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Neratinib in the Early-Stage/Extended Adjuvant Breast Cancer Patient

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Abstract: Breast cancer is the most common tumor type observed in women in the United States. The majority of patients are diagnosed at an early stage, but the disease often recurs after initial treatment. Human epidermal growth factor receptor 2 (HER2) gene amplification is present in approximately 20% to 25% of breast tumors and is associated with invasive disease and an aggressive phenotype. The addition of anti-HER2 therapy to chemotherapy has significantly improved the prognosis for patients with these aggressive tumors. However, despite the dramatic advances in survival achieved by targeting HER2, patients with these tumors are still at risk for recurrence after initial treatment. In an effort to address the risk for recurrence, recent clinical trials have evaluated the efficacy and safety of anti-HER2 antibodies and HER2 tyrosine kinase inhibitors as adjuvant or extended adjuvant therapy. Meaningful reductions have been observed in the risk for invasive and distant recurrence, particularly in certain HER2-positive breast cancer subpopulations. To optimize adjuvant treatment, therapies should be prescribed for patient subpopulations based on factors such as underlying risk profile, response to initial therapy, and patient preference. Neratinib is a small-molecule, irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4 that penetrates the blood-brain barrier. This monograph examines neratinib in the setting of early-stage/extended adjuvant breast cancer, with a focus on clinical trial data, the mechanism of action, and ways to optimize clinical use.

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Risk of Recurrence in Early-Stage, HER2-Positive Breast Cancer

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The advent of monoclonal antibody therapy for human epidermal growth factor receptor 2 (HER2)-positive, early-stage breast cancer revolutionized the approach to treatment and significantly improved outcome compared with chemotherapy alone. However, patients remain at risk for disease recurrence.

Rates of Recurrence in Clinical Trials

Breast cancer studies with up to 10 years of follow-up report that disease will recur in approximately 25% to 30% of patients, despite treatment with trastuzumab (Table 1). The risk for recurrence was approximately 25% in both the Breast Cancer International Research Group (BCIRG) trial and the joint analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 studies (Figure 1).[1,2] In the HERA study (Herceptin [Trastuzumab] in Treating Women With Human Epidermal Growth Factor Receptor [HER] 2-Positive Primary Breast Cancer), approximately 30% of patients had experienced a recurrence at 10 years of follow-up (Figure 2).[3]

A risk for recurrence was also seen with shorter follow-up in both 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) and the APHINITY study (A Study of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Participants With Human Epidermal Growth Receptor 2 [HER2]-Positive Primary Breast Cancer).[4,5] The open-label, phase 3 KATHERINE trial focused on a high-risk subset of patients: those with HER2-positive, early-stage breast cancer[4] who had received previous neoadjuvant therapy with a taxane plus trastuzumab, with or without an anthracycline, and who had residual invasive disease at the time of surgery. The patients enrolled in this trial had not achieved a pathologic complete response, and were randomly assigned to receive 14 cycles of adjuvant treatment with T-DM1 or trastuzumab. The primary endpoint of the study was invasive disease–free survival. At a 3-year interim analysis, 77.0% of patients who continued treatment with trastuzumab were free of invasive disease compared with 88.3% of those randomized to T-DM1 (hazard ratio [HR], 0.50; 95% CI, 0.39-0.64; $P<.001$). Although treatment with T-DM1 resulted in a major improvement over trastuzumab, this still left 12% of patients with an invasive recurrence at 3 years. This observation is important when considering the role of neratinib in this setting. Neratinib is a small-molecule tyrosine kinase inhibitor approved for use as a single agent for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, following adjuvant trastuzumab-based therapy. Of note, neratinib is also approved in combination with capecitabine for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2 based regimens in the metastatic setting.

Predictors of Recurrence

Findings from several studies evaluating the role of adjuvant trastuzumab, including the joint analysis of NSABP B-31 and NCCTG N9831, BCIRG 006, and HERA, indicate that lymph node status is a predictor of recurrence.[1-3] Most patients in these trials had node-positive disease, but a subset of patients were node-negative. The 10-year risk of recurrence was approximately 25% among patients with 1 to 3 positive nodes at diagnosis and up to 45% among those with a higher nodal burden at diagnosis. The APHINITY trial prospectively enrolled 4805 patients with HER-positive, node-positive breast cancer or high-risk, node-negative disease,[5] and randomized them to standard adjuvant chemotherapy plus 1 year of trastuzumab, with the addition of pertuzumab or placebo. With a median follow-up of 74 months, the rate of invasive disease–free survival at 6 years was 87.9% with pertuzumab vs 83.4% with placebo (HR, 0.73; 95% CI, 0.59-0.92) in those with node-positive disease, demonstrating a clear benefit for pertuzumab in this group of patients. Patients with high-risk, node-negative disease

Table 1. Recurrence Rates in HER2-Positive Early Breast Cancer Clinical Trials

Clinical Trial	Population	Recurrence (%)
HERA[3] (trastuzumab)	ITT at 10 years	31%[a]
Joint Analysis[1] NSABP and NCCTG N9831 (trastuzumab in combination)	ITT at 10 years	26%[a]
BCIRG-006[3] (TC and trastuzumab)	ITT at 10 years	27%[a]
BCIRG-006[3] (AC→T and trastuzumab)	ITT at 10 years	25%[a]
KATHERINE[4] (ado-trastuzumab emtansine arm)	ITT at 3 years	12%[b]
KATHERINE[4] (ado-trastuzumab emtansine arm)	Residual node-positive patients with no pCR at 3 years	17%[b]

AC, anthracycline plus cyclophosphamide; HER, human epidermal growth factor receptor; ITT, intent to treat; pCR, pathologic complete response; T, taxane; TC, taxane plus carboplatin.

[a] "Recurrence" refers to disease-free survival, defined as the time from enrollment to documentation of the first of any of these events: local, regional, or distant recurrence of breast cancer; a contralateral breast cancer; a second primary cancer; or death as a result of any cause.

[b] "Recurrence" refers to invasive disease-free survival, defined as time from randomization to the first occurrence of any of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive breast cancer, contralateral invasive breast cancer, a distant disease recurrence, or death from any cause.

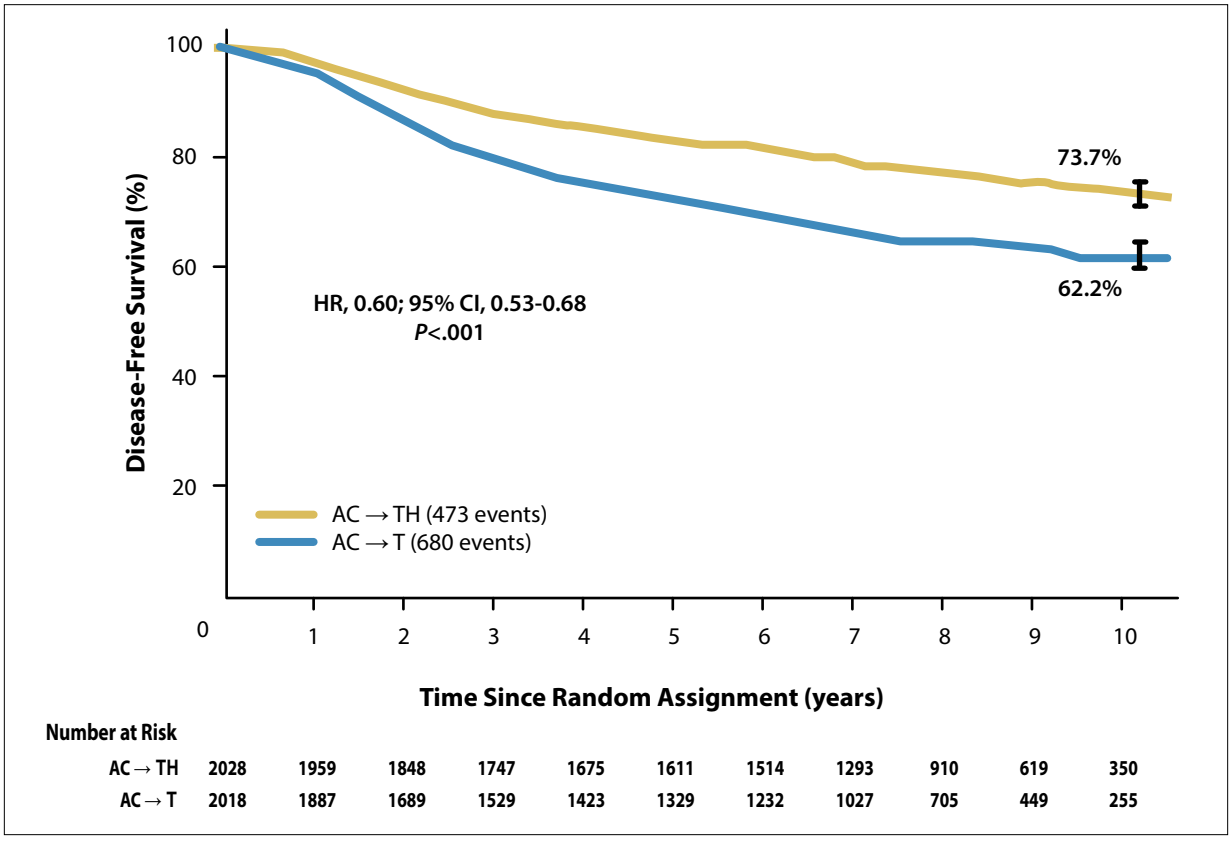

Figure 1. Disease-free survival from combined data analysis for the NCCTG N9831 and NSABP B-31 trials. AC, doxorubicin and cyclophosphamide; H, trastuzumab; HR, hazard ratio; NCCTG N9831, North Central Cancer Treatment Group Combination Chemotherapy With or Without Trastuzumab in Treating Women With HER2-Overexpressing Breast Cancer; NSABP B-31, National Surgical Adjuvant Breast and Bowel Project Doxorubicin and Cyclophosphamide Plus Paclitaxel With or Without Trastuzumab in Treating Women With Node-Positive Breast Cancer That Overexpresses HER2; T, paclitaxel. Adapted from Perez EA et al. *J Clin Oncol.* 2014;32(33):3744-3752.[1]

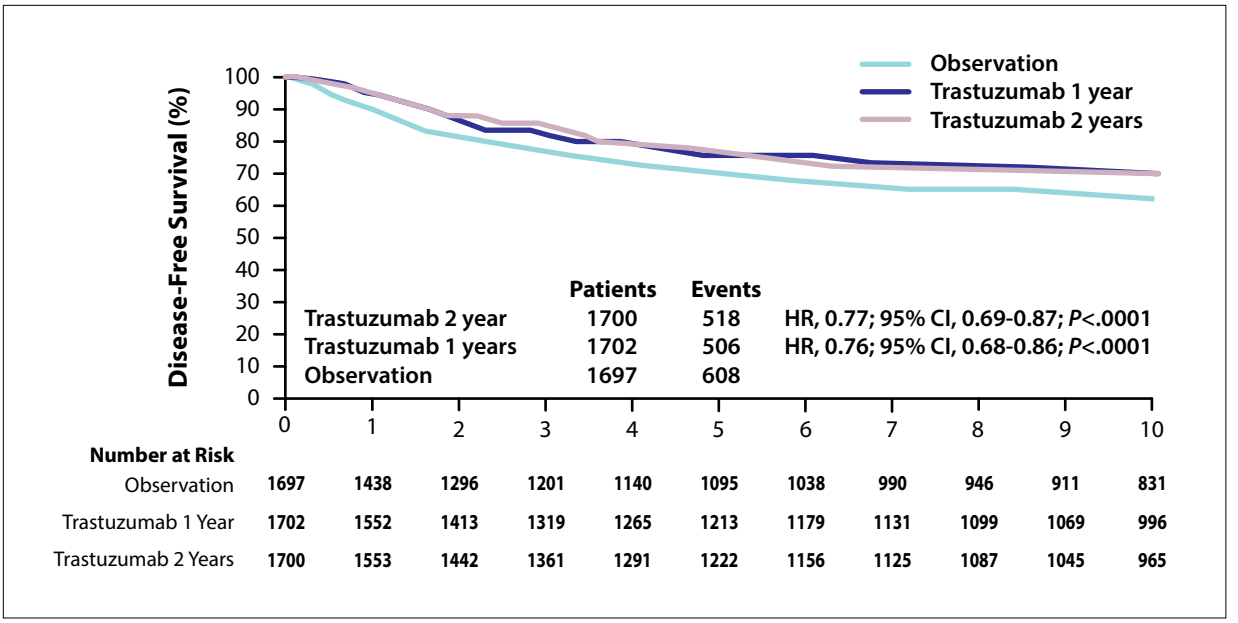

Figure 2. In the HERA study, approximately 30% of patients were experiencing a recurrence at 10 years of follow-up. HERA, Herceptin (Trastuzumab) in Treating Women With Human Epidermal Growth Factor Receptor (HER) 2-Positive Primary Breast Cancer. Adapted from Cameron D et al. *Lancet.* 2017;389(10075):1195-1205.[3]

had similar rates of recurrence of 5% for both pertuzumab and placebo (HR, 1.02; 95% CI, 0.69-1.53).

Tumor size is another factor related to the risk for recurrence. In the earlier trials that evaluated the role of adjuvant trastuzumab, the risk for recurrence increased by approximately 50% in women with tumors of 2 cm to 5 cm compared with smaller tumors, and by 81% in patients with tumors larger than 5 cm.[1] In the APHINITY trial, among the patients who received both trastuzumab and pertuzumab, the risk for recurrence was also associated with tumor size.[5] The rate of invasive disease–free survival was approximately 95% to 97% when the tumors were smaller than 2 cm, approximately 93% when the tumors were 2 cm to 5 cm, and approximately 88% when the tumors were larger than 5 cm.[5]

A recent publication from the joint analysis of NSABP B-31 and NCCTG N9831 evaluated how estrogen receptor (ER) status over time impacts the risk for recurrence.[6] Among patients with HER2-positive disease, the risk for recurrence up to 5 years after diagnosis was higher in those with ER-negative disease vs ER-positive disease. The 5-year risk for recurrence was 17.5% vs 11%, respectively (P<.001). After 5 years, however, the risk for recurrence decreases among patients with HER2-positive/ER-negative disease, leading to a similar risk in both groups over the long-term. A similar outcome was also seen in the HERA trial.[7]

The strongest predictor of disease-free survival, however, is the patient's response to neoadjuvant therapy, with studies demonstrating that those who achieve a pathologic complete response experience a significantly improved outcome. The phase 2 I-SPY 2 trial (Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer) is investigating neoadjuvant treatment in patients with locally advanced, triple-negative breast cancer, HER-positive, or HER2-negative, hormone receptor–positive breast cancer.[8] For the latter patients, enrollment was limited to those identified as high risk (based on a 70-gene microarray analysis). It is a platform trial and, to date, the investigators have reported on 14 different regimens. Data presented at the 2018 San Antonio Breast Cancer Symposium investigating the relationship between pathologic complete response and survival showed that, across the entire patient population, pathologic complete response was significantly associated with 3-year event-free survival (P<.001), regardless of therapy.[8] Among patients with HER2-positive/ER-negative disease, 3-year event-free survival was 93% in patients who achieved a pathologic complete response vs approximately 53% in those who did not. Among patients with HER2-positive/ER-positive disease, these rates were 96% vs 87%.

The KATHERINE data encouragingly demonstrate that, in patients who do not achieve a pathologic complete response, the use of T-DM1 results in an 11% improvement with T-DM1 compared with trastuzumab.[4] However, a significant risk of relapse still remains for these patients.[4] Among patients receiving T-DM1, the risk for recurrence at 3 years was just under 12%. Importantly,

distant recurrence as the first invasive disease event occurred in 10.5% of patients who received T-DM1 vs 15.9% in those who received only trastuzumab. Distant recurrence is extremely problematic.

In summary, data presented in the mid-2000s supporting the addition of adjuvant HER2-directed therapy to chemotherapy changed practice and substantially improved outcomes.[9] The KATHERINE trial showed that the risk of distant metastases could be further significantly reduced by switching to adjuvant T-DM1 in patients with residual, invasive disease after neoadjuvant therapy with trastuzumab.[4] Based on findings from the APHINITY trial, pertuzumab will likely be reserved primarily for patients with HER2-positive/hormone receptor–negative disease or those with node-positive disease.[5]

Metastatic Disease

There have been tremendous strides in the treatment of metastatic disease. The landmark analysis from the phase 3 CLEOPATRA trial (A Study to Evaluate Pertuzumab + Trastuzumab + Docetaxel vs. Placebo + Trastuzumab + Docetaxel in Previously Untreated HER2-Positive Metastatic Breast Cancer) was recently published in *Lancet Oncology*.[10] This study investigated the addition of pertuzumab or placebo to first-line treatment with trastuzumab and docetaxel in patients with HER2-positive, metastatic breast cancer. After a median follow-up of more than 8 years, the analysis showed that the addition of pertuzumab increased the median overall survival to 57.1 months, compared with 40.8 months in the placebo arm. Eight-year landmark survival rates were 37% with pertuzumab vs 23% with placebo. Randomized trials have also shown prolongation in overall survival with the use of T-DM1 and, more recently, tucatinib.[11] Nonetheless, the majority of patients who develop metastatic disease will unfortunately succumb to it.

Another important concern in patients with HER2-positive disease is the development of central nervous system (CNS) metastases. This unfortunately still represents an unmet medical need, as shown by results from the KATHERINE and APHINITY trials.[4,5] As previously discussed, the KATHERINE study demonstrated a significant reduction in the risk of recurrence with the use of adjuvant T-DM1 vs continued trastuzumab.[4] However, there was no impact of T-DM1 on the rates of CNS recurrence as first event (4.3% with trastuzumab vs 5.9% with T-DM1). Similarly, based on data from the APHINITY study, the addition of pertuzumab did not reduce the risk of CNS metastases as first event; this rate was 2% in both arms.[5] Thus, brain metastases continue to be a significant concern for patients with HER2-positive breast cancer.

Conclusion

Data from clinical trials indicate that a substantial proportion of patients with early-stage, HER2-positive breast cancer will develop recurrent disease, even with recent advances in treatment. Additional management strategies are needed for these patients.

Disclosure

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

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Neratinib in Early-Stage Breast Cancer: Clinical Trial Data

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Neratinib is a small molecule and an irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4.[1] Notably, neratinib penetrates the blood-brain barrier. Neratinib is highly effective in inhibiting the growth of HER2-positive preclinical models. Neratinib appears to effectively inhibit crosstalk between the ER and HER2 pathways.

The ExteNET Trial

The ExteNET trial (Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer) was the registration study for neratinib.[2] The study evaluated whether extended HER2 inhibition after a year of trastuzumab therapy would improve outcomes and reduce the risk for recurrence. Adjuvant trials have shown a fairly significant risk for recurrence of approximately 25% with longer follow-up. ExteNET was a double-blind, placebo-controlled, randomized phase 3 trial for patients ages 18 years or older. The trial initially recruited patients with stage 1, 2, and 3c breast cancer; it was later modified to include only higher-risk patients (stages 2-3c). All enrolled patients had HER2-positive disease. Previous treatment could include either neoadjuvant or adjuvant chemotherapy with trastuzumab. Patients had no evidence of disease recurrence or metastatic disease upon study entry. Prior to randomization, patients were stratified based on hormone receptor status (positive vs negative); nodal status (negative vs 1, 2, or 3 positive nodes vs 4 or more positive nodes); and whether the trastuzumab was given sequentially or concurrently with chemotherapy. Patients were then randomly assigned to receive extended adjuvant therapy with oral neratinib (240 mg daily) or placebo. The treatment was given continuously for a year, unless the patient developed disease recurrence or new breast cancer, experienced intolerable adverse events, or withdrew consent.

The 5-year results were published in *Lancet Oncology*.[3] Between July 2009 and October 2011, 2840 eligible women with early-stage, HER2-positive breast cancer were enrolled at institutions across 40 countries. The rate of invasive disease–free survival at 5 years was 90.2% in the neratinib arm vs 87.7% in the placebo arm (HR, 0.73; 95% CI, 0.57-0.92; *P*=.0083; Figure 3).

The results were different in the hormone receptor–positive group vs the hormone receptor–negative group. At 5 years, there was no significant difference for hormone receptor–negative cancers with neratinib vs placebo; the rates of invasive disease–free survival were 88.9% vs 86.1%, respectively (HR, 0.73; 95% CI, 0.47-1.14; *P*=.175; Figure 4).[4] In contrast, in the hormone receptor–positive group, the curves separated fairly early in favor of neratinib and continued to separate. At 5 years, the rates of invasive disease–free survival were 90.8% with neratinib vs 85.7% with placebo (HR, 0.58; 95% CI, 0.41-0.82; Figure 5).[5]

Subset Analyses

A subgroup analysis of the ExteNET trial included 1334 patients who had hormone receptor–positive breast cancer and were randomly assigned to treatment within 1 year of their last dose of trastuzumab. Among these patients, treatment with neratinib led to a 51% reduction in the risk for invasive disease recurrence or death at 2 years, and the treatment benefit was maintained at 4 years. In addition, this cohort had a prolonged time to distant recurrence with neratinib (Figure 6).

Another exploratory subset analysis focused on 295 patients with hormone receptor–positive, HER2-positive breast cancer who started treatment within 1 year of completing trastuzumab, and who were considered high risk because they did not achieve a pathologic complete response after neoadjuvant therapy. Among these patients, the 2-year invasive disease–free survival rate was 90% with neratinib vs 85% with placebo. At 5 years, this rate was 92% vs 85%, respectively (HR, 0.60; 95% CI, 0.33-1.07).

These data suggest that neratinib is particularly effective among cancers that are hormone receptor–positive. Preclinical models have shown bidirectional crosstalk between the HER2 pathway and the ER pathway.[6] HER2-positive cancer sets off phosphorylation cascades in the cells through the PI3 kinase and MAP kinase pathway,

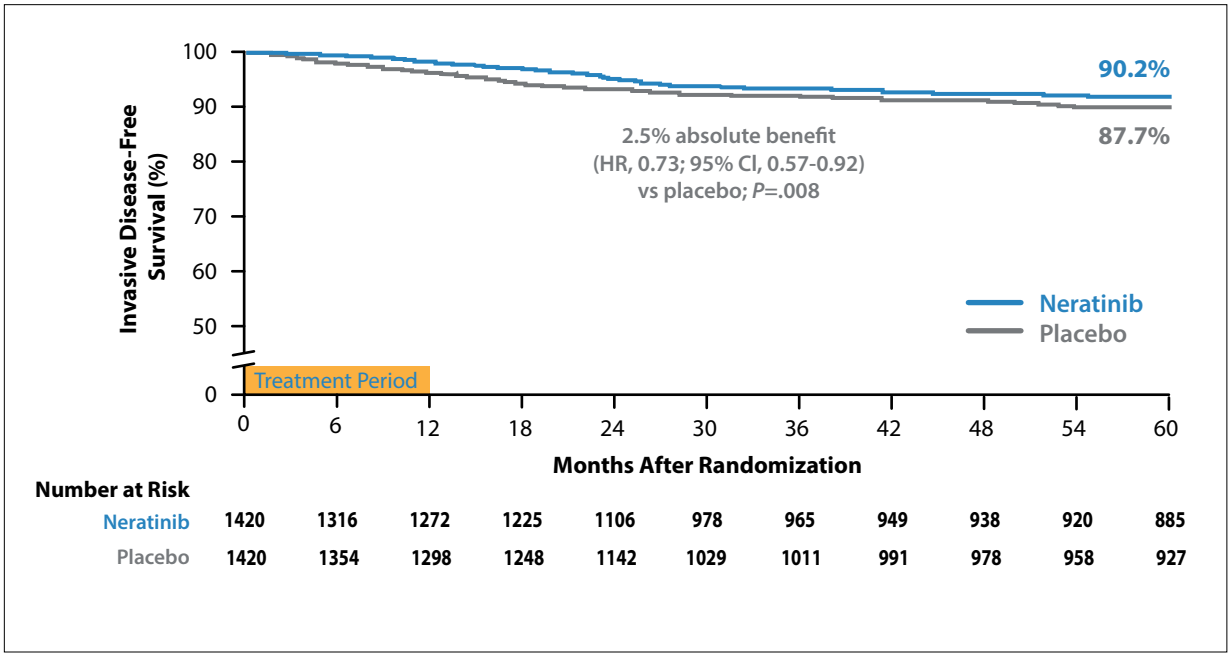

Figure 3. The rate of invasive disease–free survival at 5 years in the phase 3 ExteNET trial, which compared neratinib vs placebo in patients with early-stage, HER2-positive breast cancer. ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer; HER2, human epidermal growth factor receptor 2; HR, hazard ratio. Adapted from Martin M et al. *Lancet Oncol.* 2017;18(12):1688-1700.[3]

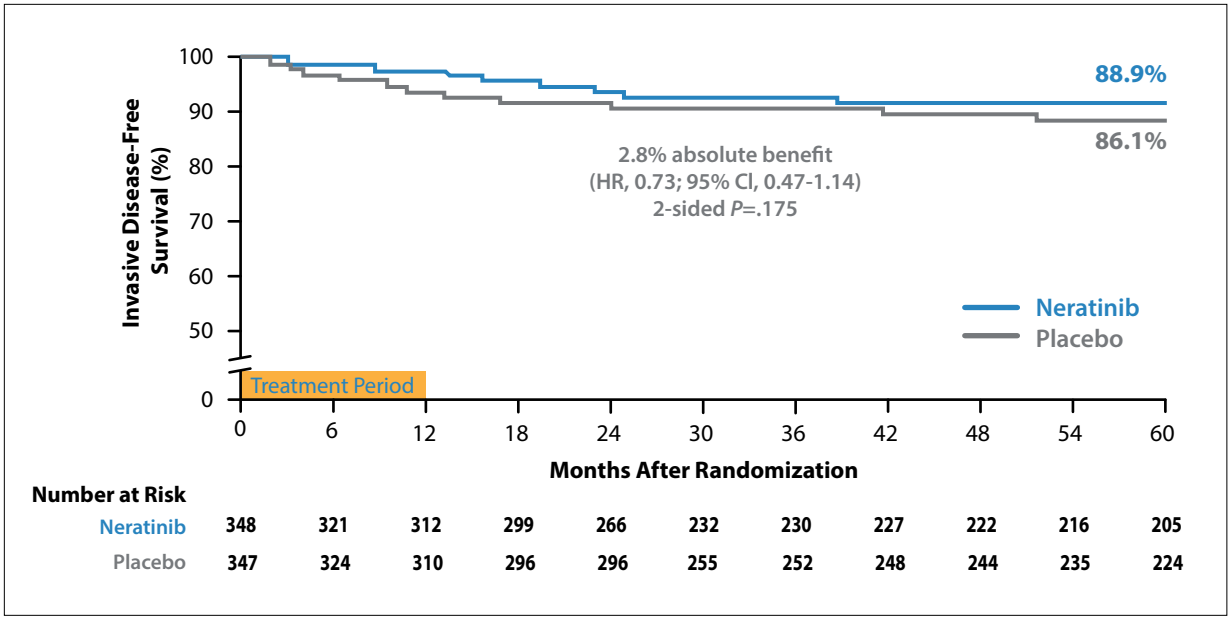

Figure 4. The rate of invasive disease–free survival at 5 years among patients with hormone receptor–negative tumors in the phase 3 ExteNET trial. ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer; HR, hazard ratio. Adapted from Ejlertsen B et al. ASCO abstract 549. *J Clin Oncol.* 2018;36(suppl).[4]

sequestering coactivators from the ER, and thereby turning off estrogen-regulated gene transcription. Conversely, blocking HER2 with an antibody or a tyrosine kinase inhibitor will turn off the phosphorylation pathways, and the coactivators will remain associated with the ER. In other words, blocking the HER2 pathway in a cancer that is both hormone receptor–positive and HER2-positive will allow the ER pathway to act as an escape mechanism. The converse is also thought to be true: Inhibition of only the ER will allow the HER2 to act as an escape pathway.

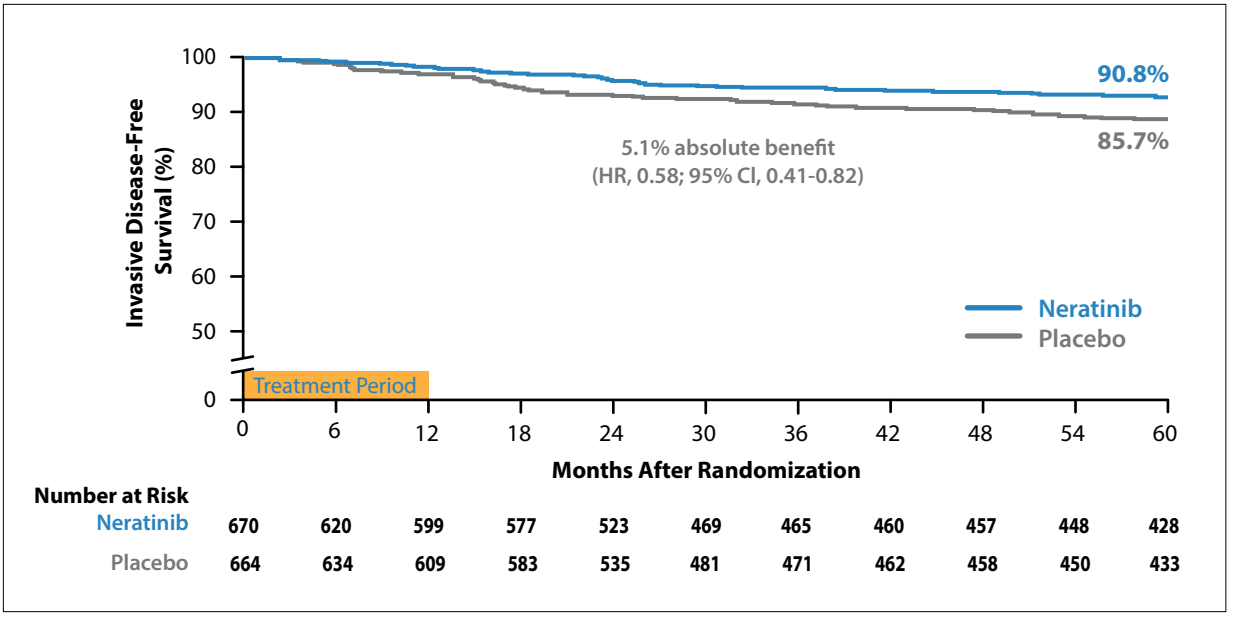

Figure 5. The rate of invasive disease–free survival at 5 years among patients with hormone receptor–positive tumors in the phase 3 ExteNET trial. ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer; HR, hazard ratio. Adapted from Gnant M et al. SABCS abstract P2-13-01. *Cancer Res.* 2018;78(4).[5]

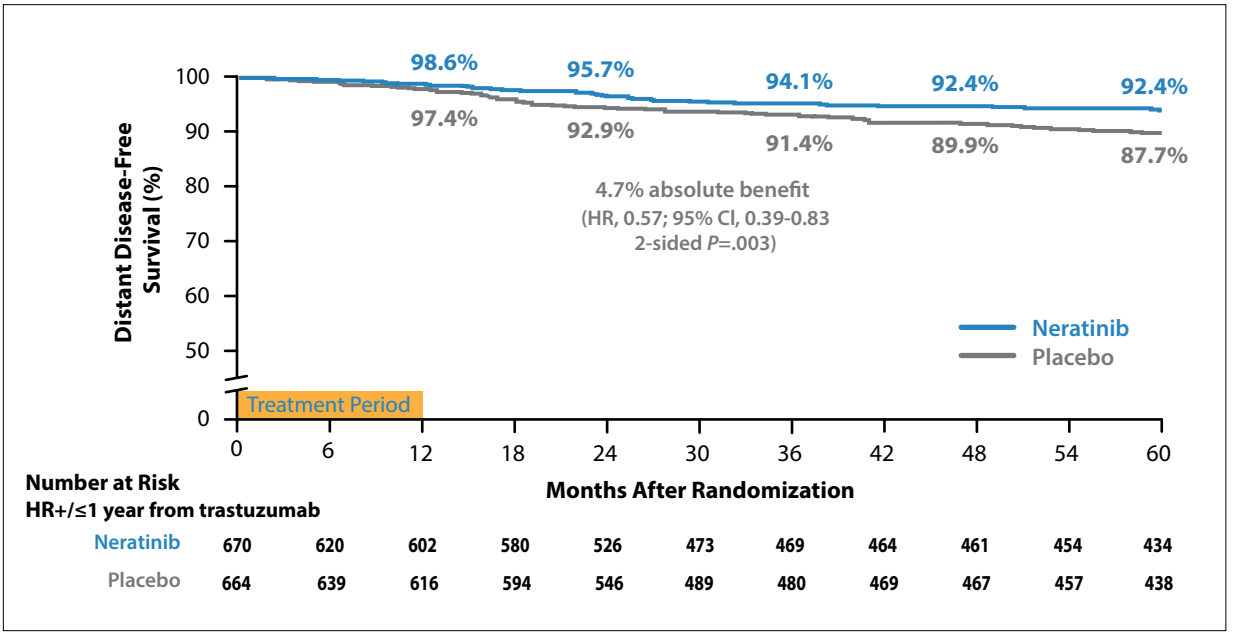

Figure 6. Distant recurrences among patients with hormone receptor–positive disease in the phase 3 ExteNET trial. ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer; HR, hazard ratio. Adapted from Gnant M et al. SABCS abstract P2-13-01. *Cancer Res.* 2018;78(4).[5]

Sudhan and colleagues examined this theory in HER2-positive, ER-positive mouse models.[7] Mice with established tumors were first treated with paclitaxel plus trastuzumab, with or without pertuzumab, for 4 weeks. They were then randomly assigned to treatment with fulvestrant, with or without neratinib. The investigators also examined cell lines that were treated with fulvestrant, neratinib, or both. They showed that blocking only the ER with fulvestrant would activate HER2 signaling. Conversely, blocking just the HER2 pathway with neratinib would activate the ER and all of its downstream genes and proteins. Therefore, it may be important to block both HER2 and the ER in some patients with HER2-positive, hormone receptor–positive tumors.

This theory could explain why data from the ExteNET study shows worse outcomes with placebo vs neratinib among patients with hormone receptor–positive cancers. In the neratinib arm, HER2 was inhibited by neratinib and ER was inhibited by endocrine therapy. In contrast, in the placebo arm, only ER is inhibited, thereby potentially allowing HER2 to provide an escape pathway. This concept was demonstrated in preclinical models by Unni and colleagues.[8] The majority of hormone receptor–positive, HER2-positive cancers are luminal B, but approximately one-third are luminal A. It is possible that crosstalk is more important in the latter group. The intriguing concept of crosstalk between the HER2 pathway and the ER pathway provides the best explanation of why the ExteNET study showed greater efficacy with neratinib in tumors that were hormone receptor–positive compared with those that were hormone receptor–negative.

Regardless of hormone receptor status, there is significant genetic heterogeneity among HER2-positive cancers. In a study from the Dana–Farber Cancer Institute, multiple biopsies were performed in patients with HER2-positive breast cancer who received preoperative T-DM1.[9] The investigators identified a large number of cancers that were heterogeneous, almost all of which were ER-positive. Interestingly, these patients had a much lower rate of pathologic complete response compared with patients with more homogenous HER2-positive cancers.

Disclosure

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Best Use of Neratinib in Patients With Early-Stage Breast Cancer

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Several subset analyses from the ExteNET trial provided important insights into the best use of neratinib.[1] In the ExteNET trial, most patients received treatment with neratinib or placebo within 2 years after they finished treatment with adjuvant trastuzumab. However, that is a long time frame during which to finish adjuvant trastuzumab, start endocrine therapy (for ER-positive patients), and then undergo randomization to treatment with neratinib or placebo.

Most of the subset analyses have focused on patients who began treatment with neratinib within a year after completion of adjuvant trastuzumab. In the intent-to-treat population of the ExteNET trial, the 5-year invasive disease–free survival rate was 90.2% with neratinib vs 87.7% with placebo, providing a delta of 2.5% in favor of neratinib.[2] A noteworthy finding that has driven practice to a large extent concerns the 5-year invasive disease–free survival in ER-positive patients, for a delta of 4.4%.

A subsequent analysis focused on patients with centrally confirmed HER2-positive disease. Enrollment into the ExteNET trial was permitted based on local confirmation of HER2-positivity. All patients also underwent central confirmation of HER2 positivity. In approximately 15% of patients, central testing failed to confirm HER2-positive disease. Similar discrepancies have been seen in other trials of adjuvant therapy. Consequently, nearly all trials now require central confirmation of HER2 before enrollment. In this retrospective analysis, the benefit in the ER-positive patients with centrally confirmed HER2-positive breast cancer was on the order of an absolute benefit of 7% to 8%. As expected, the benefit with neratinib was stronger in the intent-to-treat ER-positive population.

In the 5-year analysis of invasive disease–free survival among the hormone receptor–negative population, the Kaplan-Meier curves for neratinib vs placebo split at 12 months. The rates were 97.5% for neratinib vs 94.7% for placebo.[2] However, as soon as the patient stops neratinib, the curves merge together again. At the 2-year mark, patients in both arms were at parity. The data points then remained similar through years 2 through 5. Therefore, only a transient benefit in the ER-negative population was seen, which seemed to contradict the known biology. Subset analyses were performed to explore this issue. For example, 1334 patients in the ExteNET trial had ER-positive disease and began treatment with neratinib or placebo within 1 year of their last dose of trastuzumab. Among these patients, neratinib provided a 5.1% increase in invasive disease–free survival vs placebo at 5 years (P=.002).[3] ER-positivity was not centrally confirmed, but there was a slightly higher improvement in invasive disease–free survival in patients randomly assigned to treatment within the first year after cessation of HER2-directed therapy. For clinical practice, this finding suggests that patients can take a short break after they finish standard adjuvant therapy (with either pertuzumab or, more likely, T-DM1). Among the patients with ER-positive disease who started their treatment within a year of their last dose of trastuzumab, there was a 4.7% improvement in distant disease–free survival for neratinib compared with placebo. A 5% improvement after 5 years is important.

It is well known that among patients who receive preoperative therapy, those who do not achieve a pathologic complete response fare worse than those who do. In the ExteNET trial, 295 patients who had hormone receptor–positive disease and who had not achieved a pathologic complete response after neoadjuvant therapy with chemotherapy plus trastuzumab (pertuzumab was not available as preoperative therapy then), received neratinib starting within 1 year of their last dose of trastuzumab. In these high-risk patients, the rate of invasive disease–free survival at 5 years was 85.0% with neratinib vs 77.6% with placebo (Figure 7). This impressive difference would have been even higher if the analysis had included only patients with centrally confirmed HER2-positivity.

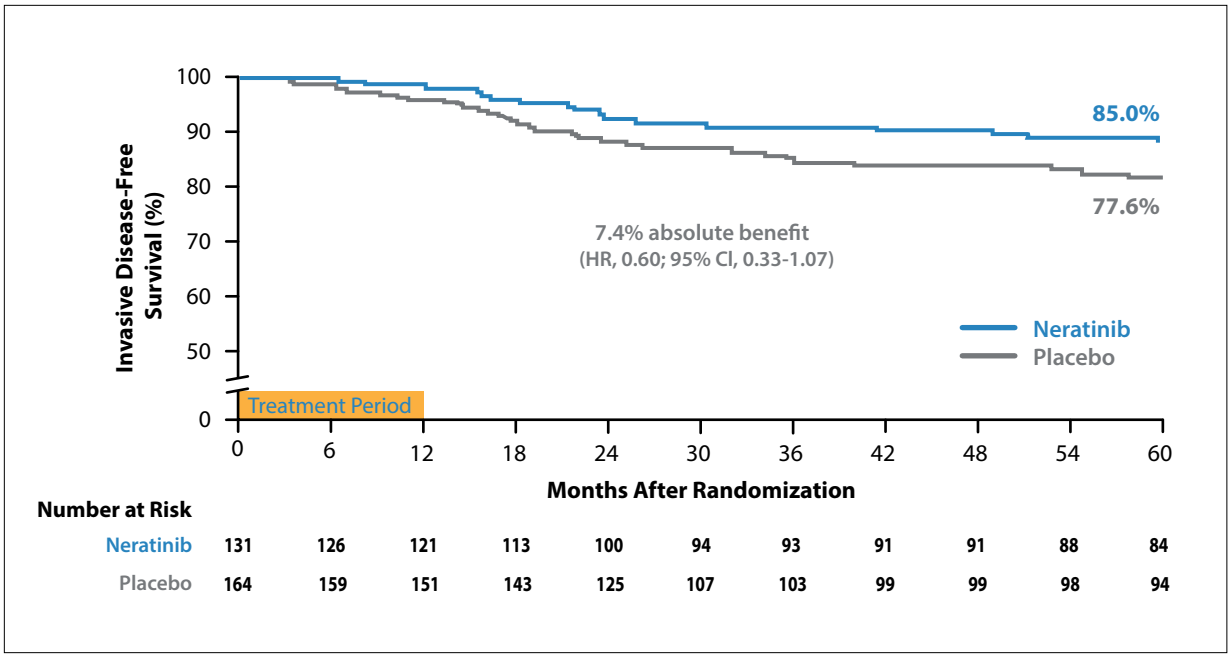


Figure 7. Rates of invasive disease–free survival among patients with hormone receptor–positive disease who received trial treatment starting within 1 year of their last dose of trastuzumab, and did not achieve a pathologic complete response after neoadjuvant therapy in the ExteNET trial. ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer; HR, hazard ratio. Adapted from Gnant M et al. SABCS abstract P2-13-01. *Cancer Res.* 2019;79(4 suppl).[3]

Another exploratory analysis of patients from ExteNET evaluated outcomes in ER-negative patients who initiated neratinib within 6 months of completing trastuzumab.[4] In practice, we would initiate neratinib therapy within 6 months after the patient finishes adjuvant therapy. In this subset of 695 patients, the rate of 5-year invasive disease–free survival was 88.9% with neratinib vs 86.1% with placebo. The results from this exploratory analysis suggest that patients with ER-negative disease who begin neratinib very soon after finishing adjuvant therapy (eg, preoperative trastuzumab and pertuzumab, followed by T-DM1) are able to benefit from treatment.

A fascinating observation from the ExteNET study is that the 295 patients with ER-positive disease received neratinib for only 1 year, but results of that adjuvant treatment were apparent across 5 years, as the Kaplan-Meier curves continued to separate. The synergy seen with dual inhibition of the ER and the HER2 was impressive. Neratinib is a 1-year therapy that pays dividends for patients for many years to come.

Another subset analysis of the ExteNET trial evaluated how the duration of neratinib therapy impacted invasive disease–free survival.[5] To reiterate, in the overall intent-to-treat population, there was a 2.5% improvement in 5-year invasive disease–free survival in favor of neratinib. Among patients who began treatment with neratinib but stopped (for any reason) within 3 months, there was essentially no difference in 5-year invasive disease–free survival (88.4% with neratinib vs 87.7% with placebo). Among patients who remained on neratinib for at least 11 months, however, the rate of 5-year invasive disease–free survival was 91.0% with neratinib vs 87.7% with placebo. Almost all of this improvement was in distant disease-free survival.

Management of Diarrhea

To optimize the efficacy of neratinib, clinicians should aim to ensure that patients can complete the full course of therapy. In an analysis by Holmes and colleagues, the difference in invasive disease-free survival between neratinib and placebo was not statistically significant at 3 months or less, but did reach significance at 11 months (Figure 8).[6] Management of toxicities is a large component of successful treatment. The main toxicity associated with neratinib is diarrhea (Table 2). Other toxicities are fatigue, which is manageable, and rare cases of rash.

The protocol for the ExteNET trial did not specify prophylaxis for diarrhea, and 95% of patients treated with neratinib experienced this adverse event.[1] Grade 4 diarrhea was nearly nonexistent, but grade 3 episodes occurred in 39.9% of patients. Diarrhea led 16.8% of patients to discontinue treatment with neratinib. To

Table 2. Adverse Events in the ExteNET Trial

	Neratinib (n=1408)		Placebo (n=1408)	
	All Grades, ≥10% (%)	Grades 3 or Higher, ≥1% (%)	All Grades, ≥10% (%)	Grades 3 or Higher, ≥1% (%)
Diarrhea	95	40 (Grade 3) 0.1 (Grade 4)	35	2
Nausea	43	2	22	0.1
Abdominal pain	36	2	15	0.4
Fatigue	27	2	20	0.4
Vomiting	26	3	8	0.4
Rash	18	0.6	9	0
Stomatitis	14	0.6	6	0.1
Decreased appetite	12	0.2	3	0
Muscle spasms	11	0.1	3	0.1
Dyspepsia	10	0.4	4	0
ALT increase	9	1 (Grade 3) 0.2 (Grade 4)	3	0.2

ALT, alanine aminotransferase; ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer. Data from Martin M et al. *Lancet Oncol.* 2017;18(12):1688-1700.[2]

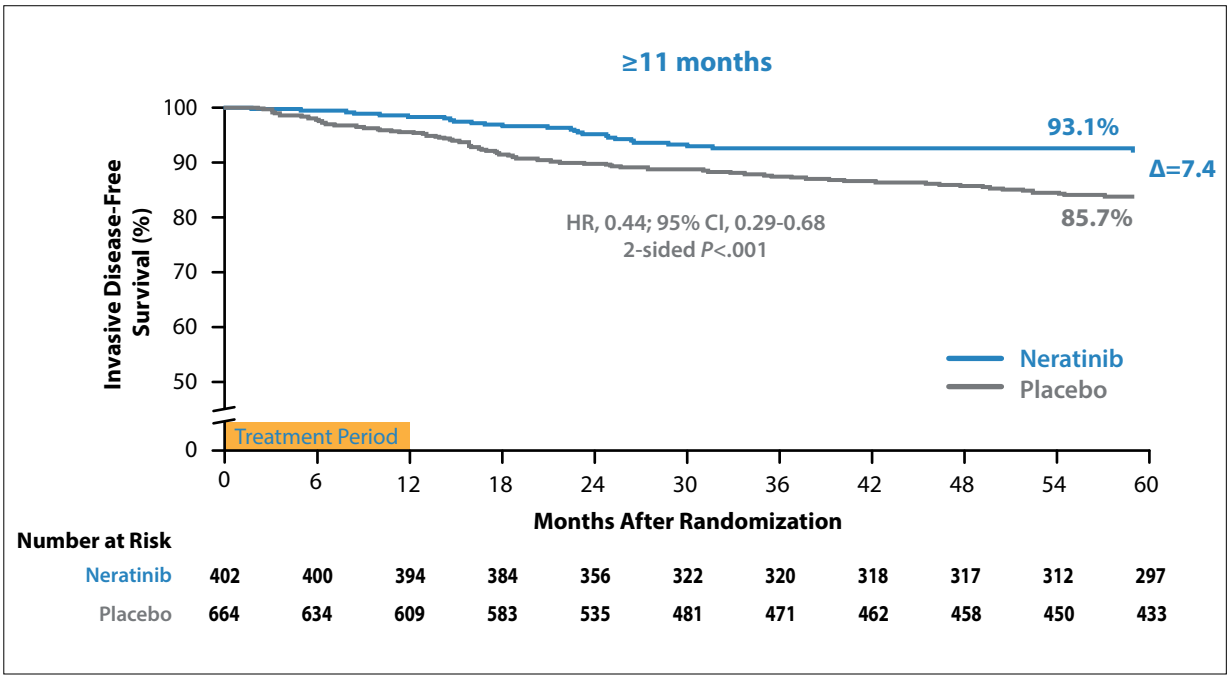


Figure 8. Invasive disease-free survival among patients who received at least 11 months of treatment in the ExteNET trial. ExteNET, Study Evaluating the Effects of Neratinib After Adjuvant Trastuzumab in Women With Early Stage Breast Cancer; HR, hazard ratio. Adapted from Holmes FA et al. Abstract 16. Presented at: the 37th Annual Miami Breast Cancer Conference; March 5-8, 2020; Miami, FL.[6]

address this issue, the open-label phase 2 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) investigated antidiarrheal prophylaxis, as well as neratinib dose escalation (Figure 9).[7,8] Rather than waiting for the onset of diarrhea, the trial evaluated administration of antidiarrheal treatments given on day 1 of neratinib. The CONTROL trial included approximately 500 breast cancer patients who had completed adjuvant trastuzumab. Neratinib (240 mg daily) was administered to all patients in the first 4 cohorts. In cohort 1, patients received loperamide prophylaxis (4 mg, 3 times daily) during cycles 1 to 2 (days 1 to 56), and then as needed. In cohort 2, patients received 2 cycles of loperamide prophylaxis plus budesonide (9 mg daily) during cycle 1. In cohort 3, patients received loperamide as described, plus colestipol (2 g, twice daily) for the first 28 days. Colestipol is an oral bile acid–binding agent. In cohort 4, patients received colestipol (2 g, twice daily) during the first cycle, plus loperamide as needed. Finally, 2 more cohorts evaluated neratinib dose escalation: Neratinib was initiated at either 120 mg daily or 160 mg daily, and was escalated to 240 mg daily thereafter. The primary endpoint was the incidence of grade 3 or higher diarrhea.

All of the preventive strategies showed a reduction in the incidence of grade 3 or higher diarrhea compared with the ExteNET trial. In the CONTROL trial, there was no grade 4 diarrhea. In the 4 cohorts that investigated loperamide, with or without budesonide or colestipol, the rate of grade 3 diarrhea ranged from 21% to 32%. In cohort 5—a neratinib dose-escalation cohort—the incidence of grade 3 diarrhea was only 15%.

The trial also showed a reduction in the severity and duration of diarrhea in patients receiving neratinib. The median cumulative duration of grade 3 or higher diarrhea events was 5 days (interquartile range, 2-9 days) in the ExteNET trial vs 2 days (interquartile range, 2-3 days) in the CONTROL trial. In the CONTROL dose-escalation cohort, only 3.3% of patients discontinued treatment owing to neratinib-associated diarrhea (vs 16.8% in the ExteNET trial). Most discontinuations due to diarrhea occurred in the first month (Figure 10).

The Use of Neratinib in Clinical Practice

Along with the use of loperamide, the strategy of starting neratinib at a lower dose and escalating to the full daily dose has been an important prophylactic measure to improve patients' ability to tolerate this treatment. Loperamide can be given 4 times daily prophylactically or

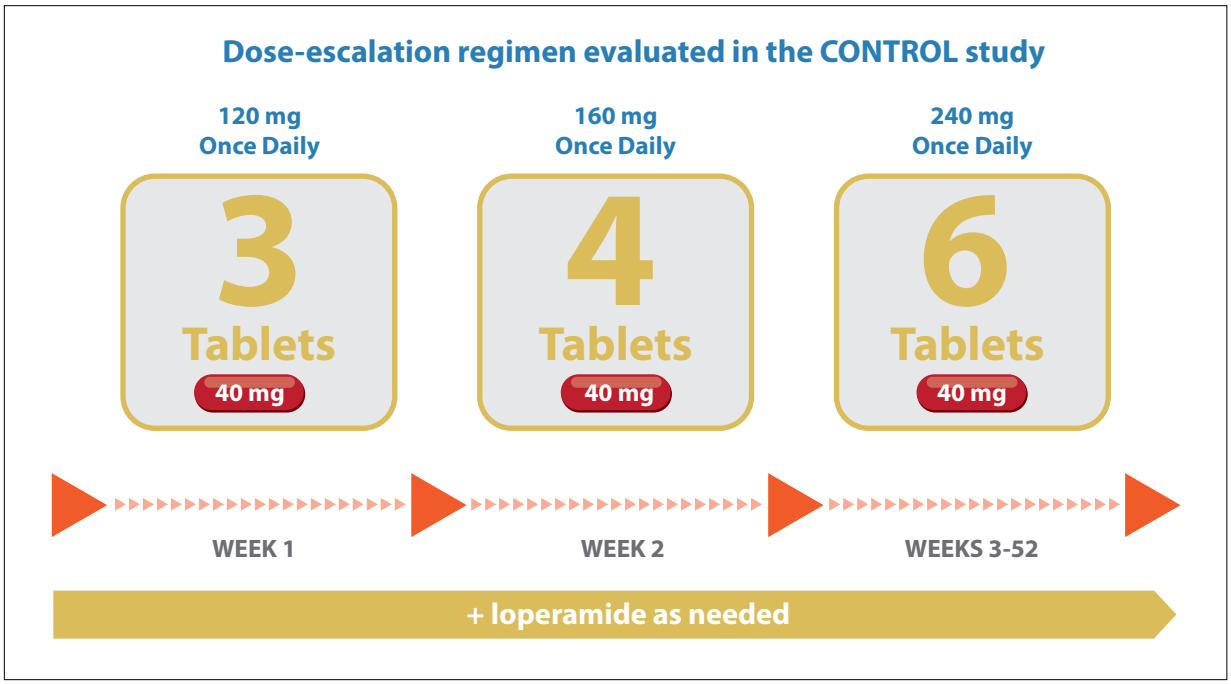
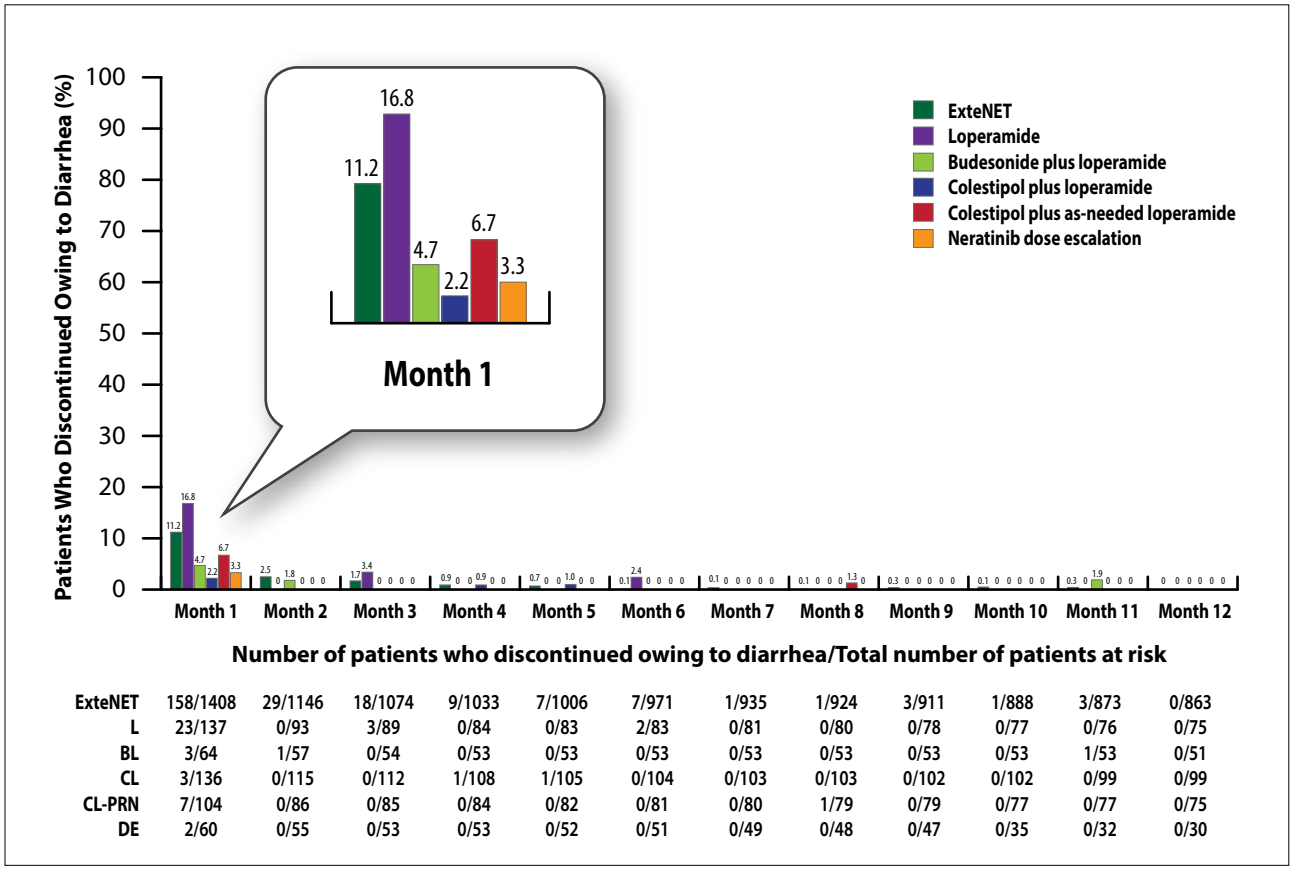


Figure 9. A neratinib dose-escalation strategy evaluated in the CONTROL trial. A second dose-escalation arm in CONTROL was still enrolling at the data cutoff date of August 26, 2019. That arm starts neratinib at 4 pills (160 mg) daily for 2 weeks, then increases to 5 pills (200 mg) daily for another 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.



	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
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 10. 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]

if diarrhea does occur. This approach is commonly taken with afatinib—another pan-HER inhibitor—in patients with lung cancer. The slow dose escalation has made a significant impact in increasing treatment adherence. In my practice, I tend to begin treatment with neratinib with a prescription of 4 pills of 40 mg each, which is equivalent to 160 mg daily. If the patient develops diarrhea, I will reduce the daily dose to 3 pills. Then, every 1 to 2 weeks, I will increase the neratinib dose by 1 pill until the full dose is reached. In some cases, a patient will need to stop at 5 pills, without further dose escalation. Treatment can still be successful with a 5-pill strategy if escalating to the full 240 mg (6 pills a day) is not feasible. The goal is to ensure that patients can continue treatment with neratinib for 1 year. Virtually no patients discontinue neratinib owing to diarrhea after the first month of neratinib; there is predictable tachyphylaxis.

When describing neratinib to patients, it is important to inform them of the potential for grade 3 diarrhea. However, clinicians should clarify that this adverse event tends to be limited to the first 1 or 2 months of treatment. After that time, patients may have no diarrhea whatsoever, or they may experience an occasional loose stool, depending on what they eat.

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.

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Neratinib in the Early-Stage/Extended Adjuvant Breast Cancer Patient: Q&A

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

Joyce A. O'Shaughnessy, MD In which settings do you recommend adjuvant neratinib? Also, how do you address treatment fatigue, which refers to patients who are reluctant to embark on another course of therapy after T-DM1?

Ruth O'Regan, MD I typically consider using neratinib in patients with hormone receptor–positive disease, particularly those without a pathologic complete response. I believe the data are compelling in these settings.[1] I have not yet prescribed neratinib after T-DM1, but this approach could be appropriate. I use little adjuvant treatment, based on the patient's risk for residual disease. I prescribe neratinib to high-risk patients, who are happy to have another treatment option. The dose-escalation strategy works well to manage the diarrhea.[2]

Claudine Isaacs, MD I follow the same approach as Dr O'Regan. One important issue to consider is treatment fatigue. Treatment for these patients is akin to a marathon. Throughout the treatment course, I remind patients that other therapies may be needed. At the start of the neoadjuvant phase, I inform patients that the choice of treatment following the neoadjuvant phase will be predicated on the tumor's response to therapy. In patients who do not achieve a pathologic complete response, I start T-DM1. Patients understandably consider T-DM1 to be something more than just antibody-targeted therapy. At the time I initiate T-DM1, I discuss with patients that, once they complete the intravenous therapy, we are planning one additional year of oral therapy with another HER2-directed agent. I remind them again partway through the T-DM1 regimen. My approach is to regularly mention the idea of another therapy along the way, as it can be understandably disconcerting for a patient to suddenly learn she will need to take another treatment after finishing T-DM1.

I usually restrict neratinib to my patients with ER-positive disease, but would consider using this agent in ER-negative patients with high-risk disease, who are at risk for recurrence. The ExteNET data were somewhat confounded by the fact that many patients started treatment with neratinib a long time after completion of adjuvant therapy.[1] Data from subset unplanned analyses indicate a benefit with neratinib in the ER-negative subset of patients who began treatment within a few months of completing adjuvant trastuzumab.

In terms of symptom management, based on data from the CONTROL trial, I have started to administer neratinib in a dose-escalation strategy.[2] This results in much better control of the diarrhea, one of the most problematic side effects of this drug.

Joyce A. O'Shaughnessy, MD I do use neratinib for the occasional ER-negative patient who did not respond well to preoperative therapy. This patient would, of course, receive T-DM1. For high-risk patients, I would not hesitate to consider neratinib, based on the subset analysis from the ExteNET trial of patients who began neratinib within 6 months of finishing adjuvant trastuzumab.[1] The curves on the Kaplan-Meier graph did stay apart. I have not yet used neratinib in this setting, but I would.

I use neratinib after T-DM1 in patients who are high risk, specifically those with positive nodes after preoperative therapy whose breast cancer is ER-positive and HER2-positive. In that case, I administer docetaxel, carboplatin, and trastuzumab plus pertuzumab (TCH+P). Patients then receive T-DM1, in addition to optimal endocrine therapy. High-risk ER-positive, HER2-positive patients are still at risk for late recurrences. If I were in their place, and a treatment offered me a 7% to 8% greater chance of invasive disease–free survival in 5 years, I would take it. Much of the benefit is from an improvement in distant disease-free survival.

In the early-stage setting, neratinib was approved for use after adjuvant trastuzumab-based therapy. Currently, there have been no studies to provide level 1 evidence showing that patients will benefit from adjuvant neratinib after other anti-HER2–based therapies, such as adjuvant or neoadjuvant pertuzumab, nor after adjuvant T-DM1. However, based on preclinical data, blocking the tyrosine kinase activity of HER1, HER2, and HER4 is not cross-resistant with antibody therapy. The National Surgical Adjuvant Breast and Bowel Project FB-10 trial investigated T-DM1 plus neratinib in patients with metastatic breast cancer that had progressed after treatment with trastuzumab plus pertuzumab and a taxane.[3] The study used a 3 + 3 expansion design and enrolled 27 patients. All patients received T-DM1 (3.6 mg/kg, every 3 weeks), and the expansion cohorts evaluated the addition of neratinib at 4 different dose levels. The response rate for 19 evaluable patients was 63%. Responses were observed at all dose levels of neratinib, and the recommended dose of neratinib was 160 mg daily. Results from the NALA trial also suggested that neratinib is probably not cross-resistant with anti-HER2 antibody therapy.[4]

Even in the metastatic setting, treatment with neratinib after many other therapies can be beneficial. This approach makes sense. Particularly among the ER-positive population, where endocrine therapy has been utilized to block the ER, there will have been upregulation of the HER family in the metastatic disease that survived trastuzumab, pertuzumab, and T-DM1.[5] Biologically, it makes a great deal of sense that anti-HER2 antibodies and the pan-HER2 tyrosine kinase inhibitor neratinib would be non–cross resistant, and the activity of neratinib in increasing disease-free survival and distant disease-free survival in the ExteNET trial following neoadjuvant trastuzumab is evidence of this.

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.

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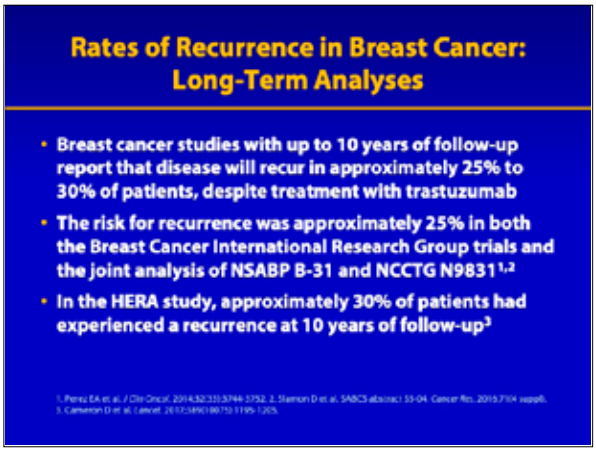

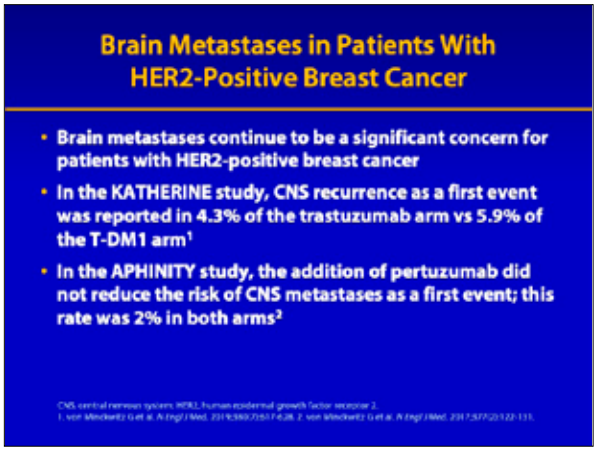

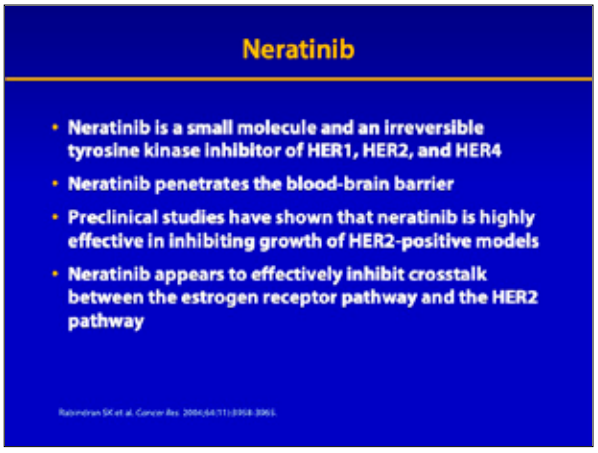

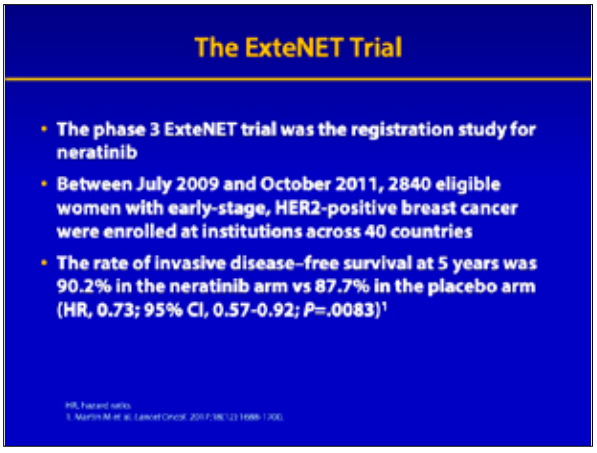

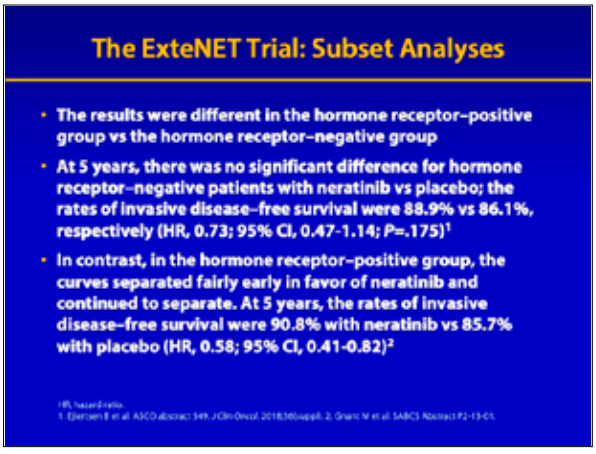

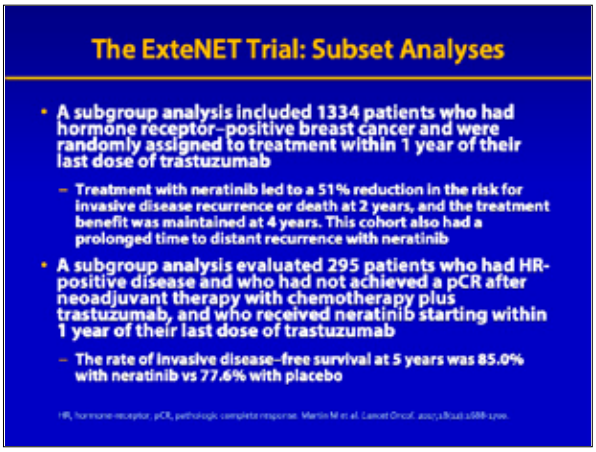

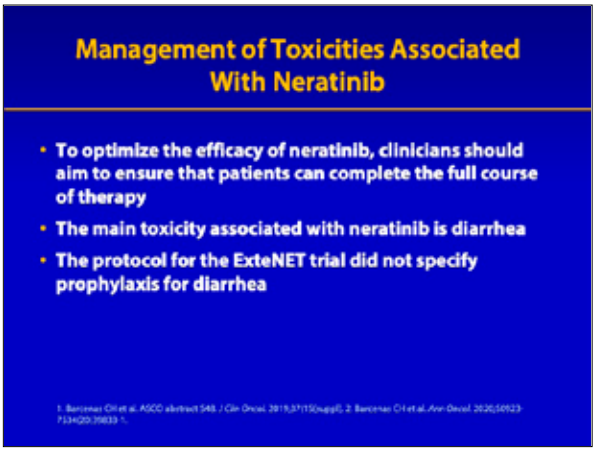

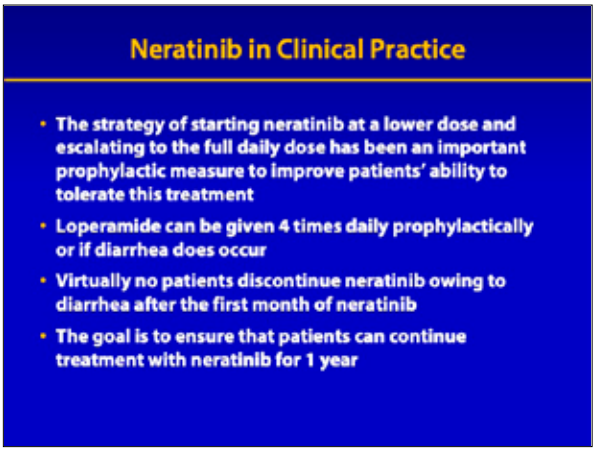

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