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A SPECIAL MEETING REVIEW EDITION

Highlights in Early and Metastatic Breast Cancer From the 2020 San Antonio Breast Cancer Symposium

A Review of Selected Presentations From the 2020 SABCS Virtual Symposium • December 8-11, 2020

Special Reporting on:

- Continued Efficacy of Neratinib in Patients With HER2-Positive Early-Stage Breast Cancer: Final Overall Survival Analysis From the Randomized Phase 3 ExteNET Trial
- First Results From a Phase 3 Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients With 1 to 3 Positive Nodes, Hormone Receptor–Positive and HER2-Negative Breast Cancer With Recurrence Score <25: SWOG S1007 (RxPONDER)
- Bringing Diarrhea Under CONTROL: Dose Escalation Reduces Neratinib-Associated Diarrhea and Improves Tolerability in HER2-Positive Early-Stage Breast Cancer
- Phase III Study of Palbociclib Combined With Endocrine Therapy in Patients With Hormone Receptor–Positive, HER2-Negative Primary Breast Cancer and With High Relapse Risk After Neoadjuvant Chemotherapy: First Results From PENELOPE-B
- Impact of Neratinib on Outcomes in HER2-Positive Metastatic Breast Cancer Patients With Central Nervous System Disease at Baseline: Findings From the Phase 3 NALA Trial
- Results From CONTESSA: A Phase 3 Study of Tesetaxel Plus a Reduced Dose of Capecitabine Versus Capecitabine Alone in Patients With HER2–, Hormone Receptor+ Metastatic Breast Cancer Who Have Previously Received a Taxane
- Cost-Effectiveness of Neratinib for the Extended Adjuvant Treatment of Adult Patients With Early-Stage, HR+, HER2-Overexpressed/Amplified Breast Cancer Who Initiated Neratinib Within 1 Year of Completing Trastuzumab in the US
- Primary Outcome Analysis of Invasive Disease–Free Survival for MonarchE: Abemaciclib Combined With Adjuvant Endocrine Therapy for High-Risk Early Breast Cancer
- The Neat-HER Virtual Registry: Results on HER2+ Breast Cancer Patients Receiving Neratinib as Extended Adjuvant Therapy
- E2112: Randomized Phase 3 Trial of Endocrine Therapy Plus Entinostat/Placebo in Patients With Hormone Receptor–Positive Advanced Breast Cancer: A Trial of the ECOG-ACRIN Cancer Research Group

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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THE FIRST AND ONLY HER2-DIRECTED SMALL MOLECULE APPROVED IN BOTH EARLY AND METASTATIC HER2+ BREAST CANCER

PREVENT

RECURRENCE[1,2,*]

(REDUCE THE RISK OF RECURRENCE IN eBC)[†]

PROTECT

AGAINST PROGRESSION[3]

(INCREASE PFS IN mBC)[‡]

ACTUAL PATIENTS

ExteNET was a pivotal phase 3, global, multicenter, randomized, double-blind, placebo-controlled study involving 2840 women with early-stage HER2+ breast cancer and locally confirmed HER2 status who had received prior trastuzumab-based therapy.[1,2,§] Of the patients with HER2+, hormone receptor-positive (HR+) disease, 95% of the HR+ study population received concurrent endocrine therapy.[2] The primary endpoint was iDFS.[‖]

NALA was a pivotal phase 3, global, multicenter, randomized, open-label study of NERLYNX + capecitabine (n=307) vs lapatinib + capecitabine (n=314) in adults with HER2+ mBC. All patients had ≥2 prior lines of HER2-directed therapy for mBC. Asymptomatic and stable brain metastases were permitted.[3,4]

INDICATIONS AND USAGE: NERLYNX is a kinase inhibitor indicated:

- As a single agent, for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
- In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

Please see IMPORTANT SAFETY INFORMATION and brief summary of Full Prescribing Information on the following pages.

*In patients randomized to NERLYNX ≤1 year from completing trastuzumab-based therapy. Results of ExteNET are supported by an exploratory analysis of 5-year follow-up, with 74.5% (2117/2840) of patients reconsented. 95% of the HR+ study population received concurrent endocrine therapy. Recurrence is defined as time from randomization to first occurrence of invasive ipsilateral tumor recurrence, invasive contralateral breast cancer, local/regional invasive recurrence, distant recurrence, or death from any cause.

†4.7% absolute benefit in distant disease-free survival vs placebo at 5 years in early-stage HER2+ HR+ breast cancer patients within 1 year of completing trastuzumab-based therapy. Distant disease-free survival was a secondary endpoint in the clinical trial.

‡Median PFS of 5.6 months with NERLYNX + capecitabine vs 5.5 months with lapatinib + capecitabine (HR=0.76; 95% CI: 0.63, 0.93; *P*=0.0059).

§Select exclusion criteria: clinically significant cardiac, GI, or psychiatric comorbidities; inability to swallow pills.

‖Invasive disease-free survival defined as the time between the date of randomization to the first occurrence of invasive recurrence (local/regional, ipsilateral, or contralateral breast cancer), distant recurrence, or death from any cause, with 2 years and 28 days of follow-up.

CI: confidence interval; eBC: early breast cancer; HER: human epidermal growth factor receptor; HR: hazard ratio; HR+: hormone receptor-positive; iDFS: invasive disease-free survival; mBC: metastatic breast cancer; PFS: progression-free survival.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: None

WARNINGS AND PRECAUTIONS:

- **Diarrhea:** Aggressively manage diarrhea. If diarrhea occurs despite recommended prophylaxis, treat with additional anti-diarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥ 2 diarrhea that occurs after maximal dose reduction.
- **Hepatotoxicity:** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities.
- **Embryo-Fetal Toxicity:** NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception.

ADVERSE REACTIONS: The most common adverse reactions (reported in ≥ 5% of patients) were:

- NERLYNX as a single agent: diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increased, nail disorder, dry skin, abdominal distention, epistaxis, weight decreased, and urinary tract infection.
- NERLYNX in combination with capecitabine: diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, weight decreased, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment, and muscle spasms.

To report SUSPECTED ADVERSE REACTIONS, contact Puma Biotechnology, Inc. at 1-844-NERLYNX (1-844-637-5969) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS:

- Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors. When patients require gastric acid reducing agents, use an H_2-receptor antagonist or antacid. Separate NERLYNX by at least 3 hours with antacids. Separate NERLYNX by at least 2 hours before or 10 hours after H_2-receptor antagonists.
- Strong CYP3A4 inhibitors: Avoid concomitant use.
- Moderate CYP3A4 and P-glycoprotein (P-gp) dual inhibitors: Avoid concomitant use.
- Strong or moderate CYP3A4 inducers: Avoid concomitant use.
- P-glycoprotein (P-gp) substrates: Monitor for adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with NERLYNX.

USE IN SPECIFIC POPULATIONS:

- **Lactation:** Advise women not to breastfeed.

Please see brief summary of Full Prescribing Information on next page.

References: 1. Gnant M, Martin M, Holmes 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 analysis from the phase III ExteNET trial. Poster presented at: 2018 San Antonio Breast Cancer Symposium (SABCS); December 4-8, 2018; San Antonio, TX. **2.** Martin M, Holmes FA, Ejlertsen B, et al. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017;18(12):1688-1700. **3.** NERLYNX [package insert]. Los Angeles, CA; Puma Biotechnology, Inc. **4.** Saura C, Oliveira M, Feng Y-H, et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥2 HER2-directed regimens: phase III NALA trial. *J Clin Oncol*. Published online July 17, 2020. doi:10.1200/JCO.20.00147

BRIEF SUMMARY OF PRESCRIBING INFORMATION

The following is a brief summary of the full prescribing information and does not include all the information needed to use NERLYNX® (neratinib) tablets safely and effectively. See full prescribing information for NERLYNX.

NERLYNX® (neratinib) tablets, for oral use

Initial U.S. Approval: 2017

INDICATION AND USAGE: NERLYNX is a kinase inhibitor indicated:

- As a single agent, for the extended adjuvant treatment of adult patients with early-stage HER2-positive breast cancer, to follow adjuvant trastuzumab-based therapy.
- In combination with capecitabine, for the treatment of adult patients with advanced or metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 based regimens in the metastatic setting.

CONTRAINDICATIONS: None. (See Section 4 of the full prescribing information.)

WARNINGS AND PRECAUTIONS:

- ***Diarrhea:*** Aggressively manage diarrhea occurring despite recommended prophylaxis with additional antidiarrheals, fluids, and electrolytes as clinically indicated. Withhold NERLYNX in patients experiencing severe and/or persistent diarrhea. Permanently discontinue NERLYNX in patients experiencing Grade 4 diarrhea or Grade ≥2 diarrhea that occurs after maximal dose reduction. (See Sections 2.3, 5.1 of the full prescribing information.)
- ***Hepatotoxicity:*** Monitor liver function tests monthly for the first 3 months of treatment, then every 3 months while on treatment and as clinically indicated. Withhold NERLYNX in patients experiencing Grade 3 liver abnormalities and permanently discontinue NERLYNX in patients experiencing Grade 4 liver abnormalities. (See Sections 2.3, 5.2 of the full prescribing information.)
- ***Embryo-Fetal Toxicity:*** NERLYNX can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (See Sections 5.3, 8.1, 8.3 of the full prescribing information.)

ADVERSE REACTIONS: The most common adverse reactions (reported in ≥ 5% of patients) were:

- NERLYNX as a single agent: diarrhea, nausea, abdominal pain, fatigue, vomiting, rash, stomatitis, decreased appetite, muscle spasms, dyspepsia, AST or ALT increased, nail disorder, dry skin, abdominal distention, epistaxis, weight decreased, and urinary tract infection.
- NERLYNX in combination with capecitabine: diarrhea, nausea, vomiting, decreased appetite, constipation, fatigue/asthenia, weight decreased, dizziness, back pain, arthralgia, urinary tract infection, upper respiratory tract infection, abdominal distention, renal impairment, and muscle spasms.

To report SUSPECTED ADVERSE REACTIONS, contact Puma Biotechnology, Inc. at 1-844-NERLYNX (1-844-637-5969) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS:

- Gastric acid reducing agents: Avoid concomitant use with proton pump inhibitors. When patients require gastric acid reducing agents, use an H_2-receptor antagonist or antacid. Separate NERLYNX by at least 3 hours with antacids. Separate NERLYNX by at least 2 hours before or 10 hours after H_2-receptor antagonists. (See Sections 2.3, 7.1 of the full prescribing information.)
- Strong CYP3A4 inhibitors: Avoid concomitant use. (See Section 7.1 of the full prescribing information.)
- Moderate CYP3A4 and P-glycoprotein (P-gp) dual inhibitors: Avoid concomitant use. (See Section 7.1 of the full prescribing information.)
- Strong or moderate CYP3A4 inducers: Avoid concomitant use. (See Section 7.1 of the full prescribing information.)
- P-glycoprotein (P-gp) substrates: Monitor for adverse reactions of narrow therapeutic agents that are P-gp substrates when used concomitantly with NERLYNX. (See Section 7.2 of the full prescribing information.)

USE IN SPECIFIC POPULATIONS:

Lactation: Advise women not to breastfeed. (See Section 8.2 of the full prescribing information.)

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PRC-US-NER-1453 03/20

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(neratinib) tablets

Continued Efficacy of Neratinib in Patients With HER2-Positive Early-Stage Breast Cancer: Final Overall Survival Analysis From the Randomized Phase 3 ExteNET Trial

Neratinib is an irreversible tyrosine kinase inhibitor of the human epidermal growth factor receptors (HER) 1, 2, and 4. The phase 3 ExteNET trial enrolled 2840 women with early-stage HER2-positive breast cancer who had completed neoadjuvant or adjuvant trastuzumab plus chemotherapy. The patients were randomly assigned to oral neratinib at 240 mg/d or placebo for 1 year.[1] Their median age was 52 years (range, 23-83). Dr Frankie Ann Holmes and colleagues reported the final analysis of overall survival (OS) from ExteNET.[2]

As previously reported, a 5-year follow-up analysis in the intention-to-treat (ITT) population showed that neratinib was associated with an absolute invasive disease–free survival (IDFS) benefit of 2.5% and a distant disease–free survival (DDFS) benefit of 1.7%.[3] Among patients with hormone receptor–positive disease who initiated neratinib treatment within 1 year of completing trastuzumab, an absolute IDFS benefit of 5.1% and a DDFS benefit of 4.7% were seen at 5 years. In the subset of the population that did not achieve a pathologic complete response (pCR) after neoadjuvant therapy, the absolute 5-year IDFS and DDFS benefits were 7.4% and 7.0%, respectively.

The current OS analysis was event-driven and powered for the ITT population, with a target of 248 events. OS was defined as the time from randomization to the date of death from any cause. Descriptive analyses were performed in the population of patients with hormone receptor–positive disease (n=1631), in those who initiated neratinib treatment within 1 year of completing trastuzumab (n=1334), and in the higher-risk subset of patients who did not achieve a pCR after neoadjuvant therapy (n=354). The analysis cutoff date was July 2019.

After a median follow-up of 8.1 years in the ITT population, deaths were reported in 8.9% of the neratinib arm and 9.6% of the placebo arm. The 8-year OS rates were 90.1% (95% CI, 88.3-91.6) in the neratinib group and 90.2% (95% CI, 88.4-91.7) in the placebo group (absolute difference at 8 years, –0.1%; stratified hazard ratio [HR], 0.95; 95% CI, 0.75-1.21; *P*=.6914). In the hormone receptor–positive population, the absolute difference in OS rates at 8 years was 1.5% (HR, 0.80; 95% CI, 0.58-1.12). In the subgroup that initiated neratinib treatment within 1 year of completing trastuzumab, the absolute difference in OS rates at 8 years was 2.1% (HR, 0.79; 95% CI, 0.55-1.13), whereas in the subgroup with no pCR

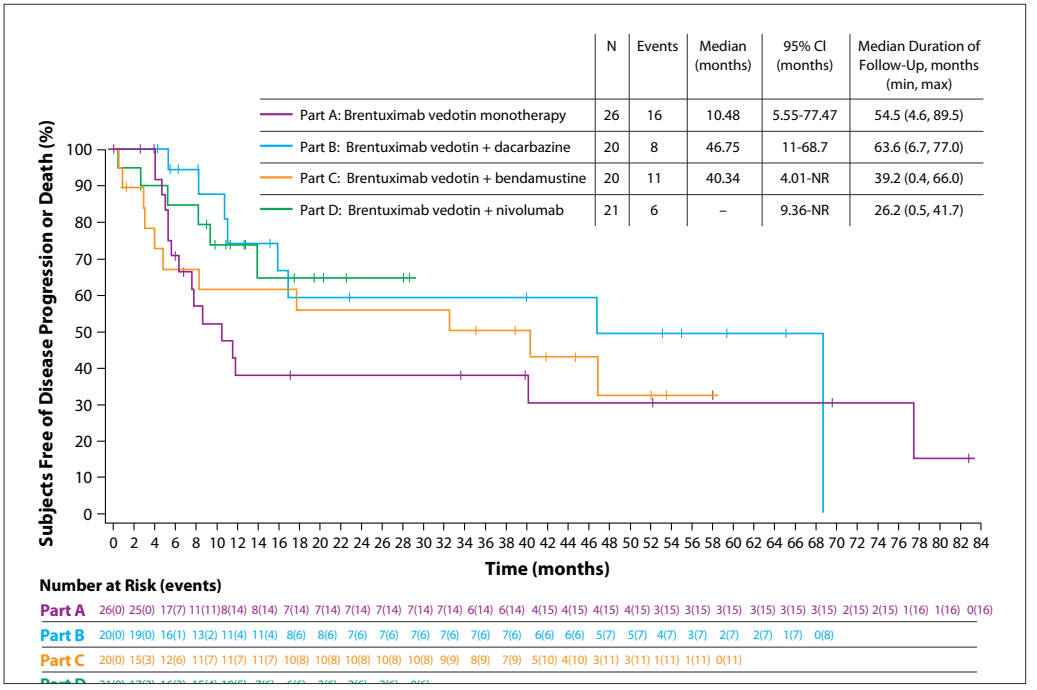

Figure 1. Overall survival among the subgroup of patients without a pathologic complete response after neoadjuvant therapy in the phase 3 ExteNET trial, which compared neratinib vs placebo in patients with early-stage HER2-positive breast cancer. HER2, human epidermal growth factor receptor 2. Adapted from Holmes FA et al. SABCS abstract PD3-03. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

after neoadjuvant therapy, the absolute difference at 8 years was 9.1% (HR, 0.47; 95% CI, 0.23-0.92; Figure 1). Neratinib did not appear to improve OS rates for patients with hormone receptor–negative disease. In the ITT group and hormone receptor–positive disease subgroups, there were fewer central nervous system (CNS) events in the neratinib arm compared with placebo; however, these differences did not reach statistical significance. Safety results in this 8-year follow-up were similar to those previously published.[2]

The investigators concluded that neratinib was not associated with a statistically significant benefit in OS over placebo in the ITT population. However, an association between neratinib treatment and OS benefit was seen in the population of patients with hormone receptor–positive disease, in the subset of patients who initiated neratinib treatment within 1 year of completing trastuzumab, and in the higher-risk subset of patients who did not achieve a pCR after neoadjuvant therapy. These findings are consistent with earlier results for IDFS and DDFS, and they support the use of neratinib in clinical practice for such patients.

References

1. 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.
2. Holmes FA, Moy B, Delaloge S, et al. Continued efficacy of neratinib in patients with HER2-positive early-stage breast cancer: final overall survival analysis from the randomized phase 3 ExteNET trial. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PD3-03.
3. 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.

First Results From a Phase 3 Randomized Clinical Trial of Standard Adjuvant Endocrine Therapy +/- Chemotherapy in Patients With 1 to 3 Positive Nodes, Hormone Receptor–Positive and HER2-Negative Breast Cancer With Recurrence Score <25: SWOG S1007 (RxPONDER)

The phase 3 SWOG S1007 RxPONDER trial compared endocrine therapy vs chemoendocrine therapy in women with hormone receptor–positive, HER2-negative breast cancer, with 1 to 3 positive lymph nodes, and a 21-gene Oncotype DX Recurrence Score of 0 to 25.[1] Patients were randomly assigned to receive endocrine therapy or chemoendocrine therapy. The primary endpoint was IDFS. The primary hypothesis was that the benefit of chemoendocrine therapy would increase as the Recurrence Score increased.

Dr Kevin Kalinsky presented the results from the primary analysis.[1] The analysis included 2506 patients treated with endocrine therapy only and 2509 patients treated with chemotherapy followed by endocrine therapy. Half of the patients treated with chemotherapy received docetaxel and cyclophosphamide (4 or 6 cycles). Premenopausal women underwent ovarian function suppression.

The baseline characteristics were well balanced between the treatment arms. In both arms, 33.2% of women were premenopausal. The Recurrence Score was 0 to 13 in 42.7% of patients in the endocrine therapy arm and 42.9% of those in the chemotherapy arm. Previous axillary lymph node dissection was reported in 62.7% vs 62.5%, respectively. In both groups, most patients had only 1 positive node (65.9% vs 65.0%). Disease risk was considered intermediate in most patients (64.1% vs 66.1%).

After a median follow-up of 5.1 years (447 IDFS events), the Recurrence Score did not predict the relative benefit of chemoendocrine therapy (P=.30). In a prespecified analysis by menopausal status, chemoendocrine therapy did not provide statistically significant benefits over endocrine therapy for postmenopausal patients. The 5-year IDFS was 91.9% with endocrine therapy vs 91.6% with chemoendocrine therapy (HR, 0.97; 95% CI, 0.78-1.22; P=.82) for postmenopausal women. In premenopausal patients, the 5-year IDFS was 94.2% with chemoendocrine therapy vs 89.0% with endocrine therapy alone (HR, 0.54; 95% CI, 0.38-0.76; P=.0004; Figure 2). Among premenopausal women, the addition of chemotherapy to endocrine therapy resulted in a 46% decrease in IDFS events. Benefits were seen across all subgroups. There was a 53% decrease in deaths, which translated to an absolute improvement in 5-year OS of 1.3%. These data suggest there is a significant differential treatment effect of chemoendocrine therapy over endocrine therapy alone based on the Recurrence Score for premenopausal women that requires further analysis.

The investigators concluded that it is likely that adjuvant chemotherapy can be omitted from treatment for postmenopausal women with 1 to 3 positive lymphoma nodes and a Recurrence Score of 0 to 25. In contrast,

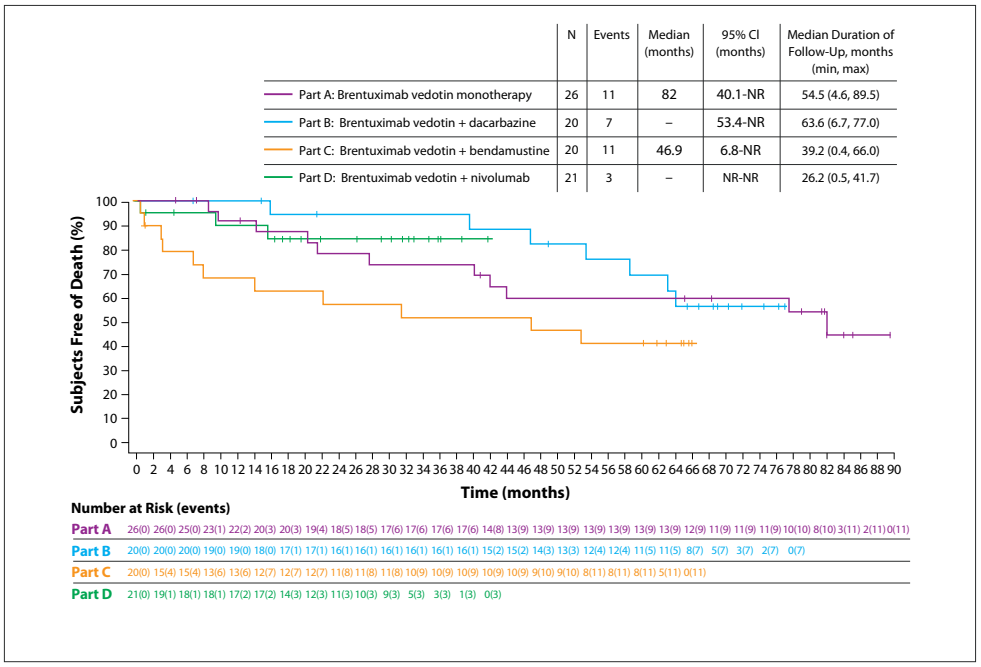

Figure 2. Invasive disease–free survival at 5 years among premenopausal women with a Recurrence Score of 0 to 25 in the phase 3 SWOG S1007 RxPONDER trial, which compared endocrine therapy vs chemoendocrine therapy in women with hormone receptor–positive, HER2-negative breast cancer. CET, chemoendocrine therapy; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDFS, invasive disease–free survival. Adapted from Kalinsky K et al. Abstract GS3-00. Presented at: the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[1]

premenopausal women with positive nodes and a Recurrence Score of 0 to 25 will likely benefit from chemotherapy. Future analysis of the study will provide data for quality of life and other outcomes.

Reference

1. Kalinsky K, Barlow W, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) <25: SWOG S1007 (RxPONDER). Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS3-00.

Bringing Diarrhea Under CONTROL: Dose Escalation Reduces Neratinib-Associated Diarrhea and Improves Tolerability in HER2-Positive Early-Stage Breast Cancer

Diarrhea is the main tolerability concern with neratinib, particularly in the first 1 to 2 months of treatment. In the phase 3 ExteNET trial, women with early-stage HER2-positive breast cancer who had completed neoadjuvant or adjuvant trastuzumab plus chemotherapy received either oral neratinib at 240 mg/d or placebo for 1 year. No mandatory prophylaxis was used, and the rate of grade 3 diarrhea was 40%.[1] The CONTROL trial is a phase 2, open-label study that is investigating several strategies to improve the tolerability of neratinib. A previous analysis of CONTROL showed that the rate, severity, and duration of neratinib-associated grade 3/4 diarrhea were improved compared with rates reported in the ExteNET trial when preemptive antidiarrheal prophylaxis with loperamide alone or in combination with budesonide or colestipol was used or when a dose-escalation strategy for neratinib was adopted.[2] Dr Manuel Ruiz-Borrego reported updated findings from 2 dose-escalation cohorts in the CONTROL trial.[3]

The CONTROL trial enrolled adults with stage I to IIIc, HER2-positive breast cancer who had received trastuzumab-based adjuvant therapy. The median age was between 49 and 53 years (depending on cohort; range, 26-86), and 99% were women. The treatment proceeded in 28-day cycles for 1 year.

There were 6 cohorts. The first cohort (n=137) received oral neratinib 240 mg/d continuously, with a tapering schedule of oral loperamide prophylaxis during cycles 1 and 2 followed by loperamide (≤16 mg/d) as needed thereafter. The second cohort (n=64) received neratinib at 240 mg/d continuously, with budesonide at 9 mg/d during cycle 1 and loperamide prophylaxis as described above. The third cohort (n=136) received neratinib at 240 mg/d continuously, with colestipol given at 2 g twice daily during cycle 1 and a tapering schedule of loperamide prophylaxis during the

Table 1. Key Diarrhea Outcomes in All Cohorts in the CONTROL Trial

	Loperamide (n=137)	Budesonide + Loperamide (n=64)	Colestipol + Loperamide (n=136)	Colestipol + Loperamide PRN (n=104)	Neratinib DE1 + Loperamide PRN (n=60)	Neratinib DE2 + Loperamide PRN[a] (n=62)
Grade 3 diarrhea, n (%)	42 (30.7)	18 (28.1)	28 (20.6)	33 (31.7)	8 (13.3)	16 (25.8)
Discontinuations due to diarrhea, n (%)	28 (20.4)	7 (10.9)	5 (3.7)	8 (7.7)	2 (3.3)	3 (4.8)

[a]The data cutoff was October 19, 2020.
DE, dose escalation; PRN, as needed.
Adapted from Ruiz-Borrego M et al. SABCS abstract PS13-20. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[3]

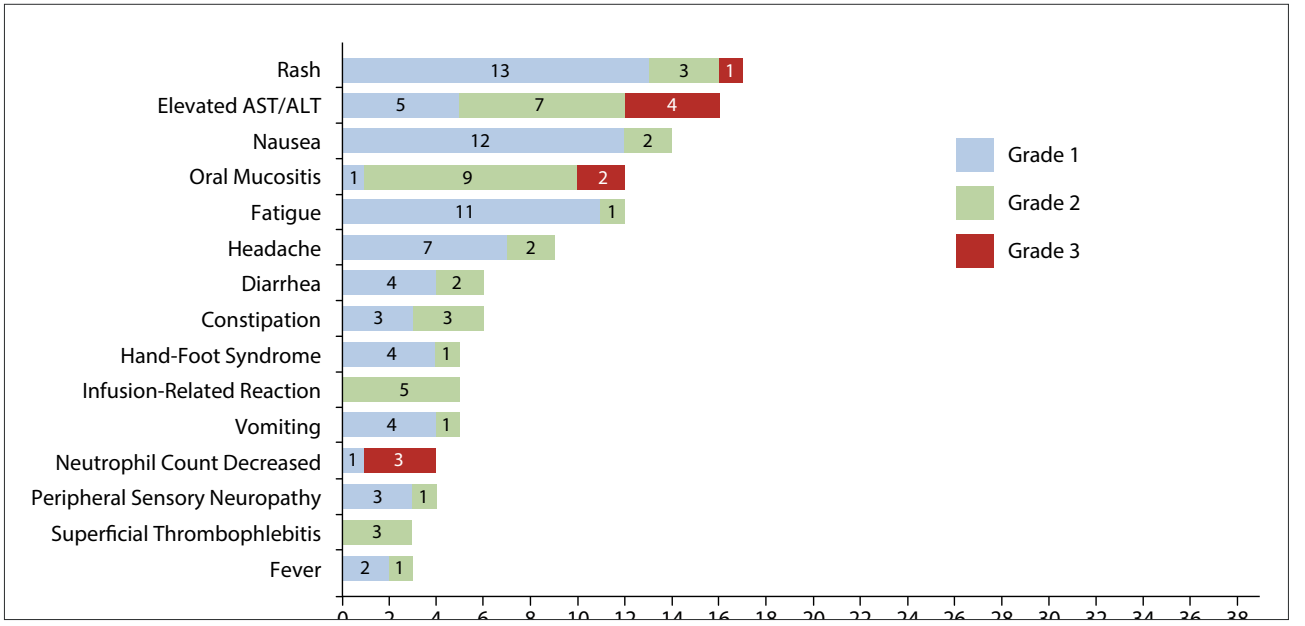

Figure 3. Treatment discontinuation owing to diarrhea according to treatment arm in the CONTROL trial. DE, dose escalation. Adapted from Ruiz-Borrego M et al. Abstract PS13-20. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[3]

first cycle only, followed by loperamide (≤16 mg/d) as needed thereafter. The fourth cohort (n=104) received neratinib at 240 mg/d continuously, with colestipol at 2 g twice daily during cycle 1, plus loperamide as needed throughout treatment. The fifth cohort (dose-escalation 1) received neratinib at 120 mg/d on days 1 to 7, 160 mg/d on days 8 to 14, and then 240 mg/d thereafter, plus loperamide as needed throughout (n=60). The sixth cohort (dose-escalation 2) received neratinib at 160 mg/d on days 1 to 14, 200 mg/d on days 15 to 28, then 240 mg/d thereafter, plus loperamide as needed throughout (n=62). The primary endpoint was the incidence of grade 3 or higher diarrhea.

As of the data cutoff (October 19, 2020), all patients in the dose-escalation 1 cohort were off-study, with a completion rate of 78.3%. In dose-escalation cohort 2, 38.7% of patients completed, 24.2% discontinued, and 37.1% had received at least 6 months of treatment and remained on treatment. Discontinuation for diarrhea occurred in 3.3% and 4.8% of patients in dose-escalation cohorts 1 and 2, respectively (Table 1). Treatment discontinuations owing to diarrhea tended to occur early among all cohorts (Figure 3). Escalation proceeded on schedule for 91.7% of patients in dose-escalation cohort 1 and 77.4% in dose-escalation cohort 2. At least 1 dose hold was required by 11.7% of patients in dose-escalation

cohort 1 and 14.5% in dose-escalation cohort 2. There were no grade 4 diarrhea events. The incidence of grade 3 diarrhea was 13.3% in dose-escalation cohort 1 and 25.8% in dose-escalation cohort 2. The median cumulative duration of grade 3 diarrhea over the 12-month treatment period was 2.5 days (range, 1-6 days) in dose-escalation cohort 1 and 2 days (range, 1-7 days) in dose-escalation cohort 2.

Compared with reported data from the phase 3 ExteNET study, the regimen in dose-escalation cohort 1 in the CONTROL study reduced the incidence, severity, and duration of neratinib-associated diarrhea.[1-3] This dose-escalation strategy, combined with loperamide administered as needed, may improve treatment adherence and completion rates.

References

1. 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.
2. Barcenas CH, Hurvitz SA, Di Palma JA, et al; CONTROL Study Investigators. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Ann Oncol.* 2020;31(9):1223-1230.
3. Ruiz-Borrego M, Chan A, Marx G, et al. Bringing diarrhea under CONTROL: dose escalation reduces neratinib-associated diarrhea and improves tolerability in HER2-positive early-stage breast cancer. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PS13-20.

Phase III Study of Palbociclib Combined With Endocrine Therapy in Patients With Hormone Receptor–Positive, HER2-Negative Primary Breast Cancer and With High Relapse Risk After Neoadjuvant Chemotherapy: First Results From PENELOPE-B

Approximately one-third of patients with hormone receptor–positive, HER2-negative primary breast cancer with residual invasive disease after neoadjuvant chemotherapy will relapse despite the use of adjuvant endocrine therapy. Palbociclib is a cyclin-dependent kinase (CDK) 4/6 inhibitor that has demonstrated highly relevant efficacy in metastatic breast cancer when combined with endocrine therapy.[1] Dr Sibylle Loibl reported final results from the PENELOPE-B trial of palbociclib.[2] This double-blind, placebo-controlled, phase 3 study enrolled women with centrally confirmed, hormone receptor–positive, HER2-negative primary breast cancer who did not achieve a pCR after taxane-containing neoadjuvant chemotherapy. The patients had a baseline Clinical-Pathologic Stage + Estrogen/Grade (CPS+EG) score of 3 or higher (or 2 or higher if there were lymph node metastases at the time of surgery). The CPS+EG score combines clinical stage before neoadjuvant treatment, pathologic stage after neoadjuvant treatment, grading, and estrogen receptor status.[3,4]

In PENELOPE-B, patients who had completed neoadjuvant chemotherapy and locoregional therapy were randomly assigned to receive 13 cycles of palbociclib 125 mg/d (n=631) or placebo (n=619) on days 1 to 21 in a 28-day cycle in addition to standard endocrine therapy.[2] Randomization was stratified by lymph node status (at surgery), age, Ki-67 expression level, global region, and CPS+EG score. The primary endpoint was IDFS, and the main secondary endpoints were IDFS

ABSTRACT SUMMARY Double-Blind, Placebo-Controlled Randomized Phase III Trial Evaluating First-Line Ipatasertib Combined With Paclitaxel for *PIK3CA/AKT1/PTEN*-Altered Locally Advanced Unresectable or Metastatic Triple-Negative Breast Cancer: Primary Results From IPATunity130 Cohort A

The IPATunity130 phase 3 trial enrolled 255 patients with chemotherapy-naive, locally advanced unresectable or metastatic triple-negative breast cancer that was *PIK3CA/AKT1*-altered and/or *PTEN*-altered (Abstract GS3-04). Patients were randomly assigned 2:1 to receive either ipatasertib at 400 mg or placebo (days 1-21), both combined with paclitaxel at 80 mg/m^2 (days 1, 8, and 15) in 28-day cycles until disease progression, unacceptable toxicity, or withdrawal. Approximately 51% had received neoadjuvant chemotherapy, 59% had visceral disease, 51% had *PIK3CA/AKT1*-activating mutations, and 49% had *PTEN* alterations only. After a median follow-up of 8.3 months, 33% of patients remained on treatment. The mean paclitaxel dose intensity was similar between the groups. There was no significant difference in PFS between treatment arms overall or in any prespecified subgroups. OS results are immature, but preliminary findings revealed no significant difference between the treatment arms. Similar proportions of patients in the study arms experienced grade 3/4 AEs, fatal AEs, or AEs leading to discontinuation of any treatment. AEs leading to dose reduction of any treatment were more common with ipatasertib.

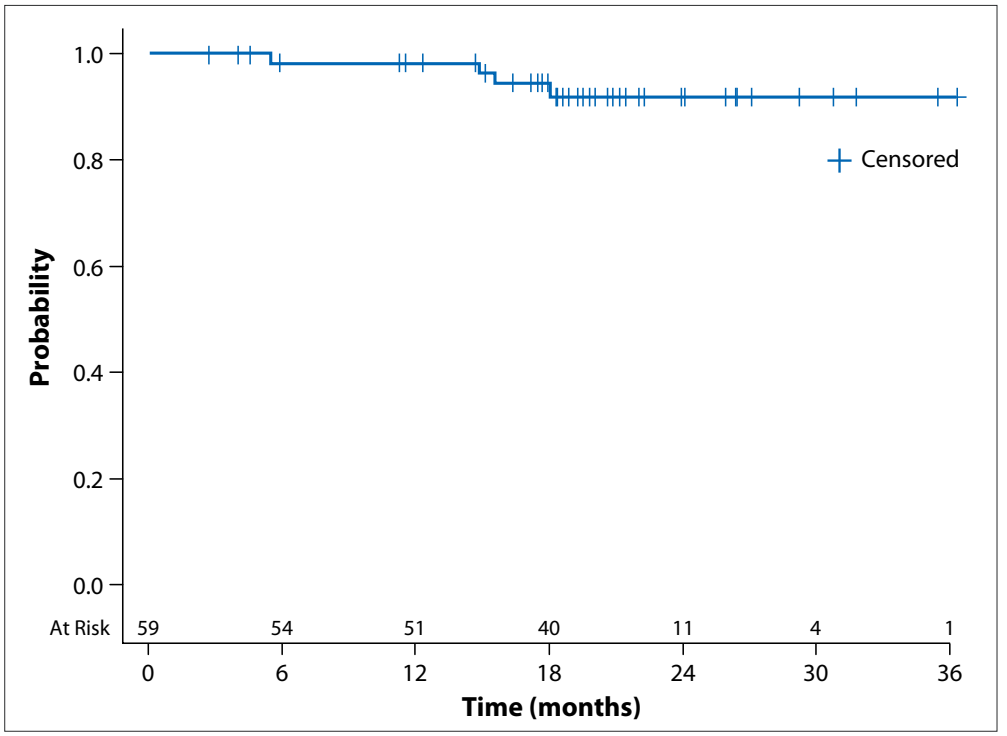

Figure 4. Invasive disease–free survival in the phase 3 PENELOPE-B trial, which compared palbociclib vs placebo among patients with hormone receptor–positive, HER2-negative primary breast cancer who did not achieve a pathologic complete response after taxane-containing neoadjuvant chemotherapy. ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IDFS, invasive disease–free survival; yr, year. Adapted from Loibl S et al. Abstract GS1-02. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

excluding second primary invasive nonbreast cancers, OS, and safety.

The median age of enrolled patients was 49.7 years (range, 19-79). Among these, 47.4% had grade 3 disease, 25.5% had a Ki-67 expression level greater than 15%, and 59.4% had a CPS+EG score of 3 or higher. After a median follow-up of 42.8 months, IDFS was not improved with palbociclib compared with placebo (stratified HR, 0.93; 95% CI, 0.74-1.16; *P*=.525; Figure 4); similar results were seen for OS (stratified HR, 0.87; 95% CI, 0.61-1.22; *P*=.420). The estimated 3-year IDFS rates were similar between groups (81.2% with palbociclib vs 77.7% with placebo), as were the estimated 3-year OS rates (93.6% with palbociclib vs 90.5% with placebo). An analysis showed that palbociclib was not significantly superior to placebo among any subgroups.

Therapy was completed by 80.5% of patients in the palbociclib arm vs 84.5% in the placebo arm. Approximately 88.6% vs 90.3% of patients, respectively, received at least 7 cycles of study treatment. The relative total dose intensity was 82% for palbociclib and 99% for placebo. In the safety analysis, the incidence of nonhematologic grade 3/4 adverse events (AEs) did not differ significantly between the arms. The incidence of hematologic grade 3/4 AEs was significantly higher in the palbociclib arm than in the placebo arm (73% vs 1.3%; *P*<.001).

References

1. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379(20):1926-1936.
2. Loibl S, Marmé F, Martin M, et al. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancer and with high relapse risk after neoadjuvant chemotherapy (NACT): first results from PENELOPE-B. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS1-02.
3. Mittendorf EA, Jeruss JS, Tucker SL, et al. Validation of a novel staging system for disease-specific survival in patients with breast cancer treated with neoadjuvant chemotherapy. *J Clin Oncol*. 2011;29(15):1956-1962.
4. Marmé F, Lederer B, Blohmer JU, et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. *Eur J Cancer*. 2016;53:65-74.

Impact of Neratinib on Outcomes in HER2-Positive Metastatic Breast Cancer Patients With Central Nervous System Disease at Baseline: Findings From the Phase 3 NALA Trial

Approximately 30% to 55% of patients with HER2-positive metastatic breast cancer develop CNS metastases, but there are few evidence-based treatments available.[1] NALA is a randomized phase 3 study comparing the combination of neratinib plus capecitabine vs the combination of lapatinib, a reversible dual tyrosine kinase inhibitor, plus capecitabine in patients with HER2-positive, metastatic breast cancer treated with at least 2 previous HER2-directed treatment regimens.[2] As previously reported, NALA enrolled 621 patients who were randomly assigned to neratinib at 240 mg once daily plus capecitabine at 750 mg/m^2 twice daily (with loperamide prophylaxis) or to lapatinib at 1250 mg once daily plus capecitabine at 1000 mg/m^2 twice daily. Neratinib and lapatinib were administered continuously, and capecitabine was administered on days 1 to 14 of 21-day cycles. Progression-free survival (PFS) was improved with the neratinib combination compared with the lapatinib combination (HR, 0.76; 95% CI, 0.63-0.93; *P*=.0059), as was the use of interventions for CNS disease (cumulative incidence, 22.8% vs 29.2%; *P*=.043).[3] The most common AEs were diarrhea (83% with the neratinib combination vs 66% with the lapatinib combination) and nausea (53% vs 42%).

Dr Cristina Saura discussed data from an exploratory analysis of patients from NALA with CNS involvement at enrollment.[4] Baseline CNS disease was documented in 51 patients in the neratinib combination arm and 50 in the lapatinib combination arm; the mean age of this cohort was 54 years (range, 25-75). No significant imbalances of baseline characteristics were noted between the treatment arms. Previous treatment with CNS radiation included whole brain radiation in 58% of patients and stereotactic radiation in 17%. Five patients (5%) had undergone CNS surgery. The median treatment duration was 5.7 months (range, 0.4-28.6) for the neratinib combination and 3.5 months (range, 0.5-20.8) for the lapatinib combination. The endpoints for this analysis were PFS, OS, time to intervention for metastatic CNS disease, and time from randomization to disease progression in the brain or death from any cause (CNS-PFS).

PFS was 7.8 months with the neratinib combination vs 5.5 months with the lapatinib combination, but this difference did not reach statistical significance (HR, 0.66; 95% CI, 0.41-1.05; *P*=.0741; Figure 5). CNS-PFS was 12.4 months vs 8.3 months, respectively, a difference that was not significant (HR, 0.62; 95% CI, 0.32-1.18; *P*=.143; Figure 6). There was no statistically significant difference between the arms for OS (16.4 months vs 15.4 months; HR, 0.90; 95% CI, 0.59-1.38; *P*=.635). The 12-month cumulative incidence for CNS disease was 25.5% vs 36.0% (*P*=.430).

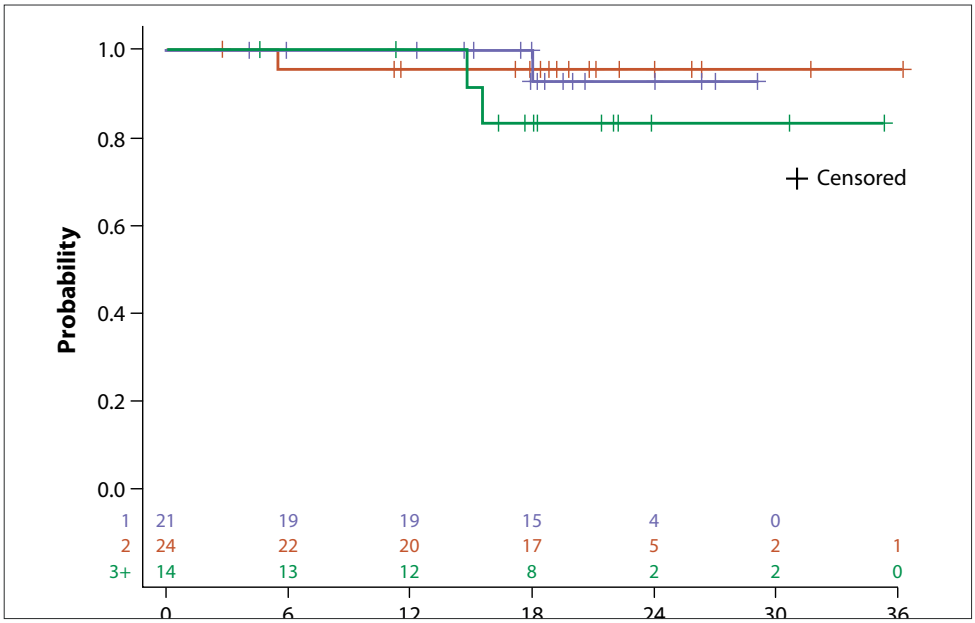

Figure 5. Progression-free survival in an exploratory analysis of patients with CNS involvement at enrollment in the phase 3 NALA trial, which compared neratinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2-positive, metastatic breast cancer treated with at least 2 previous HER2-directed treatment regimens. CNS, central nervous system; HER2, human epidermal growth factor receptor 2. Adapted from Saura C et al. Abstract PD13-09. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[4]

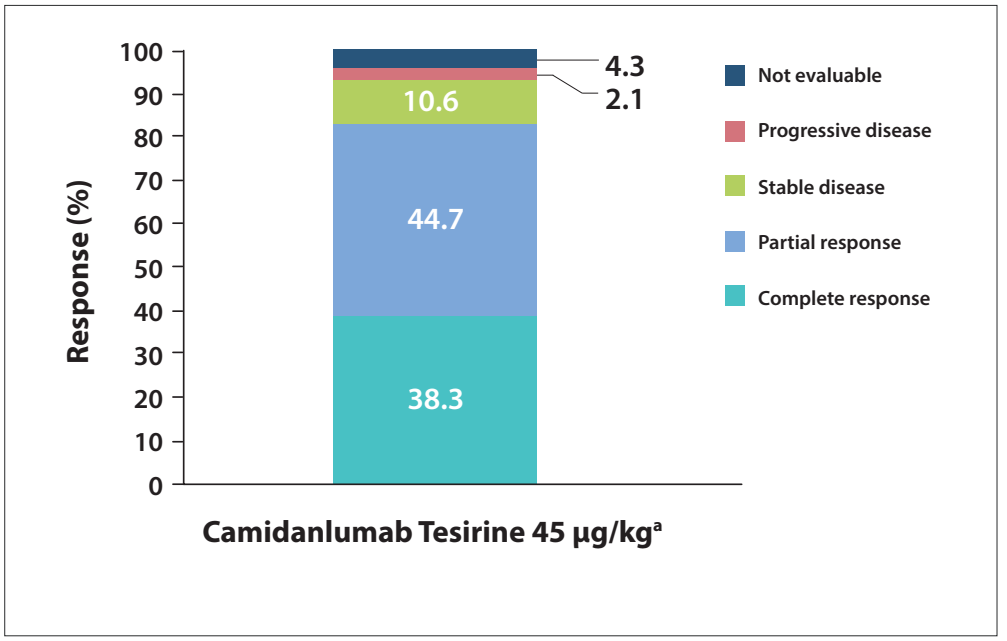

Figure 6. CNS progression-free survival in an exploratory analysis of patients with CNS involvement at enrollment in the phase 3 NALA trial, which compared neratinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2-positive, metastatic breast cancer treated with at least 2 previous HER2-directed regimens. CNS, central nervous system; HER2, human epidermal growth factor receptor 2. Adapted from Saura C et al. Abstract PD13-09. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[4]

The safety profile was similar to that reported for the overall NALA trial.[4]

References

1. Witzel I, Oliveira-Ferrer L, Müller V. Brain metastasis in breast cancer patients-need for improvement. *Cancers (Basel)*. 2020;12(11):3190.
2. 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. *J Clin Oncol*. 2020;38(27):3138-3149.
3. Awada A, Brufsky A, Saura C, et al. Impact of neratinib on development and progression of central nervous system metastases in patients with HER2-positive metastatic breast cancer: findings from the NALA, NEfERT-T, and TBCRC 022 trials. Abstract presented at: the 2019 San Antonio Breast Cancer Symposium; San Antonio, Texas; December 10-14, 2019. Abstract P2-20-01.
4. Saura C, Ryvo L, Hurvitz S, et al. Impact of neratinib on outcomes in HER2-positive metastatic breast cancer patients with central nervous system disease at baseline: findings from the phase 3 NALA trial. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PD13-09.

Results From CONTESSA: A Phase 3 Study of Tesetaxel Plus a Reduced Dose of Capecitabine Versus Capecitabine Alone in Patients With HER2–, Hormone Receptor+ Metastatic Breast Cancer Who Have Previously Received a Taxane

Tesetaxel is a novel oral taxane given every 3 weeks that has demonstrated an objective response rate (ORR) of 45% in a phase 2 trial of patients diagnosed with hormone receptor–positive, HER2-negative metastatic breast cancer.[1] Dr Joyce O'Shaughnessy presented results from a protocol-specified primary analysis of CONTESSA, an international, multicenter phase 3 trial comparing tesetaxel plus a reduced dose of capecitabine vs capecitabine monotherapy, given at the approved dose.[2] The trial enrolled patients with hormone receptor–positive, HER2-negative metastatic breast cancer who had received no more than 1 chemotherapy regimen for advanced disease and had received a taxane in the adjuvant or neoadjuvant setting.

CONTESSA randomly assigned patients to receive tesetaxel at 27 mg/m^2 on day 1 plus capecitabine at 1650 mg/m^2 per day on days 1 to 14 of a 21-day cycle (n=343), or capecitabine 2500 mg/m^2 per day on days 1 to 14 of a 21-day cycle (n=342). The median age was 56 years (range, 23-85) in the tesetaxel combination arm (n=343) and 57 years (range, 29-84) in the capecitabine arm (n=342). More than 90% of patients had previously received endocrine therapy, 80% had previously received an anthracycline, and approximately 50% had previously received a CDK4/6 inhibitor. Approximately 80% had visceral disease. The primary endpoint was independently assessed PFS. Secondary endpoints included OS, ORR, and disease control rate.

The median PFS was 9.8 months with the tesetaxel combination vs 6.9 months with single-agent capecitabine (HR, 0.716; 95% CI, 0.573-0.895; *P*=.003; Figure 7). The treatment effect was similar across the protocol-specified subgroups, including patients

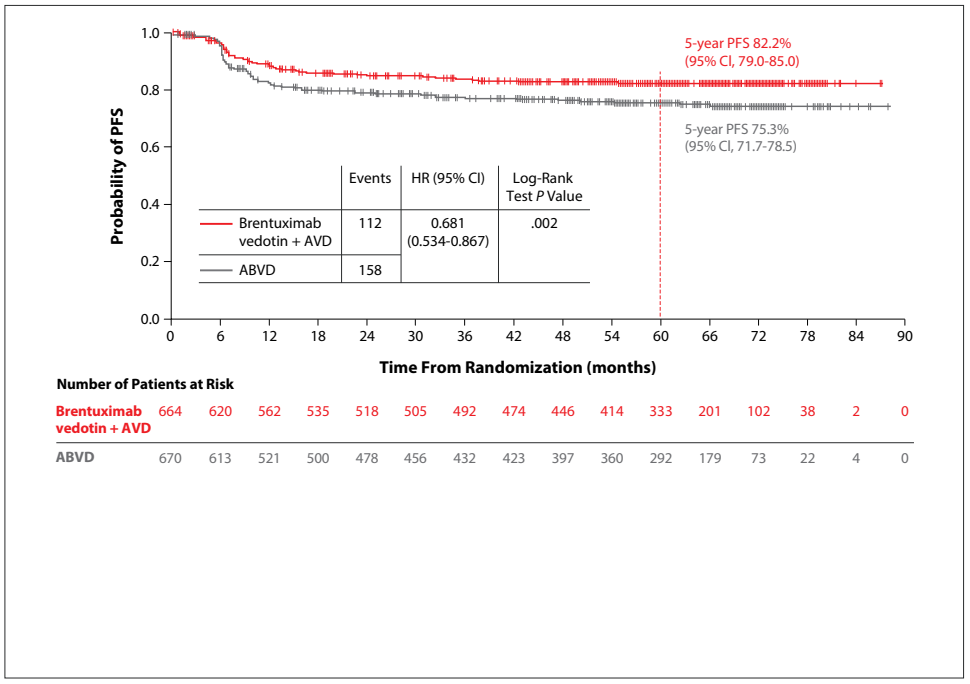

Figure 7. Progression-free survival in the phase 3 CONTESSA trial, which compared tesetaxel plus a reduced dose of capecitabine vs capecitabine alone in patients with HER2-negative, hormone receptor–positive metastatic breast cancer who had previously received a taxane. HER2, human epidermal growth factor receptor 2. Adapted from O'Shaughnessy J et al. Abstract GS4-01. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

with a disease-free interval of less than 24 months after neoadjuvant or adjuvant taxane therapy, patients who had been previously treated with a CDK4/6 inhibitor, and patients in each geographic region. The ORR was 57% in the tesetaxel combination arm vs 41% in the capecitabine-alone arm (*P*=.0002). The 24-week disease control rate was 67% in the tesetaxel combination arm vs 50% in the capecitabine-alone arm (*P*<.0001).

The most frequent grade 3/4 treatment-emergent AEs were neutropenia (which occurred in 70.9% of patients treated with tesetaxel plus capecitabine vs 8.3% of those treated with capecitabine), diarrhea (13.1% vs 8.9%), hand-foot syndrome (6.8% vs 12.2%), febrile neutropenia (13.1% vs 1.2%), fatigue (8.6% vs 4.5%), hypokalemia (8.6% vs 2.7%), leukopenia (9.8% vs 0.9%), anemia (8% vs 2.4%), nausea (6.2% vs 2.1%), and neuropathy (5.9% vs 0.9%). Grade 2 alopecia occurred in 8% of patients treated with tesetaxel plus capecitabine vs 0.3% of patients treated with capecitabine alone. Treatment discontinuation owing to any AE occurred in 23.1% of patients in the tesetaxel combination arm vs 11.9% of patients in the capecitabine monotherapy arm. Treatment-related deaths occurred in 1.8% vs 0.9%, respectively.

ABSTRACT SUMMARY PRIME 2 Randomised Trial (Postoperative Radiotherapy in Minimum-Risk Elderly): Wide Local Excision and Adjuvant Hormonal Therapy ±Whole Breast Irradiation in Women ≥65 Years With Early Invasive Breast Cancer: 10-Year Results

The PRIME 2 phase 3 trial enrolled 1326 women ages 65 years or older with hormone receptor–positive, unilateral invasive breast cancer with a tumor size of 3 cm or less and no regional lymph node involvement (Abstract GS2-03). Patients underwent breast-conserving surgery and received neoadjuvant endocrine therapy. They were randomly assigned to receive whole breast radiotherapy (n=658) or not to receive radiotherapy (n=668). The mean age was approximately 71 years. Ipsilateral breast tumor recurrence was the primary endpoint. The 10-year ipsilateral breast tumor recurrence rate was 9.8% without radiotherapy and 0.9% with radiotherapy (HR, 0.12; 95% CI, 0.05-0.31; *P*<.0001). Regional recurrence was reported in 2.3% vs 0.5%, respectively (*P*=.014). No differences were seen for subgroups such as patients with contralateral breast cancer (1% vs 2.2%; *P*=.20), distant metastases (1.4% vs 3.6%; *P*=.07), or new cancers (excluding breast cancer; 10.2% vs 8.7%; *P*=.41). Metastasis-free survival was 98.1% without radiotherapy and 96.4% with radiotherapy (*P*=.28). OS at 10 years was 80.4% vs 81.0%, respectively (*P*=.68). Most deaths were not attributable to breast cancer recurrence.

References

1. Seidman AD, Schwartzberg LS, Gudena VK, et al. Activity of tesetaxel, an oral taxane, given as a single-agent in patients (pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC) in a phase 2 study [ASCO abstract 1042]. *J Clin Oncol*. 2018;36(15 suppl).
2. O'Shaughnessy J, Schwartzberg L, Piccart M, et al. Results from CONTESSA: a phase 3 study of tesetaxel plus a reduced dose of capecitabine versus capecitabine alone in patients with HER2-, hormone receptor+ (HR+) metastatic breast cancer (MBC) who have previously received a taxane. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS4-01.

Cost-Effectiveness of Neratinib for the Extended Adjuvant Treatment of Adult Patients With Early-Stage, HR+, HER2-Overexpressed/ Amplified Breast Cancer Who Initiated Neratinib Within 1 Year of Completing Trastuzumab in the US

The phase 3 ExteNET study reported improvements in OS and IDFS with neratinib vs placebo in patients with hormone receptor–positive, HER2-positive early breast cancer who initiated neratinib less than 1 year after they completed adjuvant trastuzumab-based therapy.[1] Dr Thor-Henrik Brodtkorb presented data from a cost-effectiveness study of neratinib vs placebo in this patient population from the perspective of a third-party payer in the United States.[2] Additional analyses evaluated cost-effectiveness for the subgroup of patients in this population who did not achieve a pCR after neoadjuvant therapy.

The investigators constructed a Markov model of costs and health outcomes of neratinib and placebo over a lifetime horizon. The model consisted of 5 health states that represent the primary stages of disease in early breast cancer: disease-free, local recurrence, remission, distant recurrence, and dead. The model corresponded with the primary and secondary endpoints in the ExteNET trial.[1] The treatment effect in the model was based on 5-year data from ExteNET for IDFS, the proportion of local and distant recurrence, and the number of AEs. Statistical extrapolation of IDFS and post-distant recurrence survival were derived from the 5-year ExteNET clinical trial data to obtain lifetime transition probabilities. OS was modeled based on a combination of post–distant recurrence survival and general population mortality, assuming all cancer-related mortality would occur through the distant recurrence health state. Mortality unrelated to breast cancer was derived from US life tables.

The costs per treatment arm were calculated based on drug acquisition, administration, and monitoring, combined with the expenses associated with AE-related and health state–related use of medical resources. Quality-adjusted life-years (QALYs) were estimated per health state, and disutilities were applied per AE independent of treatment. Utility values for IDFS health state and diarrhea were estimated using the EQ-5D-3L quality-of-life data collected in ExteNET.[1] Additional health state utilities and AE disutilities were identified from the literature. Costs were adjusted to 2020 US dollars. One-way and probabilistic sensitivity analyses and scenario analyses were performed to investigate the robustness of the results.

The increased cost of neratinib compared with placebo was partially offset by decreased costs of subsequent therapy owing to improved patient

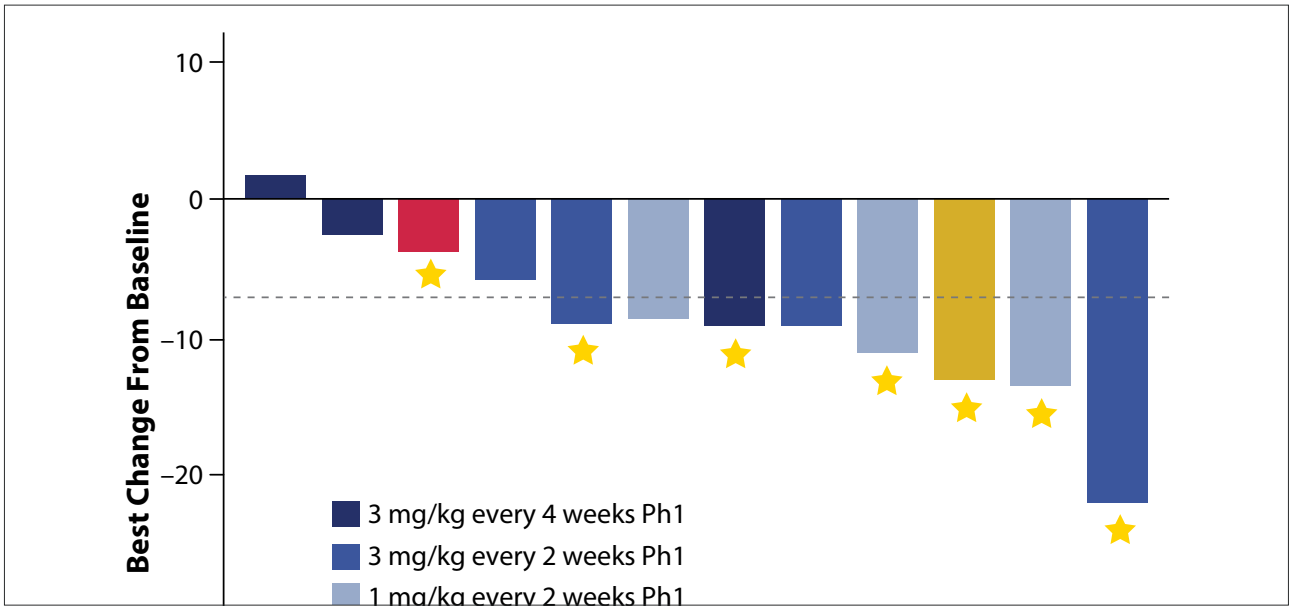

Figure 8. The cost results breakdown in an analysis of cost-effectiveness of neratinib for extended adjuvant treatment of early-stage breast cancer. Adapted from Brodtkorb T et al. Abstract PS9-33. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[2]

outcomes (Figure 8). The results of the base case analysis showed that, overall, neratinib treatment generated an additional 0.89 incremental QALYs compared with placebo, for a resulting cost per QALY gained of $62,172. The results were robust across multiple scenario analyses, with incremental cost-effectiveness ratios below $70,000. Among patients who did not achieve a pCR after neoadjuvant therapy, neratinib treatment generated an additional 1.27 incremental QALYs compared with placebo, for a resulting cost per QALY gained of $29,500. One-way sensitivity analyses found that the parameters that most influenced the results were variations in treatment-related costs, efficacy, and health state utility values. The probabilistic sensitivity analysis indicated that the probability of neratinib being cost-effective at a $100,000 per QALY threshold exceeded 74% overall, and was higher than 78% in patients without a pCR after neoadjuvant therapy.

References

1. Chan A, Moy B, Mansi J, et al. Final efficacy results of neratinib in HER2-positive hormone receptor–positive early-stage breast cancer from the phase III ExteNET Trial. *Clin Breast Cancer*. 2020;S1526-8209(20)30258-5.
2. Brodtkorb T, McDade C, Lalla D, et al. Cost-effectiveness of neratinib for the extended adjuvant treatment of adult patients with early-stage, HR+, HER2-overexpressed/amplified breast cancer who initiated neratinib within 1 year of completing trastuzumab in the US. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PS9-33.

Primary Outcome Analysis of Invasive Disease–Free Survival for MonarchE: Abemaciclib Combined With Adjuvant Endocrine Therapy for High-Risk Early Breast Cancer

Approximately 20% of patients who have hormone receptor–positive, HER2-negative, early breast cancer will develop disease recurrence within 10 years.[1] Elevated expression levels of the nuclear antigen Ki-67 are associated with higher risk.[2] Abemaciclib is an oral, continuously dosed, CDK 4/6 inhibitor that is approved for the treatment of this patient population in combination with endocrine therapy.[3] In the open-label phase 3 monarchE trial, abemaciclib combined with endocrine therapy was compared with endocrine therapy alone in 5637 patients with node-positive, hormone receptor–positive, HER2-negative, high-risk early breast cancer.[4] The patients had undergone surgery and, as indicated, radiotherapy and/or adjuvant/neoadjuvant chemotherapy. Dr Joyce A. O'Shaughnessy reported results from the primary outcome analysis for IDFS.[5]

The eligibility criteria encompassed patients with 4 or more positive nodes, 1 to 3 nodes plus either a tumor size of at least 5 cm or histologic grade 3 disease, or 1 to 3 nodes plus a centrally tested Ki-67 expression level of at least 20%. Patients were randomly assigned to adjuvant endocrine therapy with or without abemaciclib at 150 mg twice daily for 2 years. The median age of enrolled patients was 51 years (range, 22-89). The high Ki-67 subgroup included all patients with an expression level of at least 20% (n=2498). The primary endpoint was IDFS. Secondary endpoints included distant relapse–free survival, OS, and safety.

A previously reported interim analysis found a 2-year IDFS rate of 92.2% with abemaciclib plus endocrine therapy vs 88.7% with endocrine therapy alone (HR, 0.747; 95% CI, 0.598-0.932; *P*=.0096).[4] For the current analysis, the cutoff date was July 8, 2020. The 2-year IDFS rates were 92.3% with abemaciclib plus endocrine therapy and 89.3% with endocrine therapy alone (HR, 0.713; 95% CI, 0.583-0.871; *P*=.0009; Figure 9). This benefit was consistently seen across prespecified subgroups, including baseline number of nodes, histologic tumor grade, tumor size, and tumor stage. Two-year distant relapse–free survival rates were 93.8% with abemaciclib plus endocrine therapy vs 90.8% with endocrine therapy alone (HR, 0.687; 95% CI, 0.551-0.858; *P*=.0009). A key secondary endpoint was efficacy in the subpopulation with high Ki-67 expression levels. The 2-year IDFS rate was 91.6% with abemaciclib plus endocrine therapy vs 87.1% with endocrine therapy alone (HR, 0.691; 95% CI, 0.519-0.920; *P*=.0111) for this subpopulation.

Treatment-emergent AEs that were more common with abemaciclib included diarrhea (82.6% vs 7.8%), neutropenia (45.2% vs 5.2%), fatigue (39.2% vs 16.6%), leukopenia (37.2% vs 6.3%), abdominal pain (34.4% vs 9.0%), nausea (28.5% vs 8.3%), anemia (23.5% vs 3.4%), venous thrombosis events (2.4% vs 0.6%), and interstitial lung disease (2.9% vs 1.2%). Treatment discontinuation was required by 27.7% of patients who received abemaciclib plus endocrine therapy vs 14.6% of those who received endocrine therapy alone.

The investigators concluded that abemaciclib combined with endocrine therapy continued to confer a clinically meaningful improvement in IDFS and distant relapse–free survival compared with endocrine therapy alone for patients with hormone receptor–positive, HER2-negative, node-positive, high-risk early breast cancer, including those with Ki-67 expression levels of

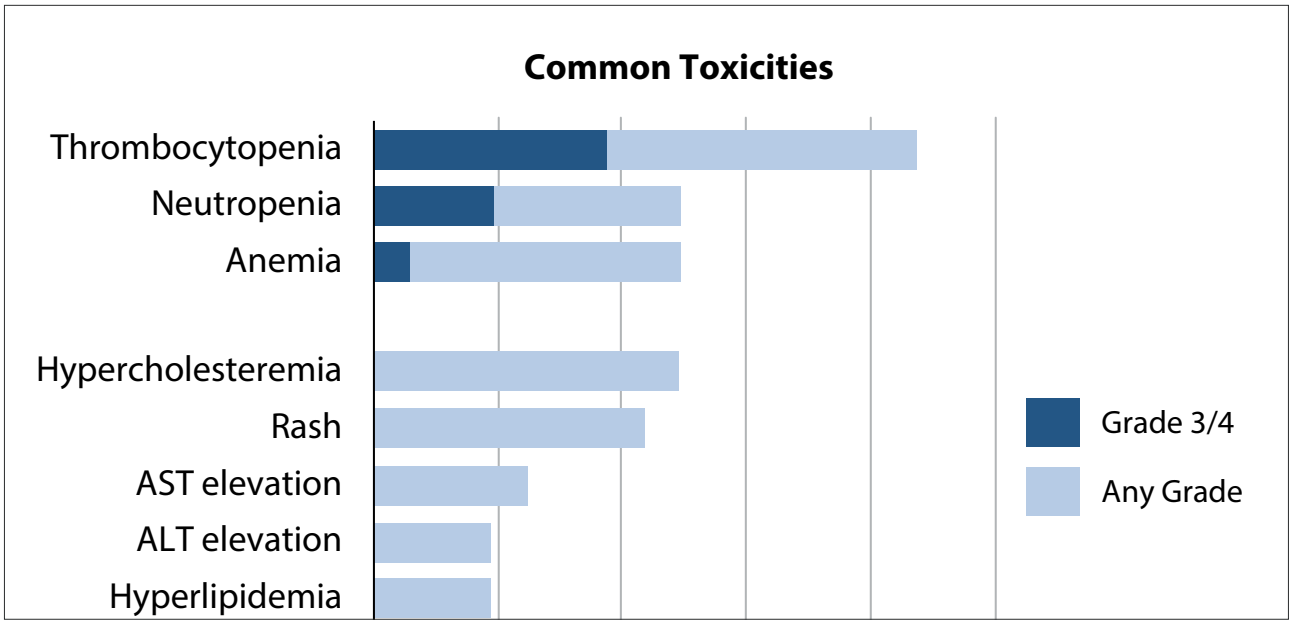

Figure 9. Invasive disease–free survival in the phase 3 monarchE trial, which compared abemaciclib plus endocrine therapy vs endocrine therapy alone in patients with high-risk early breast cancer. ET, endocrine therapy; HR, hazard ratio; IA2, second interim analysis; IDFS, invasive disease–free survival. Adapted from O'Shaughnessy J et al. Abstract GS1-01. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[5]

20% or higher. The safety profile of the combination therapy was tolerable and similar to that reported in previous analyses. The monarchE study is ongoing, and will continue until the final assessment of OS.

References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*. 2015;386(10001):1341-1352.
2. Dowsett M, Nielsen TO, A'Hern R, et al; International Ki-67 in Breast Cancer Working Group. Assessment of Ki67 in breast cancer: recommendations from the International Ki67 in Breast Cancer working group. *J Natl Cancer Inst*. 2011;103(22):1656-1664.
3. Corona SP, Generali D. Abemaciclib: a CDK4/6 inhibitor for the treatment of HR+/HER2- advanced breast cancer. *Drug Des Devel Ther*. 2018;12:321-330.
4. Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998.
5. O'Shaughnessy JA, Johnston S, Harbeck N, et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS1-01.

The Neat-HER Virtual Registry: Results on HER2+ Breast Cancer Patients Receiving Neratinib as Extended Adjuvant Therapy

Neat-HER is a virtual registry based in the United States that is currently enrolling patients with HER2-positive, early-stage breast cancer who are receiving neratinib as extended adjuvant therapy. The Neat-HER registry is designed to assess the characteristics and treatment history of these patients; evaluate treatment patterns, such as diarrhea prophylaxis; and inform clinical practice and quality of care. Dr Hope S. Rugo reported on the registry design and early data from the first 22 patients enrolled.[1]

Patients ages 18 years and older who are currently receiving neratinib as extended adjuvant therapy for HER2-positive, early-stage breast cancer are eligible. Those participating in a clinical trial or with metastatic disease are excluded. Recruitment is occurring through email, private social media groups, treating clinicians, and a texting program.

Enrolled patients authorize investigators to request and collect medical records from providers on their behalf. Patient data are then extracted from medical records and organized into a data schema using optical character recognition and named entity recognition. Medical records for breast cancer-related treatment are included from the time of diagnosis to 1-year after enrollment in the registry. The data collected include demographics, medical history, visit information, medications, comorbid conditions, laboratory results, vital sign measures, procedures,

imaging, tumor characteristics, breast cancer surgery, receipt of therapy (eg, radiotherapy, adjuvant therapy), neratinib duration, and diarrhea prophylaxis. Patients have digital access to their own consolidated medical records for the duration of the study. De-identified longitudinal patient data sets will undergo statistical analysis.

Since December 2018, 22 patients have been enrolled. The median age is 51 years (range, 32-73). Of these, 73% have hormone receptor–positive disease, and 73% have node-positive disease. Adjuvant therapies include trastuzumab plus paclitaxel in 9%, and trastuzumab plus pertuzumab in 91% (all but 1 patient also received docetaxel). At month 12, 50% of patients had completed neratinib treatment, whereas 23% had discontinued treatment early, and 27% were still receiving ongoing treatment at the time of data cutoff. Dose holds were reported for 27%, and dose modifications were reported for 18% during the course of neratinib treatment. Most patients (95%) had discussed diarrhea prophylaxis with their health care providers before the start of neratinib.

The investigators concluded that the Neat-HER virtual registry is feasible and provides useful information on patient/tumor characteristics and treatment patterns in a real-world cohort of patients receiving extended adjuvant neratinib. Validation of this method is needed and could be used to evaluate important trends such as the frequency of neoadjuvant therapy and associated outcomes in a larger population.

Reference

1. Rugo HS, Vidal GA, Oestreicher N, et al. The Neat-HER Virtual Registry: results on HER2+ breast cancer patients receiving neratinib as extended adjuvant therapy. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PS7-61.

E2112: Randomized Phase 3 Trial of Endocrine Therapy Plus Entinostat/Placebo in Patients With Hormone Receptor–Positive Advanced Breast Cancer: A Trial of the ECOG-ACRIN Cancer Research Group

Preclinical models suggest that resistance to endocrine therapy can be overcome with the use of histone deacetylase (HDAC) inhibitors that inhibit growth factor signaling pathways and normalize gene expression of the estrogen receptor.[1] Previous results of the phase 2 ENCORE 301 study showed improvements in PFS and OS with the addition of entinostat, an oral class I HDAC inhibitor, to exemestane, a steroidal aromatase inhibitor, in patients with advanced hormone receptor–positive, HER2-negative breast cancer.[2] Protein lysine acetylation in peripheral blood mononuclear cells was associated with prolonged PFS in the entinostat arm.

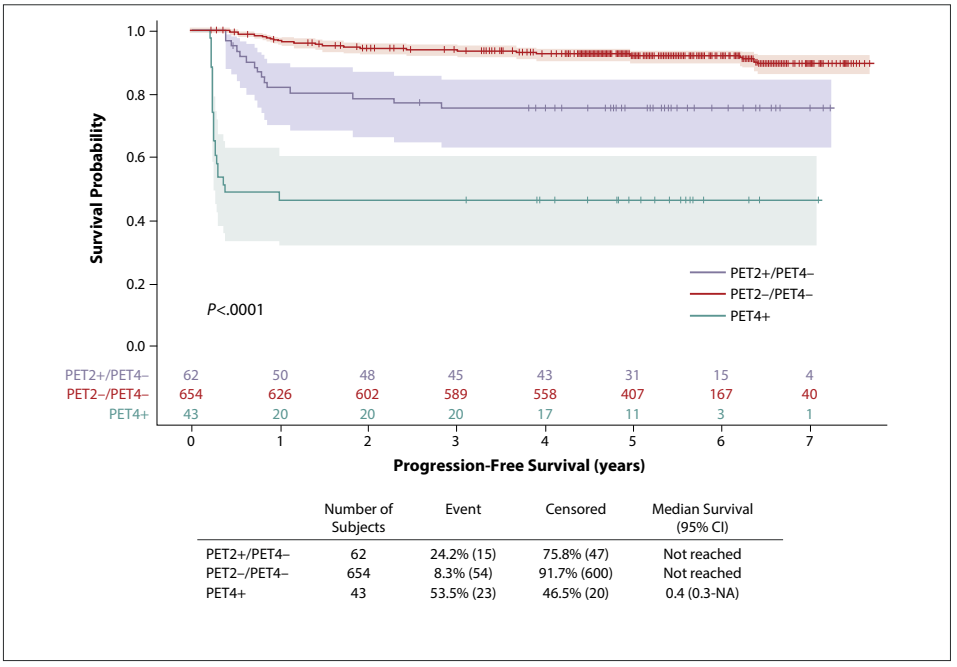

Figure 10. Progression-free survival for entinostat plus exemestane vs placebo plus exemestane in the phase 3 E2112 trial of patients with hormone receptor–positive advanced breast cancer. Adapted from Connolly RM et al. Abstract GS4-02. Presented at the 2020 San Antonio Breast Cancer Symposium; December 8-11, 2020.[3]

Dr Roisin M. Connolly presented results from E2112, a phase 3 study that enrolled 608 patients with hormone receptor–positive, HER2-negative advanced breast cancer whose disease had progressed during treatment with a nonsteroidal aromatase inhibitor in the adjuvant or metastatic setting. The median age was 63 years (range, 29-91).[3] All patients received exemestane at 25 mg daily; additionally, patients were randomly assigned to either entinostat 5 mg weekly or placebo. The patient characteristics were well balanced between the study arms. The co–primary endpoints were PFS and OS. The secondary endpoints included safety, ORR, and changes in protein lysine acetylation status in peripheral blood mononuclear cells from baseline.

Entinostat plus exemestane failed to show benefit over placebo plus exemestane in this study. The median PFS was 3.3 months in the entinostat arm vs 3.1 months in the placebo arm (HR, 0.87; 95% CI, 0.67-1.13; *P*=.30; Figure 10). The median OS was 23.4 months vs 21.7 months, respectively (HR, 0.99; 95% CI, 0.82-1.21; *P*=.94). The ORR was 4.6% in the entinostat arm and 4.3% in the placebo arm.

The pharmacodynamic analysis confirmed that HDAC inhibition was increased in the entinostat arm. The median change from baseline in lysine acetylation in peripheral blood mononuclear cells was approximately 1.5-fold in the entinostat arm and 1-fold in the placebo arm (*P*<.001). Grade 3/4 AEs with a higher incidence in the entinostat arm than the placebo arm included neutropenia (20% vs <1%), hypophosphatemia (14% vs 1%), anemia (8% vs 2%), leukopenia (6% vs 1%), fatigue (4% vs 1%), diarrhea (4% vs <1%), and thrombocytopenia (3% vs 1%).

References

1. Sabnis GJ, Goloubeva OG, Kazi AA, Shah P, Brodie AH. HDAC inhibitor entinostat restores responsiveness of letrozole-resistant MCF-7Ca xenografts to aromatase inhibitors through modulation of Her-2. *Mol Cancer Ther*. 2013;12(12):2804-2816.
2. Yardley DA, Ismail-Khan RR, Melichar B, et al. Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. *J Clin Oncol*. 2013;31(17):2128-2135.
3. Connolly RM, Zhao F, Miller KD, et al. E2112: randomized phase 3 trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor–positive advanced breast cancer. A trial of the ECOG-ACRIN cancer research group. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS4-02.

Highlights in Early and Metastatic Breast Cancer From the 2020 San Antonio Breast Cancer Symposium: Commentary

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In December 2020, the San Antonio Breast Cancer Symposium (SABCS) was presented in a virtual format. Important data in both early and metastatic disease were provided for treatments such as neratinib, the cyclin-dependent kinase 4/6 (CDK4/6) inhibitors abemaciclib and palbociclib, tesetaxel, entinostat, and ipatasertib plus paclitaxel. Studies also evaluated optimal use of neo/adjuvant chemotherapy and radiotherapy.

Early Disease

Neratinib

The phase 3 ExteNET trial evaluated the efficacy and safety of 12 months of neratinib administered after trastuzumab-based adjuvant therapy in patients with early-stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer.[1,2] More than 2800 patients were randomly assigned to treatment with oral neratinib at 240 mg per day or placebo. After 5 years of follow-up, treatment with neratinib led to an absolute benefit in invasive disease–free survival (IDFS) of 2.5% and an improvement in distant disease–free survival of 1.7%.[2]

At the 2020 SABCS, Dr Frankie Holmes presented the final overall survival analysis of the ExteNET trial.[3] The median follow-up was 8 years. The key finding that is relevant to clinical practice concerns the group of patients

with estrogen receptor (ER)-positive/HER2-positive breast cancer who were receiving preoperative therapy and still had residual disease. Within a year of finishing adjuvant trastuzumab, the patients received neratinib or placebo. Among these patients, neratinib was associated with a 9% absolute improvement in overall survival. This finding is drawn from an exploratory analysis of a small cohort of patients (n=295). However, it is the key cohort of clinical interest. This improvement in survival is important. One issue with the ExteNET trial is that the patients had not received preoperative pertuzumab nor trastuzumab emtansine (T-DM1) in the adjuvant setting. Data from the NALA trial showed that in the metastatic setting, neratinib is non–cross-resistant with pertuzumab and T-DM1.[4] Based on these data in the metastatic setting, it would therefore be expected that treatment with a pan-HER tyrosine kinase inhibitor would be non–cross-resistant with antibody-based therapy. Extrapolating the metastatic data to the curative setting, it appears likely that neratinib would have a positive impact on outcome even after treatment with prior pertuzumab and T-DM1 among high-risk hormone receptor (HR)-positive patients. Given the improvement in survival, albeit in an exploratory subset analysis, I believe that 1 year of neratinib should be offered to high-risk patients who have residual disease that is node-positive or larger cancers that are node-negative after treatment with preoperative chemotherapy, trastuzumab, pertuzumab, and T-DM1, in combination with endocrine therapy.

Dr Manuel Ruiz-Borrego provided updated data from the CONTROL trial, which examined strategies to control diarrhea associated with neratinib.[5] An earlier report of the CONTROL trial showed that antidiarrheal prophylaxis or a dose-escalation schedule reduced the rate, severity, and duration of grade 3 or higher diarrhea, as compared with findings from the ExteNET trial.[2,6] The CONTROL trial is evaluating 2 dose-escalation strategies. Dr Ruiz-Borrego provided data for the first regimen, which begins with 120 mg (3 pills), increases to 160 mg (4 pills), and then continues with 240 mg (6 pills), with loperamide given as needed. The dose was increased every week. There was the option to increase the dose more slowly, with increases made only if the patient was tolerating the lower dose. With this regimen, the rate of grade 3 diarrhea was 13%, as opposed to approximately 40% in the ExteNET study,[2] a dramatic reduction. The duration of grade 3 diarrhea was short, at 2.5 days. The percentage of patients who had to stop neratinib because of diarrhea was 3.3%. It is important for the patient to take loperamide after each loose stool.

The dose-escalation scheme has been a sea change in terms of the feasibility and tolerability of neratinib. An important finding from the ExteNET trial is that, with just 1 year of adjuvant neratinib, high-risk patients accrue a reduced risk of recurrence and death that increases after completing neratinib.[2] Therefore, patients continue to receive more benefit as the years go on, which is very important. This observation speaks to the synergy of inhibiting the HER family along with the ER. Neratinib represents an important therapeutic opportunity for high-risk patients who still have considerable residual disease after standard preoperative therapy.

Dr Thor-Henrik Brodtkorb presented a cost-effectiveness analysis of extended adjuvant neratinib, based on data from the ExteNET trial.[7] The analysis showed that neratinib is cost-effective among patients in the ExteNET trial at highest risk, meaning those who are HR-positive/HER2-positive and who had residual disease after prior adjuvant trastuzumab-based therapy. These high-risk patients are those most relevant to clinical practice. The cost of a quality-adjusted life-year was approximately $29,000. This is a favorable cost-effectiveness analysis in a very high–risk population. The results make sense; prevention of a metastatic recurrence should lead to a large cost savings. Although there is additional expense associated with a year of treatment with neratinib, the effect on the overall cost to the health care system is favorable.

Dr Hope Rugo is the principal investigator of the Neat-HER Virtual Registry.[8] This prospective virtual registry is gathering data from patients with early-stage HER2-positive breast cancer treated with neratinib in the extended adjuvant setting. Patients are recruited from physicians' practices or through social media. Patients provide informed consent for the investigators to compile medical records to assess factors such as demographics, tumor characteristics, treatments, outcomes, and dose modifications. Using artificial intelligence methods, the data are extracted virtually from the patient's records and entered into this virtual registry.

The goals are to examine real-world evidence among patients receiving extended adjuvant neratinib. These data will be used to evaluate the feasibility of delivering neratinib, including the use of dose-escalation strategies and loperamide to ameliorate diarrhea, the percentage of patients who reach and maintain the upper dose levels, the duration of neratinib, the need for dose reductions and treatment discontinuation, and outcome. Now that there is an effective approach to decreasing the serious diarrhea that can interfere with administration of neratinib, it will be interesting to see the data from this registry.

CDK4/6 Inhibitors

The monarchE trial was an important study of adjuvant treatment with the CDK4/6 inhibitor abemaciclib.[9] My colleagues and I presented the primary outcome analysis of IDFS per protocol specification. The median follow-up

was 19 months. The 2-year rate of IDFS was 92.3% with abemaciclib plus endocrine therapy vs 89.3% with endocrine therapy alone. The hazard ratio was 0.713, which was statistically significant (*P*=.0009). The analyses also showed that the Ki-67 level does not impact the benefit seen with abemaciclib. The level of Ki-67 was prognostic, but not predictive of abemaciclib benefit. The risk of early recurrence was increased in patients with a higher Ki-67 (≥20%) and decreased in those with a lower Ki-67. These data from the primary outcome analysis of IDFS are encouraging. Longer follow-up is needed because at the time of this analysis, most patients were still receiving adjuvant abemaciclib. The investigators will assess outcome after abemaciclib treatment ends.

Dr Sibylle Loibl presented results from the phase 3 PENELOPE-B trial, which evaluated the CDK4/6 inhibitor palbociclib plus endocrine therapy in patients with hormone-receptor–positive, HER2-negative primary breast cancer at high risk of relapse after neoadjuvant chemotherapy.[10] These high-risk patients had received preoperative chemotherapy for ER-positive/HER2-negative breast cancer and had residual disease at definitive surgery. They were randomly assigned to receive endocrine therapy with 1 year of palbociclib or placebo. The primary endpoint was IDFS. The results of PENELOPE-B showed an early improvement with palbociclib that was not sustained. Unfortunately, there was no statistically significant improvement. This sobering result suggests that palbociclib appears to lack a cytotoxic mechanism that would lead to a durable impact on IDFS.

It is not known whether the same outcome will be seen with abemaciclib, another CDK4/6 inhibitor. In the monarchE trial, abemaciclib will be given for 2 years.[9] The population enrolled in the monarchE trial is at even higher risk than that in the PENELOPE-B trial.[9,10] The patients in monarchE are likely to have early recurrence of disease. Abemaciclib and palbociclib are different CDK4/6 inhibitors. Abemaciclib is administered continuously, and it has a broader spectrum of action beyond CDK4/6, inhibiting other CDKs and additional kinases. Based on results from PENELOPE-B,[10] as well as the PALLAS trial,[11] adjuvant palbociclib does not improve the outcome of early-stage breast cancer patients. Mature results are awaited from monarchE, as well as the ongoing NATALEE trial evaluating 3 years of adjuvant ribociclib.[12]

Adjuvant Chemotherapy and the Recurrence Score

Dr Kevin Kalinsky provided results from the SWOG S1007 RxPONDER trial.[13] This important phase 3 trial enrolled premenopausal and postmenopausal women with hormone receptor–positive/HER2-negative disease and 1 to 3 positive lymph nodes. Patients had a recurrence score between 0 and 25. They were randomly assigned to chemotherapy followed by endocrine therapy or endocrine therapy alone. The primary endpoint was to determine the effect of chemotherapy on IDFS and to assess whether the effect corresponds with the recurrence score. In the overall population, IDFS was 92.4% in the chemotherapy arm vs 91.0% in the control arm (*P*=.026). An analysis according to menopausal status showed that premenopausal women benefited from chemotherapy. The absolute difference in the 5-year rate of IDFS was 3.9% in premenopausal patients with a recurrence score of 0 to 13 and 6.2% in those with a recurrence score of 14 to 25. Postmenopausal women did not derive any benefit from adjuvant chemotherapy, regardless of their recurrence score.

These results raise the question of whether treatment with endocrine therapy that included a luteinizing hormone-releasing hormone (LHRH) agonist would have decreased the impact of chemotherapy if the main benefit of chemotherapy was derived from ovarian suppression. In the RxPONDER trial, only 16% of patients in the endocrine therapy–alone arm received an LHRH agonist. Therefore, the patients did not receive the current definition of optimal endocrine therapy. It is necessary to individualize treatment for premenopausal patients because not all will require chemotherapy. Chemotherapy will probably not benefit premenopausal women with 1 or 2 nodes and an otherwise indolent biology of grade 1 or 2 disease, whose breast cancers are strongly ER-positive/progesterone receptor–positive and have a low Ki-67, and who are willing to undergo oophorectomy or receive an LHRH agonist together with an aromatase inhibitor, which is the optimal endocrine therapy. Data from the RxPONDER trial suggest that chemotherapy had a cytotoxic effect on the ovaries in some premenopausal patients. Interestingly, a recent study showed that high recurrence scores are driven by less sensitivity to endocrine therapy, in other words, less ER transcriptional activity in the breast cancer.[14] This study showed that high recurrence scores are not driven predominantly by proliferation, but rather by the expected endocrine therapy sensitivity of the cancer. The cassette of ER-related genes in the recurrence score are less highly expressed. Therefore, the higher the recurrence score, the less that patients will benefit from endocrine therapy and the more they will need the chemotherapy. Patients with lower recurrence scores may still have a risk of recurrence because they have node-positive disease, but they have higher expression and biologic activity of the ER pathway. In my view, data from the RxPONDER trial suggest that optimal endocrine therapy is an option for premenopausal patients with 1 to 3 positive lymph nodes who have lower recurrence scores.

Another point raised by the RxPONDER trial is that among the

overall population, the magnitude of the benefit of chemotherapy did not correspond with rising recurrence scores. The data showed that prognosis was worse among patients with higher recurrence scores, and these patients obtained a greater absolute benefit from chemotherapy even though the proportional impact on disease-free survival was the same across the spectrum of the recurrence scores. Among patients with a higher risk of recurrence, chemotherapy will lead to a higher absolute improvement in disease-free survival, even though proportional risk reduction is the same in women with high and low recurrence scores. In the RxPONDER trial, the recurrence score was not predictive of chemotherapy benefit, but it was prognostic.

Breast Radiotherapy

Dr Ian Kunkler presented results of the PRIME 2 trial, which evaluated whether postoperative whole breast radiotherapy can be omitted in low-risk older patients.[15] The study enrolled patients ages 65 years and older with early breast cancer that was HR-positive. Patients had grade 1 or 2 breast cancer that was node-negative. They had already undergone definitive surgery, and the breast cancer tumor was no larger than 3 cm. All patients received adjuvant endocrine therapy with wide local excision with clear margins. They were randomly assigned to receive treatment with whole breast radiation or no radiotherapy. The 10-year rate of local recurrence was 9.8% without radiotherapy vs 0.9% with radiotherapy. Therefore, the risk of an in-breast recurrence was approximately 1% per year among patients who did not receive whole breast radiation. There was no impact on overall survival.

These data corroborate other studies and support the current standard of care,[16] where we have the option to discuss omitting radiation therapy in low-risk patients ages 70 years and older. In a healthy 65-year-old woman, a 10% risk of in-breast recurrence over 10 years—with the potential for a continued increased risk out to 20 years—is too high. In contrast, for a 65-year-old woman with substantial comorbidities, with a life expectancy of less than 10 years, a 10% risk over 10 years may be acceptable. For a woman ages 80 years or older with grade 1 or 2, node-negative breast cancer sized 3 cm or less, with clear margins, the decision to forgo radiation therapy may be very reasonable, as long as she is able to tolerate endocrine therapy. Radiation therapy tends to be recommended to women who are younger and healthier, and who have a longer lifespan, particularly now with the availability of accelerated whole breast radiation and partial breast irradiation options that shorten treatment duration.

Metastatic Disease

Neratinib

Dr Cristina Saura provided updated data from the phase 3 NALA trial of neratinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer.[4,17] This analysis evaluated patients who entered the study with stable treated brain metastases. Progression-free survival was improved with neratinib compared with lapatinib among patients with central nervous system (CNS) metastases. In addition, neratinib had a greater impact on control of CNS disease. The overall analysis of the NALA trial found that progression-free survival was significantly higher with neratinib plus capecitabine.[4] This improvement was maintained in patients with brain metastasis. This analysis of the NALA trial supports the combination of neratinib and capecitabine as an effective option for patients with CNS metastases.

Tesetaxel

The CONTESSA trial evaluated the novel oral taxane tesetaxel,[18] which is not extruded from cells via P-glycoprotein (Pgp). Tesetaxel is absorbed from the gastrointestinal (GI) tract and is not extruded back into the GI tract by Pgp, leading to improved oral bioavailability of tesetaxel. In the CONTESSA trial, the addition of tesetaxel to capecitabine led to a significant improvement in progression-free survival of approximately 3 months compared with capecitabine alone among patients with ER-positive, HER2-negative metastatic breast cancer that is resistant to endocrine therapy. Tesetaxel was administered as 27 mg/m^2 orally once every 3 weeks with capecitabine 825 mg/m^2 orally twice daily for 14 days of a 21-day cycle.

The safety profile was acceptable. Approximately 13% of patients treated with tesetaxel plus capecitabine developed febrile neutropenia. This toxicity can be ameliorated by holding capecitabine during the neutrophil nadir if patients develop concomitant GI toxicity. Dose reductions of tesetaxel and/or the use of granulocyte colony–stimulating factor in the capecitabine off-days were successful in preventing treatment delays and discontinuations. Tesetaxel was associated with low rates of neurotoxicity and alopecia (28% overall, with grade 2 cases in 8%).

If tesetaxel is approved by the US Food and Drug Administration, it will be helpful to have the combination of capecitabine plus tesetaxel as an all-oral therapeutic option in ER-positive, HER2-negative patients who require combination chemotherapy. A second oral taxane regimen consists of oral paclitaxel plus oral encequidar.[19] Encequidar inhibits Pgp, allowing for GI absorption of paclitaxel. Currently, oral paclitaxel with encequidar is administered 3 times weekly, and involves a higher pill burden. Tesetaxel is given as a regimen of 2 to 5 pills once every 3 weeks. Overall, the oral taxanes will be a welcome addition as treatment options, postponing the need for central venous access and intravenous chemotherapy.

Entinostat

Dr Roisin Connolly presented long-awaited results from the phase 3 E2112 trial, which compared entinostat plus exemestane vs exemestane plus placebo in patients with metastatic breast cancer that was resistant to a nonsteroidal aromatase inhibitor.[20] Unfortunately, the addition of entinostat did not improve progression-free survival or overall survival in this trial. The ENCORE trial had previously shown that adding the histone deacetylase (HDAC) inhibitor entinostat to exemestane favorably impacted survival in patients whose breast cancer was resistant to a nonsteroidal aromatase inhibitor.[21] Preclinically, entinostat remodels the chromatin and can overcome endocrine therapy resistance.[22]

The reason for the difference in outcome between the E2112 trial and the ENCORE trials is not known. Previous use of a CDK4/6 inhibitor was reported in 37% of patients in the entinostat arm and 33% of patients in the placebo arm. The ENCORE trial was conducted before the availability of CDK4/6 inhibitors, while approximately one-third of patients in the E2112 trial had received a prior CDK4/6 inhibitor. Whether the weekly administration of entinostat inhibited HDAC enough to increase the response to endocrine therapy will be evaluated through analysis of blood biomarkers of histone acetylation in patients who received entinostat.

Ipatasertib and Paclitaxel

Dr Rebecca Dent presented primary results from cohort A of the phase 3 IPATunity130 trial, which evaluated first-line therapy with the selective AKT inhibitor ipatasertib plus paclitaxel vs paclitaxel plus placebo.[23] The trial enrolled patients with a genomic alteration that activated the phosphoinositide 3-kinase pathway, including mutations in *PIK3CA*, *AKT1*, or *PTEN*. Ipatasertib plus paclitaxel did not improve progression-free survival or overall survival compared with paclitaxel alone. This outcome differed from that of the LOTUS trial, which demonstrated a favorable impact on progression-free survival, as well as a trend toward improvement in overall survival with combined paclitaxel plus ipatasertib.[24] The negative results of the IPATunity130 trial do not necessarily mean that ipatasertib, and inhibition of the AKT, is a failed strategy in triple-negative breast cancers. AKT is active and promotes therapy resistance in a majority of triple-negative breast cancers. An earlier phase 1b trial by Professor Peter Schmid evaluated a triplet combination of ipatasertib, atezolizumab, and paclitaxel or nab-paclitaxel as first-line therapy for metastatic triple-negative breast cancer patients.[26] The response rate was 73%, which is encouraging, and additional trials of this triplet utilizing nab-paclitaxel are ongoing. Another AKT inhibitor, capivasertib, is undergoing evaluation in combination with paclitaxel in triple-negative breast cancer patients in a phase 3 trial enrolling a nongenomically selected population.[25]

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. 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.
2. 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.
3. Holmes FA, Moy B, Delaloge S, et al. Continued efficacy of neratinib in patients with HER2-positive early-stage breast cancer: final overall survival analysis from the randomized phase 3 ExteNET trial. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PD3-03.
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. *J Clin Oncol*. 2020;38(27):3138-3149.
5. Ruiz-Borrego M, Chan A, Marx G, et al. Bringing diarrhea under CONTROL: dose escalation reduces neratinib-associated diarrhea and improves tolerability in HER2-positive early-stage breast cancer. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PS13-20.
6. Barcenas CH, Hurvitz SA, Di Palma JA, et al; CONTROL Study Investigators. Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. *Ann Oncol*. 2020;31(9):1223-1230.
7. Brodtkorb T, McDade C, Lalla D, et al. Cost-effectiveness of neratinib for the extended adjuvant treatment of adult patients with early-stage, HR+, HER2-overexpressed/amplified breast cancer who initiated neratinib within 1 year of completing trastuzumab in the US. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PS9-33.
8. Rugo HS, Vidal GA, Oestreicher N, et al. The Neat-HER Virtual Registry: results on HER2+ breast cancer patients receiving neratinib as extended adjuvant therapy. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PS7-61.
9. O'Shaughnessy JA, Johnston S, Harbeck N, et al. Primary outcome analysis of invasive disease-free survival for monarchE: abemaciclib combined with adjuvant endocrine therapy for high risk early breast cancer. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS1-01.
10. Loibl S, Marmé F, Martin M, et al. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancer and with high relapse risk after neoadjuvant chemotherapy (NACT): first results from PENELOPE-B. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS1-02.
11. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2021;22(2):212-222.
12. Slamon DJ, Fasching PA, Patel R, et al. NATALEE: phase III study of ribociclib (RIBO) + endocrine therapy (ET) as adjuvant treatment in hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) early breast cancer (EBC) [ASCO abstract TPS597]. *J Clin Oncol*. 2010;37(5 suppl).
13. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes,

hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer (BC) with recurrence score (RS) < 25: SWOG S1007 (RxPONDER). Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS3-00.

14. Dowsett M, Sestak I, Cuzick J. Calibration of CTS5 in women with early estrogen receptor-positive breast cancer. *J Clin Oncol*. 2021;39(4):338-339.

15. Kunkler IH, Williams LJ, Jack W, et al. Prime 2 randomised trial (postoperative radiotherapy in minimum-risk elderly): wide local excision and adjuvant hormonal therapy +/- whole breast irradiation in women =/> 65 years with early invasive breast cancer: 10 year results. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS2-03.

16. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: long-term follow-up of CALGB 9343. *J Clin Oncol*. 2013;31(19):2382-2387.

17. Saura C, Ryvo L, Hurvitz S, et al. Impact of neratinib on outcomes in HER2-positive metastatic breast cancer patients with central nervous system disease at baseline: findings from the phase 3 NALA trial. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PD13-09.

18. O'Shaughnessy J, Schwartzberg L, Piccart M, et al. Results from CONTESSA: a phase 3 study of tesetaxel plus a reduced dose of capecitabine versus capecitabine alone in patients with HER2-, hormone receptor + (HR+) metastatic breast cancer (MBC) who have previously received a taxane. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS4-01.

19. Umanzor G, Rugo HS, Barrios FJ, et al. Oral paclitaxel and encequidar (oPac+E) versus IV paclitaxel (IVPac) in the treatment of metastatic breast cancer (mBC) patients (study KX-ORAX-001): progression free survival (PFS) and overall survival (OS) updates. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract PD1-08.

20. Connolly RM, Zhao F, Miller KD, et al. E2112: randomized phase 3 trial of endocrine therapy plus entinostat/placebo in patients with hormone receptor-positive advanced breast cancer. A trial of the ECOG-ACRIN cancer research group. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS4-02.

21. Yardley DA, Ismail-Khan RR, Melichar B, et al. Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. *J Clin Oncol*. 2013;31(17):2128-2135.

22. Connolly RM, Rudek MA, Piekarz R. Entinostat: a promising treatment option for patients with advanced breast cancer. *Future Oncol*. 2017;13(13):1137-1148.

23. Dent R, Kim SB, Oliveira M, et al. Double-blind placebo (PBO)-controlled randomized phase III trial evaluating first-line ipatasertib (IPAT) combined with paclitaxel (PAC) for *PIK3CA/AKT1/PTEN*-altered locally advanced unresectable or metastatic triple-negative breast cancer (aTNBC): primary results from IPATunity130 Cohort A. Abstract presented at: the San Antonio Breast Cancer Symposium 2020 Virtual Meeting; December 8-11, 2020. Abstract GS3-04.

24. Kim SB, Dent R, Im SA, et al; LOTUS investigators. Ipatasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer (LOTUS): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2017;18(10):1360-1372.

25. Schmid P, Abraham J, Chan S, et al. Capivasertib plus paclitaxel versus placebo plus paclitaxel as first-line therapy for metastatic triple-negative breast cancer: the PAKT trial. *J Clin Oncol*. 2020;38(5):423-433.

26. Schmid P, Loirat D, Savas P, et al. Phase Ib study evaluating a triplet combination of ipatasertib (IPAT), atezolizumab (atezo), and paclitaxel (PAC) or nab-PAC as first-line (1L) therapy for locally advanced/metastatic triple-negative breast cancer (TNBC) [AACR abstract CT049]. *Can Res*. 2019;79(13 suppl).