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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Breast Cancer From the 2019 San Antonio Breast Cancer Symposium

A Review of Selected Presentations From the 2019 SABCS • December 10-14, 2019 • San Antonio, Texas

Special Reporting on:

- Tucatinib vs Placebo, Both Combined With Capecitabine and Trastuzumab, for Patients With Pretreated HER2-Positive Metastatic Breast Cancer With and Without Brain Metastases (HER2CLIMB)
- [Fam-] Trastuzumab Deruxtecan (T-DXd; DS-8201a) in Subjects With HER2-Positive Metastatic Breast Cancer Previously Treated With T-DM1: A Phase 2, Multicenter, Open-Label Study (DESTINY-Breast01)
- Results From the PEARL Study (GEICAM/2013-02_CECOG/BC.1.3.006): A Phase 3 Trial of Palbociclib in Combination With Endocrine Therapy Versus Capecitabine in Hormonal Receptor (HR)-Positive/Human Epidermal Growth Factor Receptor (HER) 2-Negative Metastatic Breast Cancer Patients Whose Disease Progressed on Aromatase Inhibitors
- Oral Paclitaxel With Encequidar: The First Orally Administered Paclitaxel Shown to Be Superior to IV Paclitaxel on Confirmed Response and Survival With Less Neuropathy: A Phase III Clinical Study in Metastatic Breast Cancer
- Durvalumab Compared to Maintenance Chemotherapy in Patients With Metastatic Breast Cancer: Results From the Phase II Randomized Trial SAFIR02-IMMUNO
- Phase 3 SOPHIA Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies: Second Interim Overall Survival Analysis

PLUS Meeting Abstract Summaries

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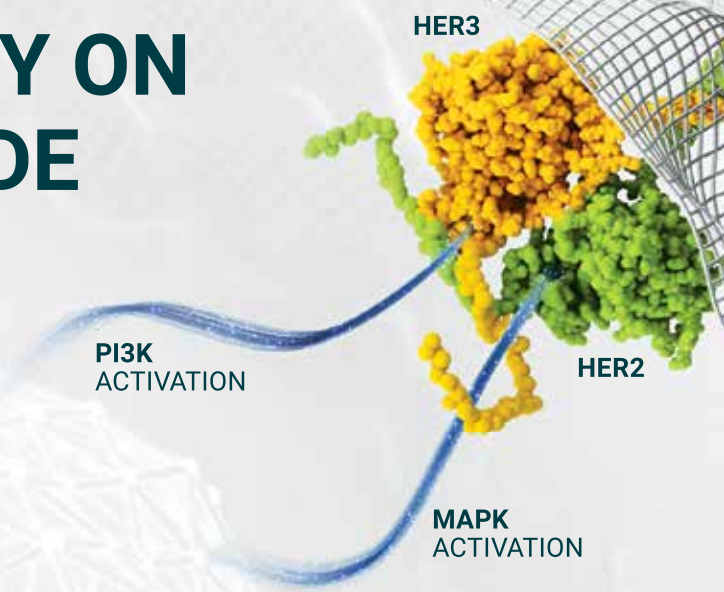
GET THE INSIDE AND OUTSIDE STORY ON HER2 BLOCKADE



Targeting HER2 intracellularly or extracellularly alone may lead to resumption of signaling and resistance to therapies that target HER2.[1-4]

Nonspecific inhibition of HER family members (eg, EGFR) does not suppress functional HER2 signaling, has limited evidence of clinical benefit, and may result in off-target toxicities.[5-9]

New approaches are needed to selectively and comprehensively block HER2 signaling for patients with HER2+ MBC.[3]

ASCO = American Society of Clinical Oncology; CNS = central nervous system; EGFR = epidermal growth factor receptor; HER = human epidermal growth factor receptor; MAPK = mitogen-activated protein kinase; MBC = metastatic breast cancer; PI3K = phosphoinositide 3-kinase.

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DESPITE ADVANCES IN HER2 TARGETED TREATMENTS, HER2+ MBC ALMOST INVARIABLY PROGRESSES[10]

- The most common sites of metastasis in HER2+ MBC are liver, lung, bone, and brain[11]

Up to 50% of patients with HER2+ MBC will develop brain metastases during the course of their disease[12-15]

- Compared with non-CNS metastases, brain metastases are associated with faster disease progression and shorter overall survival[15,16]

ASCO guidelines recommend clinicians should have a low threshold for performing brain imaging due to the high incidence of brain metastases in HER2+ MBC.[17]

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Tucatinib vs Placebo, Both Combined With Capecitabine and Trastuzumab, for Patients With Pretreated HER2-Positive Metastatic Breast Cancer With and Without Brain Metastases (HER2CLIMB)

Therapeutic options are limited for patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer whose disease progresses after treatment with multiple HER2-targeted agents. Many of these patients develop brain metastases. Tucatinib is an investigational, oral tyrosine kinase inhibitor that targets the HER2 tyrosine kinase. This drug is highly selective for the kinase domain of HER2, achieving more than 1000-fold selectivity for HER2 relative to epidermal growth factor receptor in vitro.[1,2] A phase 1b study in metastatic breast cancer showed activity when tucatinib was combined with trastuzumab and/or capecitabine.[3] Among patients with measurable disease at baseline, an objective response was seen in 83% of the tucatinib and capecitabine arm, 40% of the tucatinib and trastuzumab arm, and 61% of the tucatinib, capecitabine, and trastuzumab arm. These preclinical and early clinical results led to the HER2CLIMB trial (A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer), which investigated tucatinib added to trastuzumab and capecitabine in patients with HER2-positive metastatic breast cancer.[4] Dr Rashmi K. Murthy and colleagues presented results at the 2019 San Antonio Breast Cancer Symposium (SABCS).[4] Results were simultaneously published in the *New England Journal of Medicine*.[5]

This randomized, double-blind, placebo-controlled, active comparator trial enrolled patients from 155 sites across 15 different countries.[4] Patients had received prior treatment with trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1). Their baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 or 1. Patients underwent brain magnetic resonance imaging at baseline. The trial limited enrollment to the following types of patients: those with previously treated and stable brain metastases, those with untreated brain metastases not needing immediate local therapy, those with previously treated progressing brain metastases not needing immediate local therapy, and those with no evidence of brain metastases.[4]

Patients were randomly assigned in a 2-to-1 fashion to receive either tucatinib (300 mg twice daily) or placebo, both in combination with trastuzumab (6 mg/kg every 3 weeks following a loading dose of 8 mg/kg) and capecitabine (1000 mg/m^2 twice daily on days 1-14). At randomization, patients were stratified according to the presence of brain metastases, ECOG performance status, and geographic region.[4]

The primary endpoint was progression-free survival (PFS) assessed by blinded independent central review among the first 480 patients who underwent randomization. Secondary endpoints, evaluated in the total population of 612 patients, included overall survival (OS), PFS in patients with brain metastases, confirmed objective response rate (ORR), and safety.

The patients' baseline demographics and disease characteristics were well balanced between the tucatinib (n=410) and placebo (n=202) arms. The patients' median age was 55.0 years and 54.0 years, respectively. ECOG performance status was divided equally between 1 and 2 in the tucatinib arm. In the placebo arm, more patients had a performance status of 2 (54%). Hormone receptor–positive disease was reported in 60% of the tucatinib arm and 63% of the placebo arm. Current

ABSTRACT SUMMARY A Multicenter Phase II Study Evaluating the Efficacy of Nivolumab Plus Paclitaxel Plus Bevacizumab Triple-Combination Therapy as a First-Line Treatment in Patients With HER2-Negative Metastatic Breast Cancer: WJOG9917B NEWBEAT trial

An investigator-initiated, multicenter, single-arm phase 2 trial evaluated the efficacy and safety of a triplet combination of nivolumab, paclitaxel, and bevacizumab in patients with metastatic breast cancer (Abstract PD1-03). The trial enrolled 57 patients from 8 institutions throughout Japan. Thirty-nine patients (68%) were hormone receptor–positive, and 18 patients (32%) had TNBC. ORR based on investigator assessment was 70% (95% CI, 55.9-81.2), meeting the primary endpoint. The disease control rate was 98%. ORR was 74% in patients with hormone receptor–positive disease and 59% in those with TNBC. Investigator-assessed median PFS was 14.8 months. The median OS was not reached. A biomarker analysis suggested that PD-L1 positivity did not correspond to efficacy. The adverse events were manageable and consistent with the known safety profiles of the drugs. An AE of grade 3 or higher occurred in 65% of patients. Any-grade immune-related AEs occurred in 75%. An AE led to treatment discontinuation in 9%. A phase 3 trial of the triplet combination is planned.

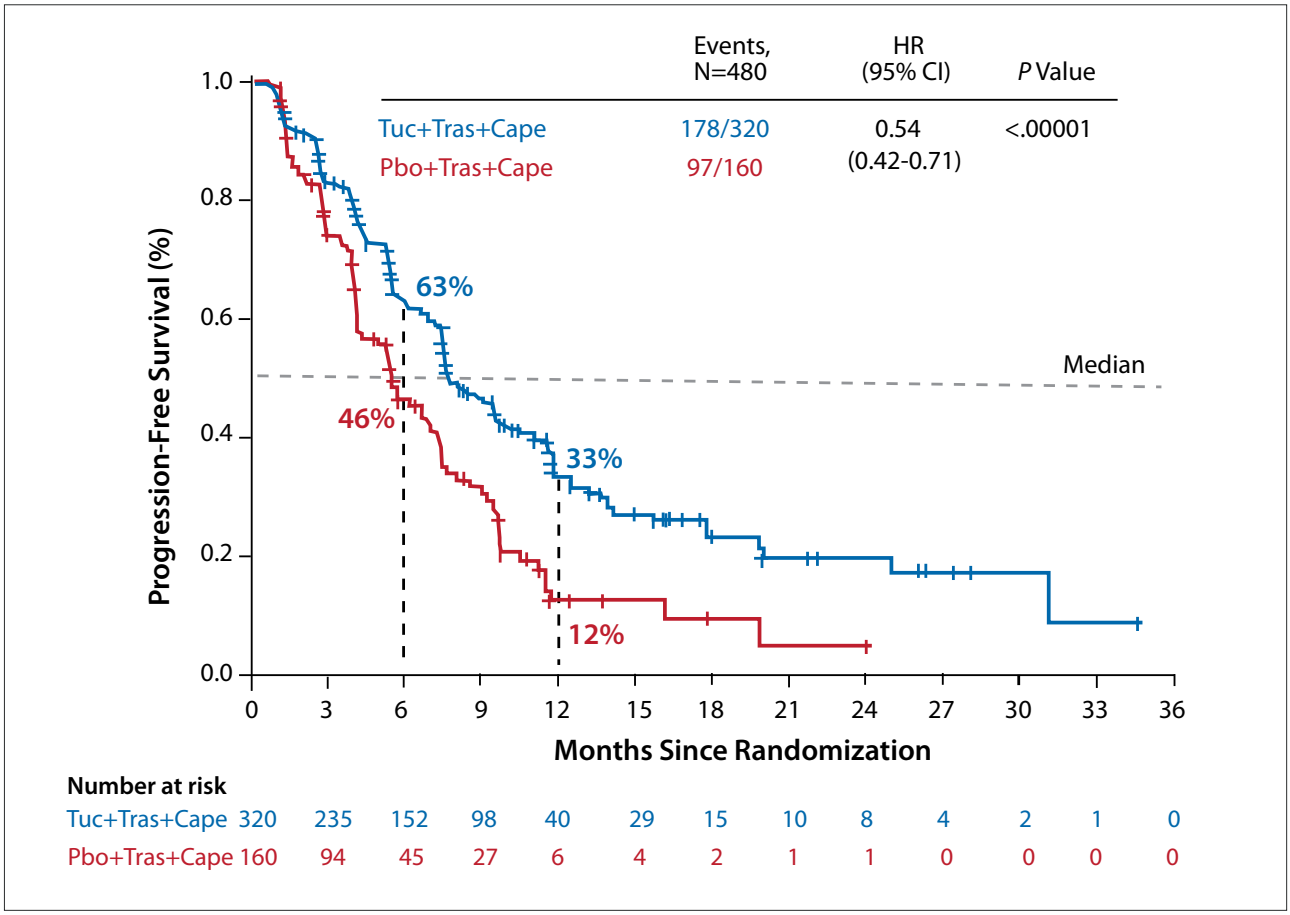

Figure 1. Progression-free survival in the HER2CLIMB trial, which evaluated the addition of tucatinib to trastuzumab and capecitabine in patients with HER2-positive metastatic breast cancer. Cape, capecitabine; HER2, human epidermal growth factor receptor 2; HER2CLIMB, A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer; HR, hazard ratio; Tras, trastuzumab; Tuc, tucatinib. Adapted from Murthy RK et al. Abstract GS1-01. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[4]

or prior brain metastases were present in 48% and 46% of patients, respectively. Among these patients, brain metastases were treated and stable in approximately 59% in both arms.[4]

In the primary endpoint population of 480 patients, median PFS by blinded independent central review was 7.8 months with tucatinib plus trastuzumab and capecitabine vs 5.6 months with placebo plus trastuzumab and capecitabine (hazard ratio [HR], 0.54; 95% CI, 0.42-0.71; *P*<.00001; Figure 1).[4] The 1-year PFS rate was 33% vs 12%, respectively. The investigators noted that treatment with trastuzumab reduced the risk for progression or death by 46% in the primary endpoint population. The benefit in PFS with tucatinib was observed across all prespecified patient subgroups. Among the 291 patients with brain metastases, median PFS was 7.6 months in the tucatinib arm vs 5.4 months in the control arm (HR, 0.48; 95% CI, 0.34-0.69; *P*<.00001).

In the overall study population, median OS was 21.9 months in the tucatinib arm vs 17.4 months in the placebo arm (HR, 0.66; 95% CI, 0.50-0.88; *P*=.00480; Figure 2). The 1-year OS rate was 45% vs 27%, respectively. As with PFS, the benefit in OS with tucatinib was observed across all prespecified patient subgroups.

In the overall study population, the confirmed ORR was 41% in the tucatinib arm vs 23% in the control arm (*P*=.00008; Figure 3). Most of the responses were partial responses (PRs). In addition, 46% of patients in the tucatinib arm and 59% of patients in the control arm achieved stable disease.

Grade 3 or higher adverse events were reported in 55% of the tucatinib arm and 49% of the control arm. Adverse events led to discontinuation of tucatinib in 6% and of placebo in 3%. Diarrhea was the most common adverse event reported in both arms (81% of the tucatinib arm and 53% of the control arm). Grade 3 or higher cases of diarrhea occurred in 13% of the tucatinib arm and 9% of the control arm. Liver transaminase elevations were reported in both arms, and were primarily low-grade, transient, and

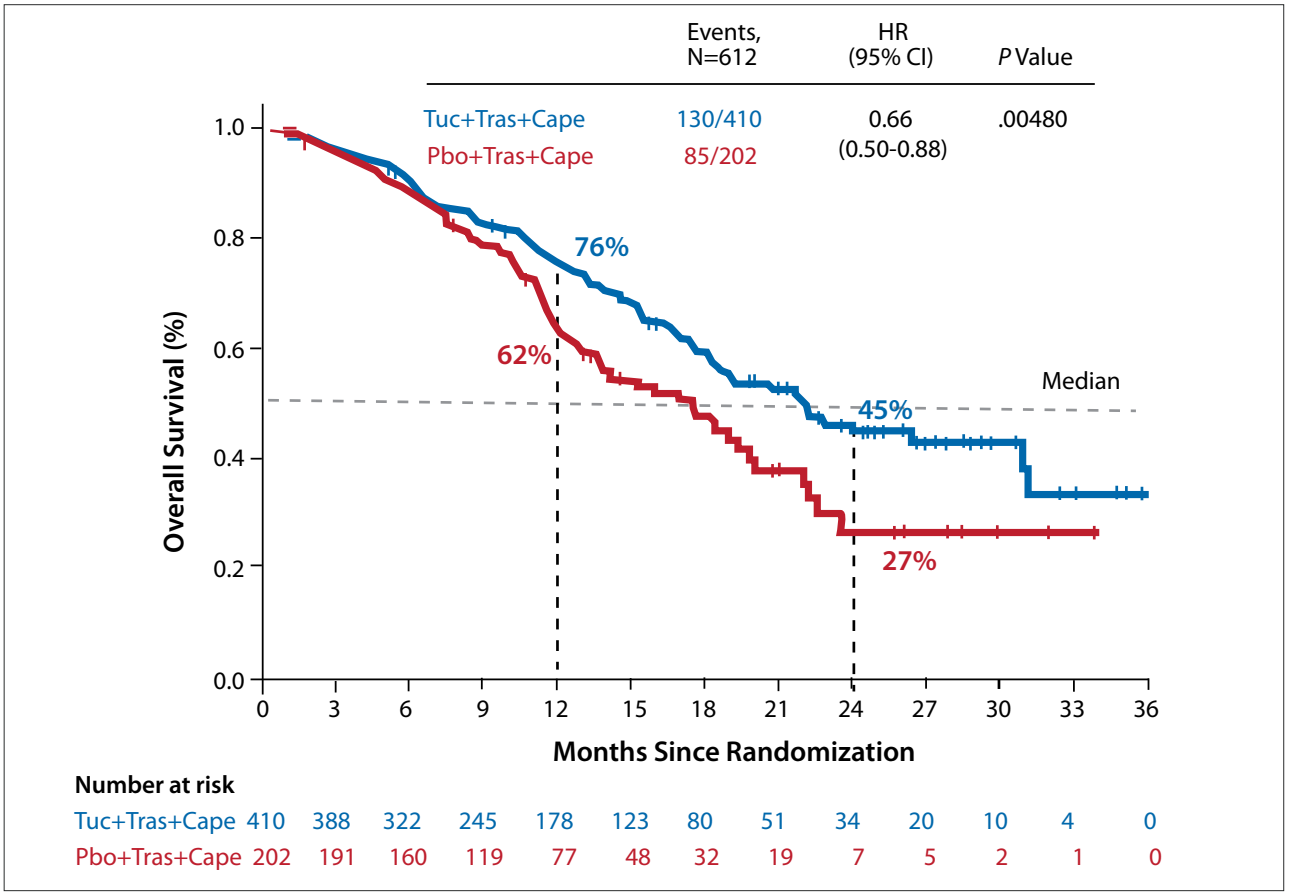

Figure 2. Overall survival in the HER2CLIMB trial, which evaluated the addition of tucatinib to trastuzumab and capecitabine in patients with HER2-positive metastatic breast cancer. Cape, capecitabine; HER2, human epidermal growth factor receptor 2; HER2CLIMB, A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer; HR, hazard ratio; Pbo, placebo; Tras, trastuzumab; Tuc, tucatinib. Adapted from Murthy RK et al. Abstract GS1-01. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[4]

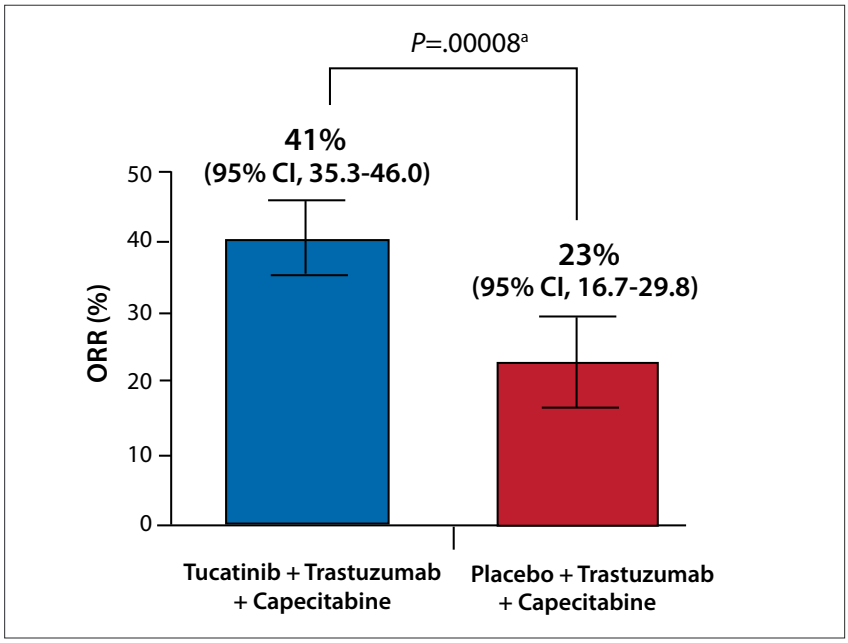

Figure 3. Overall response in the HER2CLIMB trial, which evaluated the addition of tucatinib to trastuzumab and capecitabine in patients with HER2-positive metastatic breast cancer. [a]Stratified Cochran–Mantel–Haenszel *P* value for ORR. HER2, human epidermal growth factor receptor 2; HER2CLIMB, A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer; ORR, objective response rate. Adapted from Murthy RK et al. Abstract GS1-01. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[4]

reversible. Grade 3 or higher aspartate transaminase elevations occurred in 4.5% of the tucatinib arm and 0.5% of the control arm. Grade 3 or higher alanine transaminase elevations occurred in 5.4% vs 0.5% of patients, respectively. Palmar-plantar erythrodysesthesia syndrome was reported in 63% of the tucatinib arm and 53% of the placebo arm. Grade 3 or higher events occurred in 13% vs 9%. The investigators noted that palmar-plantar erythrodysesthesia is a known side effect of capecitabine, and that the longer duration of exposure in the tucatinib arm likely contributed to the difference observed with this toxicity.

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[Fam-] Trastuzumab Deruxtecan (T-DXd; DS-8201a) in Subjects With HER2-Positive Metastatic Breast Cancer Previously Treated With T-DM1: A Phase 2, Multicenter, Open-Label Study (DESTINY-Breast01)

Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate consisting of 3 components: a humanized anti-HER2 monoclonal antibody with the same amino acid sequence as trastuzumab, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor that is the cytotoxic payload.[1,2] In a phase 1 dose-finding study, most patients with advanced HER2-positive metastatic breast cancer achieved a response with trastuzumab deruxtecan.[3] At the 2019 SABCS, Dr Ian Krop and colleagues reported on the efficacy and safety of trastuzumab deruxtecan in the DESTINY-Breast01 trial (DS-8201a in Human Epidermal Growth Factor Receptor 2 [HER2]-Positive Breast Cancer), which was designed to confirm the outcomes observed in the phase 1 trial and to identify a recommended dose in patients with HER2-positive metastatic breast cancer previously treated with trastuzumab emtansine.[4] Results were published simultaneously in the *New England Journal of Medicine*.[5]

DESTINY-Breast01 was a 2-part, open-label, multicenter phase 2 study that enrolled patients with unresectable and/or metastatic HER2-positive breast cancer previously treated with T-DM1. The trial enrolled patients with stable, treated brain metastases, but excluded those with a history of significant interstitial lung disease. The first part of the study evaluated 3 different doses of trastuzumab deruxtecan to establish a recommended dose; the second part evaluated the efficacy and safety of this recommended dose (5.4 mg/kg). The primary endpoint was ORR according to independent central review. Key secondary endpoints were the investigator-assessed ORR, disease control rate, duration of response, clinical benefit rate, PFS, OS, pharmacokinetics, and safety.[4]

A total of 184 patients received trastuzumab deruxtecan at the 5.4 mg/kg dose throughout either part of the DESTINY-Breast01 study.[4] Their median age was 55 years. Patients were from Europe (37.0%), Asia (34.2%), and North America (28.8%). Most patients had an ECOG performance status of 0 (55.4%) or 1 (44.0%). The disease was hormone receptor–positive in 52.7% and hormone receptor–negative in 45.1%. (Hormone receptor status was unknown in 2.2%.) All patients had HER2-positive disease, but the degree of expression varied; 83.7% of patients had immunohistochemistry 3+ expression. Visceral disease was present in 91.8% of patients, and 13.0% had a history of brain metastases. Patients were heavily pretreated. The median number of prior lines of cancer therapy was 6 (range, 2 to 27).

The ORR, as confirmed by independent central review, was 60.9% (95% CI, 53.4-68.0). The rate of complete response (CR) was 6.0%, and the rate of PR was 54.9%. An additional 36.4% of patients achieved stable disease, for a disease control rate of 97.3%. ORR according to a subgroup analysis is shown in Figure 4. The median duration of response was 14.8 months (95% CI, 13.8-16.9), and the clinical benefit rate (defined as the rate of CR, PR, and stable disease for at least 6 months) was 76.1%. The median time to response was

		ORR (%)	95% CI
All Patients[a]	**N=184**	60.9	53.4-68.0
Prior pertuzumab	Yes (n=121)	64.5	55.2-73.0
	No (n=63)	54.0	40.9-66.6
Hormone receptors	Positive (n=97)	57.7	47.3-67.7
	Negative (n=83)	66.3	55.1-76.3
Brain metastasis	Yes (n=24)	58.3	36.6-77.9
	No (n=160)	61.3	53.2-68.8
Presence of visceral disease	Yes (n=169)	60.4	52.6-67.8
	No (n=15)	66.7	38.4-88.2
Region	Asia (n=63)	58.7	45.6-71.0
	North America (n=53)	62.3	47.9-75.2
	Europe (n=68)	61.8	49.2-73.3
ECOG performance status	0 (n=102)	65.7	55.6-74.8
	1 (n=81)	55.6	44.1-66.6
HER2-positive	IHC 3+ (n=154)	63.0	54.8-70.6
	IHC 1+/2+ (n=28)	46.4	27.5-66.1

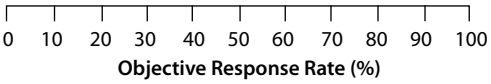

Figure 4. Objective response according to subgroups in the DESTINY-Breast01 study of trastuzumab deruxtecan in patients with unresectable and/or metastatic HER2-positive breast cancer. [a]Patients who received trastuzumab deruxtecan at 5.4 mg/kg. ECOG, Eastern Cooperative Oncology Group; DESTINY-Breast01, DS-8201a in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate. Adapted from Krop I et al. Abstract GS1-03. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[4]

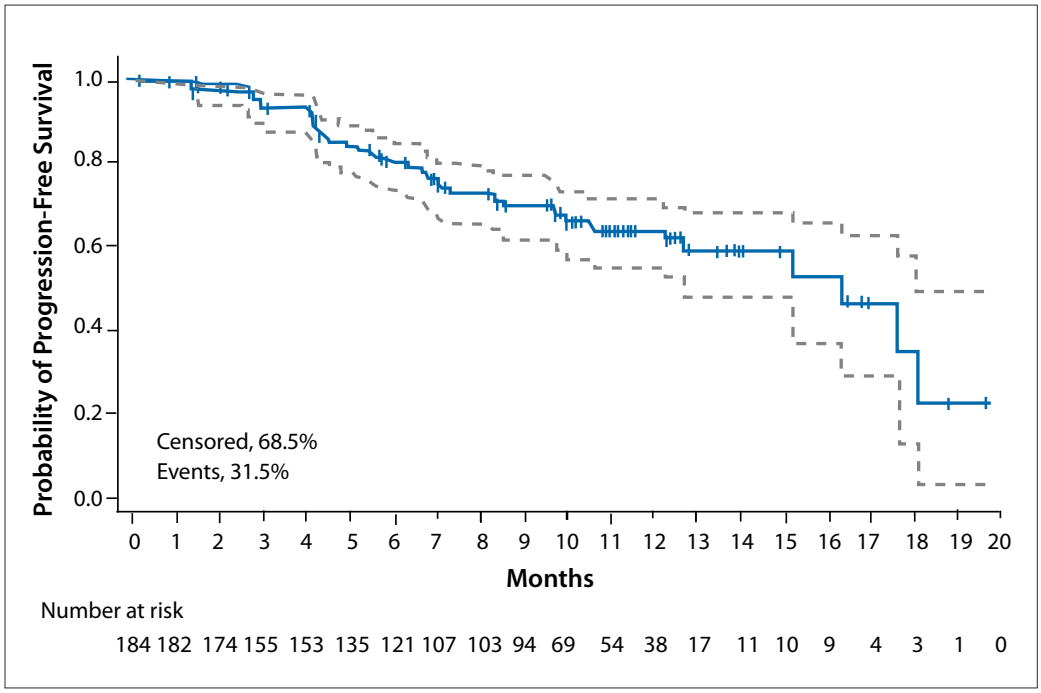

Figure 5. Probability of progression-free survival in the DESTINY-Breast01 study of trastuzumab deruxtecan in patients with unresectable and/or metastatic HER2-positive breast cancer. DESTINY-Breast01, DS-8201a in Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer; HER2, human epidermal growth factor receptor 2. Adapted from Krop I et al. Abstract GS1-03. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[4]

1.6 months (95% CI, 1.4-2.6).

A survival analysis was performed after a median follow-up of 11.1 months (range, 0.7-19.9). The median PFS was 16.4 months (95% CI, 12.7 to not estimable; Figure 5), and the median OS was not reached (95% CI was not estimable). Notably, among patients with brain metastases (n=24), the median PFS was 18.1 months (95% CI, 6.7-18.1).

Grade 3 or higher treatment-emergent adverse events considered related to the study drug occurred in 48.4% of patients. Treatment-emergent adverse events that led to treatment discontinuation included pneumonitis (n=11) and interstitial lung disease (n=5). Interstitial lung disease was reported in 25 patients (13.6%). Among these 25 patients, the median time to investigator-reported onset was 193 days (range, 42-535). Twenty patients had a grade 2 or higher case of interstitial lung disease (most often treated with corticosteroids). Four patients died from interstitial lung disease. Another adverse event of special interest was a decrease in the left ventricular ejection fraction. There were no cases of cardiac failure with left ventricular ejection fraction decline. Additionally, no patients had a left ventricular ejection fraction of less than 40% or a decrease of 20% or more. There were 5 cardiac events, most of which were mild or moderate.

In December 2019, the US Food and Drug Administration (FDA) granted accelerated approval to fam-trastuzumab deruxtecan-nxki among patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2–based regimens in the metastatic setting.[6] For this approval, the efficacy of trastuzumab deruxtecan was supported by data from the DESTINY-Breast01 trial, whereas safety was supported by a pooled analysis of DESTINY-Breast01 and the study DS8201-A-J101.[7]

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Results From the PEARL Study (GEICAM/2013-02_CECOG/BC.1.3.006): A Phase 3 Trial of Palbociclib in Combination With Endocrine Therapy Versus Capecitabine in Hormonal Receptor (HR)-Positive/Human Epidermal Growth Factor Receptor (HER) 2-Negative Metastatic Breast Cancer Patients Whose Disease Progressed on Aromatase Inhibitors

Dr Miguel Martin and colleagues presented results from the PEARL study (Phase III Palbociclib With Endocrine Therapy vs. Capecitabine in HR+/HER2- MBC With Resistance to Aromatase Inhibitors). This trial compared the cyclin dependent kinase 4/6 inhibitor palbociclib combined with endocrine therapy vs capecitabine in patients with hormone receptor–positive/HER2-negative metastatic breast cancer.[1] The trial evaluated 2 palbociclib-based strategies in separate cohorts. In cohort 1, patients were randomly assigned to receive either palbociclib plus the aromatase inhibitor exemestane or single-agent capecitabine. Patients in cohort 2 were randomly assigned to receive either palbociclib plus the selective estrogen receptor degrader fulvestrant or single-agent capecitabine. The latter cohort was planned after the study design was modified based on emerging data showing that patients with *ESR1* mutations—which occur at a high frequency in patients previously treated with aromatase inhibitors for metastatic disease—seem to derive little benefit from further aromatase inhibitor therapy.[2] Instead, fulvestrant may be more active in *ESR1*-mutated tumors.[3]

The trial enrolled patients whose disease had recurred or progressed during or within 12 months of prior

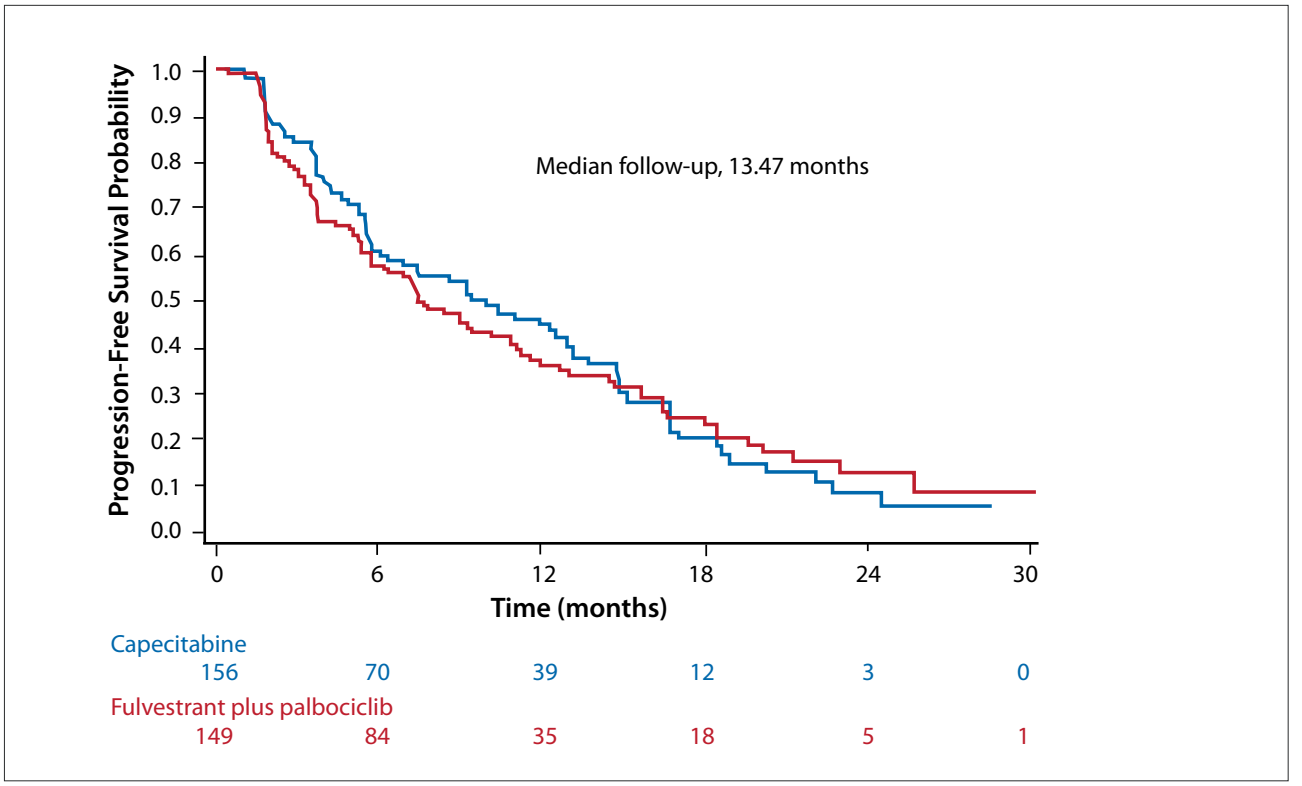

Figure 6. Probability of progression-free survival in the PEARL study, which compared palbociclib combined with endocrine therapy vs capecitabine in patients with hormone receptor–positive/HER2-negative metastatic breast cancer. HER2, human epidermal growth factor receptor 2; PEARL, Phase III Palbociclib With Endocrine Therapy vs. Capecitabine in HR+/HER2- MBC With Resistance to Aromatase Inhibitors. Adapted from Martin M et al. Abstract GS2-07. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[1]

aromatase inhibitor therapy. Patients could have received 1 prior line of chemotherapy for metastatic breast cancer, but they were excluded if they had received prior capecitabine or exemestane (in cohort 1) or fulvestrant (in cohort 2). In both cohorts, patients were stratified by the type of metastasis (visceral vs nonvisceral), prior sensitivity to hormonal treatment, whether they had received prior chemotherapy for metastatic disease, and their country. Treatment continued until disease progression, symptomatic deterioration, or development of unacceptable toxicity.

The PEARL study had 2 co–primary objectives.[1] The first was PFS of palbociclib plus fulvestrant vs capecitabine in cohort 2, regardless of the patient's *ESR1* mutational status. The second was PFS of palbociclib plus endocrine therapy (either exemestane or fulvestrant) vs capecitabine in patients with *ESR1* wild-type tumors. *ESR1* mutational status was determined via circulating tumor DNA prior to treatment initiation. Secondary objectives included PFS of palbociclib plus endocrine therapy (either exemestane or fulvestrant) vs capecitabine in all patients regardless of *ESR1* mutational status, as well as other efficacy measures, including OS, ORR, clinical benefit rate, and duration of response.

In cohort 1 (n=296), the median age in both arms was 60 years. Most patients had visceral disease (67%), and the most frequent metastatic sites were bone (70%), lymph nodes (39%), the liver (43%), and the lungs (28%). In cohort 2 (n=305), the median age was 62 years in the combination arm and 60 years in the capecitabine arm. Most patients had visceral disease (65%), with the most frequent metastatic sites being bone (69%), lymph nodes (43%), the liver (42%), and the lungs (28%). *ESR1* mutations were detected in 26% of cohort 1 and 28% of cohort 2. Insensitivity to prior hormonal therapy was reported in 29% vs 21%, respectively.

After a median follow-up of 13.47 months, an analysis of the first co–primary objective in cohort 2 showed a median PFS of 7.5 months with palbociclib plus fulvestrant vs 10.0 months with capecitabine (HR, 1.09; 95% CI, 0.83-1.44; *P*=.537; Figure 6). For the second co–primary objective (all *ESR1* wild-type patients from both cohorts, n=393), the median follow-up was 18.89 months. At that point, median PFS was 8.0 months with palbociclib plus endocrine therapy vs 10.6 months with capecitabine (HR, 1.08; 95% CI, 0.85-1.36; *P*=.526). Overall, subgroup

ABSTRACT SUMMARY A "Real World" Experience of CDK4/6 Inhibition With Ribociclib and Endocrine Therapy in Hormone Receptor–Positive Metastatic Breast Cancer in Australia

An analysis of a medicine access program in Australia evaluated the use of ribociclib and endocrine therapy in patients with hormone receptor–positive metastatic breast cancer (Abstract OT2-02-01). Data for 62 patients were reported. The median duration of therapy was 19.0 months. The median PFS was not reached, but ranged from 1.6 months to 29.5+ months. At the time of the analysis, 69% of patients had required at least 1 dose interruption during treatment. At least 1 dose reduction was needed by 55%. The most common reasons for dose reduction were neutropenia (65%) and abnormal liver function tests (26%). No dose reductions or interruptions were attributed to a cardiac event (eg, QT prolongation). Among the 24 patients who discontinued treatment, the reasons were disease progression in 79% and toxicity in 21%.

analysis for both objectives favored capecitabine in most cases.

At a median follow-up of 17.64 months for both cohorts combined (irrespective of *ESR1* mutation status; a secondary objective), the median PFS was 7.4 months for patients treated with palbociclib plus endocrine therapy and 9.4 months for patients treated with capecitabine (HR, 1.09; 95% CI, 0.90-1.31; *P*=.380). An analysis of PFS by intrinsic breast cancer subtypes in cohort 2 found no significant difference between the 2 treatment regimens in patients with luminal A or B subtype, both luminal subtypes combined, or nonluminal subtypes. This observation remained consistent when the analysis of PFS by intrinsic subtype was further limited to patients with *ESR1* wild-type disease.

The ORR and clinical benefit rate did not differ between the randomized groups in cohort 2 or in the *ESR1* wild-type subgroup.[1] The ORR in cohort 2 was 27% with palbociclib plus fulvestrant vs 33% with capecitabine (odds ratio, 0.73; 95% CI, 0.42-1.27). The ORR in patients with *ESR1* wild-type tumors from both cohorts was 28% with palbociclib plus endocrine therapy vs 37% with capecitabine (odds ratio, 0.67; 95% CI, 0.42-1.08).

Adverse events leading to study drug discontinuation were more common in the capecitabine arm (12.8%) vs the palbociclib plus exemestane (2.0%) and palbociclib plus fulvestrant (5.4%) arms.[1] Grade 3 or higher decreases in neutrophil count occurred more frequently with palbociclib plus exemestane (57.3%) and palbociclib plus fulvestrant (55.7%) vs capecitabine (5.5%). Grade 3 or higher adverse events that were more frequent with capecitabine were palmar-plantar erythrodysesthesia syndrome (23.5%), diarrhea (7.6%), fatigue (5.5%), and anemia (3.5%).

The investigators concluded that the PEARL study did not meet its 2 co–primary endpoints. Palbociclib plus endocrine therapy was not superior to capecitabine in terms of PFS. However, treatment with palbociclib plus endocrine therapy was generally better tolerated than capecitabine, with fewer serious adverse events and less frequent treatment discontinuations.

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Oral Paclitaxel With Encequidar: The First Orally Administered Paclitaxel Shown to Be Superior to IV Paclitaxel on Confirmed Response and Survival With Less Neuropathy: A Phase III Clinical Study in Metastatic Breast Cancer

In metastatic breast cancer, the use of paclitaxel is limited by the need for intravenous (IV) administration. Oral administration of paclitaxel would permit at-home dosing, remove the need for IV access, and eliminate the risk for infusion hypersensitivity reactions and the associated use of prophylactic corticosteroids.[1,2] However, oral paclitaxel is not well absorbed owing to its excretion by the P-glycoprotein drug transporter pump.[3] Encequidar is an investigational inhibitor of P-glycoprotein. In a preclinical study in rats, administration of encequidar

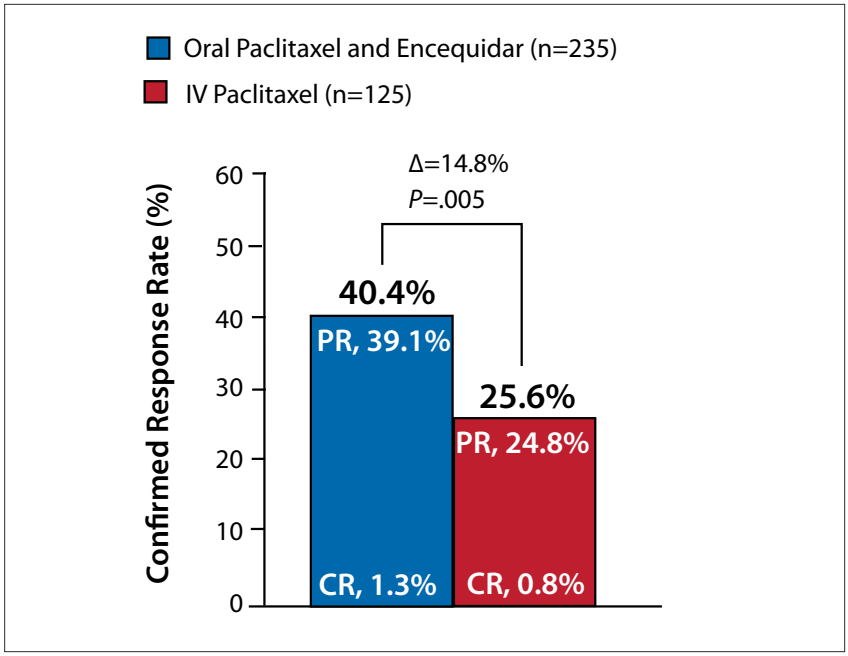

Figure 7. Confirmed response rate in a prespecified modified ITT population in a trial comparing oral paclitaxel plus encequidar vs standard IV paclitaxel in patients with metastatic breast cancer. CR, complete response; ITT, intention-to-treat; IV, intravenous; PR, partial response. Adapted from Umanzor G et al. Abstract GS6-01. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[5]

increased the oral bioavailability of paclitaxel from 3.4% to 41.3%.[4] A phase 3 trial compared oral paclitaxel plus encequidar (OPE) vs standard IV-administered paclitaxel in patients with metastatic breast cancer.[5] Two previously reported studies provided evidence to support the dosing of OPE used in the phase 3 trial.[6,7] In a phase 1 pharmacokinetics study, OPE at a dose of 205 mg/m^2 of paclitaxel plus 15 mg of encequidar, administered once daily for 3 consecutive days per week, was bioequivalent to 80 mg/m^2 of IV paclitaxel and resulted in a similar area under the curve.[6] In a phase 2 single-arm, multicenter, open-label study, this dose of OPE showed clinical activity in patients with metastatic breast cancer (42.3% PR rate and 46.2% stable disease rate), with an area under the curve similar to that previously reported with weekly IV paclitaxel.[7]

The phase 3 trial enrolled patients with metastatic breast cancer who had measurable target lesions according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and an ECOG performance status of 0 or 1.[5] Patients with central nervous system metastases were excluded from the study, as were patients treated with taxanes within a year of enrollment (in either the metastatic or adjuvant settings). The patients were randomly assigned in a 2-to-1 ratio to treatment with OPE at the previously established dose of 205 mg/m^2 of paclitaxel plus 15 mg of encequidar, administered once daily for 3 consecutive days per week, or IV paclitaxel at a dose of 175 mg/m^2 once every 3 weeks. Patients received six 3-week cycles of each study drug, then were analyzed for the primary endpoint of confirmed tumor response and the secondary endpoints of PFS and OS. Confirmed tumor responses were defined by 2 consecutive imaging scans showing either a PR or CR (according to RECIST version 1.1). Tumor assessment was blinded and adjudicated by central independent review.

The trial randomly assigned treatment to 402 patients, who formed the intention-to-treat (ITT) population.[5] Among these patients, 360 were considered evaluable and categorized as the prespecified modified ITT population. In the modified ITT population, 235 patients received OPE and 125 received IV paclitaxel. Patients in the modified ITT population had a baseline evaluable scan with a metastatic lesion identified upon central review, and received at least 7 doses of OPE or 1 dose of IV paclitaxel.

The baseline patient demographics and disease characteristics were relatively well balanced between the 2 treatment arms. The median age was 57.2 years in the OPE arm and 55.7 years in the IV paclitaxel arm. The disease was hormone receptor–positive/HER2-negative in 56% of the OPE arm and 49% of the IV paclitaxel arm. The disease was hormone receptor–positive/HER2-positive in 9% vs 8%, respectively. Triple-negative breast cancer (TNBC) was reported in 8% vs 15%.[5]

In the prespecified modified ITT population, the confirmed response rate was 40.4% with OPE vs 25.6% with IV paclitaxel (*P*=.005; Figure 7). In both arms, most responses were partial (39.1% in the OPE arm vs 24.8% in the IV paclitaxel arm). Data for patients with a confirmed response are shown in Figure 8. The response rate was improved with OPE compared with IV paclitaxel across all patient subgroups evaluated, with the exception of the small number of patients (n=17 overall) with hormone receptor–positive/HER2-positive disease.

Median PFS was 9.3 months with OPE vs 8.3 months with IV paclitaxel, a difference that did not reach statistical significance (HR, 0.760; 95% CI, 0.551-1.049; log-rank test *P*=.0773). Median OS was 27.9 months with OPE vs 16.9 months with IV paclitaxel

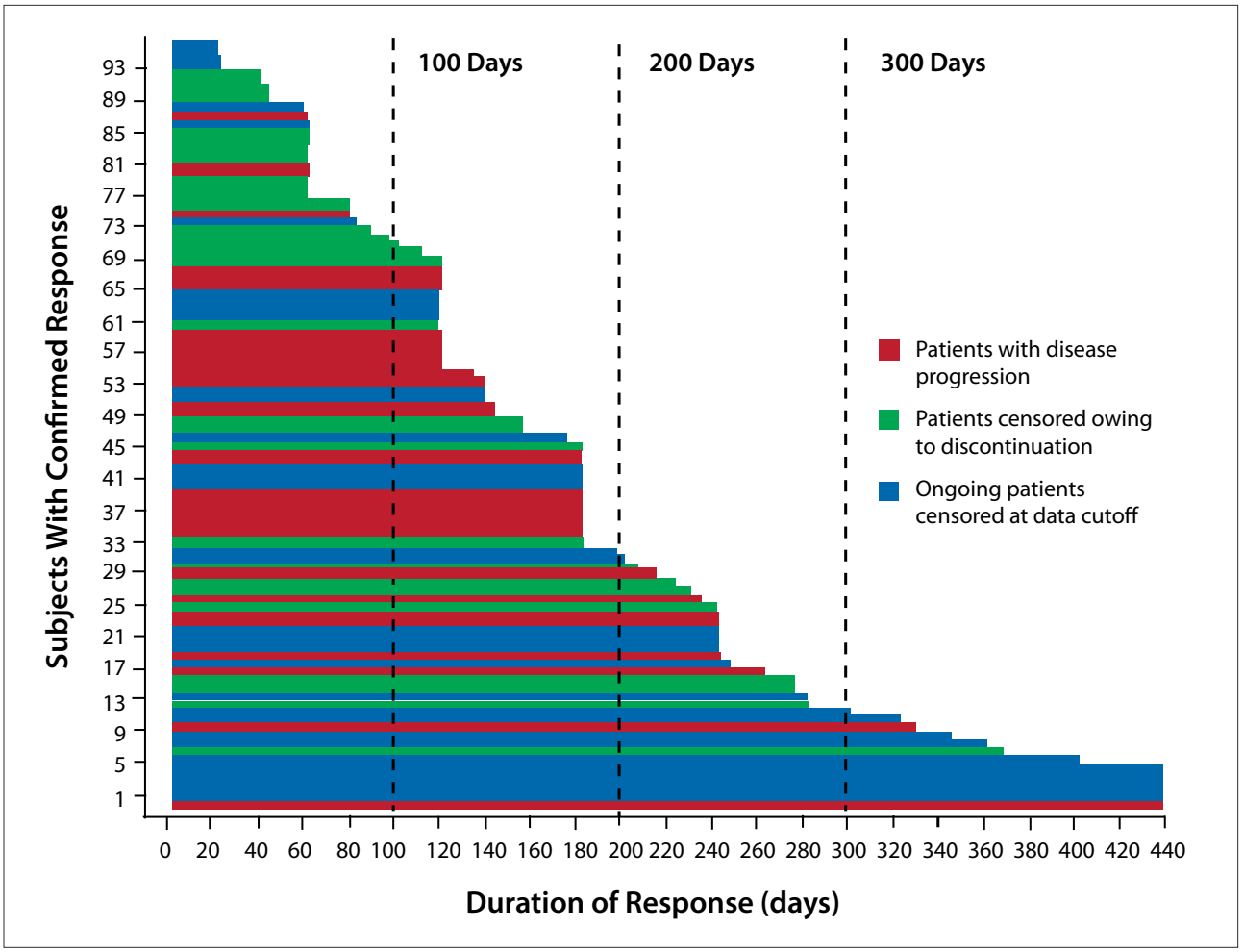

Figure 8. Patients with a confirmed response in a prespecified modified ITT population in a trial comparing oral paclitaxel plus encequidar vs standard IV paclitaxel in metastatic breast cancer. ITT, intention-to-treat; IV, intravenous. Adapted from Umanzor G et al. Abstract GS6-01. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[5]

(HR, 0.684; 95% CI, 0.475-0.985; log-rank test *P*=.0353).

The safety population consisted of 399 patients. Grade 2 or higher treatment-emergent adverse events included neuropathy, which occurred in 31.1% of the IV paclitaxel group vs 7.6% of the OPE group, as well as alopecia (48.1% vs 28.8%) and pain (33.3% vs 14.8%).[5] In contrast, gastrointestinal treatment-emergent adverse events were more frequent with OPE vs IV paclitaxel. These events included diarrhea (24.2% vs 8.1%), nausea (23.1% vs 5.2%), vomiting (17.0% vs 4.4%), and abdominal pain (13.6% vs 4.4%). Grade 2 or higher hematologic treatment-emergent adverse events included neutropenia (38.3% with OPE and 33.3% with IV paclitaxel) and anemia (19.7% vs 10.4%). Urinary tract infections occurred in 18.9% of patients in the OPE arm and 11.9% in the IV paclitaxel arm.

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Durvalumab Compared to Maintenance Chemotherapy in Patients With Metastatic Breast Cancer: Results From the Phase II Randomized Trial SAFIR02-IMMUNO

The use of maintenance chemotherapy in patients with metastatic breast cancer may prolong duration of response and improve outcomes, but it can also worsen quality of life.[1] At the 2019 SABCS, Dr Florence Dalenc and colleagues presented results from SAFIR02-IMMUNO, a substudy of the larger SAFIR02_Breast trial (Efficacy of Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Breast Cancer), which explored other potential therapies in the maintenance setting.[2,3] The open-label, multicenter, randomized phase 2 SAFIR02_Breast trial enrolled 1462 patients with advanced breast cancer (locally advanced or metastatic). All patients were HER2-negative and resistant to endocrine therapy (if hormone receptor–positive). They had received chemotherapy in either the first-line or second-line settings. Patients who achieved a response (complete or partial) or stable disease underwent high throughput next-generation sequencing. Genomic analysis was employed as a therapeutic decision tool to identify targetable molecular alterations in tumor specimens. Those patients with a targetable molecular anomaly (n=240) proceeded into substudy 1, in which they were randomly assigned to maintenance treatment with either an individualized targeted therapy or chemotherapy. Substudy 1 is ongoing, and will be reported at a later time.[2,3]

Patients who did not have a targetable molecular anomaly (n=199) proceeded into substudy 2 (SAFIR02-IMMUNO). These patients were then randomly assigned in a 2-to-1 ratio to maintenance treatment with the immunotherapy durvalumab (10 mg/kg every 2 weeks; n=131) or chemotherapy (n=68). At randomization, patients were stratified by whether they had received chemotherapy in the first-line or second-line setting, and by their response to chemotherapy (CR/PR vs stable disease). The investigators noted that because SAFIR02-IMMUNO is a secondary objective of the SAFIR02-Breast trial, all subgroup analyses should be considered exploratory.[3]

Baseline demographic and disease characteristics were well balanced in the treatment arms of SAFIR02-IMMUNO.[3] The median age of patients in both arms was 56 years, and 55% of patients had an ECOG performance status of 0. A total of 43% of patients had 3 or more metastatic

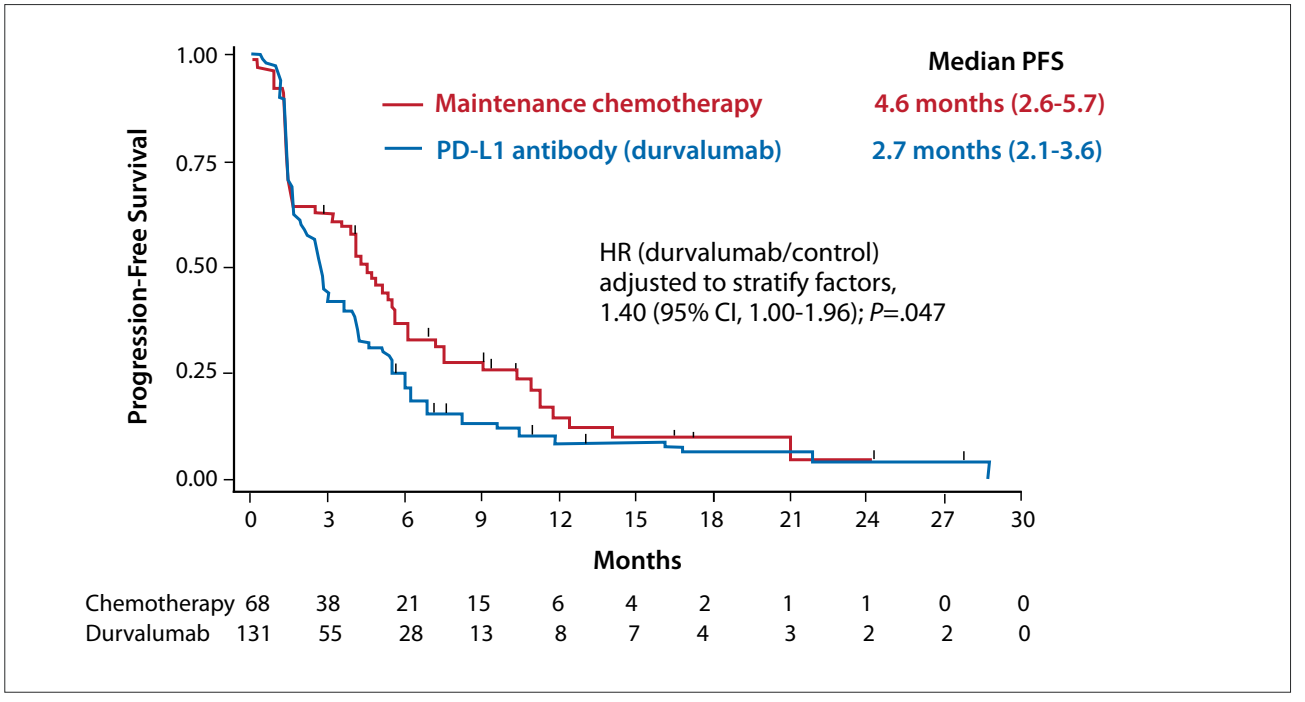

Figure 9. Progression-free survival in the SAFIR02-IMMUNO trial, a substudy of the SAFIR02_Breast trial. Patients without a targetable molecular anomaly received maintenance treatment with chemotherapy or durvalumab. PD-L1, programmed death ligand 1; SAFIR02_Breast - Efficacy of Genome Analysis as a Therapeutic Decision Tool for Patients With Metastatic Breast Cancer. Adapted from Dalenc F et al. Abstract GS3-02. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[3]

lesions, with liver (48%) and lung (28%) metastases the most prevalent. The immunohistochemistry subtype of the primary tumor was known in 192 of the 199 patients; 56% of the patients had hormone receptor–positive/HER2-negative disease and 43% had TNBC. Two patients randomly assigned to the durvalumab arm had a HER2-positive primary tumor. Following induction chemotherapy, 41% of patients had achieved an objective response prior to randomization.

Expression levels of programmed death ligand 1 (PD-L1) were assessable in 133 patients. Positive PD-L1 expression (≥1% of immune cells with PD-L1 expression by immunohistochemistry) was reported in 32.6% of the durvalumab arm and 34.0% of the chemotherapy arm. Among patients with TNBC, PD-L1 expression status was positive in 52.4% and negative in 47.6%. In the non-TNBC cohort, 85% of patients were PD-L1–negative and 14.9% were PD-L1–positive. Hormone receptor status was unknown in 5 of the PD-L1 expression samples tested.

Among the overall population of the SAFIR02-IMMUNO trial, PFS was 4.6 months with maintenance chemotherapy vs 2.7 months with maintenance durvalumab (Figure 9). The hazard ratio of the risk for disease progression with durvalumab vs chemotherapy was 1.40 (95% CI, 1.00-1.96; *P*=.047). Chemotherapy was associated with longer PFS across most patient subgroups, with 2 notable exceptions. The hazard ratio for disease progression with durvalumab vs chemotherapy was 0.75 (95% CI, 0.38-1.49) in 44 patients with PD-L1–positive expression status and 0.87 (95% CI, 0.54-1.42) in 82 patients with TNBC.

Median OS was 21.7 months with durvalumab vs 17.9 months with chemotherapy, a difference that did not reach statistical significance (HR, 0.85; 95% CI, 0.54-1.29; *P*=.42).[3] However, 2 patient subgroups seemed to benefit from maintenance durvalumab. In the patients with PD-L1–positive expression, median OS was 26 months with durvalumab vs 12 months with chemotherapy (unadjusted HR, 0.42; 95% CI, 0.17-1.05; *P*=.0552). Among the patients with TNBC, median OS was 21 months with durvalumab vs 14 months with chemotherapy (unadjusted HR, 0.54; 95% CI, 0.30-0.97; *P*=.0377).

Adverse events considered related to maintenance therapy were reported in 82.2% of the durvalumab arm and 77.8% of the chemotherapy arm. Grade 3 or 4 adverse events considered related to the maintenance therapy occurred in 13.2% vs 15.9%, respectively. A serious adverse event was reported in 18.6% vs 1.6%. Discontinuations owing to an adverse event occurred in 6.2% vs 9.5%. No deaths were reported.

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Phase 3 SOPHIA Study of Margetuximab + Chemotherapy vs Trastuzumab + Chemotherapy in Patients With HER2+ Metastatic Breast Cancer After Prior Anti-HER2 Therapies: Second Interim Overall Survival Analysis

At the 2019 SABCS, Dr Hope S. Rugo and colleagues presented data from the second interim analysis of the SOPHIA study (Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of HER2+ Metastatic Breast Cancer), a phase 3 trial evaluating the efficacy and safety of the investigational agent margetuximab plus chemotherapy in patients with HER2-positive metastatic breast cancer who had received prior anti-HER2 therapies and required systemic treatment for disease progression.[1] Both hormone receptor–positive and –negative tumors were allowed. All patients had received prior treatment with 1 to 3 lines of therapy in the metastatic setting. In addition, patients had received at least 2 anti-HER2–directed agents, one of which was pertuzumab, in either the neoadjuvant or metastatic setting. Patients had developed progressive disease during or after their most recent line of therapy. The trial enrolled patients with treated and stable brain metastases, but excluded those with untreated brain metastases. Patients with a history of clinically significant cardiovascular disease were also excluded, as were patients with clinically significant pulmonary compromise.

Patients were randomly assigned to treatment with either margetuximab (15 mg/kg; n=266) or trastuzumab (6 mg/kg after an 8 mg/kg loading dose; n=270), both administered in 3-week cycles with the investigator's choice of chemotherapy (capecitabine, eribulin, gemcitabine, or vinorelbine). At ran-

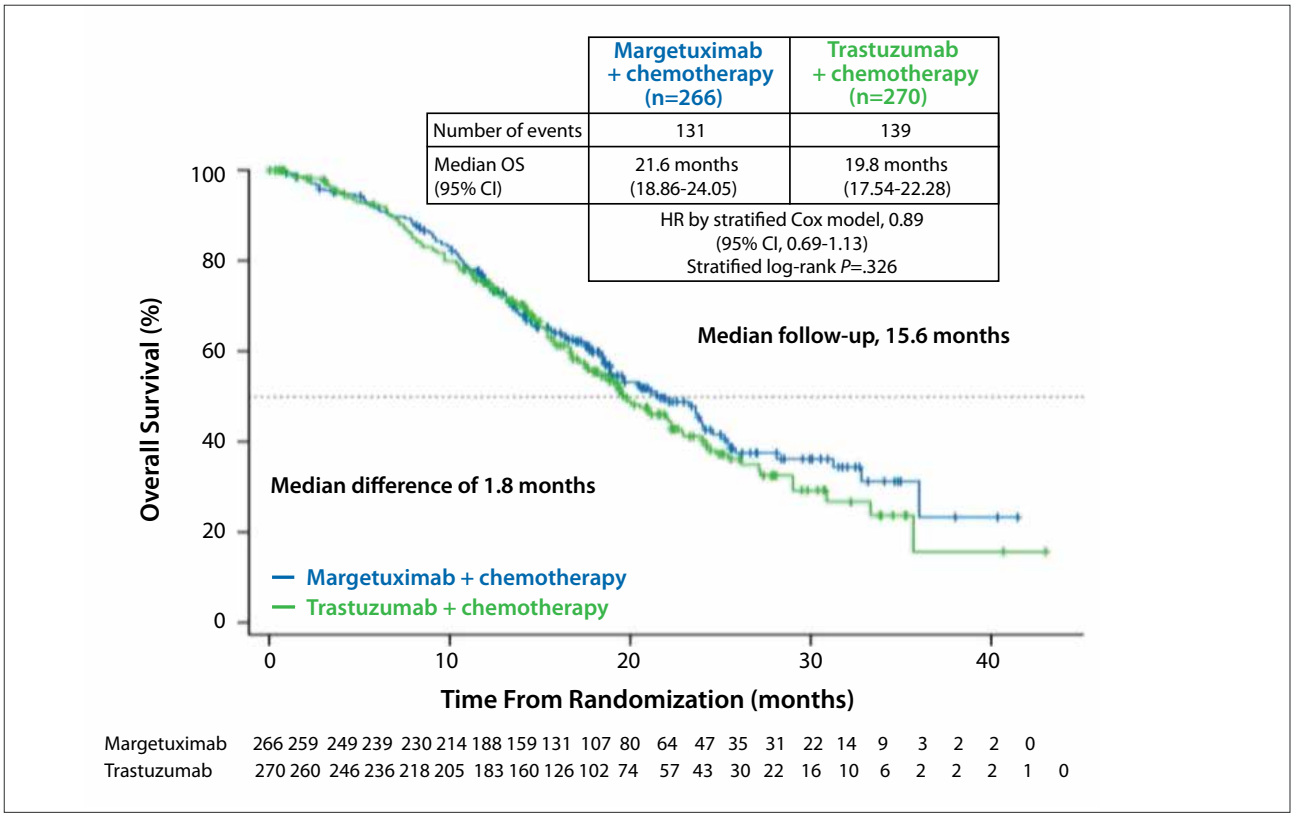

Figure 10. Overall survival in an updated analysis of the SOPHIA trial of margetuximab plus chemotherapy vs trastuzumab plus chemotherapy in patients with HER2-positive advanced (locally advanced or metastatic) breast cancer. HER2, human epidermal growth factor receptor 2; HR, hazard ratio; PFS, progression-free survival; SOPHIA, Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of HER2+ Metastatic Breast Cancer. Adapted from Rugo HS et al. Abstract GS1-02. Presented at: the 2019 San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX.[1]

domization, patients were stratified by choice of chemotherapy, prior therapies (≤2 vs >2), and number of metastatic sites (≤2 vs >2). The SOPHIA trial had 2 sequential primary endpoints: PFS (by central blinded analysis) and OS. Secondary endpoints were investigator-assessed PFS and ORR (by central blinded analysis). The trial design had several tertiary and exploratory endpoints, including investigator-assessed ORR, clinical benefit rate, duration of response, and safety. Additionally, the trial examined the effect of CD16A, CD32A, and CD32B expression on efficacy.

The baseline characteristics were well balanced in the ITT population (N=536). The SOPHIA trial is ongoing. The last patient was randomly assigned to a treatment arm in October 2018. Patients had a median age of approximately 55 years, and were from Europe (54%), North America (35%), or another region (11%). Approximately two-thirds of patients (62%) had hormone receptor–positive cancer. All patients had received prior trastuzumab and pertuzumab; other prior HER2-directed therapies included T-DM1 (91%) and lapatinib (15%).

The primary endpoint of PFS by central blinded analysis was based on a cutoff of October 2018. These data, previously reported at the American Society of Clinical Oncology 2019 Annual Meeting, showed a statistically significant 24% reduction in the risk for disease progression favoring margetuximab compared with trastuzumab.[2] The median PFS was 5.8 months vs 4.9 months, respectively (HR, 0.76; 95% CI, 0.59-0.98; *P*=.033). Central blinded PFS data collection continues, and analysis of mature data is planned.

The second primary endpoint, OS, was reported at the 2019 SABCS.[1] With a September 2019 data cutoff, the median follow-up was 15.6 months. The second interim analysis included 270 events, which was 70% of the 385 events required for the final OS analysis. The median OS was 21.6 months with margetuximab vs 19.8 months with trastuzumab, a difference that was not statistically significant (HR, 0.89; 95% CI, 0.69-1.13; *P*=.326; Figure 10).

PFS as assessed by the investigators (September 2019 cutoff) showed a statistically significant 29% reduction in the risk for disease progression with margetuximab vs trastuzumab. The median PFS was 5.7 months vs

4.4 months, respectively (HR, 0.71; 95% CI, 0.58-0.86; *P*=.0006). The ORR was 25.2% in the margetuximab arm vs 13.7% in the trastuzumab arm (*P*=.0006). Responses were partial in 23.3% vs 12.2%, respectively. Stable disease was reported in 53.8% vs 58.5%. The clinical benefit rate was 48.1% with margetuximab vs 35.6% with trastuzumab (*P*=.0025). The duration of response was similar in the 2 arms, at 6.9 months (range, 5.45-7.49) with margetuximab and 7.0 months (range, 5.55-8.15) with trastuzumab (*P*=.7400).

A prespecified exploratory analysis evaluated OS among patients who were CD16A 158F carriers (either homozygous F/F or heterozygous V/F). The analysis showed an absolute improvement in OS of 4.3 months with margetuximab vs trastuzumab. Median OS was 23.7 months vs 19.4 months, respectively (HR, 0.79; 95% CI, 0.61-1.04; *P*=.087). Patients homozygous for the V/V genotype did not appear to benefit from margetuximab compared with trastuzumab. For these patients, the median OS was 19.7 months vs 33.3 months, respectively (HR, 1.65; 95% CI, 0.82-3.32; *P*=.157). However, this analysis was restricted to a small group of 69 patients, whose baseline clinical characteristics were imbalanced and favored the trastuzumab arm.

Overall safety profiles were similar between the 2 treatment arms. Infusion-related reactions were increased with margetuximab (all-grade, 13.3%; grade ≥3, 1.5%) as compared with trastuzumab (all-grade, 3.4%; grade ≥3, 0%). The rate of left ventricular dysfunction was equivalent across the 2 groups (1.5% and 2.3%, respectively). Grade 3 or higher adverse events attributed to either margetuximab or trastuzumab occurred in 12.9% of the margetuximab arm and 8.3% of the trastuzumab arm. The rates of discontinuations owing to adverse events were 3.0% vs 2.6%, respectively.

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Highlights in Metastatic Breast Cancer From the 2019 San Antonio Breast Cancer Symposium: Commentary

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Presentations at the 2019 San Antonio Breast Cancer Symposium (SABCS) provided important insights into the management of patients with breast cancer. Studies in metastatic breast cancer evaluated novel therapies such as tucatinib, trastuzumab deruxtecan, and oral paclitaxel with encequidar.

Novel Regimens in Metastatic Breast Cancer

The phase 3 HER2CLIMB trial (A Study of Tucatinib vs. Placebo in Combination With Capecitabine & Trastuzumab in Patients With Advanced HER2+ Breast Cancer) evaluated the oral agent tucatinib in patients with metastatic disease that could include treated or untreated brain metastases.[1,2] Tucatinib is a pure inhibitor of human epidermal growth factor receptor 2 (HER2) tyrosine kinase that penetrates the blood-brain barrier.[2] This study is the first randomized, phase 3 trial to enroll patients with brain metastases that had not been treated and were even progressing. (Patients with symptomatic brain metastases were excluded.) Approximately half of the patients in the trial had brain metastases. All patients had received prior treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (T-DM1). Approximately two-thirds of patients had received prior pertuzumab for metastatic disease. Patients were randomly assigned to treatment with capecitabine, trastuzumab, and tucatinib or capecitabine, trastuzumab, and placebo.

The addition of tucatinib significantly improved overall survival and progression-free survival in patients with or without brain metastasis. It was striking to see this survival advantage in this poor-prognosis population. The median overall survival was 21.9

months in the tucatinib arm vs 17.4 months in the control arm, for a 34% reduction in the risk of death. The median progression-free survival was significantly increased at 7.8 months in the tucatinib arm vs 5.6 months in the control arm, for a 46% reduction in the risk of progression or death. The response rates were also higher, at 41% in the tucatinib arm vs 23% in the control arm. Among patients with brain metastases, the median progression-free survival was significantly improved at 7.6 months vs 5.4 months, respectively.

Treatment with the triplet was tolerable. The rates of treatment discontinuation were low, at 6% in the tucatinib arm and 3% in the control arm. There was some grade 2/3 diarrhea with tucatinib, but less than that seen with other oral anti-HER2 tyrosine kinase inhibitors. Low-grade transaminitis was also observed.

Based on this study, the triplet regimen of capecitabine, trastuzumab, and tucatinib is an important option for patients with brain metastasis, as well as for patients who have received previous treatment with T-DM1. Capecitabine, trastuzumab, and tucatinib will likely become the standard of care in these settings after approval from the US Food and Drug Administration (FDA).

Tucatinib is being evaluated in ongoing trials. In the metastatic setting, tucatinib is being combined with T-DM1.[3] Per the KATHERINE trial (A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy), T-DM1 is being administered in the adjuvant setting to patients with residual disease following preoperative chemotherapy plus trastuzumab and pertuzumab.[4] An ongoing randomized trial is evaluating whether the addition of tucatinib to adjuvant T-DM1 will improve progression-free survival and decrease the incidence of brain metastases in early-stage patients.[5]

Dr Ian Krop presented results from the phase 2 DESTINY-Breast01 trial (DS-8201a in Human Epidermal Growth Factor Receptor 2 [HER2]-Positive Breast Cancer) of trastuzumab deruxtecan (DS-8201) in patients with HER2-positive metastatic breast cancer previously treated with T-DM1.[6,7] This trial led to the FDA approval in December 2019 of trastuzumab deruxtecan for patients with unresectable or metastatic HER2-positive breast cancer treated with at least 2 prior anti–HER2-based regimens in the metastatic setting.[8] Trastuzumab deruxtecan is an antibody-drug conjugate that consists of trastuzumab conjugated to deruxtecan, a triple isomerase 1 inhibitor. This antibody-drug conjugate has 8 molecules of deruxtecan per every 1 molecule of trastuzumab, so the ratio of drug to antibody is high.[9] Trastuzumab deruxtecan has a membrane permeable payload, and it exerts a bystander effect. Once cleaved in the interstitial space between breast cancer cells, trastuzumab deruxtecan diffuses into any cells that are HER2-negative. In addition, trastuzumab deruxtecan is internalized and cleaved in HER2-positive cells, and then can kill any neighboring HER2-negative cells. Deruxtecan can therefore kill cells that are not HER2-positive via these bystander effects.

This single-arm trial enrolled heavily pretreated patients who had already received trastuzumab and T-DM1. Previous treatment included pertuzumab in 65.8% of patients. The objective response rate was high, at 61%. Progression-free survival was long, at a median of 16.4 months. The median overall survival was not reached, but the early data are encouraging.

Trastuzumab deruxtecan was generally well-tolerated. This treatment is associated with one important toxicity: interstitial lung disease. Four patients (2%) died from interstitial lung disease in the study. All-grade interstitial lung disease was reported in 13.6% of patients, with rates of 2.7% for grade 1, 8.2% for grade 2, and 0.5% for grade 3. (There were no grade 4 cases.) Many treatments for breast cancer, including everolimus and T-DM1, can cause interstitial lung disease.[10,11] Early detection of interstitial lung disease is critical, and clinicians should be alert to symptoms, including cough and dyspnea on exertion. Patients with symptoms should undergo a computed tomography scan of the chest, and any abnormal finding should trigger pulmonary consultation and consideration of high-dose corticosteroid treatment. The risk of interstitial lung disease associated with trastuzumab deruxtecan requires vigilance, but is manageable. Ongoing phase 3 trials are evaluating trastuzumab deruxtecan in earlier lines of treatment for HER2-positive metastatic breast cancer.[12,13] Trastuzumab deruxtecan also has excellent antitumor activity in patients whose metastatic breast cancer is HER2-low (HER2 1+ or 2+), and a phase 3 trial of trastuzumab deruxtecan vs chemotherapy of the physician's choice is ongoing in this setting.

Dr Miguel Martin presented results from the phase 3 Spanish Breast Cancer Research Group (GEICAM) PEARL trial (Phase III Palbociclib With Endocrine Therapy vs. Capecitabine in HR+/HER2- MBC With Resistance to Aromatase Inhibitors), which compared palbociclib plus endocrine therapy vs capecitabine among patients with metastatic hormone receptor (HR)-positive, HER2-negative disease.[14] Patients could have received up to 1 prior chemotherapy regimen for metastatic disease. Patients were randomly assigned to treatment with exemestane plus palbociclib vs capecitabine. The hypothesis behind the study was that the combination of exemestane and palbociclib would improve progression-free survival overall and/or in patients with estrogen receptor 1 (*ESR1*) wild-type tumors. After treatment of the first cohort, the

study protocol was amended to allow a second cohort to receive fulvestrant with palbociclib instead of exemestane vs capecitabine.

The study found that progression-free survival was identical between the investigational arms vs the control arm for the study population overall and in patients with *ESR1* wild-type or *ESR1*-mutant tumors. Palbociclib was associated with less toxicity and was better tolerated than capecitabine. Adverse events leading to study drug continuation were reported in 2.0% of the exemestane/palbociclib arm, 5.4% of the fulvestrant/palbociclib arm, and 12.8% of the capecitabine arm. Serious treatment-related adverse events were reported in 4.0%, 3.4%, and 10.4%, respectively. The implication of this study is that nearly all patients, except those with visceral crisis, are better served with first-line endocrine therapy plus cyclin-dependent kinase inhibitor therapy instead of chemotherapy.

A randomized phase 3 clinical trial evaluated a novel taxane regimen consisting of oral paclitaxel with encequidar (OPE) in patients with metastatic breast cancer.[15] Encequidar is an oral agent that blocks P-glycoprotein, and allows for absorption of oral paclitaxel through the gastrointestinal tract. OPE was given daily for 3 days each week continuously. The control arm consisted of intravenous paclitaxel given every 3 weeks.

The patients had triple-negative, estrogen receptor–positive, HER2-negative, or HER2-positive metastatic breast cancer and could have received prior chemotherapy. The trial provided data for 360 evaluable patients. The study analyzed data from a prespecified, modified intention-to-treat population consisting of patients who had received at least 7 doses of OPE or 1 dose of intravenous paclitaxel.

The primary endpoint, objective response rate, was 40.4% with OPE vs 25.6% with intravenous paclitaxel, a statistically significant improvement (P=.005). The median overall survival was also significantly improved with OPE, at 27.9 months vs 16.9 months with intravenous paclitaxel (P=.0353). The median PFS was 9.3 months vs 8.3 months, a difference that did not reach statistical significance (P=.0773).

There was considerably less neuropathy with OPE, but more gastrointestinal toxicity.

OPE is a promising treatment. If it becomes commercially available, it will be particularly suitable for patients who are at high risk for developing peripheral neuropathy or who have preexisting neuropathy. It would also be an option for patients who prefer an oral therapy and would rather avoid a central venous access device.

Disclosure

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

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