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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Breast Cancer From the 2021 San Antonio Breast Cancer Symposium

A Review of Selected Presentations From the 2021 SABCS
December 7-10, 2021 • San Antonio, Texas

Special Reporting on:

- Updated Data From AMEERA-1: Phase 1/2 Study of Amcenestrant (SAR439859), an Oral Selective Estrogen Receptor Degrader, Combined With Palbociclib in Postmenopausal Women With ER+/HER2– Advanced Breast Cancer
- Overall Survival Subgroup Analysis by Metastatic Site From the Phase 3 MONALEESA-2 Study of First-Line Ribociclib + Letrozole in Postmenopausal Patients With Advanced HR+/HER2– Breast Cancer
- Datopotamab Deruxtecan in Advanced/Metastatic HER2– Breast Cancer: Results From the Phase 1 TROPION-PanTumor01 Study
- Correlative Analysis of Overall Survival by Intrinsic Subtype Across the MONALEESA-2, -3, and -7 Studies of Ribociclib + Endocrine Therapy in Patients With HR+/HER2– Advanced Breast Cancer
- Elacestrant, an Oral Selective Estrogen Receptor Degrader, vs Investigator's Choice of Endocrine Monotherapy for ER+/HER2– Advanced/Metastatic Breast Cancer Following Progression on Prior Endocrine and CDK4/6 Inhibitor Therapy: Results of the EMERALD Phase 3 Trial
- Trastuzumab Deruxtecan (DS-8201a) vs Trastuzumab Emtansine in Patients With HER2+ Metastatic Breast Cancer: Subgroup Analyses From the Randomized Phase 3 Study DESTINY-Breast03
- Fulvestrant-Palbociclib vs Continuing Aromatase Inhibitor-Palbociclib Upon Detection of Circulating ESR1 Mutation in HR+ HER2– Metastatic Breast Cancer Patients: Results of PADA-1, a UCBG-GINECO Randomized Phase 3 Trial
- Neratinib + Fulvestrant + Trastuzumab for Hormone Receptor-Positive, HER2-Mutant Metastatic Breast Cancer and Neratinib + Trastuzumab for Triple-Negative Disease: Latest Updates From the SUMMIT Trial

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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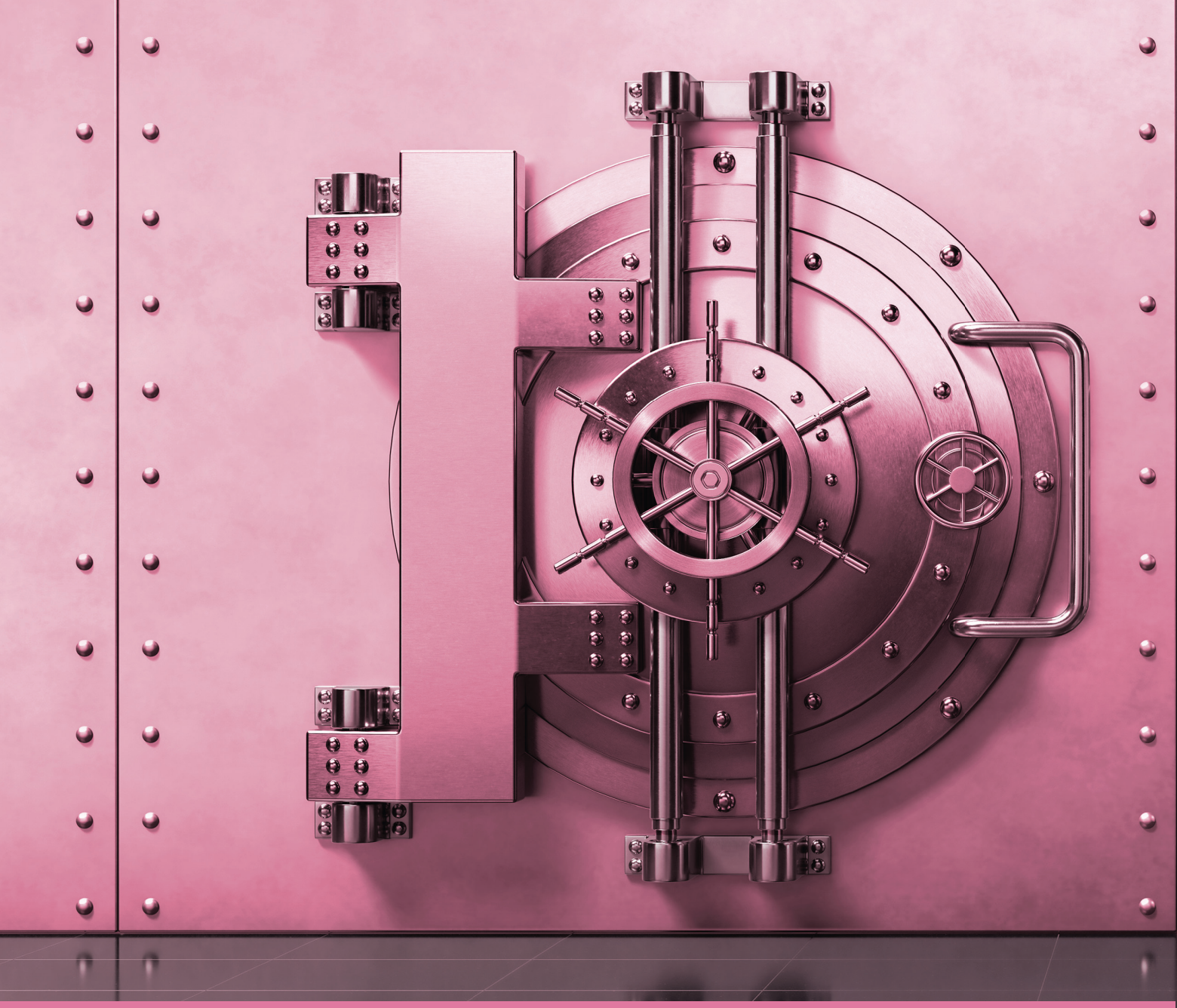

IN ER+/HER2- METASTATIC BREAST CANCER (mBC)

CAN IMPROVING ER ANTAGONISM AND DEGRADATION UNLOCK A BRIGHTER FUTURE?

Complex mechanisms of estrogen receptor (ER) signaling have been associated with tumor growth.[1-3]

In ER+/HER2– mBC, the ER pathways are involved in tumor progression and treatment escape mechanisms that enable endocrine resistance.[1,2,4,5]

To strengthen the fight against resistance, could advancements in ER antagonism and degradation help decrease the ER pathway's downstream effects?

Reveal more at UnlockmBC.com

HER2=human epidermal growth factor receptor 2.

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SANOFI GENZYME

Updated Data From AMEERA-1: Phase 1/2 Study of Amcenestrant (SAR439859), an Oral Selective Estrogen Receptor Degrader, Combined With Palbociclib in Postmenopausal Women With ER+/HER2– Advanced Breast Cancer

For patients with advanced breast cancer that is estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative, standard-of-care therapy consists of endocrine therapy in combination with an inhibitor of cyclin-dependent kinase 4/6 (CDK4/6).[1,2] However, up to 40% of patients develop resistance to endocrine therapy. Amcenestrant is an oral selective estrogen receptor degrader (SERD). Arm 2 of the open-label phase 1/2 AMEERA-1 trial investigated the efficacy and safety of amcenestrant (200 mg/day) plus palbociclib (125 mg, 21 days on/7 days off) in patients with ER-positive/HER2-negative advanced breast cancer that had progressed during treatment with endocrine therapy in the adjuvant or advanced setting.[3-5]

The 39 patients were a median age of 59 years (range, 33-86 years).[5] Most patients (89.7%) had visceral metastases, and all patients had exhibited resistance to prior endocrine therapy.

After a median follow-up of 14.8 months, the objective response rate (ORR) was 32.4% (11/34), and the clinical benefit rate was 73.5% (25/34; Table 1). The median progression-free survival (PFS) was 14.7 months, and the 12-month PFS rate was 59.4% (Figure 1). The median time to first response was 16.3 weeks (range, 8-32 weeks). Two patients experienced 100% shrinkage of their target lesions. *ESR1* mutations were more common among patients whose most recent

Table 1. Antitumor Activity in the Response-Evaluable Population Receiving Amcenestrant at the Recommended Phase 2 Dose in the AMEERA-1 Trial

	Response-Evaluable Population (Parts C + D; N=34)
Objective Response Rate,[a] n (%) (90% CI)[b]	11 (32.4%) (19.3%-47.8%)
Clinical Benefit Rate,[c] n (%) (90% CI)[b]	25 (73.5%) (58.4%-85.4%)
Median follow-up,[d] months	14.8
Median PFS (90% CI),[e] months	14.7 (11.0-22.3)
Number of events, n (%)	17 (50%)
Number of censoring, n (%)	17 (50%)
PFS rate (%) at 12 months (90% CI)[e]	59.4 (43.8%-72.0%)

CR, complete response; PFS, progression-free survival; PR, partial response; SD, stable disease. [a]Confirmed CR or confirmed PR; [b]Estimated by Clopper–Pearson method; [c]CR, PR, or SD≥24 weeks, [d]Based on the reverse Kaplan-Meier method; [e]Kaplan-Meier estimates. CIs were computed using the log-log method.

Adapted from Chandarlapaty S et al. SABCS abstract 1-17-11. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[5]

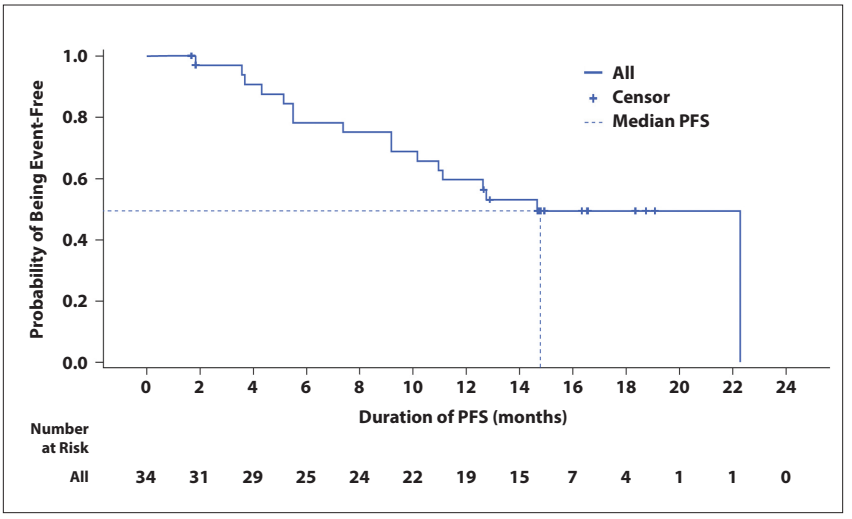

Figure 1. Progression-free survival among patients evaluable for response in arm 2 of the AMEERA-1 trial, which evaluated amcenestrant plus palbociclib in postmenopausal women with endocrine-resistant ER-positive/HER2-negative advanced breast cancer. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival. Adapted from Chandarlapaty S et al. SABCS abstract 1-17-11. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[5]

prior therapy was in the advanced setting (43.3% [13/30]) compared with patients whose most recent prior therapy was in the neoadjuvant setting (6.7% [1/15]). In most patients with the baseline *ESR1* mutation, allele frequency decreased after 2 cycles of study treatment.

The median relative dose intensity was 99.6% for amcenestrant and 97.4% for palbociclib. Two patients discontinued treatment because of treatment-related adverse events (AEs). Treatment-related AEs of grade 3 or higher occurred in 12.8% (amcenestrant-related) and 48.7% (palbociclib-related) of patients.

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Overall Survival Subgroup Analysis by Metastatic Site From the Phase 3 MONALEESA-2 Study of First-Line Ribociclib + Letrozole in Postmenopausal Patients With Advanced HR+/HER2– Breast Cancer

The phase 3 MONALEESA-2 study investigated letrozole combined with ribociclib vs letrozole combined with placebo in postmenopausal women with hormone receptor–positive/HER2-negative advanced breast cancer.[1,2] Enrolled patients had not received prior therapy for their advanced disease; however, prior use of adjuvant or neoadjuvant endocrine therapy was allowed. The trial randomly assigned 668 patients to receive ribociclib at 600 mg daily or placebo on a schedule of 3 weeks on, 1 week off, plus letrozole at 2.5 mg daily. The primary endpoint was PFS assessed locally and based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Overall survival (OS) was a key secondary endpoint.[3]

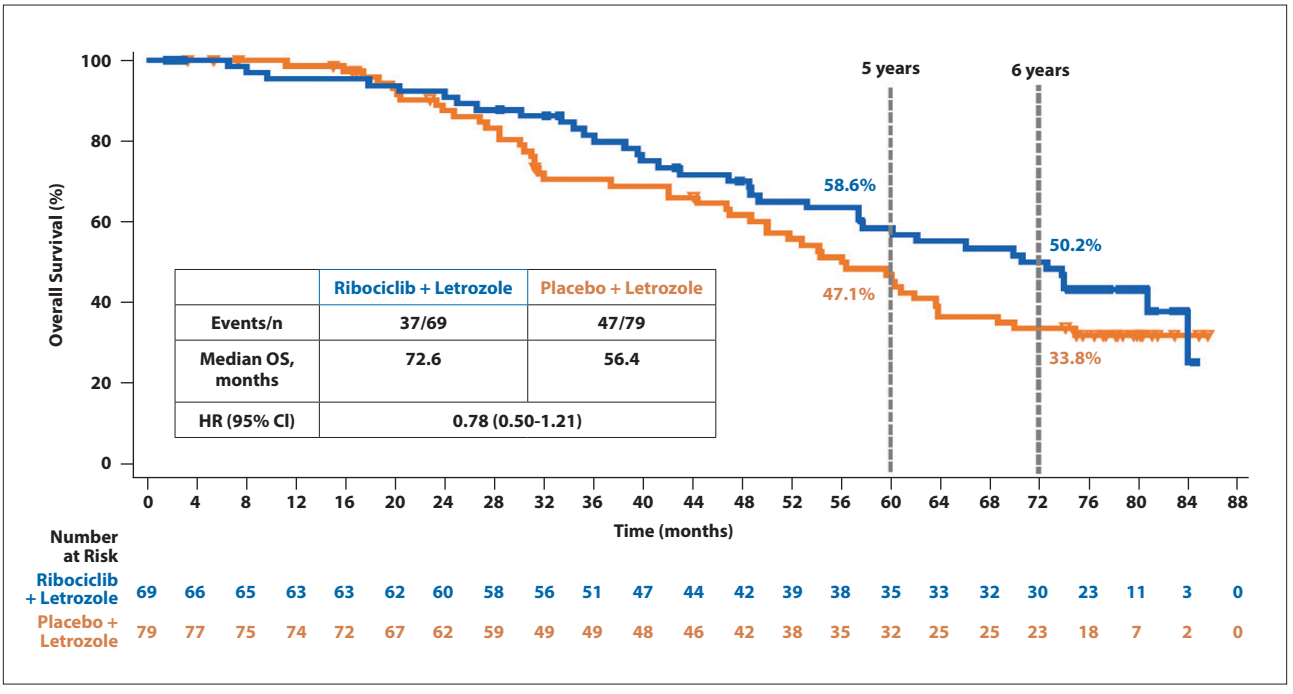

Figure 2. Overall survival in the phase 3 MONALEESA-2 study among patients with metastases in the bone only. HR, hazard ratio; OS, overall survival. Adapted from O'Shaughnessy J et al. SABCS abstract GS2-01. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[1]

After a median follow-up of 79.7 months, the median OS was 63.9 months in the ribociclib arm vs 51.4 months in the control arm (hazard ratio [HR], 0.76; 95% CI, 0.63-0.93; *P*=.004).[2] The median OS achieved with ribociclib plus letrozole was the longest reported in any phase 3 clinical trial for advanced breast cancer and the first to exceed 5 years. The estimated 6-year OS rates were 44.2% with ribociclib vs 32.0% with placebo.

Exploratory analyses evaluated outcomes in prespecified subgroups.[1] In patients with metastases in the bone only, the 5-year survival rate was 58.6% with ribociclib vs 47.1% with placebo (Figure 2). Ribociclib also conferred a benefit over placebo in patients without bone-only metastases (5-year OS, 50.6% vs 43.0%; HR, 0.81; 95% CI, 0.54-1.24). Among patients with metastases in the liver only, the 5-year OS was 48.2% with ribociclib vs 45.4% with placebo. At 6 years, OS showed a greater difference between the groups: 40.5% with ribociclib vs 31.2% with placebo. Among patients without liver-only metastases, the 5-year OS was 55.2% with ribociclib vs 48.3% with placebo, and the 6-year OS was 46.8% vs 35.7%, respectively (HR, 0.77; 95% CI, 0.62-0.97). Among patients with metastases in the liver or lung, the 5-year OS was 48.2% with ribociclib vs 45.4% with placebo, and the 6-year OS rates were 40.5% vs 31.2%, respectively (HR, 0.81; 95% CI, 0.62-1.05). Among patients without liver or lung metastases, ribociclib also conferred a survival benefit (5-year OS, 57.1% vs 41.9%; 6-year OS, 48.6% vs 33.2%; HR, 0.71; 95% CI, 0.53-0.96).

The analysis also showed an OS benefit with ribociclib vs placebo in the subset of patients with fewer than 3 metastatic sites and those with 3 or more metastatic sites; in patients who had received prior adjuvant or neoadjuvant chemotherapy, and in those who had not; in patients who had received prior aromatase inhibitor therapy; in patients who had received prior treatment with tamoxifen (with or without an aromatase inhibitor); and in patients with no prior endocrine therapy. Ribociclib has consistently demonstrated an OS benefit in the MONALEESA-2, -3, and -7 trials, irrespective of endocrine therapy partner, line of therapy, or menopausal status.[4-6]

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Datopotamab Deruxtecan in Advanced/Metastatic HER2– Breast Cancer: Results From the Phase 1 TROPION-PanTumor01 Study

Few treatment options are available for patients with advanced triple-negative breast cancer (TNBC) that has progressed on systemic therapy. TROP2 is a calcium signal transducer that promotes the growth of tumor cells and is highly expressed in breast cancer and other malignancies.[1,2] In breast and other tumors, increased TROP2 expression correlates with reduced OS. Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of a humanized, anti-TROP2, immunoglobulin G1 monoclonal antibody with a topoisomerase I inhibitor covalently attached by means of a cleavable, tetrapeptide-based linker.[3] The antibody-drug conjugate delivers a high-potency payload with an optimized drug:antibody ratio and a short systemic half-life. TROPION-PanTumor01 is a phase 1 study that evaluated the safety and efficacy of Dato-DXd among patients with various solid tumor types and relapsed or refractory disease.[4-6] Patients were not selected based on TROP2 expression. Enrolled patients were adults with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and measurable disease according to RECIST 1.1.[7] The study included 44 patients with TNBC, and these patients were treated with Dato-DXd at a dose of 8 mg/kg (n=2) or 6 mg/kg (n=42) on day 1 of every 3-week cycle. The primary objectives were the safety and tolerability of the study treatment.

At baseline, the 44 patients with TNBC were a median age of 53 years (range, 32-82 years).[5] Five patients (11%) had brain metastases. The median number of prior therapies was 3 (range, 1-10 prior therapies), and 30% of patients had received prior treatment with a topoisomerase I–based antibody-drug conjugate. After a median follow-up of 7.6 months (range, 4-13 months), the ORR was 34% by blinded independent central review, and the disease control rate was 77% (Figure 3). Among 27 patients without prior exposure to a

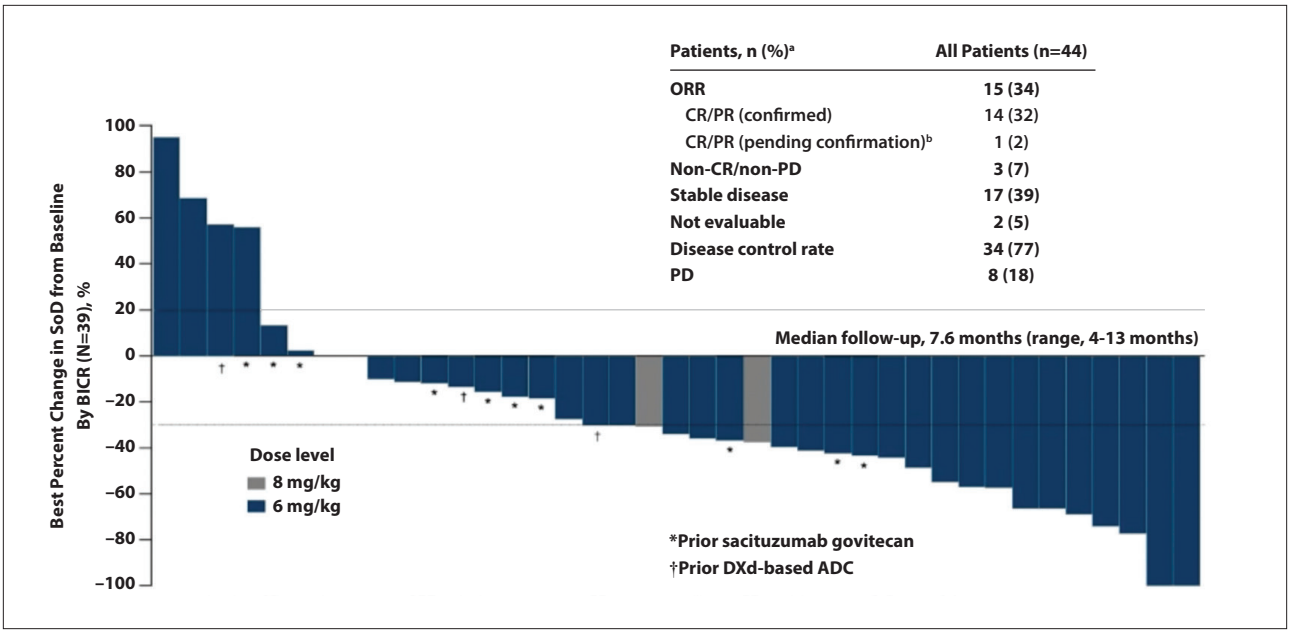

Figure 3. Tumor responses among patients with triple-negative breast cancer treated with datopotamab deruxtecan in the phase 1 TROPION-PanTumor01 study. [a]Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or who discontinued treatment. Postbaseline tumor assessments were not yet available for 2 patients at data cutoff. Three patients were not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD. [b]Includes patients with an unconfirmed response but who were receiving ongoing treatment. ADC, antibody-drug conjugate; BICR, blinded independent central review; DXd, deruxtecan; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SoD, sum of diameters. Adapted from Krop I et al. SABCS abstract GS1-05. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[5]

topoisomerase I–based antibody-drug conjugate, the ORR was 52%, and the disease control rate was 81%. The median duration of response was not reached (range, 3.7-7.4+ months).

Treatment-related AEs of grade 3 or higher were observed in 23% of patients, 18% required a dose reduction owing to an AE, and 2% discontinued treatment owing to an AE. No new safety signals emerged. A phase 3 trial of Dato-DXd in patients with TNBC is planned.

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ABSTRACT SUMMARY Final Results of KEYNOTE-355: Randomized, Double-Blind, Phase 3 Study of Pembrolizumab + Chemotherapy vs Placebo + Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer

The KEYNOTE-355 study compared chemotherapy plus pembrolizumab vs placebo in patients with previously untreated, locally recurrent, inoperable, or metastatic TNBC (Abstract GS1-02). The study randomly assigned 566 patients to the pembrolizumab arm and 281 to the placebo arm. The final analysis of the intention-to-treat population yielded a median OS of 17.2 months with pembrolizumab vs 15.5 months with placebo (HR, 0.89; 95% CI, 0.76-1.05). Among patients with a PD-L1 combined positive score (CPS) of at least 1, the median OS was 17.6 months with pembrolizumab vs 16.0 months with placebo (HR, 0.86; 95% CI, 0.72-1.04; *P*=.0563). In patients with a CPS of 10 or higher, the median OS was 23.0 months with pembrolizumab vs 16.1 months with placebo (HR, 0.66; 95% CI, 0.50-0.88; *P*=.0093). Pembrolizumab yielded a superior median PFS in the intention-to-treat population (HR, 0.82; 95% CI, 0.70-0.98), in patients with a CPS of at least 1 (HR, 0.75; 95% CI, 0.62-0.91), and in patients with a CPS of at least 10 (HR, 0.66; 95% CI, 0.50-0.88).

Correlative Analysis of Overall Survival by Intrinsic Subtype Across the MONALEESA-2, -3, and -7 Studies of Ribociclib + Endocrine Therapy in Patients With HR+/HER2− Advanced Breast Cancer

A retrospective, exploratory analysis investigated the association between intrinsic subtype and OS in patients treated with ribociclib plus endocrine therapy in the MONALEESA-2, -3, and -7 trials.[1-4] Intrinsic subtyping was performed with a set of 152 genes selected through the original Prediction Analysis of Microarray 50 (PAM50) training set and based on the ability to identify the PAM50 subtype in 48 independent tumors. The retrospective analysis included 585 samples from patients treated with ribociclib plus endocrine therapy and 412 from patients treated with placebo plus endocrine therapy. Seventy-one percent (71%) of samples were from primary tumors. In the data set pooled from the 3 MONALEESA trials, subtypes included luminal A (54.4%), luminal B (27.9%), HER2-enriched (14.7%), and basal-like (3%).

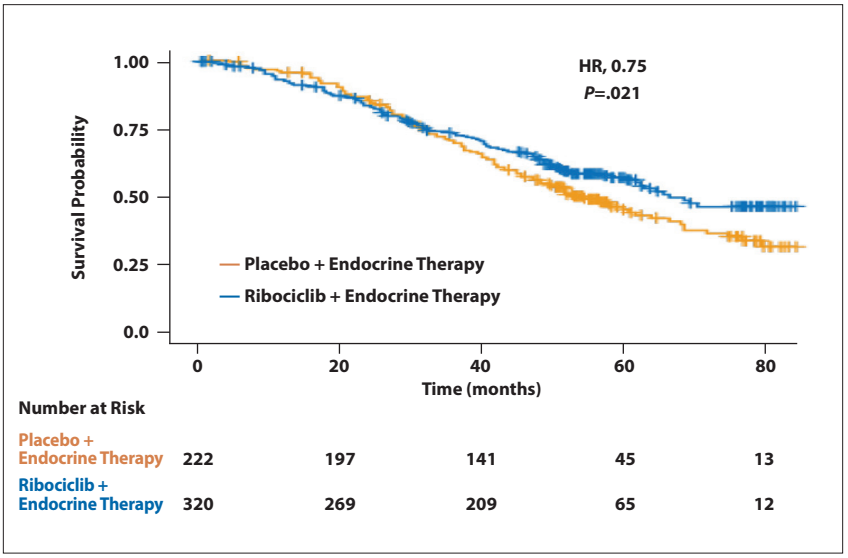

Figure 4. Overall survival among patients with luminal A disease treated with ribociclib plus endocrine therapy in the MONALEESA-2, -3, and -7 studies. HR, hazard ratio. Adapted from Carey LA et al. SABCS abstract GS2-00. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[1]

Ribociclib showed an OS benefit in the 997 patients included in the retrospective analysis (HR, 0.75; 95% CI, 0.63-0.89; *P*=.0012), and a similar OS benefit among the intention-to-treat population of 2066 patients (HR, 0.76; 95% CI, 0.67-0.86; *P*<.0001).[1] Results in the placebo arm reflected the strong association between intrinsic subtype and OS. In this group, the median OS was 54.6 months with the luminal A subtype, 44.9 months with the luminal B subtype, 29.4 months with the HER2-enriched subtype, and 21.2 months with the basal-like subtype. Compared with placebo, the median OS was prolonged with ribociclib treatment in patients with the luminal A (68.0 months), luminal B (58.8 months), and HER2-enriched (40.3 months) subtypes, but not the basal-like subtype (19.4 months). In multivariable models, the intrinsic subtype was associated with OS. Using luminal A as the referent population, the adjusted HR for death in the placebo arm was 1.47 for the luminal B subtype (95% CI, 1.08-2.00; *P*=.013), 2.87 for the HER2-enriched subtype (95% CI, 1.93-4.26; *P*<.0001), and 2.35 for the basal-like subtype (95% CI, 1.20-4.58; *P*=.012). In patients treated with ribociclib, the adjusted HR was 1.16 for the luminal B subtype (95% CI, 0.86-1.57; *P*=.32), 1.83 for the HER2-negative enriched subtype

ABSTRACT SUMMARY Ongoing Cohorts in the Phase 1/2 AMEERA-1 Trial

The ongoing AMEERA-1 trial is recruiting patients for arms 3, 4, and 5 of the open-label, noncomparative, dose-escalation and expansion study (Abstracts OT2-11-02, OT2-11-03, and OT2-11-04). Eligible patients are postmenopausal women with ER-positive/HER2-negative advanced or metastatic breast cancer. Patients in arm 3 are required to have *PIK3CA*-mutated disease and will receive treatment with amcenestrant plus alpelisib. Patients in arm 4 will receive treatment with amcenestrant plus everolimus. Patients in arm 5 will be treated with amcenestrant plus abemaciclib. Each arm will enroll 6 to 12 patients for a safety run-in phase (arm 3) or a dose-escalation phase (arms 4 and 5). Subsequently, patients in each arm will be treated at the recommended phase 2 dose of amcenestrant plus the respective second drug. The primary endpoints are the safety and tolerability of the recommended phase 2 dose of the 2-drug combinations.

(95% CI, 1.33-2.52; *P*=.00023), and 7.06 for the basal-like subtype (95% CI, 3.73-13.40; *P*<.0001). Kaplan-Meier curves also demonstrated the benefit with ribociclib vs placebo in the subtypes of luminal A (HR, 0.75; *P*=.021; Figure 4), luminal B (HR, 0.69; *P*=.023), and HER2-enriched (HR, 0.60; *P*=.018), but not in the basal-like subtype (HR, 1.89; *P*=.148). The interaction test between tumor subtype and treatment arm was significant in the overall analysis (*P*=.016), but not when the basal-like subtype was removed (*P*=.47).

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2. Hortobagyi G, Stemmer SM, Burris HA, et al. Overall survival (OS) results from the phase III MONALEESA-2 (ML-2) trial of postmenopausal patients (pts) with hormone receptor positive/human epidermal growth factor receptor 2 negative (HR+/HER2–) advanced breast cancer (ABC) treated with endocrine therapy (ET) ± ribociclib (RIB) [ESMO abstract LBA17_PR]. *Ann Oncol*. 2021;32(suppl 5).
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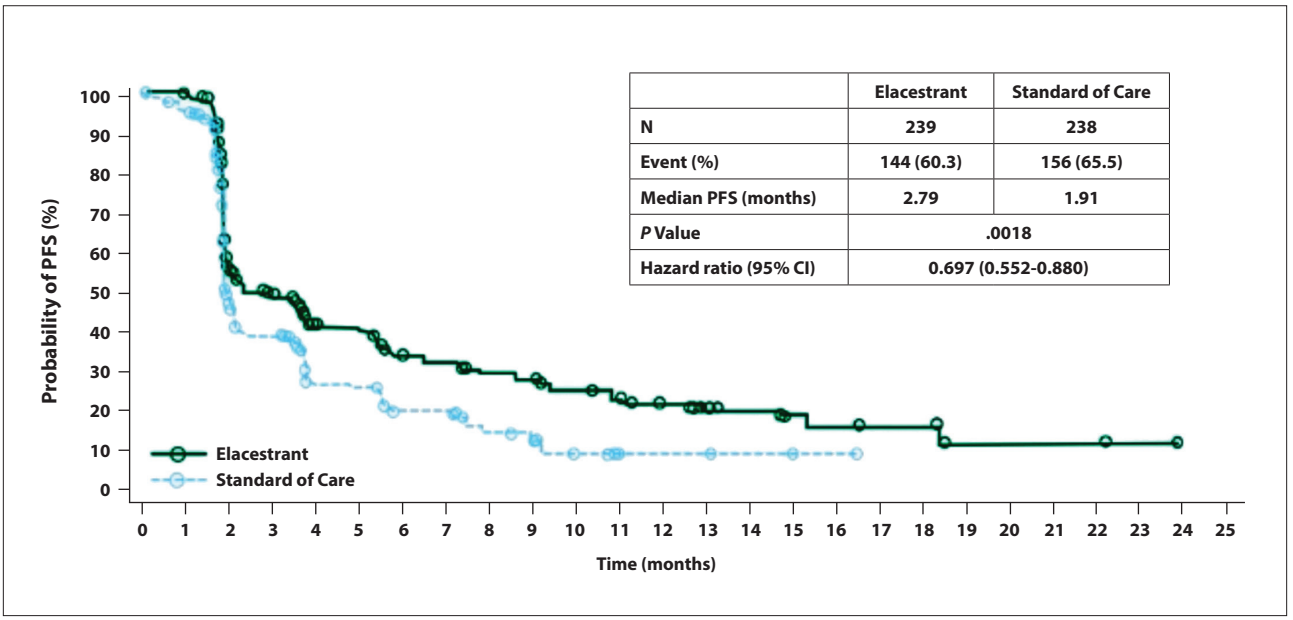
4. Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med*. 2020;382(6):514-524.

Elacestrant, an Oral Selective Estrogen Receptor Degrader, vs Investigator's Choice of Endocrine Monotherapy for ER+/HER2– Advanced/Metastatic Breast Cancer Following Progression on Prior Endocrine and CDK4/6 Inhibitor Therapy: Results of the EMERALD Phase 3 Trial

Most patients with ER-positive/HER2-negative metastatic breast cancer eventually progress on their first-line therapy. The poor median PFS associated with fulvestrant monotherapy as second-line and later treatment underscores the need for better endocrine therapy to treat this patient population.[1-3] Elacestrant (RAD1901) is an oral SERD that reduces the downstream activity of the ER, inhibiting estradiol-dependent cellular proliferation more potently than fulvestrant.[4] In a phase 1 study of postmenopausal women with ER-positive/HER2-negative metastatic breast cancer, elacestrant yielded confirmed partial responses (PRs) in heavily pretreated patients.[5]

The phase 3 EMERALD study compared elacestrant monotherapy vs the investigator's choice of therapy in previously treated men and postmenopausal women diagnosed with



	Elacestrant	Standard of Care
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P Value	.0018	
Hazard ratio (95% CI)	0.697 (0.552-0.880)	

Figure 5. Progression-free survival among patients treated with elacestrant or a standard of care in the phase 3 EMERALD trial. PFS, progression-free survival. Adapted from Bardia A et al. SABCS abstract GS2-02. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[6]

advanced or metastatic, ER-positive/HER2-negative breast cancer.[6] Eligible patients had progressed on or relapsed after treatment with 1 or 2 lines of endocrine therapy for advanced disease. Patients had experienced disease progression during treatment with a CDK4/6 inhibitor. Previous treatment with chemotherapy was limited to 1 line. Patients in the experimental arm received elacestrant at 400 mg daily. Patients in the control arm received fulvestrant, anastrozole, letrozole, or exemestane. The trial's co–primary endpoints were PFS in all patients and PFS in patients with an *ESR1* mutation according to independent review.

The trial enrolled 239 patients in the elacestrant arm (115 with the *ESR1* mutation), and 238 in the control arm (113 with the *ESR1* mutation).[6] Patient characteristics were well balanced between the 2 arms. Approximately 70% of patients had visceral metastases, and approximately 22% had received 1 prior line of chemotherapy, reflecting the aggressive tumor biology.

The trial met its primary endpoint, demonstrating a median PFS of 2.79 months with elacestrant vs 1.91 months with standard-of-care therapy (HR, 0.697; 95% CI, 0.552-0.880; *P*=.0018; Figure 5) in the entire study population. The risk of progression or death was also reduced with elacestrant vs the standard of care in the population of patients with the *ESR1* mutation (HR, 0.54; *P*=.005). In the overall study population, 12-month PFS was 22.3% with elacestrant vs 9.4% with standard-of-care therapy. Among patients with the *ESR1* mutation, 12-month PFS was 26.9% with elacestrant vs 8.2% with the standard of care therapy. The PFS benefit with elacestrant was observed in numerous prespecified subgroups, including those with visceral metastasis (HR, 0.665; 95% CI, 0.607-0.869) and those treated with 1 line of prior endocrine therapy (HR, 0.705; 95% CI, 0.527-0.959) or 2 lines of prior endocrine therapy (HR, 0.597; 95% CI, 0.423-0.841). Elacestrant was generally well tolerated, with a safety profile similar to that of other endocrine therapies. Treatment-emergent AEs required discontinuation of treatment in 6.3% of patients in the elacestrant arm vs 4.4% in the control arm. No treatment-related deaths occurred in either arm.

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Trastuzumab Deruxtecan (DS-8201a) vs Trastuzumab Emtansine in Patients With HER2+ Metastatic Breast Cancer: Subgroup Analyses From the Randomized Phase 3 Study DESTINY-Breast03

The multicenter, open-label, phase 3 DESTINY-Breast03 trial compared trastuzumab deruxtecan (T-DXd) vs trastuzumab emtansine (T-DM1) in patients with previously treated unresectable or metastatic breast cancer.[1,2] Eligible patients had received prior treatment with trastuzumab and a taxane. Enrollment included patients with clinically stable, treated brain metastases. Stratification factors included hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. The trial randomly assigned 524 patients to receive T-DXd at 5.4 mg/kg every 3 weeks or T-DM1 at 3.6 mg/kg every 3 weeks. The primary endpoint was PFS according to blinded independent review.

The baseline characteristics were generally well balanced between the 2 arms.[2] Patients were a median age of 54 years (range, 20-83 years). Most patients (88%-90%) had a HER2 expression level of 3+ according to immunohistochemistry. A history of brain metastases was reported in 23.8% of the T-DXd arm and 19.8% of the T-DM1 arm. Baseline imaging showed brain metastases in 16.5% vs 14.8%, respectively. Prior pertuzumab therapy was noted in 62.1% of patients in the T-DXd arm and 60.1% of patients in the T-DM1 arm.

After a median follow-up of 15.9 months, the median PFS was not reached (95% CI, 18.5 months to not estimable) in the T-DXd arm vs 6.8 months (95% CI, 5.6-8.2) in the T-DM1 arm (HR, 0.28; 95% CI, 0.22-0.37; $P=7.8 \times 10^{-22}$). The risk of disease progression or death was reduced by at least 67% in all subgroups, including those based on HR status, prior pertuzumab treatment, visceral disease, prior lines of therapy, and brain metastases. Across the same subgroups,

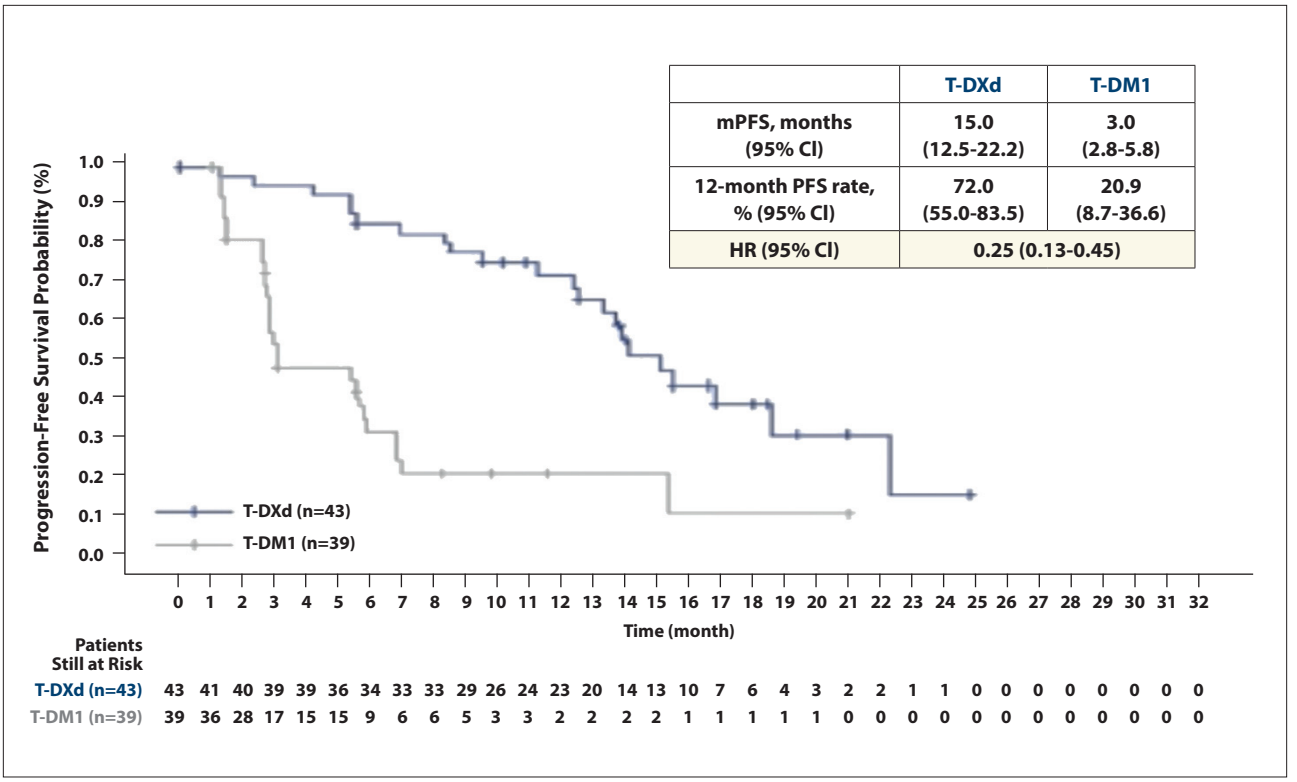

Figure 6. Progression-free survival among patients with confirmed brain metastases at baseline in the phase 3 DESTINY-Breast03 trial of trastuzumab deruxtecan vs trastuzumab emtansine. T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; HR, hazard ratio; PFS, progression-free survival. Adapted from Hurvitz S et al. SABCS abstract GS3-01. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[2]

the difference in the proportion of confirmed ORRs with T-DXd vs T-DM1 ranged from 39.1% to 51.6%, all favoring T-DXd. Among patients with confirmed brain metastases at baseline, the median PFS was 15.0 months with T-DXd vs 3.0 months with T-DM1 (HR, 0.25; 95% CI, 0.13-0.45; Figure 6). Among patients without brain metastases at baseline, the median PFS was not estimable in the T-DXd group vs 7.1 months in the T-DM1 group (HR, 0.30; 95% CI, 0.22-0.040).

In the overall study population, the confirmed ORR was 79.7% with T-DXd vs 34.2% with T-DM1, with complete response (CR) rates of 16.1% vs 8.7%, respectively. Among patients with brain metastases at baseline, the confirmed ORR was 67.4% with T-DXd vs 20.5% with T-DM1, with CR rates of 4.7% vs 0%. Thirty-six patients in each arm had brain metastases at baseline, and in these patients, intracranial responses with T-DXd vs T-DM1 included a CR rate of 27.8% vs 2.8% and a PR rate of 36.1% vs 30.6%, respectively.

The median duration of treatment was 14.3 months (range, 0.7-29.8 months) with T-DXd vs 6.9 months (range, 0.7-25.1 months) with T-DM1. Owing to the large difference in exposure to study drug in the T-DXd arm compared with the T-DM1 arm, AEs were evaluated based on the exposure-adjusted incidence rate per patient-year (EAIR). Compared with the T-DM1 arm, patients in the T-DXd arm were less likely to experience a treatment-emergent AE of any grade (EAIR, 0.87 vs 1.43), a treatment-emergent AE of at least grade 3 (EAIR, 0.46 vs 0.72), or a serious treatment-emergent AE (EAIR, 0.17 vs 0.27). The rates of treatment-emergent AEs associated with treatment discontinuation, dose reduction, or death were similar in both arms based on EAIR analysis. The most common AEs of grade 3 or higher in the T-DXd arm were neutropenia (19.1%) and thrombocytopenia (7.0%), followed by leukopenia and nausea at 6.6% each. Rates of interstitial lung disease or pneumonitis were similar in patients from Asia and non-Asian regions.

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Fulvestrant-Palbociclib vs Continuing Aromatase Inhibitor-Palbociclib Upon Detection of Circulating *ESR1* Mutation in HR+ HER2– Metastatic Breast Cancer Patients: Results of PADA-1, a UCBG-GINECO Randomized Phase 3 Trial

In patients with ER-positive metastatic breast cancer, mutations in *ESR1* promote resistance to aromatase inhibitors while retaining sensitivity to ERα degradation by SERDs.[1] Mutations in *ESR1* can be detected by analyzing cell-free circulating DNA in the blood. Although these mutations are rare at diagnosis, they are more frequently detected in patients with disease that progresses during first-line treatment with an aromatase inhibitor. The phase 3 PADA-1 trial compared treatment with fulvestrant plus palbociclib vs an aromatase inhibitor plus palbociclib upon detection of an *ESR1* mutation in the blood among patients with hormone receptor–positive/HER2-negative metastatic breast cancer.[2] Eligible patients had received no prior therapy for their metastatic disease and had not relapsed within 12 months of adjuvant treatment with an aromatase inhibitor. Stratification factors included the time of inclusion to the detection of an increasing *ESR1* mutation in the blood and the presence of visceral metastases. Patients with a rising *ESR1* mutation in the absence of synchronous disease progression were randomly assigned into the 2 treatment arms. The co–primary endpoints were safety based on hematologic AEs of grade 3 or higher and investigator-assessed PFS based on RECIST 1.1.[3]

The study enrolled 1017 patients who received treatment with an aromatase inhibitor plus palbociclib.[2] An increasing level of *ESR1* mutation in the blood was identified in 279 patients during the initial therapy. Among these patients, 172 patients had an increasing blood *ESR1* mutation level and no synchronous disease progression. The patient characteristics were well balanced between the 2 arms. In the cohort of 84 patients who continued with an aromatase inhibitor plus palbociclib, the median age was 60 years (range, 30-80 years), and 49% had visceral metastasis. The time to rising

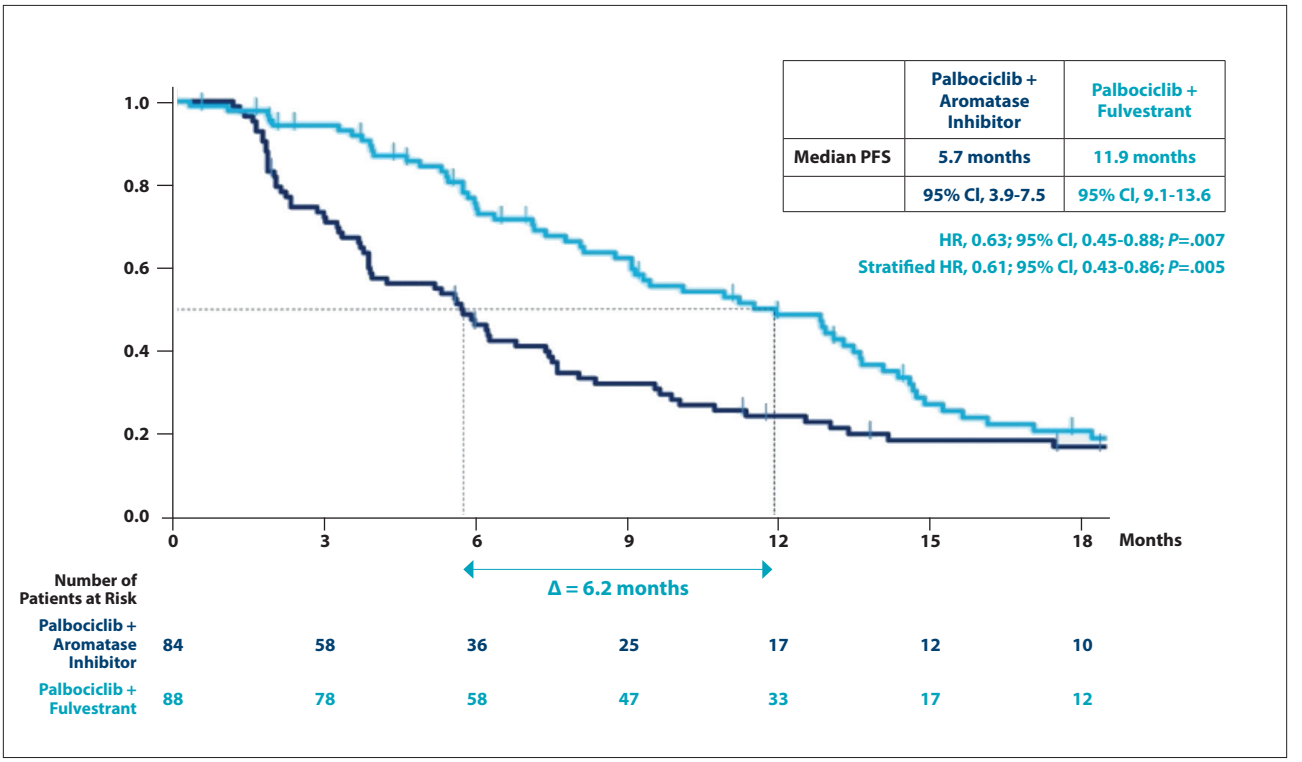

Figure 7. Progression-free survival in the phase 3 PADA-1 trial, which compared treatment with fulvestrant plus palbociclib vs continuing aromatase inhibitor-palbociclib upon detection of the circulating *ESR1* mutation. Adapted from Bidard FC et al. SABCS abstract GS3-05. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[2]

blood *ESR1* mutations was less than 12 months in 35% of patients and 12 months or longer in 65% of patients. For the 88 patients who were randomly assigned to treatment with fulvestrant plus palbociclib, the median age was 62 years (range, 23-88 years) and 48% had visceral metastasis. The time to rising blood *ESR1* was less than 12 months in 39% of patients and 12 months or more in 61% of patients. After a median follow-up of 26 months, the median PFS was 11.9 months with fulvestrant plus palbociclib vs 5.7 months with an aromatase inhibitor plus palbociclib (stratified HR, 0.61; 95% CI, 0.43-0.86; *P*=.005; Figure 7). Few grade 3/4 AEs were observed, and no new safety signals were raised.

ABSTRACT SUMMARY Clinical Utility of Molecular Tumor Profiling: Results From the Randomized Trial SAFIR02-BREAST

The European Society for Molecular Oncology Scale for Clinical Actionability of Molecular Targets (ESCAT) classifies molecular alterations in tumors based on the availability of a matched targeted therapy and the likelihood of clinical activity. This analysis included 113 breast cancer patients from the SAFIR02-BREAST and SAFIR-PI3K trials, plus 2 patients who were screened locally, who were designated with ESCAT I or II level mutations (Abstract GS1-10). These 115 patients received targeted therapy that was matched to the genomic alteration. The median PFS in these patients was 9.1 months compared with 2.8 months in the control group of patients who were treated with maintenance chemotherapy (HR, 0.41; 95% CI, 0.27-0.61; *P*<.001). In contrast, in an analysis of 238 patients who received either maintenance chemotherapy or targeted therapy in the absence of ESCAT I/II classification, the median PFS was 5.5 months with targeted treatment vs 2.9 months with maintenance chemotherapy (HR, 0.77; 95% CI, 0.56-1.06; *P*=.109).

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Neratinib + Fulvestrant + Trastuzumab for Hormone Receptor-Positive, *HER2*-Mutant Metastatic Breast Cancer and Neratinib + Trastuzumab for Triple-Negative Disease: Latest Updates From the SUMMIT Trial

Breast cancer tumors that lack overexpression of HER2 as assessed by immunohistochemistry or fluorescence in situ hybridization may harbor *HER2* mutations that can be targeted by tyrosine kinase inhibitors (TKIs).[1,2] Xenograft studies suggest that tumor killing may be enhanced by treatment with a TKI plus an anti-HER2 antibody.[3,4] The SUMMIT trial initially evaluated neratinib monotherapy in patients with a variety of tumor types, including breast tumors, with a documented *HER2* mutation.[5] The trial excluded patients who had received prior treatment with any pan-HER TKI.

In an initial analysis, neratinib monotherapy led to a median PFS of 3.6 months in 18 patients with hormone receptor–positive/HER2-negative, *HER2*-mutant metastatic breast

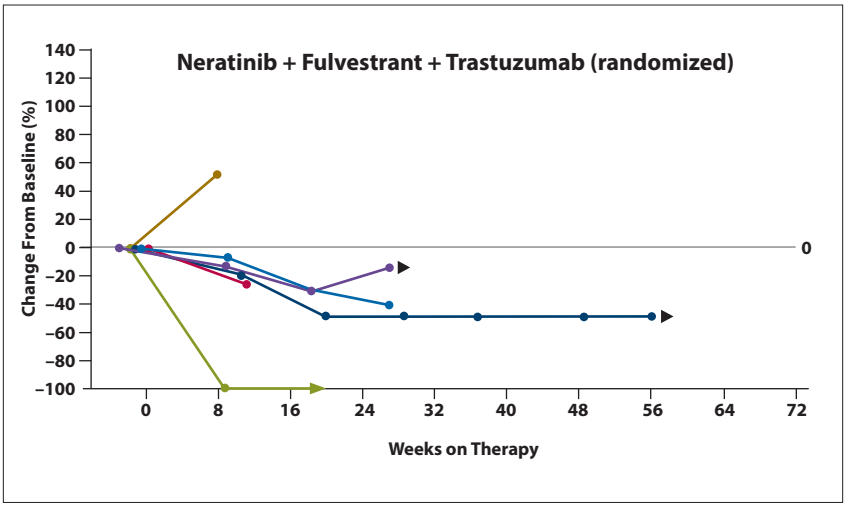

Figure 8. Response and duration of treatment among patients with hormone-receptor–positive breast tumors who received neratinib, fulvestrant, and trastuzumab in the SUMMIT trial. Each colored line represents a patient. An arrow indicates that the patient was still receiving treatment at the time of the report. Adapted from Jhaveri K et al. SABCS abstract GS4-10. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[5]

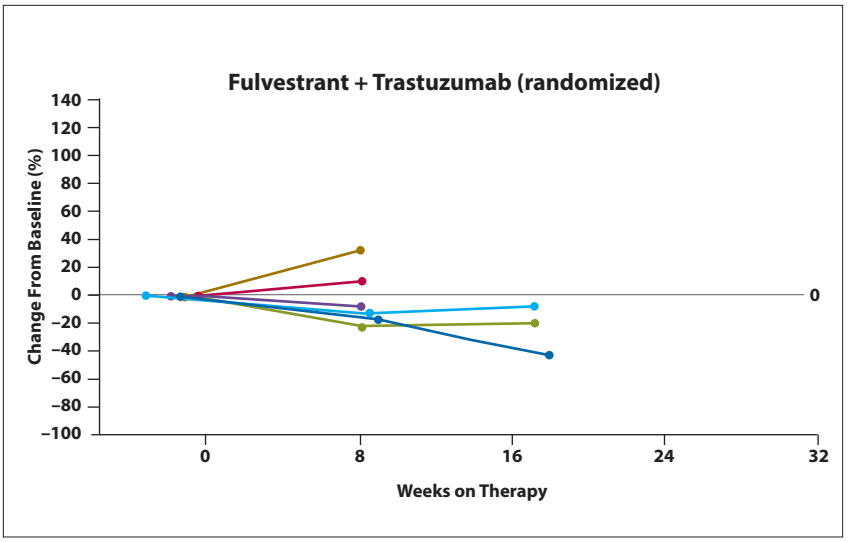

Figure 9. Response and duration of treatment among patients with hormone-receptor–positive breast tumors who received fulvestrant and trastuzumab in the SUMMIT trial. Each colored line represents a patient. Adapted from Jhaveri K et al. SABCS abstract GS4-10. Presented at: the 2021 San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, TX.[5]

cancer and of 2.0 months in 10 TNBC patients. Subsequently, fulvestrant was added to neratinib for the treatment of hormone receptor–positive/HER2-negative, *HER2*-mutant patients. The dual therapy yielded a PFS of 5.4 months in 39 patients. In the next stage of treatment for breast cancer patients in the trial, trastuzumab was added to neratinib plus fulvestrant. Inclusion criteria were updated to require prior treatment with a CDK4/6 inhibitor to reflect the current standard of care for patients with hormone receptor–positive disease.

There were greater decreases in tumor size and longer treatment durations among the patients treated with neratinib, fulvestrant, and trastuzumab vs fulvestrant and trastuzumab (Figures 8 and 9). Thirty-three patients with hormone-receptor–positive breast tumors received neratinib, fulvestrant, and trastuzumab.[5] The patients were heavily pretreated, with a median of 5 prior lines of therapy. Prior treatment with fulvestrant was reported in 82%. Triple-drug therapy yielded an ORR of 42.4%, including 1 CR (3.0%). The median PFS was 7.0 months (range, 4.2-12.7 months). Although patients were required to take loperamide as prophylaxis, diarrhea was the most common treatment-emergent AE among the 33 patients who received neratinib, fulvestrant, and trastuzumab. Any-grade diarrhea occurred in 90.9% of patients, and grade 3 diarrhea occurred in 45.5% of patients. (There were no cases of grade 4.) The median time to the first diarrhea event was 4 days (range, 1-68 days), and the median duration of each episode of grade 3 diarrhea was 2 days (range, 1-23 days). One patient (3.0%) discontinued study treatment owing to diarrhea, and 1 patient each discontinued owing to asthenia or nausea (6.0%).

Eighteen patients with TNBC in the SUMMIT trial received neratinib plus trastuzumab. The median number of prior lines of therapy was 3.5 (range, 1-7). The ORR was 33.3%, including 1 CR (5.6%), and the median PFS was 6.2 months (range, 2.1-8.2 months). The most common AE of any grade was diarrhea (88.9%). Grade 3 diarrhea was noted in 16.7% of patients, with no grade 4 diarrhea reported.

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Highlights in Metastatic Breast Cancer From the 2021 San Antonio Breast Cancer Symposium: Commentary

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Presentations in metastatic breast cancer at the 2021 San Antonio Breast Cancer Symposium (SABCS) provided important insights into management. New data were presented for treatments such as the selective estrogen receptor degraders (SERDs) amcenestrant and elacestrant, ribociclib combinations, pembrolizumab, datopotamab deruxtecan, trastuzumab deruxtecan (T-DXd), fulvestrant regimens, and nivolumab plus ipilimumab, as well as strategies for genomic profiling.

SERDs

The ongoing phase 1/2 AMEERA-1 trial is evaluating the oral SERD amcenestrant as monotherapy and in combination with targeted therapies in heavily pretreated postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. An analysis presented at the 2021 American Society of Clinical Oncology annual meeting provided data for the combination regimen of amcenestrant plus palbociclib.[1] This analysis showed a clinical benefit rate of 74% and an objective response rate of 34% among 35 evaluable patients enrolled in the dose-escalation phase (part C) and the dose-expansion phase (part D). At the 2021 SABCS, Dr Sarat Chandarlapaty presented updated data.[2] For the combination regimen, the dose of amcenestrant was reduced to 200 mg (vs 400 mg as monotherapy), given in combination with palbociclib at 125 mg, 21 days on, then 7 days off. The updated analysis showed that the combination was safe and effective. At a median follow-up of 14.8 months, the median progression-free survival (PFS) was 14.7 months (90% CI, 11.0-22.3). The objective response rate was 32.4%, and the clinical benefit rate was 73.5%.

These results underpin the ongoing phase 3 AMEERA-5 trial, which is comparing letrozole plus palbociclib vs amcenestrant plus palbociclib for the first-line treatment of patients with ER-positive/HER2-negative metastatic breast cancer.[3] The trial quickly completed accrual.

There were several posters that described different, ongoing arms of the AMEERA-1 trial. These arms are evaluating amcenestrant combination regimens in postmenopausal women with ER-positive/HER2-negative metastatic breast cancer. The regimen is amcenestrant plus alpelisib in arm 3 (parts F and G),[4] amcenestrant plus everolimus in arm 4 (part H),[5] and amcenestrant in combination with abemaciclib in arm 5 (parts J and K).[6] There are no data yet available for these arms. Amcenestrant is being developed broadly in the ER-positive, HER2-negative metastatic setting in combination with the key agents typically used in this population.

Elacestrant is another oral SERD. The phase 3 EMERALD study compared elacestrant vs investigator's choice of fulvestrant, anastrozole, letrozole, or exemestane in patients with ER-positive, HER2-negative metastatic breast cancer.[7] The study had 2 primary endpoints: PFS among all patients and PFS among patients with an *ESR1* mutation. In the intention-to-treat population, elacestrant reduced the risk of progression or death by 30%. This rate was higher among patients with an *ESR1* mutation, at 45%. Among all patients, elacestrant led to a statistically significant but modest improvement in median PFS of 2.79 months compared with 1.91 months with standard endocrine therapy.

Among patients with an *ESR1* mutation, the PFS rate at 12 months was 26.8% with elacestrant vs 8.2% with the standard of care. It appears that patients with mutant *ESR1* breast cancers that are sensitive to endocrine therapy derive more benefit from elacestrant than fulvestrant, based on the results of this head-to-head study. Elacestrant does not appear to overcome resistance in patients whose breast cancers are resistant to endocrine therapy, but rather prolongs the duration of benefit with ER-targeted therapy.

These encouraging results support the development of oral SERDs in breast cancer. These agents may be particularly helpful in patients whose breast cancers harbor an *ESR1* mutation, who represent an unmet need.

Ribociclib Combinations

I presented overall survival data in preplanned subsets from the randomized phase 3 MONALEESA-2 trial, which evaluated first-line ribociclib plus letrozole in postmenopausal patients with hormone receptor (HR)–positive, HER2-negative advanced breast cancer.[8] The analyses showed similar survival advantages regardless of prior endocrine therapy and among clinically relevant subsets such as patients with liver metastases, bone metastases, or lung and liver metastases. There was no subgroup that did not benefit from the addition of ribociclib to letrozole.

Dr Lisa Carey presented an analysis of the MONALEESA-2, -3, and -7 studies that focused on overall survival according to intrinsic subtype.[9] These studies evaluated ribociclib plus endocrine therapy in patients with HR-positive, HER2-negative advanced breast cancer. The analysis showed that the addition of ribociclib to endocrine therapy was beneficial in patients with luminal A, luminal B, and HER2-enriched breast cancer. The addition of ribociclib was not beneficial in the small fraction of patients with ER-positive, HER2-negative basal-like breast cancer.

It is not necessary to perform intrinsic subtyping on metastatic breast cancers, as this knowledge currently would not influence practice. However, these interesting data raise questions about how well the cyclin-dependent kinase 4/6 (CDK4/6) inhibitors work in patients with ER-positive, HER2-negative breast cancers that have the homologous recombination deficiency. Approximately 15% to 20% of HR-positive HER2-negative breast cancers may have this deficiency.

Pembrolizumab

A subgroup analysis of the phase 3 KEYNOTE-355 trial evaluated outcome according to patients' combined positive score (CPS).[10] A CPS of 10 or higher was reported in 38% of patients in the trial. The analyses showed that the addition of pembrolizumab to chemotherapy of physician's choice conferred a survival benefit only in those patients with a CPS of 10 or higher. Therefore, it is necessary to limit this treatment to these patients.

Datopotamab Deruxtecan

The single-arm phase 1/1b TROPION study showed very promising results for datopotamab deruxtecan in patients with triple-negative breast cancer.[11] This antibody-drug conjugate targets TROP2, and has the topoisomerase 1 payload (deruxtecan) for patients with triple-negative breast cancer. The objective response rate was 34% in a heavily pretreated population. Prior treatment with sacituzumab govitecan or another topoisomerase 1 inhibitor–based antibody-drug conjugate was reported in 30% of patients. When these patients were excluded from the analysis, the objective response rate increased to 54%. Datopotamab deruxtecan is therefore not fully cross-resistant with sacituzumab govitecan, an encouraging finding. An analysis of the overall population showed that the duration of disease control was not reached. The main adverse events were nausea, vomiting, stomatitis, and fatigue. The main toxicities seen with sacituzumab govitecan are myelosuppression and diarrhea.

Datopotamab deruxtecan had an encouraging level of activity in these generally heavily pretreated patients. A phase 3 trial is planned to evaluate datopotamab deruxtecan in patients with triple-negative breast cancer earlier in the course of their metastatic disease.

Trastuzumab Deruxtecan (T-DXd)

Dr Sara Hurvitz presented an update of data from the DESTINY-Breast03 trial that focused on patients with or without brain metastases.[12] This phase 3 study compared T-DXd vs trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer. Enrollment included patients with stable, treated brain metastases. Among this population, the PFS advantage seen with T-DXd vs TDM1 was maintained, with a hazard ratio of 0.25. This improvement is dramatic. The intracranial objective response rate was 63.9% for T-DXd vs 33.4% for T-DM1. These interesting data show that T-DXd has very promising activity in the brain.

ABSTRACT SUMMARY NIMBUS: A Phase 2 Trial of Nivolumab Plus Ipilimumab for Patients With Hypermutated *HER2*-Negative Metastatic Breast Cancer

The phase 2 NIMBUS trial evaluated treatment with nivolumab at 3 mg/kg every 2 weeks plus ipilimumab at 1 mg/kg every 6 weeks in patients with metastatic breast cancer with hypermutated *HER2* and no *HER2* amplification (Abstract GS2-10). Patients had received a median of 1.5 prior lines of therapy (range, 0-3), 70.1% of patients were negative for PD-L1 expression, and 83% of patients had a total mutation burden score of at least 9 and less than 14. The ORR was 16.7%, with no CRs. Among the 5 patients with an objective response, 3 patients had hormone receptor–positive disease and 2 patients had TNBC. After a median follow-up of 9.7 months, the median duration of response was 12.1 months, the median PFS was 1.4 months, and the median OS was 19.3 months. No new toxicities were identified, and no grade 4/5 AEs were reported.

Fulvestrant Combinations

The PADA-1 trial explored whether it is helpful to detect subclinical progression of disease with the emergence of an *ESR1* mutation in patients receiving an aromatase inhibitor plus palbociclib.[13] It may be possible to learn at an early time point when cancer cells become resistant to an aromatase inhibitor. The trial evaluated whether patients with HR-positive metastatic breast cancer found to have mutant *ESR1* on circulating tumor DNA (ctDNA) and no synchronous progressive disease would benefit if treatment with an aromatase inhibitor and palbociclib were switched to fulvestrant plus palbociclib. This strategy improved PFS by 6.2 months compared with continuing an aromatase inhibitor plus palbociclib until disease progression. However, the overall PFS improvement with the early-switch strategy was only 2.7 months compared with patients who switched to fulvestrant plus palbociclib when scans showed progression. This improvement is of questionable clinical utility. We await results of survival analyses from the PADA-1 trial, which should indicate whether an earlier change in therapy will improve survival. Currently, it is not clear whether the 2.7-month improvement in median PFS justifies an early switch to fulvestrant, while continuing the CDK4/6 inhibitor, upon the emergence of a ctDNA-detected *ESR1* mutation.

Dr Komal Jhaveri presented updated results from the SUMMIT trial, which evaluated the combination of neratinib, fulvestrant, and trastuzumab in patients with HR-positive, *HER2*-mutant metastatic breast cancer and neratinib plus trastuzumab among patients with *HER2*-mutated metastatic triple-negative disease.[14] The response rate was 42.4% in the HR-positive, HER2-negative, *HER2*-mutant cohort, with a median PFS of 7.0 months. Among patients with triple-negative breast cancer, which is associated with substantial intratumoral heterogeneity, the response rate was 33.3%, with a median PFS of 6.2 months. With such high levels of activity, these regimens will likely become a new standard of care for patients with *HER2*-mutant metastatic breast cancer.

Nivolumab Plus Ipilimumab

The phase 2 NIMBUS trial is evaluating nivolumab plus ipilimumab among patients with HER2-negative metastatic breast cancer, regardless of receptor status.[15] Most patients (70%) were HR-positive, and the remainder had triple-negative breast cancer. All patients' cancers had a tumor mutation burden of at least 9 mutations per megabase. Among all patients, the objective response rate was 16.7%. Among patients with very high tumor mutation burden (≥14 mutations per megabase) cancers, the response rate was 60%. PFS was also substantially improved among patients with very high tumor mutation burden. Among these patients with cancers that have very high tumor mutation burden, the median PFS was 9.5 months. In comparison, the median PFS was 1.4 months in patients with fewer than 14 mutations per megabase. The numbers of patients were small; only 5 patients had 14 or more mutations per megabase. The benefit with ipilimumab plus nivolumab seen in patients with high tumor-mutation–burden cancers raises the question of whether monotherapy with a checkpoint inhibitor would be equally effective. Pembrolizumab is approved for patients with metastatic breast cancer with high tumor-mutation–burden cancers. A randomized clinical trial would be needed to confirm whether the addition of the CTLA-4 agonist is additionally beneficial.

Genomic Profiling

The phase 2 SAFIR02 study evaluated the clinical utility of genomic profiling among patients with triple-negative or HR-positive/HER2-negative metastatic breast cancer.[16] Patients who were responding to standard chemotherapy were randomly assigned to continue the same chemotherapy or to switch to a targeted agent that, in some cases, matched a genomic alteration in the patients' cancers. The study evaluated effectiveness based on categories established by the European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets (ESCAT), which separate genomic alteration–drug matches into tiers based on levels of evidence.[17] There was an observed improvement in PFS in favor of switching to a targeted therapy, but only with agents categorized as ESCAT tier 1 (the alteration–drug match is associated with improved outcome in clinical trials) or tier 2 (the match is associated with antitumor activity, but the magnitude of benefit is unknown). In patients who received tier 1/2 agents, the median PFS improved from 2.8 months with maintenance chemotherapy to 9.1 months with targeted therapy. In the intention-to-treat population of patients, some of whom received non–tier 1/2 targeted therapies, there was no significant improvement in PFS.

These results are interesting. When the treatment plan involves targeting a genomic alteration, oncologists should ensure there is a high level of evidence supporting effectiveness of the targeted agent in the metastatic setting.

Disclosure

Dr O'Shaughnessy has received honoraria for consulting and advisory boards from AbbVie, Agendia, Amgen Biotechnology, AstraZeneca, Daiichi Sankyo, Bristol Myers Squibb, Eisai, Genentech, Gilead, Lilly, Merck, Myriad Genetics, Exact Sciences, Novartis, Odonate Therapeutics, Pfizer, Puma Biotechnology, Roche, Tempus, Theranostics Health, and Seagen.

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