be used in earlier settings.

Review of Clinical Trial Data

The CLEOPATRA trial reported positive results with adding pertuzumab to trastuzumab and docetaxel.[4] In the EMILIA trial (A Study of Trastuzumab Emtansine Versus Capecitabine + Lapatinib in Participants With HER2-Positive Locally Advanced or Metastatic Breast Cancer), T-DM1 was beneficial in the second-line setting (Figure 1).[9,10] More recently, the HER2CLIMB trial (A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer) evaluated tucatinib, a potent HER2 tyrosine kinase inhibitor.[11,12] Tucatinib targets HER2 with little impact on the epidermal growth factor receptor (EGFR). The trial enrolled patients with pretreated HER2-positive metastatic breast cancer. The patients had received trastuzumab, pertuzumab, and T-DM1 prior to study entry. All patients had a brain magnetic resonance image obtained at baseline. They were eligible for enrollment if they had previously treated stable brain metastases, untreated brain metastases that did not require immediate therapy, or previously treated progressing brain metastases. Patients without brain metastasis were also eligible for the study.

Treatment consisted of trastuzumab and capecitabine alone or with tucatinib. Patients were randomly assigned 2-to-1 to treatment with tucatinib vs placebo. Progression-free survival (PFS) improved by almost 50% among the patients who received tucatinib. The hazard ratio (HR) for progression or death was 0.54 (P<.001). The 1-year PFS was 33.1% in the tucatinib arm vs 12.3% in the control arm (Figure 2). The median PFS improved from 6 months with placebo to up to 8 months with tucatinib. A benefit was observed across all prespecified subgroups. The overall survival also was significantly improved, with a median

duration of 22 months with tucatinib vs 17 months with placebo (HR, 0.66; *P*=.0048). The confirmed objective response rate (ORR) was 40.6% in the tucatinib arm vs 22.8% in the placebo arm (*P*=.0008). Among the 291 patients with brain metastases, the median PFS was 7.6 months in the tucatinib arm vs 5.4 months in the control arm (HR, 0.48; *P*<.00001). An updated analysis also showed that tucatinib improved outcome among patients with stable or progressing brain metastases.[13]

Rates of toxicity in the trial were as expected. Tucatinib causes less diarrhea than some of the other tyrosine kinase inhibitors. Tucatinib is now approved, in combination with trastuzumab and capecitabine, for second-line or later treatment of patients with metastatic, HER2-positive breast cancer.[14]

The combination of neratinib plus capecitabine was recently approved for the treatment of adult patients with advanced or metastatic breast cancer who have received 2 or more prior anti-HER2–based regimens in the metastatic setting. Approval was based on results from the phase 3 NALA trial (A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting), which compared neratinib plus capecitabine vs lapatinib plus capecitabine. Data from the NALA trial showed that PFS was significantly longer among patients treated with neratinib plus capecitabine vs lapatinib plus capecitabine.[15] The 12-month PFS rate was 29% with neratinib/capecitabine vs 15% with lapatinib/capecitabine (HR, 0.76; *P*=.0059). The duration of response was longer among patients in the neratinib arm. Neratinib plus capecitabine also showed activity against refractory, HER2-positive breast cancer brain metastases. Neratinib may be uniquely suited for the management of patients with brain metastases. The next article in this monograph details these clinical trial data. Ongoing trials are evaluating neratinib in combination with other agents.

Novel Therapies

Margetuximab is a HER2-directed antibody with a different mechanism of action from trastuzumab. The SOPHIA trial (Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of HER2+ Metastatic Breast Cancer) investigated margetuximab in patients with HER2-positive metastatic breast cancer.[8,16] Patients had received at least 2 prior HER2-directed therapies, including pertuzumab, as well as 1 to 3 prior lines of treatment for metastatic disease. Patients with prior brain metastases were permitted to enroll if the metastases were treated and stable. All patients received their investigator's choice of chemotherapy, which could be capecitabine, eribulin, gemcitabine, or vinorelbine. The study randomly assigned 536 patients to receive margetuximab as the HER2-directed therapy, with the investigator's choice of chemotherapy, or trastuzumab plus chemotherapy. Patients were stratified based on the type of chemotherapy, the number of prior therapies, and the metastatic sites.

The median PFS was 4.9 months in the trastuzumab arm vs 5.6 months in the margetuximab arm (HR, 0.76; *P*=.033). The Kaplan-Meier curves separated in favor of margetuximab. The investigator-assessed ORR improved from 13.7% in the trastuzumab arm to 25.2% in the margetuximab arm (nominal *P*=.0006). The clinical benefit rate improved from 35.6% with trastuzumab to 48.1% with margetuximab (nominal *P*=.0025). Overall survival data are not yet mature. However, at the second interim analysis, overall survival was numerically prolonged in patients treated with margetuximab (18.9 vs 17.2 months; *P*=.758). Margetuximab is currently going through the FDA approval process.

An exciting therapy is the antibody-drug conjugate trastuzumab deruxtecan. The antibody portion consists of a humanized anti-HER2, immunoglobulin G1 monoclonal antibody with an amino acid sequence similar to that of trastuzumab. The antibody is conjugated to the topoisomerase I inhibitor, a derivative of exatecan, by a cleavable tetrapeptide linker. This structure is used to allow direct deposition of the topoisomerase inhibitor into the breast cancer cells.

The drug was initially evaluated in a phase 1, dose-expansion study of 115 patients with HER2-positive breast cancer.[17] All of the patients had received prior treatment with trastuzumab. Trastuzumab deruxtecan monotherapy was associated with a high response rate of 60% and a manageable safety profile in this population of heavily pretreated patients. The phase 2 DESTINY-Breast01 trial (A Study of DS-8201a in Metastatic Breast Cancer Previously Treated With Trastuzumab Emtansine [T-DM1]) was designed to confirm the results of the phase 1 trial.[18,19] The study had an initial stage to determine the recommended phase 2 dose, followed by a second stage to evaluate safety and efficacy. All patients had HER2-positive metastatic breast cancer and had received prior treatment with T-DM1. Patients with stable, treated brain metastases were permitted to enroll. The majority of patients had disease that was refractory to T-DM1; only a small number had resistant disease.

The data were impressive. The ORR was 61%, consisting of complete responses in 6% and partial responses in 55%. The median response duration was 14.8 months. According to the waterfall plot, almost all of the patients benefitted from this drug. The median PFS was 16.4 months. Response rates were consistent across subgroups, including those based on hormone receptor status and

brain metastases. The drug was generally well-tolerated. However, there were rare reports of pulmonary toxicity, which can be serious and even fatal. Trastuzumab deruxtecan is approved for the treatment of HER2-positive breast cancer in patients who have received at least 2 prior anti-HER2–based regimens for their metastatic disease.[20]

Conclusion

Overall, the number of therapies available to treat HER2-positive metastatic breast cancer has improved outcome. The median overall survival was almost 5 years in the CLEOPATRA study,[4] and that was achieved without the use of several of the newer agents. The hope is that the newer agents will prolong survival even further. Importantly, the toxicity profile for most of these agents is favorable. The primary goal is to keep these patients alive while maintaining their quality of life.

Disclosure

Dr O'Regan has received grant/research support from Eisai, Pfizer, Novartis, and Cascadian. She is a consultant for Pfizer, Genomic Health, Biotheranostics, Novartis, Puma, Genentech, Immunomedics, and MacroGenics.

References

1. Cesca MG, Vian L, Cristóvão-Ferreira S, Pondé N, de Azambuja E. HER2-positive advanced breast cancer treatment in 2020. *Cancer Treat Rev.* 2020;88:102033.
2. Perez EA, Romond EH, Suman VJ, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol.* 2014;32(33):3744-3752.
3. Slamon D, Eiermann W, Robert NJ, et al. Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer [SABCS abstract S5-04]. *Cancer Res.* 2016;71(4 suppl).
4. Swain SM, Miles D, Kim SB, et al; CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(4):519-530.
5. Ren D, Cheng H, Wang X, et al. Emerging treatment strategies for breast cancer brain metastasis: from translational therapeutics to real-world experience [published online June 30, 2020]. *Ther Adv Med Oncol*. 2020;12:1758835920936151.
6. Martin AM, Cagney DN, Catalano PJ, et al. Brain metastases in newly diagnosed breast cancer. A population-based study. *JAMA Oncol.* 2017;(8):1069-1077.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Breast Cancer. Version 5.2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated July 15, 2020. Accessed August 11, 2020.
8. Rugo H, Im SA, Shaw Wright GL, et al. SOPHIA primary analysis: a phase 3 (P3) study of margetuximab (M) + chemotherapy (C) versus trastuzumab (T) + C in patients (pts) with HER2+ metastatic (met) breast cancer (MBC) after prior anti-HER2 therapies (Tx) [ASCO abstract 1000]. *J Clin Oncol.* 2019;37(15 suppl).
9. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(6):732-742.
10. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-1791.
11. Murthy R, Loi S, Okines A, et al. Tucatinib vs placebo, both combined with capecitabine and trastuzumab, for patients with pretreated HER2-positive metastatic breast cancer with and without brain metastases (HER2CLIMB) [SABCS abstract GS1-01]. *Cancer Res.* 2019;79(suppl 4).
12. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med.* 2020;382(7):597-609.
13. Lin NU, Borges V, Anders C, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J Clin Oncol.* 2020;38(23):2610-2619.
14. Tukysa [package insert]. Bothell, WA: Seattle Genetics, Inc; 2020.
15. Saura C, Oliveira M, Feng YH, et al; NALA Investigators. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with >/= 2 HER2-directed regimens: phase III NALA trial [published online July 17, 2020]. *J Clin Oncol*. 2020:JCO2000147. doi:10.1200/JCO.20.00147.
16. Rugo H, Im SA, Cardoso F, et al. Phase III SOPHIA study of margetuximab + chemotherapy vs trastuzumab + chemotherapy in patients with HER2+ metastatic breast cancer after prior anti-HER2 therapies: second interim overall survival analysis [SABCS abstract GS1-02]. *Cancer Res.* 2019;79(suppl 4).
17. Tamura K, Tsurutani J, Takahashi S, et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol.* 2019;20(6):816-826.
18. Krop I, Saura C, Yamashita T, et al. [Fam-] trastuzumab deruxtecan (T-DXd; DS-8201a) in subjects with HER2-positive metastatic breast cancer previously treated with T-DM1: a phase 2, multicenter, open-label study (DESTINY-Breast01) {SABCS abstract GS1-03]. *Cancer Res.* 2019;79(suppl 4).
19. Modi S, Saura C, Yamashita T, et al; DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N Engl J Med.* 2020;382(7):610-621.
20. Enhertu [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc; 2019.

Neratinib: Clinical Trial Data in HER2-Positive Metastatic Breast Cancer

Joyce A. O'Shaughnessy, MD

Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
Texas Oncology
US Oncology
Dallas, Texas

Neratinib is FDA-approved in early-stage and metastatic HER2-positive breast cancer.[1] In the early-stage setting, neratinib is approved as a single agent for the extended adjuvant treatment of adult patients who already received treatment with adjuvant trastuzumab-based therapy. The combination of neratinib plus capecitabine is approved for the treatment of adult patients with advanced or metastatic breast cancer who have received 2 or more prior anti-HER2–based regimens in the metastatic setting. Neratinib is an oral pan-HER inhibitor that binds covalently to the kinase site, providing irreversible binding.[1] These features are useful in the metastatic setting. With pan-HER blockade, it is possible to overcome mechanisms of resistance that can occur with agents that primarily block HER2, such as compensatory upregulation of other HER2 family members, including HER1 and HER3. Data show that neratinib is non–cross-resistant with trastuzumab in the metastatic setting.[2] Another important attribute is that neratinib crosses the blood-brain barrier.[3] In addition to preclinical studies that demonstrate this activity, there are now 3 clinical trials in the metastatic setting that have shown activity in the brain.[4-7]

The phase 2 NEfERT-T trial (Study Evaluating Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in ErbB-2 Positive Advanced Breast Cancer) evaluated the combination of neratinib and paclitaxel vs trastuzumab and paclitaxel in the first-line metastatic breast cancer setting.[8] Enrolled patients had HER2-positive disease. The primary endpoint of median PFS was 12.9 months in both arms (*P*=.89). The ORR was 74.8% with neratinib/paclitaxel vs 77.6% with trastuzumab/paclitaxel (*P*=.52). The clinical benefit rate was 88.4% vs 85.2%, respectively (*P*=.24). A significant difference was seen in the percentage of patients who developed symptomatic or progressive central nervous system (CNS) metastasis while receiving treatment. This rate was 8.3% with neratinib vs 17.3% with trastuzumab (relative risk, 0.48; *P*=.002). A competing risks model analysis showed that the 2-year estimated cumulative incidence of CNS recurrence was 10.1% among patients treated with neratinib/paclitaxel vs 20.2% among those treated with

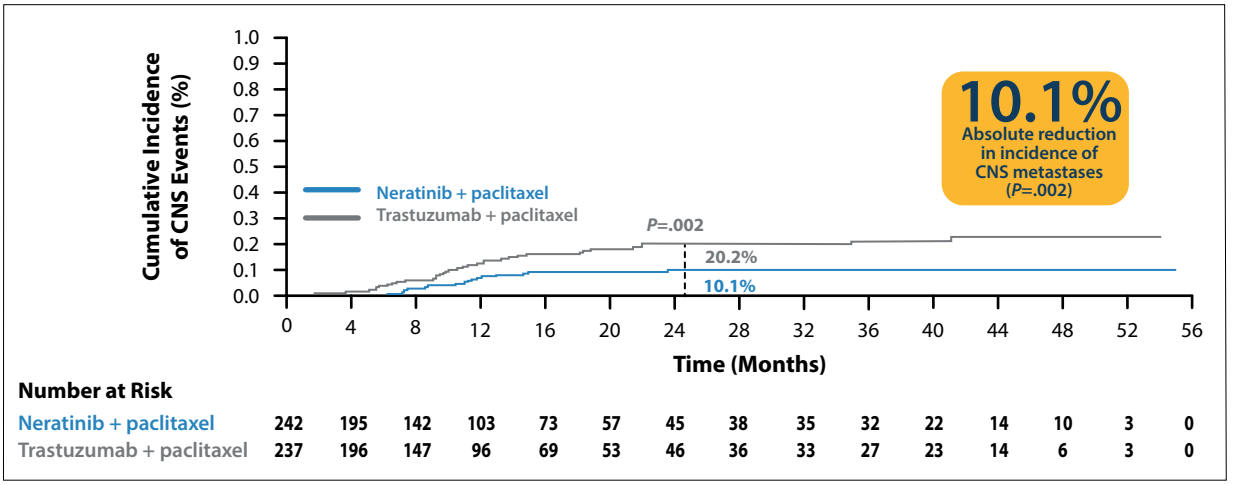


Figure 3. CNS events in the phase 2 NEfERT-T trial. CNS, central nervous system; NEfERT-T, Study Evaluating Neratinib Plus Paclitaxel vs Trastuzumab Plus Paclitaxel in ErbB-2 Positive Advanced Breast Cancer. Awada A et al. *JAMA Oncol.* 2016;2(12):1557-1564.[8]

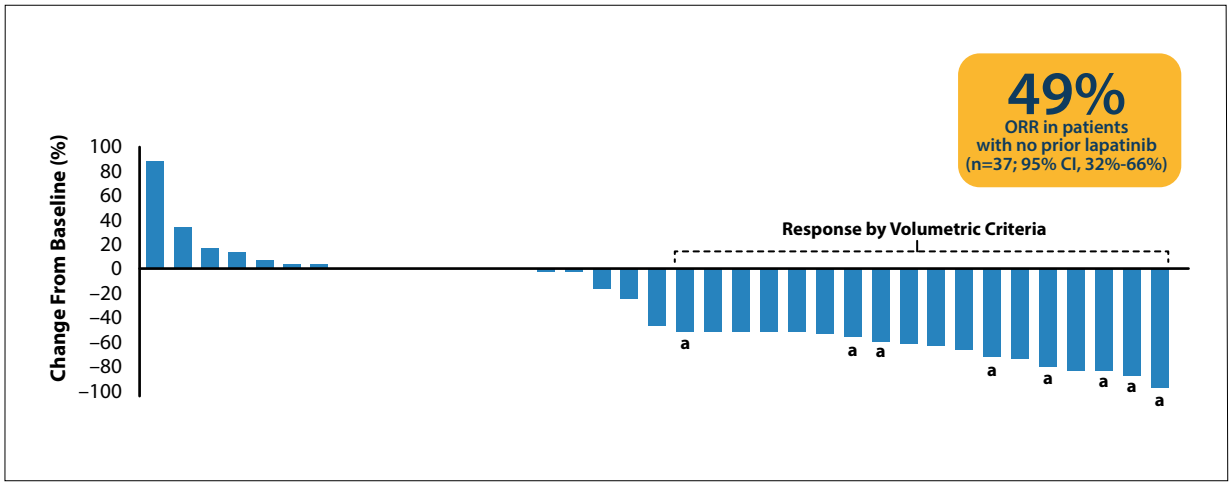


Figure 4. Best central nervous system volumetric response among lapatinib-naive patients in the phase 2 TBCRC 022 trial, which evaluated neratinib plus capecitabine. TBCRC 022, Translational Breast Cancer Research Consortium; A Phase II Trial of HKI-272 (Neratinib), Neratinib and Capecitabine, and Ado-Trastuzumab Emtansine for Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer and Brain Metastases. Adapted from Freedman RA et al. *J Clin Oncol.* 2019;37(13):1081-1089.[4]

trastuzumab/paclitaxel (*P*=.002; Figure 3). Therefore, the benefits of neratinib were equivalent to trastuzumab in patients with non-CNS systemic disease and superior among patients with CNS disease. The median time to a CNS event was not reached for neratinib/paclitaxel vs 18 months for trastuzumab/paclitaxel, an encouraging observation. The results from this trial suggest that the use of neratinib earlier in the disease course might prevent the emergence of clinical CNS metastatic disease. Data from the NEfERT-T trial led to the inclusion of neratinib plus paclitaxel in the NCCN guidelines as treatment for HER2-positive CNS disease.[9]

The phase 2 TBCRC 022 trial (Translational Breast Cancer Research Consortium; A Phase II Trial of HKI-272 [Neratinib], Neratinib and Capecitabine, and Ado-Trastuzumab Emtansine for Patients With Human Epidermal Growth Factor Receptor 2 [HER2]-Positive Breast Cancer and Brain Metastases) focused on brain metastases in patients with HER2-positive breast cancer.[4] The study evaluated a full dose of neratinib (240 mg daily) combined with capecitabine (750 mg/m^2, twice daily; 14 days on, 7 days off). The capecitabine dose was lower than usual because the goal was to use a full dose of neratinib to impact the CNS. The enrolled patients had measurable, progressive, HER2-positive brain metastases. They had received a median of 1 prior chemotherapy regimen for metastatic disease, and nearly half had received 2. Patients had received prior brain irradiation or stereotactic radiosurgery, and approximately one-third had undergone 2 rounds of CNS irradiation.

There were 2 cohorts in the single-arm trial. Patients in cohort A were lapatinib-naive, and those in cohort B had received prior treatment with lapatinib. Patients in cohort A had a composite CNS ORR of 49% (Figure 4), and a median PFS of 5.5 months.[4] In cohort B, the CNS ORR was 33%, and the median PFS was 3.1 months. The CNS response rate of nearly 50% seen with neratinib in lapatinib-naive patients, combined with controlled systemic disease, indicates an impressive level of anti-tumor activity, particularly in a group of patients who had received prior CNS radiation and treatment for systemic disease.

These results led to a registration trial for capecitabine and neratinib in the metastatic setting. The approval of neratinib in the extended adjuvant setting was based on results from the ExteNET trial (Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer).[5] The phase 3 NALA trial (A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting) compared neratinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer.[6,7] Because T-DM1 had improved survival compared with the latter combination in earlier studies,[10] the trial evaluated the study treatments as third-line therapy. Treatment in the investigational arm consisted of neratinib at 240 mg/day, plus capecitabine at 750 mg/m^2 given twice daily. Patients in the neratinib arm also received prophylactic loperamide. In the control arm, the dose of lapatinib was 1250 mg/day, and the dose of capecitabine was 1000 mg/m^2, given twice daily. Eligible patients had centrally confirmed HER2-positive disease. They had received at least 2 lines of HER2-directed therapy for metastatic disease. The trial enrolled patients with stable, treated, asymptomatic brain metastases. The study's co–primary endpoints were centrally confirmed

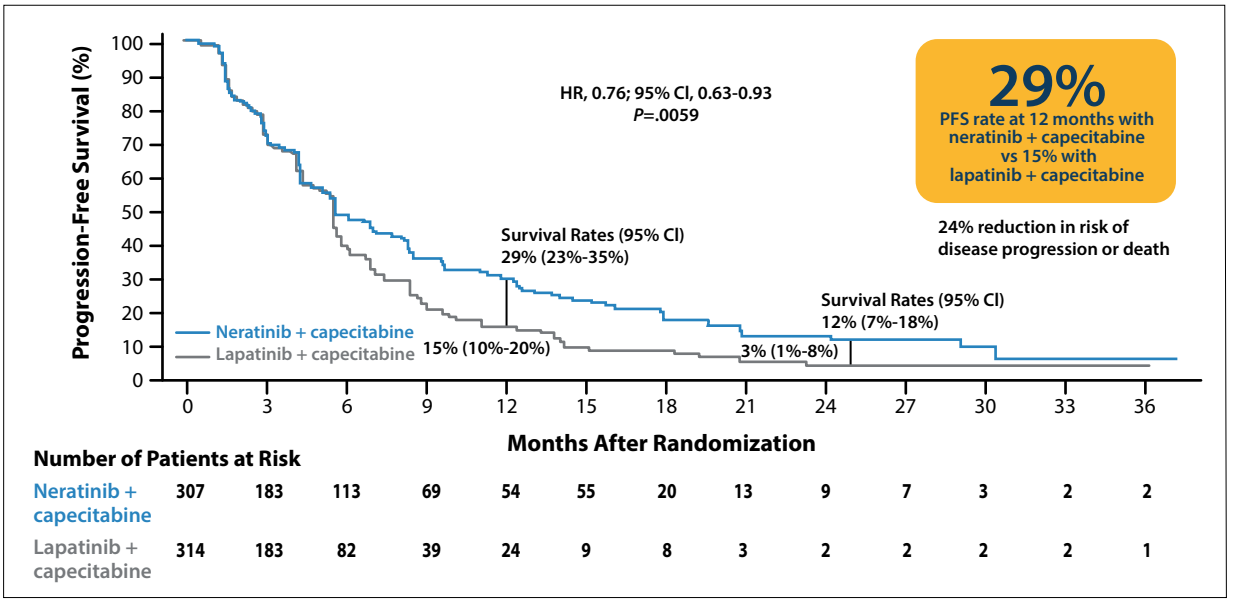


Figure 5. Progression-free survival in the phase 3 NALA trial, which compared neratinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer treated with at least 2 prior HER2-directed regimens in the metastatic setting. HR, hazard ratio; NALA, A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting. Adapted from Saura C et al. *J Clin Oncol.* 2020:JCO2000147.[6]

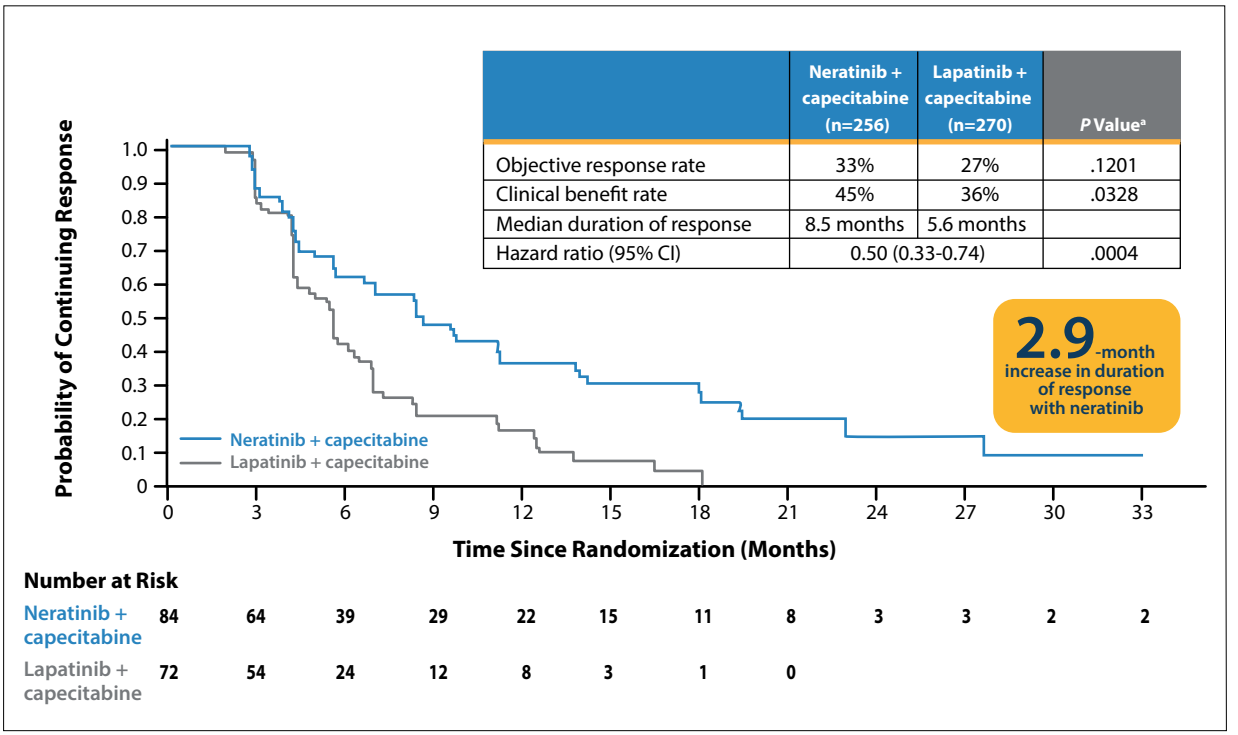


Figure 6. Duration of response in the NALA trial. NALA, A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting. Data from Saura C et al. *J Clin Oncol.* 2020:JCO2000147.[6] Data on file; Puma Biotechnology.

PFS and overall survival. Most of the patients (69%) had received 2 lines of prior HER2-directed therapies for metastatic breast cancer. Prior HER2-targeted regimens included trastuzumab monotherapy in 38%; trastuzumab, pertuzumab, and T-DM1 in 35%; trastuzumab plus T-DM1 in 20%; and trastuzumab plus pertuzumab

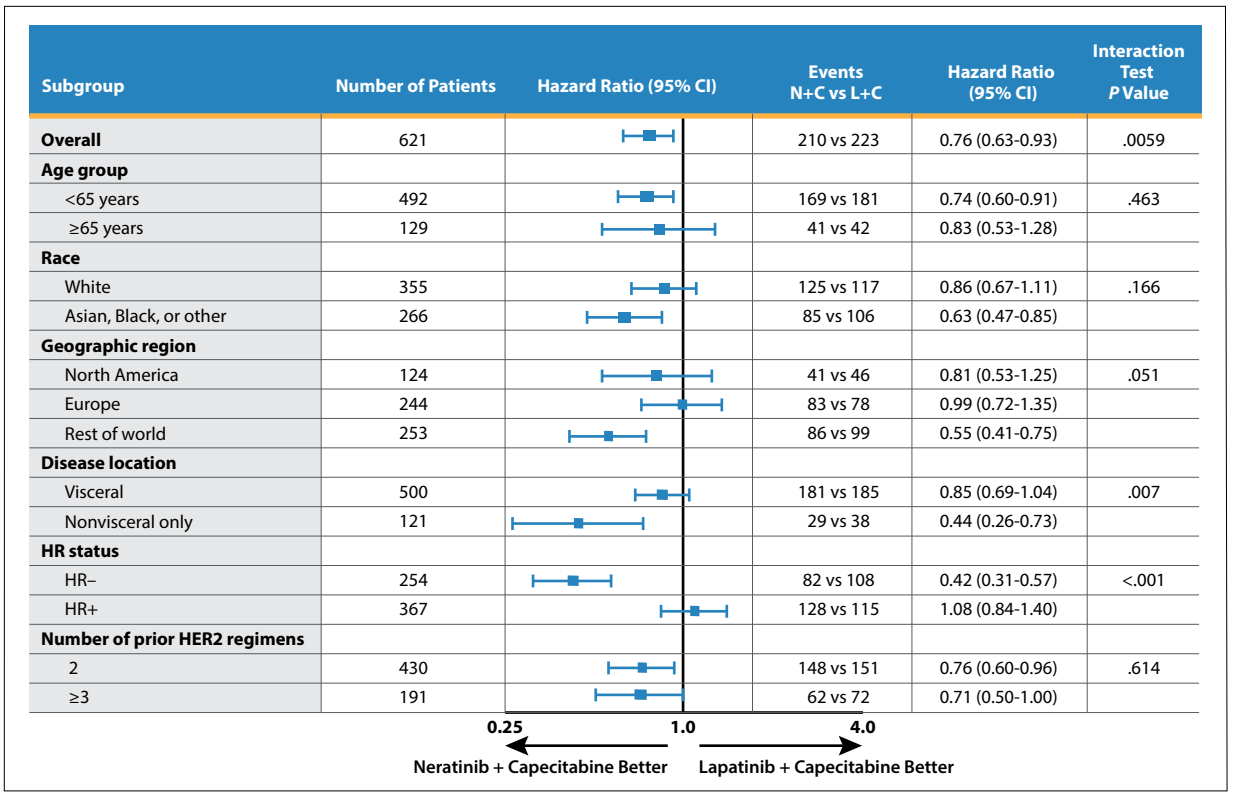


Figure 7. Benefits among subgroups in the NALA trial. HER2, human epidermal growth factor receptor 2; NALA, A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting. Adapted from Saura C et al. *J Clin Oncol.* 2020:JCO2000147.[6]

in 7.5%. Approximately 60% of the patients were estrogen receptor (ER)-positive.

The trial met the primary endpoint of PFS, showing 12-month PFS rates of 29% with neratinib/capecitabine vs 15% with lapatinib/capecitabine (HR, 0.76; *P*=.0059; Figure 5). The duration of response was longer with neratinib vs lapatinib (Figure 6). Benefits were seen across multiple subgroups (Figure 7). The overall survival data are immature (HR, 0.88; *P*=.2).

The results were interesting in light of the lower dose of capecitabine used with neratinib. The trial provided a good way to compare the activities of lapatinib, which inhibits EGFR/HER1 and HER2, with that of neratinib, which is a pan-HER inhibitor, blocking HER2 and EGFR/HER1 as well as HER4, while preventing emergence of resistance through HER3.[11]

In the NALA trial, the rate of grade 3 diarrhea was 24% with neratinib vs 13% with lapatinib.[6,7] Rates of grade 2 diarrhea were 28% vs 18%, respectively. However, these episodes of grade 2 or 3 diarrhea did not occur every day. The cumulative duration of grade 2 or 3 diarrhea was 7 days with neratinib vs 9 days with lapatinib. Patients either adjusted to therapy, or their dose of treatment was reduced. Most importantly, the rates of treatment discontinuation owing to diarrhea were only 2.6% with neratinib and 2.3% with lapatinib. This toxicity was therefore manageable.

Another important observation from the NALA trial was the time to intervention for symptomatic CNS disease. A need to intervene for CNS metastases was reported in 22.8% of the neratinib arm vs 29.2% of the lapatinib arm (*P*=.043).[6,7] This result mainly reflects a reduction in the use of radiation therapy for CNS progression. Although lapatinib was beneficial in treating the CNS, the improvement seen with neratinib was statistically significantly greater compared with lapatinib (*P*=.043).

In the NALA trial, the combination of neratinib/capecitabine was associated with a strong benefit among patients who had hormone receptor–negative disease (*P*<.001).[6,7] There was no significant difference between the treatment arms among patients with hormone receptor–positive disease. In contrast, in the ExteNET trial, the combination of neratinib plus endocrine therapy was very effective in patients with hormone receptor–positive disease, but less effective in the ER-negative population.[5] This observation suggests that blockade/inhibition of ER is important when treating patients who have hormone receptor–positive and HER2-positive disease with neratinib. In summary, based on the NALA

trial, neratinib plus capecitabine has supplanted lapatinib plus capecitabine.

The ongoing phase 2 SUMMIT trial (Neratinib HER Mutation Basket Study) is investigating neratinib combinations in patients with solid tumors that have the *HER2* mutation—not *HER2* amplification.[12] Results from an interim analysis of patients with metastatic breast cancer treated with neratinib plus fulvestrant were presented in 2018.[12] Patients had received a median of 3 prior therapies. The trial showed a median duration of response of 9.2 months and a median PFS of 5.4 months. The ORR was approximately 30%, and the clinical benefit rate was 47%. There was substantial improvement in tumor burden in the majority of patients with *HER2*-mutant breast cancer, most of whom were ER-positive. The incidence of *HER2* mutations increases in patients with the lobular subtype, up to approximately 10% to 15% in the metastatic setting. Among breast cancer patients without *HER2* amplification, approximately 5% to 8% of those with metastatic disease have an activating *HER2* mutation. *HER2* mutations are rarely seen in primary breast cancers. They arise as an acquired mutation in the context of resistance to endocrine therapy.

The single-arm FB-10 trial from the National Surgical Adjuvant Breast and Bowel Project evaluated the combination of T-DM1 (3.6 mg/kg every 3 weeks) plus escalating doses of neratinib (up to 240 mg daily).[13] Enrolled patients had shown resistance to previous treatment with pertuzumab plus trastuzumab, so this trial investigated potential cross-resistance with neratinib plus T-DM1. The drug combination was safe. Among the 19 patients evaluable for response, the trial yielded an ORR of 63%, including 3 complete responses and 9 partial responses, which was substantially better than the ORR of 43.6% reported with single-agent T-DM1 in the EMILIA trial.[10,13] The median PFS was also robust, and longer than that reported with T-DM1 in the EMILIA trial. The FB-10 trial evaluated the important issue of the extent of cross-resistance with neratinib among patients who had already received pertuzumab and/or T-DM1. These data in metastatic patients suggest that neratinib is not cross-resistant with pertuzumab and T-DM1. In the NALA trial, neratinib showed superior activity vs lapatinib in heavily pretreated patients. It is reassuring to see additional benefits with neratinib, beyond what would be expected with T-DM1. Neratinib has also proven to be highly effective in the extended adjuvant setting among hormone receptor-positive, HER2-positive patients who did not achieve a complete pathologic response with trastuzumab plus chemotherapy.[14] Oncologists are now recommending neratinib, along with endocrine therapy, in high-risk ER-positive, HER2-positive patients after adjuvant T-DM1 when a pathologic complete response was not obtained with neoadjuvant chemotherapy plus trastuzumab/pertuzumab.

Disclosure

Dr O'Shaughnessy has received honoraria for consulting and advisory boards from AbbVie, Agendia, Amgen Biotechnology, AstraZeneca, Bristol Myers Squibb, Celgene Corporation, Eisai, Genentech, Genomic Health, GRAIL, Immunomedics, Heron Therapeutics, Ipsen Biopharmaceuticals, Jounce Therapeutics, Lilly, Merck, Myriad Genetics, Novartis, Odonate Therapeutics, Pfizer, Puma Biotechnology, Prime Oncology, Roche, Seattle Genetics, Syndax Pharmaceuticals, and Takeda.

References

1. Nerlynx [package insert]. Los Angeles, CA: Puma Biotechnology, Inc; 2020.
2. Burstein HJ, Sun Y, Dirix LY, et al. Neratinib, an irreversible ErbB receptor tyrosine kinase inhibitor, in patients with advanced ErbB2-positive breast cancer. *J Clin Oncol.* 2010;28(8):1301-1307.
3. Nagpal A, Redvers RP, Ling X, et al. Neoadjuvant neratinib promotes ferroptosis and inhibits brain metastasis in a novel syngeneic model of spontaneous HER2+ve breast cancer metastasis. *Breast Cancer Res.* 2019;21(1):94.
4. Freedman RA, Gelman RS, Anders CK, et al; Translational Breast Cancer Research Consortium. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol.* 2019;37(13):1081-1089.
5. Chan A, Delaloge S, Holmes FA, et al; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2016;17(3):367-377.
6. Saura C, Oliveira M, Feng YH, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: findings from the multinational, randomized, phase III NALA trial [ASCO abstract 1002]. *J Clin Oncol.* 2019;37(15 suppl).
7. Saura C, Oliveira M, Feng YH, et al; NALA Investigators. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with >/= 2 HER2-directed regimens: phase III NALA trial [published online July 17, 2020]. *J Clin Oncol.* 2020:JCO2000147.
8. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol.* 2016;2(12):1557-1564.
9. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers. Version 2.2020. https://www. nccn.org/professionals/physician_gls/pdf/cns.pdf. Updated April 30, 2020. Accessed August 11, 2020.
10. Verma S, Miles D, Gianni L, et al; EMILIA Study Group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med.* 2012;367(19):1783-1791.
11. Xia W, Petricoin EF III, Zhao S, et al. An heregulin-EGFR-HER3 autocrine signaling axis can mediate acquired lapatinib resistance in HER2+ breast cancer models. *Breast Cancer Res.* 2013;15(5):R85.
12. Smyth LM, Piha-Paul SA, Saura C, et al. Neratinib + fulvestrant for HER2-mutant, HR-positive, metastatic breast cancer: updated results from the phase 2 SUMMIT trial [SABCS abstract PD3-06]. *Cancer Res.* 2018;78(suppl 4).
13. Abraham J, Montero AJ, Jankowitz RC, et al. Safety and efficacy of T-DM1 plus neratinib in patients with metastatic HER2-positive breast cancer: NSABP foundation trial FB-10. *J Clin Oncol.* 2019;37(29):2601-2609.
14. Gnant M, Martin M, Holmeset FA, et al. Efficacy of neratinib in hormone receptor-positive patients who initiated treatment within 1 year of completing trastuzumab-based adjuvant therapy in HER2+ early stage breast cancer: subgroup analyses from the phase III ExteNET trial [SABCS abstract P2-13-01]. *Cancer Res.* 2018;78(suppl 4).

Incorporating Neratinib Into Clinical Practice for Patients With HER2-Positive Metastatic Breast Cancer

Claudine Isaacs, MD

Professor of Medicine and Oncology
Lombardi Comprehensive Cancer Center
Georgetown University Medical Center
Washington, DC

Neratinib is FDA-approved in 2 settings: in the extended adjuvant setting and in the metastatic setting for patients who have received 2 or more lines of therapy for metastatic disease.[1] These indications are based primarily on the results from the ExteNET and NALA trials, respectively.[2-4] Data from the TBCRC 022 and NEfERT-T trials also supported the efficacy of neratinib for the treatment of brain metastasis in HER2-positive disease.[5,6] The NCCN includes neratinib in their guidelines for breast cancer, as well as for CNS cancers. The combination of neratinib plus capecitabine is given a category 2A designation, based on the data from the NALA and TBCRC 022 trials.[3] Neratinib plus paclitaxel was given a category 2B designation, based on data from the NEfERT-T trial.

As discussed above, the NALA trial enrolled patients who had received 2 or more lines of HER2-directed therapy for metastatic, HER2-positive disease. The trial permitted enrollment of patients with asymptomatic or stable brain metastases. The trial results support the use of neratinib in this group of patients. The TBCRC 022 and NEfERT-T trials provide further evidence of activity of this agent for CNS disease, an important finding.[5,6]

There are still questions regarding how to manage the toxicity of neratinib. One of the main toxicities is diarrhea. Although diarrhea is common, it has a relatively short duration. Several strategies have been developed to mitigate the diarrhea. In the NALA trial, diarrhea of any grade was observed in 83.2% of patients treated with neratinib plus capecitabine vs 66.2% for lapatinib plus capecitabine (Table 1).[4] Treatment-emergent grade 3 diarrhea occurred in 24.4% vs 12.5%, respectively. An important point is that the NALA trial required prophylaxis with loperamide starting with cycle 1. The rate of discontinuation owing to diarrhea was 2.6% in those receiving neratinib plus capecitabine vs 2.3% of those receiving lapatinib plus capecitabine. The rate of discontinuation of any study drug owing to any treatment-emergent adverse event was 13.9% in the neratinib arm vs 18.0% in the lapatinib arm. With new drugs, tolerability and ease of toxicity management are key, especially when the drug is an oral therapy that the patient takes at home. Diarrhea, even relatively low-grade cases, is disruptive to the patient's daily quality of life. Grade 3 diarrhea can severely limit a patient's ability to engage in normal activities.

The CONTROL trial (An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients With Early-Stage HER2+ Breast Cancer Treated With Neratinib and Loperamide) evaluated different mechanisms to control the diarrhea associated with neratinib among patients with early HER2-positive breast cancer.[8] This open-label, phase 2 trial investigated various interventions, including administration of loperamide alone, colestipol plus loperamide, colestipol plus loperamide, and budesonide plus loperamide. In addition, 2 arms investigated dose escalation of neratinib. Rather than starting out immediately with 240 mg daily, the dose was ramped up gradually (Figure 8). Patients started with 3 pills of 40 mg each for the first week. Patients who could tolerate that starting dose received 4 tablets (160 mg total) for the second week, and then a full dose of 240 mg daily from week 3 on. Patients in the dose-escalation arms used loperamide as needed. With this approach, the percent of patients who discontinued neratinib owing to diarrhea in month 1 was only 3.3%, and no patients did so in subsequent months (Figure 9).[8] Another issue identified by the CONTROL trial is that patients were experiencing both severe constipation secondary to prophylactic loperamide and severe diarrhea, from neratinib. The dose-escalation strategy—with loperamide given only as needed—addresses this concern.

Although the CONTROL trial was conducted in patients with early-stage breast cancer, the results are also applicable to patients with metastatic disease. Based on

Table 1. The Most Common Treatment-Emergent Adverse Events in the NALA Trial

	Neratinib + Capecitabine (n=303)		Lapatinib + Capecitabine (n=311)	
	All Grades (%)	Grades ≥3 (%)	All Grades (%)	Grades ≥3 (%)
Diarrhea	252 (83.2)	74 (24.4)[a]	206 (66.2)	39 (12.5)[a]
Nausea	161 (53.1)	13 (4.3)	132 (42.4)	9 (2.9)
PPE syndrome	139 (45.9)	29 (9.6)	175 (56.3)	35 (11.3)
Vomiting	138 (45.5)	12 (4.0)	97 (31.2)	6 (1.9)
Decreased appetite	107 (35.3)	8 (2.6)	67 (21.5)	7 (2.3)
Fatigue	104 (34.3)	9 (3.0)	97 (31.2)	10 (3.2)
Constipation	94 (31.0)	4 (1.3)	41 (13.2)	1 (0.3)
Stomatitis	62 (20.5)	6 (2.0)	83 (26.7)	8 (2.6)
Weight decreased	60 (9.8)	1 (0.3)	41 (13.2)	2 (0.6)
Rash	30 (9.9)	0	69 (22.2)	2 (0.6)
Anemia	45 (14.9)	6 (2.0)	51 (16.4)	11 (3.5)
Dizziness	43 (14.2)	1 (0.3)	31 (10.0)	2 (0.6)
Cough	37 (12.2)	0	34 (10.9)	0
Abdominal pain	36 (11.9)	3 (1.0)	45 (14.5)	6 (1.9)
Asthenia	36 (11.9)	8 (2.6)	36 (11.6)	5 (1.6)
Hypokalemia	35 (11.9)	14 (4.6)	44 (14.1)	20 (6.4)
Paronychia	35 (11.6)	2 (0.7)	49 (15.8)	3 (1.0)
Pyrexia	33 (10.9)	0	32 (10.3)	1 (0.3)
Headache	32 (10.6)	1 (0.3)	51 (16.4)	3 (1.0)

[a]There were no reports of grade 4 diarrhea. NALA, A Study of Neratinib Plus Capecitabine Versus Lapatinib Plus Capecitabine in Patients With HER2+ Metastatic Breast Cancer Who Have Received Two or More Prior HER2 Directed Regimens in the Metastatic Setting. PPE, palmar-plantar erythrodysesthesia. Adapted from Saura C et al. *J Clin Oncol.* 2020:JCO2000147.[4]

data from the CONTROL trial, many clinicians now increase the neratinib dose more slowly, even going from 4 tablets in one week to 5 tablets the next week, and then moving to 6 tablets the next week only if the drug was well-tolerated. Thus, the dose-escalation approach can be successfully used to help manage the side effects of this therapy.

In the NALA trial, some other adverse events were higher with neratinib/capecitabine vs lapatinib/capecitabine.[6] Gastrointestinal events were more common in the neratinib arm, but most cases were grade 1/2. Diarrhea occurred in 83.2% of the neratinib/capecitabine arm vs 66.2% of the lapatinib/capecitabine arm. Nausea was a bit more common, occurring in 53.1% vs 42.4%, but cases were generally low grade. Rash was somewhat less common in the neratinib arm (9.9% vs 22.2%). Patients in the neratinib arm also had higher rates of constipation (31.0% vs 13.2%), but this event resulted from overcompensation of the management of diarrhea.

Administration of oral agents, particularly when given on different schedules, requires careful patient education. The regimen can be complicated, as neratinib is taken every day throughout the treatment course, whereas capecitabine is taken for 14 days followed by 1 week off. As some of the toxicities of capecitabine and neratinib overlap, the doses of one or both drugs may need to be reduced, held, or stopped altogether.

Clinical Scenarios for Neratinib

Neratinib is an appropriate treatment for the third-line setting and beyond, and—given its demonstrated activity in CNS—neratinib is also an option for patients with brain metastases. The NALA, TBCRC 022, and NEfERT-T trials have all shown efficacy in this group of patients.[3-6]

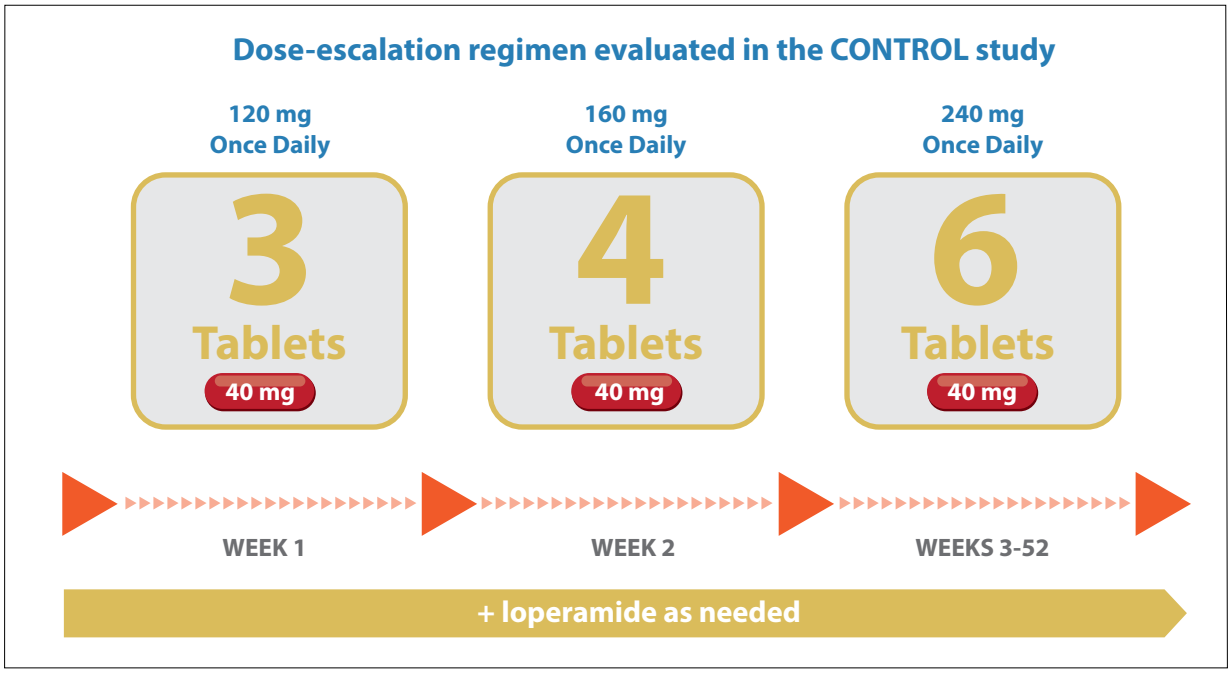
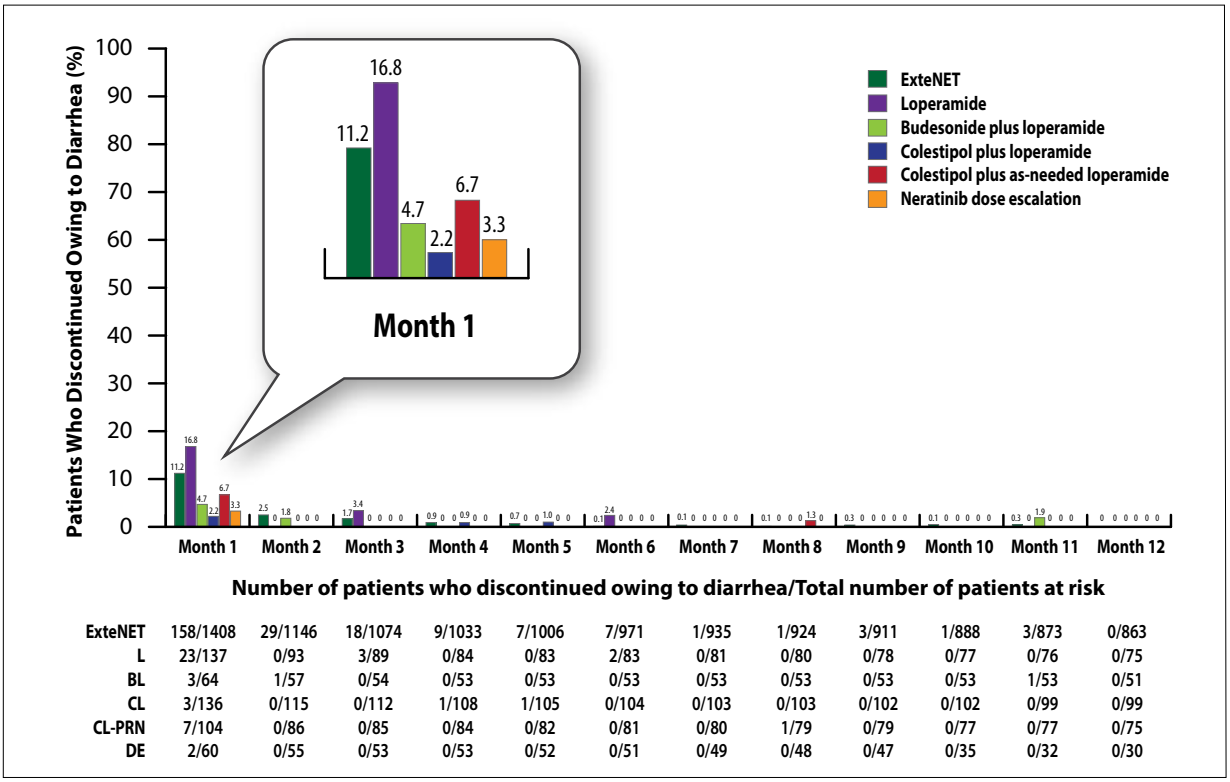


Figure 8. A dose-escalation strategy for neratinib evaluated in the CONTROL trial. A second dose-escalation arm in the trial was still enrolling at the data cutoff date of August 26, 2019. That arm starts neratinib at 4 pills (160 mg) daily for 2 weeks, then increases to 5 pills (200 mg) daily for another 2 weeks, then increases to the full dose of 6 pills (240 mg) daily for the rest of the year. CONTROL, An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients With Early-Stage HER2+ Breast Cancer Treated With Neratinib and Loperamide.



ExteNET	158/1408	29/1146	18/1074	9/1033	7/1006	7/971	1/935	1/924	3/911	1/888	3/873	0/863
L	23/137	0/93	3/89	0/84	0/83	2/83	0/81	0/80	0/78	0/77	0/76	0/75
BL	3/64	1/57	0/54	0/53	0/53	0/53	0/53	0/53	0/53	0/53	1/53	0/51
CL	3/136	0/115	0/112	1/108	1/105	0/104	0/103	0/103	0/102	0/102	0/99	0/99
CL-PRN	7/104	0/86	0/85	0/84	0/82	0/81	0/80	1/79	0/79	0/77	0/77	0/75
DE	2/60	0/55	0/53	0/53	0/52	0/51	0/49	0/48	0/47	0/35	0/32	0/30

Figure 9. Treatment discontinuations related to treatment-emergent diarrhea in the ExteNET and CONTROL trials. BL, budesonide plus loperamide; CL, colestipol plus loperamide; CL-PRN, colestipol plus as-needed loperamide; CONTROL, An Open-Label Study to Characterize the Incidence and Severity of Diarrhea in Patients With Early-Stage HER2+ Breast Cancer Treated With Neratinib and Loperamide; L, loperamide; DE, neratinib dose escalation; ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer. Adapted from Barcenas CH et al. *Ann Oncol.* 2020;S0923-7534(20)39833-1.[8]

Additionally, the SUMMIT trial demonstrated activity of neratinib in combination with fulvestrant and trastuzumab in patients with hormone receptor–positive metastatic breast cancer with *HER2* mutations.[9,10] SUMMIT is a "basket" trial that includes patients with HER2 mutations across tumor types; 25% of the patients had breast cancer. Of note, the patients did not have HER2 amplification. The ORR at week 8 in breast cancer patients was 32%. Thus, when molecular profiling reveals these rare HER2 mutations, neratinib should be considered.

Disclosure

Dr Isaacs is a member of the speakers bureau for Genentech. She has consultancies with Genentech, Puma, Seattle Genetics, AstraZeneca, and Novartis.

References

1. Nerlynx [package insert]. Los Angeles, CA: Puma Biotechnology, Inc; 2020.
2. Chan A, Delaloge S, Holmes FA, et al; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2016;17(3):367-377.
3. Saura C, Oliveira M, Feng YH, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥2 HER2-directed regimens: findings from the multinational, randomized, phase III NALA trial [ASCO abstract 1002]. *J Clin Oncol.* 2019;37(15 suppl).
4. Saura C, Oliveira M, Feng YH, et al; NALA Investigators. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with >/= 2 HER2-directed regimens: phase III NALA trial [published online July 17, 2020]. *J Clin Oncol.* 2020:JCO2000147. doi:10.1200/JCO.20.00147.
5. Freedman RA, Gelman RS, Anders CK, et al; Translational Breast Cancer Research Consortium. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol.* 2019;37(13):1081-1089.
6. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol.* 2016;2(12):1557-1564.
7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers. Version 2.2020. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf. Updated April 30, 2020. Accessed August 11, 2020.
8. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial. *Ann Oncol.* 2020;10.1016/j.annonc.2020.05.012.
9. Hyman DM, Piha-Paul SA, Won H, et al. HER kinase inhibition in patients with HER2- and HER3-mutant cancers. *Nature*. 2018;554(7691):189-194.
10. Smyth LM, Piha-Paul SA, Saura C, et al. Neratinib + fulvestrant for HER2-mutant, HR-positive, metastatic breast cancer: updated results from the phase 2 SUMMIT trial [SABCS abstract PD3-06]. *Cancer Res.* 2018;78(suppl 4).

Neratinib: An Option for HER2-Positive Metastatic Breast Cancer—Q&A

Joyce O'Shaughnessy, MD, Ruth O'Regan, MD, and Claudine Isaacs, MD

Joyce O'Shaughnessy, MD I would like to discuss the settings where we tend to use neratinib plus capecitabine in metastatic disease. The FDA approval of neratinib is relatively new.[1] I tend to use neratinib in the extended adjuvant setting because we want to do everything possible to prevent the development of metastatic disease in high-risk patients. Unfortunately, there are patients who present with de novo metastatic disease, and who will need a variety of therapies. For patients who have received the CLEOPATRA regimen and T-DM1, the survival advantage in the HER2CLIMB trial is compelling, as is the efficacy regarding brain metastasis.[2-4] I think tucatinib and capecitabine plus trastuzumab will become the go-to third-line regimen, particularly for patients with brain metastasis, but arguably even without, given the advantage in overall survival.

Data for trastuzumab deruxtecan are limited, but quite compelling overall. Among the 24 patients with CNS metastases at baseline enrolled in the DESTINY-Breast01 trial, treatment with trastuzumab deruxtecan was associated with a median overall PFS—not PFS in the brain—of 18 months, comparable to what was reported in the overall intention-to-treat population.[5] It may be possible that trastuzumab deruxtecan controlled CNS disease as well.

Among patients with brain metastases, there are much more data for neratinib, with either paclitaxel or capecitabine.[6,7] For these patients, after treatment with the tucatinib regimen, I would aim to begin neratinib and continue capecitabine. There is also the potential to use neratinib with paclitaxel, if the patient had not received paclitaxel in the metastatic setting.

I am intrigued by the combination of endocrine therapy plus neratinib, given the strong data in the ExteNET study.[6] An important finding from the study was that simply blocking pan-HER inhibition will allow escape of the cancer cells through the ER over time, with selective pressure. Therefore, I would consider using a combination of an endocrine agent plus neratinib among estrogen-positive patients with brain metastases after treatment with tucatinib. Among patients without brain metastases, I probably would administer trastuzumab deruxtecan after tucatinib, and then prescribe a neratinib combination later. I would use the combination of neratinib plus fulvestrant among patients whose cancers have an activating HER2 mutation.

Ruth O'Regan, MD I agree with these strategies. My first-line treatment is usually the CLEOPATRA regimen.[4] I use T-DM1 as second-line treatment. It will be interesting to see whether data for new agents leads to their earlier use. The choice of treatment also depends on which regimens patients received in the adjuvant setting.

Patients with ER-positive/HER2-positive disease should be managed differently from those with ER-negative/HER2-positive disease. There has been much interest in treating patients with ER-positive/HER2-positive disease with nonchemotherapy regimens. However, given the impressive results from the CLEOPATRA trial,[4] it is hard not to recommend chemotherapy with HER2-directed agents in the first-line setting. Further research is required in this area.

As mentioned, neratinib seems to effectively block HER2, potentially allowing ER to act as an escape mechanism. It is important to think about blocking ER as well in this scenario.

I have been using trastuzumab deruxtecan in the third-line setting because I think the results from DESTINY-Breast01 are impressive.[5] However, if a patient has brain metastasis, I would be much more likely to use a tyrosine kinase inhibitor, either neratinib or tucatinib.

Claudine Isaacs, MD As usual, I agree with my colleagues. I have grappled with the issues Dr O'Regan has mentioned, as well. Do all patients with hormone receptor–positive/HER2-positive breast cancer require chemotherapy, per the CLEOPATRA trial? I usually lean toward that approach, given the impressive survival benefit and my concern that I might lose that benefit if I do not start with chemotherapy. Thus, I typically start with a CLEOPATRA-type regimen.[4] For patients who have hormone receptor–positive disease, when I stop chemotherapy after about 6 cycles, I then add endocrine therapy and continue the trastuzumab and pertuzumab. My second-line treatment has typically been T-DM1.

Treatment in the third-line setting is less clear. The past 6 months have seen the advent of many treatment options supported by strong clinical trial data. We are all learning how to apply this new information to the management of patients. Given the survival benefit observed with tucatinib, I would probably lean toward using it first, followed by trastuzumab deruxtecan. In addition, I would consider neratinib in combination with fulvestrant based on the strong data we have just reviewed. Among patients with hormone receptor–positive/HER2-positive disease who had already received capecitabine plus tucatinib, I would lean toward endocrine therapy plus neratinib. Another option is neratinib plus capecitabine.

In the extended adjuvant setting, the impressive data for T-DM1 from the KATHERINE trial (A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy) led some clinicians to believe that there might not be a role for neratinib.[8] However, while T-DM1 has made a significant impact on outcome, even with this therapy, patients who did not achieve a pathologic complete response still had a 3-year risk of invasive disease recurrence of approximately 11% to 12%. This is still a fairly large risk, and I believe there remains room for improvement. For my patients who have hormone receptor–positive/HER2-positive disease who do not achieve a pathologic complete response, I do recommend neratinib after T-DM1.

I also consider neratinib for some patients with very high-risk hormone receptor–negative disease. An unplanned analysis from the ExteNET study showed a benefit when neratinib was initiated shortly after completion of HER2-directed therapy in this setting.[6]

Joyce O'Shaughnessy, MD The SUMMIT trial is adding trastuzumab to fulvestrant and neratinib.[9] The data are immature because the study currently lacks enough patients, but the preliminary data are encouraging. HER2CLIMB investigated the triplet of trastuzumab, capecitabine, and tucatinib.[2] Based on the SUMMIT trial, there may be another triplet combination, consisting of trastuzumab, neratinib, and fulvestrant.

Neratinib is the only option to prevent brain metastases in the curative setting. Unfortunately, in the KATHERINE trial, T-DM1 did not prevent brain metastases.[8] In this trial, half of the recurrences were in the brain in both treatment arms. We have to do better than that. Tucatinib combined with T-DM1 is also undergoing evaluation.[10]

The FDA has approved neratinib for both early and metastatic breast cancer. Forthcoming data from the ExteNET study will provide insight into the impact of neratinib on brain metastases. There is an opportunity to decrease the incidence of brain metastases. Ample data in the metastatic setting show that neratinib has activity in the brain. The potential for neratinib to reduce the incidence of brain metastases is important, especially in high-risk patients with stage 3 disease or node-positive disease. It is most important to utilize neratinib in the appropriate patients in the extended adjuvant setting.

Claudine Isaacs, MD The NCCN guidelines for the management of CNS cancers list capecitabine plus neratinib and paclitaxel plus neratinib for the management of brain metastases in patients with HER2-positive breast cancer.[11] When you prescribe capecitabine with neratinib,

how do you manage diarrhea? This adverse event can be associated with both of these treatments.

Ruth O'Regan, MD I find that dose escalation and antidiarrheal treatments work well for many patients. Although the dose-escalation strategy was studied in patients with early-stage breast cancer, it is also appropriate for patients with metastatic disease.

Joyce O'Shaughnessy, MD The dose-escalation strategy is absolutely essential.

Claudine Isaacs, MD I agree.

Joyce O'Shaughnessy, MD There were 2 separate dose-escalation schemas in the CONTROL trial: 120 mg/day for the first week, 160 mg/day for the second week, and 240 mg/day for weeks 3 to 52; and 160 mg/day for 2 weeks, 200 mg/day for weeks 3 and 4, and then 240 mg/daily for weeks 5 to 52.[12] The CONTROL study enrolled patients with early-stage disease, but I also follow the dose-escalation strategy in my patients with metastatic disease. In a middle-aged or younger patient, I start with 4 pills of neratinib, then I increase to 5 pills, and then 6 pills. I will take 1 or 2 weeks per dose level to ensure the patient is doing well. For older patients, I will start with 3 pills. Then I will go to 4 pills. As Dr Isaacs mentioned earlier, I will increase to 5 pills and take my time to reach 6 pills if the treatment is tolerated. The key is to keep patients on treatment.

I follow a similar strategy with capecitabine. I will start with a lower dose. In an older woman, I might start with 3 or 4 pills a day, and increase the dosage over time. I would try to reach the full dose of neratinib first. Oftentimes, neratinib is the most non–cross-resistant drug available. We expect that neratinib will overcome resistance in HER2 signaling. In the NALA trial, neratinib at 240 mg/day was combined with a lower dose of capecitabine: 1500 mg/m^2/day.[13,14] I carefully escalate the doses of both drugs. This strategy appears useful.

Claudine Isaacs, MD Yes, I agree. I tend to start with low doses of both neratinib and capecitabine, and work my way up.

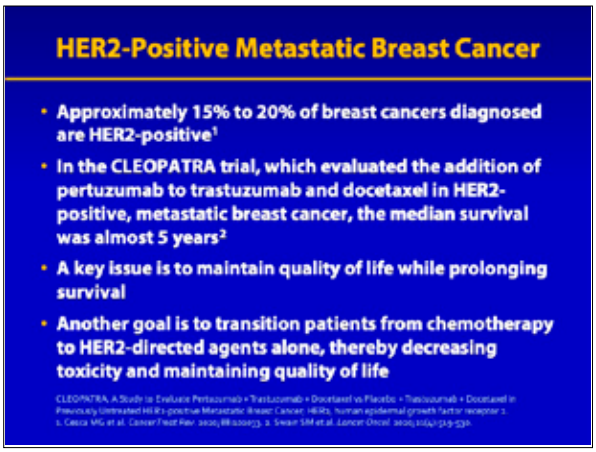
Disclosures

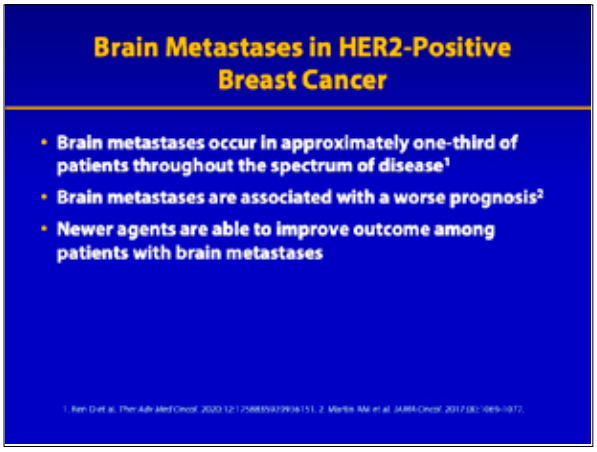
Dr O'Shaughnessy has received honoraria for consulting and advisory boards from AbbVie, Agendia, Amgen Biotechnology, AstraZeneca, Bristol Myers Squibb, Celgene Corporation, Eisai, Genentech, Genomic Health, GRAIL, Immunomedics, Heron Therapeutics, Ipsen Biopharmaceuticals, Jounce Therapeutics, Lilly, Merck, Myriad Genetics, Novartis, Odonate Therapeutics, Pfizer, Puma Biotechnology, Prime Oncology, Roche, Seattle Genetics, Syndax Pharmaceuticals, and Takeda. Dr O'Regan has received grant/research support from Eisai, Pfizer, Novartis, and Cascadian. She is a consultant for Pfizer, Genomic Health, Biotheranostics, Novartis, Puma, Genentech, Immunomedics, and MacroGenics. Dr Isaacs is a member of the speakers bureau for Genentech. She has consultancies with Genentech, Puma, Seattle Genetics, AstraZeneca, and Novartis.

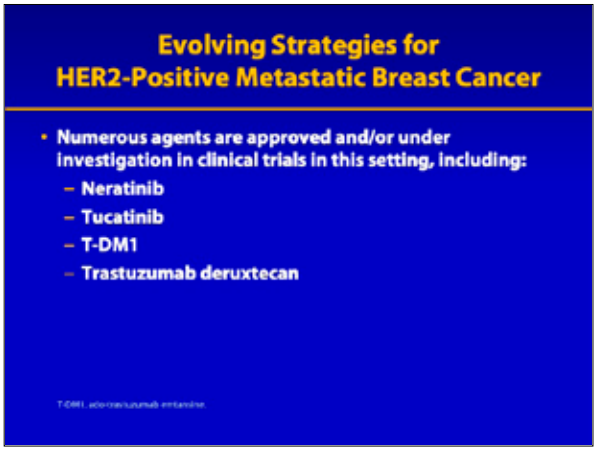
References

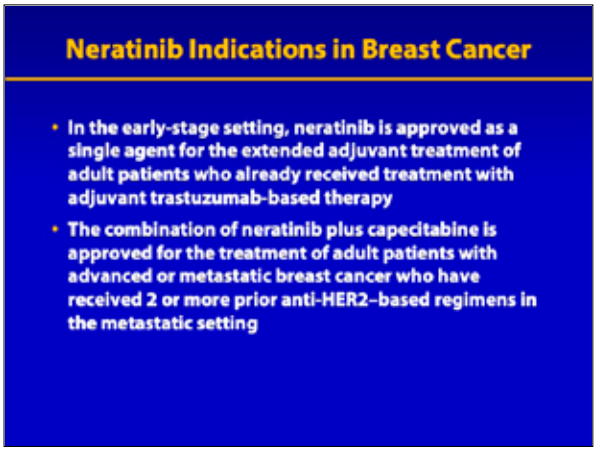
1. Nerlynx [package insert]. Los Angeles, CA: Puma Biotechnology, Inc; 2020.
2. Murthy R, Loi S, Okines A, et al. Tucatinib vs placebo, both combined with capecitabine and trastuzumab, for patients with pretreated HER2-positive metastatic breast cancer with and without brain metastases (HER2CLIMB) [SABCS abstract GS1-01]. *Cancer Res*. 2019;79(suppl 4).
3. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med.* 2020;382(7):597-609.
4. Swain SM, Miles D, Kim SB, et al; CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2020;21(4):519-530.
5. Jerusalem G, Park YH, Yamashita T, et al. CNS metastases in HER2-positive metastatic breast cancer treated with trastuzumab deruxtecan: DESTINY-Breast01 subgroup analyses [ESMO abstract 1380]. *Ann Oncol.* 2020;31(suppl 2):S63-S64.
6. Martin M, Holmes FA, Ejlertsen B, et al; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2017;18(12):1688-1700.
7. Awada A, Colomer R, Inoue K, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. *JAMA Oncol.* 2016;2(12):1557-1564.
8. von Minckwitz G, Huang CS, Mano MS, et al; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380(7):617-628.
9. Smyth LM, Piha-Paul SA, Saura C, et al. Neratinib + fulvestrant for HER2-mutant, HR-positive, metastatic breast cancer: updated results from the phase 2 SUMMIT trial [SABCS abstract PD3-06]. *Cancer Res*. 2018;78(suppl 4).
10. Borges VF, Ferrario C, Aucoin N, et al. Tucatinib combined with ado-trastuzumab emtansine in advanced ERBB2/HER2-positive metastatic breast cancer: a phase 1b clinical trial. *JAMA Oncol.* 2018;4(9):1214-1220.
11. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Central Nervous System Cancers. Version 2.2020. https://www. nccn.org/professionals/physician_gls/pdf/cns.pdf. Updated April 30, 2020. Accessed August 11, 2020.
12. Barcenas CH, Hurvitz SA, Di Palma JA, et al. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: diarrheal toxicity in the CONTROL trial. *Ann Oncol.* 2020;10.1016/j.annonc.2020.05.012.
13. Saura C, Oliveira M, Feng YH, et al; NALA Investigators. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with >/= 2 HER2-directed regimens: phase III NALA trial [published online July 17, 2020]. *J Clin Oncol.* 2020:JCO2000147. doi:10.1200/JCO.20.00147.
14. Saura C, Oliveira M, Feng YH, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: findings from the multinational, randomized, phase III NALA trial [ASCO abstract 1002]. *J Clin Oncol.* 2019;37 (15 suppl).

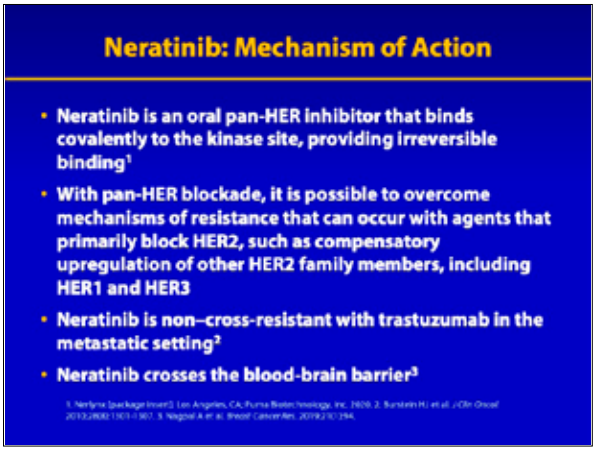
Slide Library

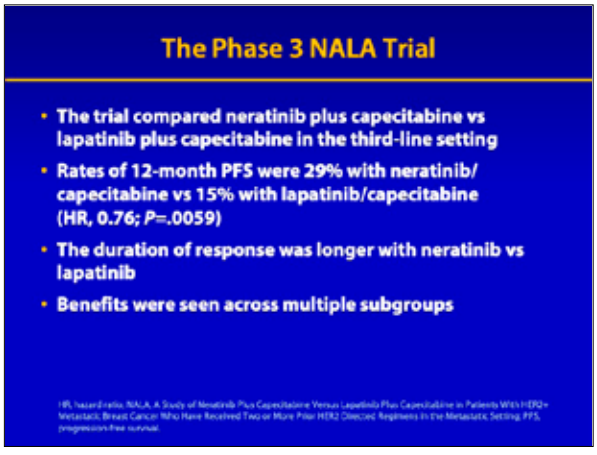


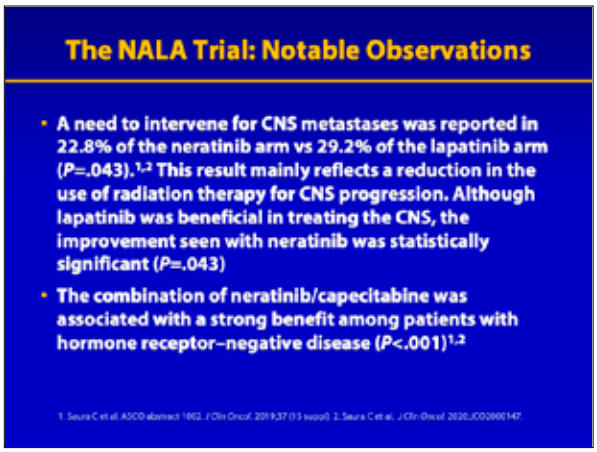


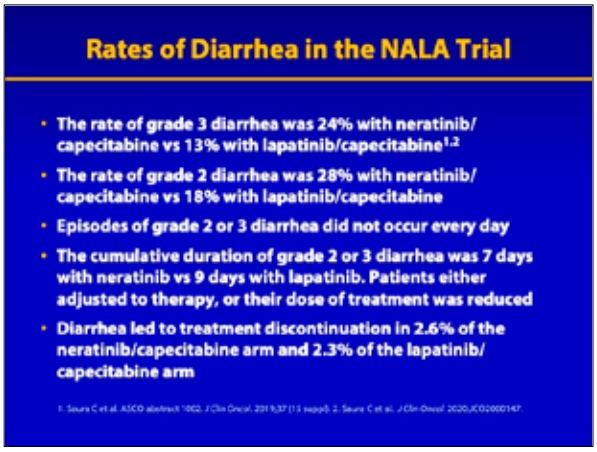


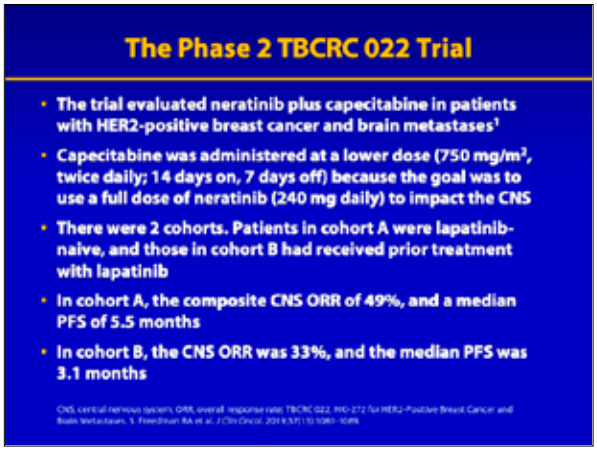


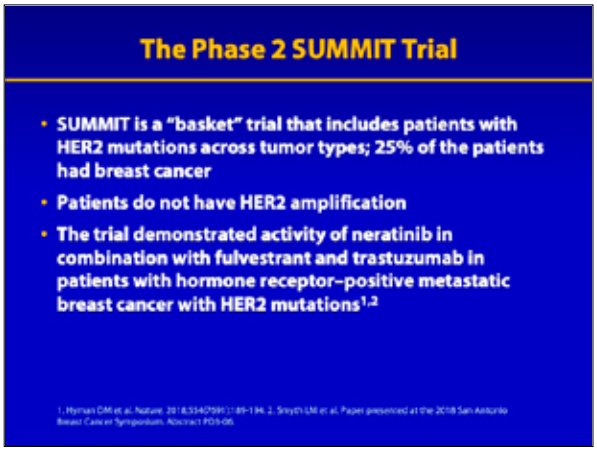












For a free electronic download of these slides, please direct your browser to the following web address:

http://www.hematologyandoncology.net