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Highlights in Metastatic Breast Cancer from the 2022 San Antonio Breast Cancer Symposium

A Review of Selected Presentations from SABCS 2022 • San Antonio, TX • December 6-10, 2022

Special Reporting on:

- EMERALD Phase 3 Trial of Elacestrant Versus Standard of Care Endocrine Therapy in Patients With ER+/HER2- Metastatic Breast Cancer: Updated Results by Duration of Prior CDK4/6i in Metastatic Setting
- Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2– Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy
- Sacituzumab Govitecan vs Treatment of Physician's Choice: Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients With HR+/HER2– Metastatic Breast Cancer
- Trastuzumab Deruxtecan vs Physician's Choice in Patients With HER2+ Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab Emtansine: Primary Results of the Randomized, Phase 3 Study DESTINY-Breast02
- Capivasertib and Fulvestrant for Patients With Aromatase Inhibitor-Resistant Hormone Receptor-Positive/ Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Phase III CAPItello-291 Trial

PLUS Additional Abstract Summaries

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EMERALD Phase 3 Trial of Elacestrant Versus Standard of Care Endocrine Therapy in Patients With ER+/HER2- Metastatic Breast Cancer: Updated Results by Duration of Prior CDK4/6i in Metastatic Setting

In breast tumors that express the estrogen receptor (ER), excess growth is mediated by estrogen binding to the receptor. For patients with ER-positive/human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer, standard first-line therapy comprises endocrine therapy plus a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor.[1] However, tumors often develop resistance to endocrine therapy through mutation in genes such as estrogen receptor 1 (*ESR1*). Novel therapies for hormone-resistant disease with improved efficacy and a tolerable safety profile are desired.

Elacestrant is a next-generation selective estrogen receptor downregulator (SERD) that causes degradation of the ER, thus inhibiting ER-mediated growth. The phase 3 EMERALD trial investigated elacestrant vs standard of care (SOC) therapy in patients with ER-positive/HER2-negative advanced or metastatic breast cancer.[2] In this open-label, international trial, eligible patients were men or postmenopausal women who had experienced disease progression during or after treatment with endocrine therapy and a CDK4/6 inhibitor. Patients who had received 0 or 1 prior lines of chemotherapy were allowed, and prior therapy with fulvestrant was also allowed. Patients were randomized 1:1 to receive oral elacestrant (400 mg daily) or single-agent endocrine therapy, consisting of fulvestrant, anastrozole, letrozole, or exemestane. The 2 primary endpoints were progression-free survival (PFS) in all patients and PFS in patients with tumors characterized by *ESR1* mutation.

The EMERALD trial randomized 239 patients to each arm. Baseline characteristics were well balanced between the 2 arms. *ESR1* mutation was noted in 115 patients (48%) in the elacestrant arm and 113 patients (47%) in the SOC arm. Key baseline characteristics in the elacestrant vs SOC arms included visceral metastases (68% vs 71%), 2 prior lines of endocrine therapy (46% vs 41%), prior fulvestrant therapy (29% vs 31%), and 1 prior line of chemotherapy (20% vs 25%), respectively. Initial results revealed a significant improvement in median PFS with elacestrant vs SOC therapy (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.55-0.88; *P*=.002).

In updated results presented at the 2022 San Antonio Breast Cancer Symposium (SABCS), elacestrant

Table 1. EMERALD Trial: Progression-Free Survival by Duration of CDK4/6i for All Patients

Duration on CDK4/6i in the metastatic setting						
	At least 6 months (87.5%)		**At least 12 months (66.7%)**		**At least 18 months (46.7%)**	
	Elacestrant (n=202)	SOC Hormonal Therapy (n=205)	Elacestrant (n=150)	SOC Hormonal Therapy (n=160)	Elacestrant (n-98)	SOC Hormonal Therapy (n=119)
Median PFS, months (95% CI)	**2.79** (1.94-3.78)	**1.91** (1.87-2.14)	**3.78** (2.33-6.51)	**1.91** (1.87-3.58)	**5.45** (2.33-8.61)	**3.29** (1.87-3.71)
PFS rate at 6 months, % (95% CI)	34.40 (26.70-42.10)	19.88 (12.99-26.76)	41.56 (32.30-50.81)	21.72 (13.65-29.79)	44.72 (33.24-56.20)	25.12 (15.13-35.10)
PFS rate at 12 months, % (95% CI)	21.00 (13.57-28.43)	6.42 (0.75-12.09)	25.64 (16.49-34.80)	7.38 (0.82-13.94)	26.70 (15.61-37.80)	8.23 (0.00-17.07)
PFS rate at 18 months, % (95% CI)	16.24 (8.75-23.74)	3.21 (0.00-8.48)	19.34 (9.98-28.70)	3.69 (0.00-9.77)	21.03 (9.82-32.23)	4.11 (0.00-11.33)
Hazard ratio (95% CI)	**0.688** (0.535-0.884)		**0.613** (0.453-0.828)		**0.703** (0.482-1.019)	

CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; PFS, progression-free survival; SOC, standard of care (investigator's choice).
Presented at the 2022 San Antonio Breast Cancer Symposium, December 6-10, 2022, San Antonio, Texas.[3]

Table 2. EMERALD Trial: Progression-Free Survival by Duration of CDK4/6i for Patients With *ESR1*-mut Tumors

Duration on CDK4/6i in the metastatic setting						
	At least 6 months (92.3%)		**At least 12 months (71.6%)**		**At least 18 months (50.0%)**	
	Elacestrant (n=103)	SOC Hormonal Therapy (n=102)	Elacestrant (n=78)	SOC Hormonal Therapy (n=81)	Elacestrant (n=55)	SOC Hormonal Therapy (n=56)
Median PFS, months (95% CI)	**4.14** (2.20-7.79)	**1.87** (1.87-3.29)	**8.61** (4.14-10.84)	**1.91** (1.87-3.68)	**8.61** (5.45-16.89)	**2.10** (1.87-3.75)
PFS rate at 6 months, % (95% CI)	42.43 (31.15-53.71)	19.15 (9.95-28.35)	55.81 (42.69-68.94)	22.66 (11.63-33.69)	58.57 (43.02-74.12)	27.06 (13.05-41.07)
PFS rate at 12 months, % (95% CI)	26.02 (15.12-36.92)	6.45 (0.00-13.65)	35.81 (21.84-49.78)	8.39 (0.00-17.66)	35.79 (19.54-52.05)	7.73 (0.00-20.20)
PFS rate at 18 months, % (95% CI)	20.70 (9.77-31.63)	0.00	28.49 (14.08-42.89)	0.00	30.68 (13.94-47.42)	0.00
Hazard ratio (95% CI)	**0.517** (0.361-0.738)		**0.410** (0.262-0.634)		**0.466** (0.270-0.791)	

CDK4/6i, cyclin-dependent kinase 4 and 6 inhibitor; CI, confidence interval; PFS, progression-free survival; SOC, standard of care (investigator's choice). Presented at the 2022 San Antonio Breast Cancer Symposium, December 6-10, 2022, San Antonio, Texas.[3]

continued to yield superior survival outcomes at specified landmark timepoints compared with SOC.[3] The median PFS was evaluated in subgroups based on the duration of prior therapy with a CDK4/6 inhibitor. A consistent benefit was observed across all subgroups with elacestrant vs SOC, regardless of the duration of prior exposure to CDK4/6 inhibitor treatment (Table 1). In patients with at least 6 months of prior CDK4/6 inhibitor therapy, the median PFS with elacestrant vs SOC, respectively, was 2.79 vs 1.91 months (HR, 0.688; 95% CI, 0.535-0.884), and among patients with *ESR1* mutation, the median PFS was 4.14 months vs 1.87 months (HR, 0.517; 95% CI, 0.361-0.738; Table 2). Similar results were observed in subgroups with at least 12 months or at least 18 months of prior exposure to a CDK4/6 inhibitor. No new safety signals were raised.

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Primary Results From the Randomized Phase II RIGHT Choice Trial of Premenopausal Patients With Aggressive HR+/HER2− Advanced Breast Cancer Treated With Ribociclib + Endocrine Therapy vs Physician's Choice Combination Chemotherapy

Ribociclib is a CDK4/6 inhibitor that has demonstrated prolonged PFS and overall survival (OS) in combination with endocrine therapy vs endocrine therapy alone in phase 3 trials of patients with advanced hormone receptor (HR)–positive/HER2-negative breast cancer.[1] The open-label, international, phase 2 RIGHT Choice trial investigated ribociclib plus endocrine therapy vs the investigator's choice of combination chemotherapy (CC) in HR-positive/HER2-negative advanced breast cancer.[2] Eligible patients were pre- or perimenopausal women with aggressive, HER2-negative breast cancer, at least 10% expression of the ER, and measurable disease based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[3] In addition to goserelin, all patients in the experimental arm received ribociclib (600 mg daily, 3 weeks on followed

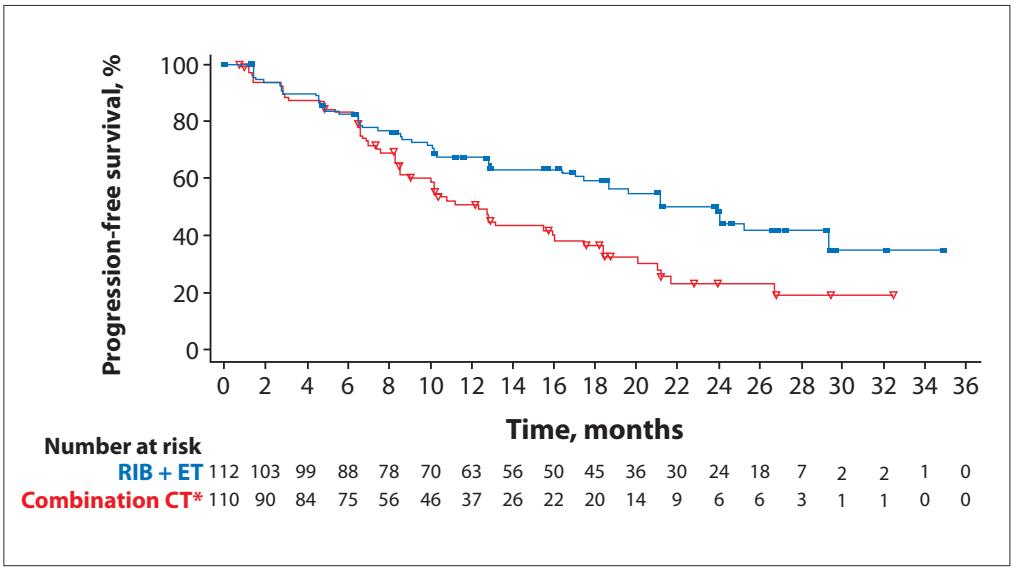

Figure 1. RIGHT Choice trial: progression-free survival among patients with aggressive, hormone receptor–positive, human epidemical growth factor receptor–negative, advanced breast cancer treated with first-line ribociclib (RIB) + endocrine therapy (ET) or combination chemotherapy (CT). Adapted from a presentation at the 2022 San Antonio Breast Cancer Symposium, December 6-10, 2022, San Antonio, Texas.[2]

by 1 week off) plus letrozole or anastrozole. Patients in the control arm received the investigator's choice of docetaxel plus capecitabine, paclitaxel plus gemcitabine, or capecitabine plus vinorelbine. The primary endpoint was locally assessed PFS based on RECIST 1.1. A prespecified analysis of PFS was planned after disease progression or death in approximately 110 patients.

The RIGHT Choice study randomized 112 patients into the ribociclib plus endocrine therapy arm and 110 patients into the CC arm. Baseline characteristics were well balanced between the 2 arms. In the experimental vs the comparator arm, grade 3 histology was noted in 31% vs 26% of patients; at least 50% ER expression was observed in 85% vs 86% of patients; symptomatic visceral metastasis was observed in 66% vs 69% of patients; and visceral crisis was noted in 55% vs 50% of patients, respectively. After a median follow-up of 24.1 months, treatment was ongoing in 46% vs 24% of patients in the experimental vs the comparator arm, respectively. The combination of ribociclib plus endocrine therapy yielded a significant and clinically meaningful increase in median PFS benefit of approximately 1 year compared with CC (24.0 vs 12.3 months; HR, 0.54; 95% CI, 0.36-0.79; $P<.007$; Figure 1). Subgroup analysis revealed a significant improvement in median PFS with the addition of ribociclib to endocrine therapy vs CC, including subgroups with a disease-free interval of at least 2 years (HR, 0.52; 95% CI, 0.34-0.78), with liver metastases (HR, 0.60; 95% CI, 0.36-1.01), and with at least 50% ER expression (HR, 0.54; 95% CI, 0.35-0.82). Treatment with ribociclib plus endocrine therapy also yielded a longer time to treatment failure (HR, 0.45; 95% CI, 0.32-0.63). No new safety signals arose among patients treated with ribociclib plus endocrine therapy. Treatment with ribociclib plus endocrine therapy was associated with fewer dose reductions and fewer treatment-related adverse events (AEs) than with CC.

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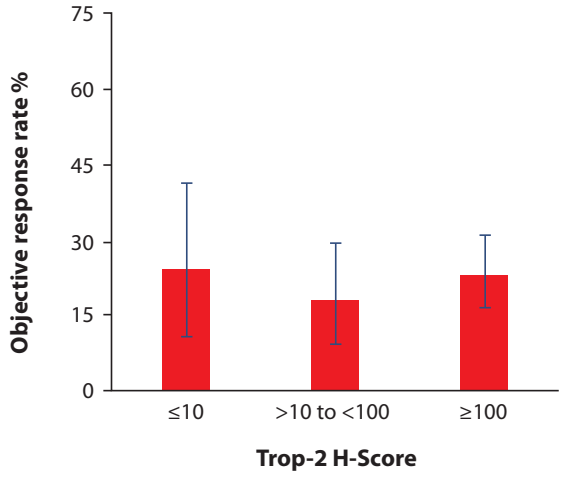
Sacituzumab Govitecan vs Treatment of Physician's Choice: Efficacy by Trop-2 Expression in the TROPiCS-02 Study of Patients With HR+/HER2– Metastatic Breast Cancer

Sacituzumab govitecan is a first-in-class antibody drug conjugate (ADC) that binds to Trop-2, an antigen that is highly expressed across breast tumor subtypes. The ADC comprises the SN-38 topoisomerase inhibitor linked to the antibody by a pH-sensitive linker. The international phase 3 TROPiCS-02 trial



Trop2 expression, H-score	ORR, n (%)	CBR, n (%)*	Median DOR, mo (95% CI)
≤10 (n=34)	8 (24)	11 (32)	7.5 (2.5-NR)
>10 to <100 (n=62)	11 (18)	17 (27)	7.4 (4.1-NR)
≥100 (n-142)	33 (23)	55 (39)	8.5 (5.9-16.9)

*Response was also observed in the small Trop-2 negative subgroup (H-score=0, n=10).

Figure 2. TROPiCS-02 trial: sacituzumab govitecan versus treatment of physician's choice: objective response rates. CBR, clinical benefit rate; CI, confidence interval; DOR, duration of response; H-score, histochemical score; ORR, objective response rate. Presented at the 2022 San Antonio Breast Cancer Symposium, December 6–10, 2022, San Antonio, Texas.[4]

investigated sacituzumab govitecan vs treatment of physician's choice (TPC) in patients with unresectable, locally advanced or metastatic HR-positive/HER2-negative breast cancer.[1,2] Eligibility criteria included disease progression after treatment with at least 1 endocrine therapy, 1 taxane, and 1 CDK4/6 inhibitor in any setting; prior treatment with 2 to 4 lines of chemotherapy for their metastatic disease; and measurable disease by RECIST 1.1.[3] After stratification, 543 patients were randomized 1:1 to receive either sacituzumab govitecan (10 mg/kg on days 1 and 8) in 21-day cycles or TPC consisting of capecitabine, vinorelbine, gemcitabine, or eribulin. The primary endpoint was PFS based on blinded independent central review.

In the intention-to-treat population, the median PFS was 5.5 months (95% CI, 4.2-7.0) with sacituzumab govitecan vs 4.0 months (95% CI, 3.1-4.4) with TPC (HR, 0.66; 95% CI, 0.53-0.83; *P*=.0003). The median OS was also significantly prolonged with sacituzumab govitecan compared with TPC (14.4 vs 11.2 months; HR, 0.79; 95% CI, 0.65-0.96; *P*=.020). Patients in all Trop-2 subgroups responded to sacituzumab govitecan, including those with very low Trop-2 expression (H-score ≤10; Figure 2)

An exploratory, post hoc analysis was conducted to evaluate the potential relationship between Trop-2 expression and efficacy with sacituzumab govitecan vs TPC among patients in the TROPiCS-02 trial.[4] Levels of Trop-2 expression were determined by means of a validated research immunohistochemistry (IHC) assay. Tumor samples with IHC data were available from 238 patients (88%) in the sacituzumab govitecan arm and 224 patients (83%) in the TPC arm. The majority of patients had an IHC expression level (H-score) of at least 100 (58%), and only 5% of patients had an H-score of 0. Among all subgroups of patients based on H-score, the median PFS was superior with sacituzumab govitecan compared with TPC, even in patients with very low expression levels of Trop-2. Owing to small subgroup sizes and the retrospective nature of the analysis, the results must be interpreted with caution. In this patient setting, treatment with sacituzumab govitecan yielded a manageable safety profile; safety outcomes did not appear to be affected by expression levels of Trop-2.

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Trastuzumab Deruxtecan vs Physician's Choice in Patients With HER2+ Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab Emtansine: Primary Results of the Randomized, Phase 3 Study DESTINY-Breast02

Trastuzumab deruxtecan (T-DXd) is an ADC that consists of a humanized anti-HER2 antibody covalently attached to a topoisomerase I inhibitor by a cleavable linker.[1-3] The phase 3 DESTINY-Breast02 trial investigated T-DXd monotherapy vs TPC in patients with HER2-positive, unresectable or metastatic breast cancer.[4] In this multicenter, open-label trial, eligible patients received prior treatment with trastuzumab emtansine and had radiographic evidence of disease progression during or after the most recent therapy. Central confirmation of disease status was a requirement of enrollment. Patients were randomized 2:1 to receive T-DXd (5.4 mg/kg every 3 weeks) or TPC, consisting of trastuzumab or lapatinib, in combination with capecitabine. The primary endpoint was PFS determined by blinded independent central review.

The study randomized 406 patients into the T-DXd arm and 202 patients into the TPC arm. Baseline characteristics were well balanced between the T-DXd and TPC arms, based on median age (54 vs 55 years), HER2 status of IHC 3+ (80% vs 79%), brain metastases (18% in both arms), and presence of visceral disease (78% vs 79%), respectively. Patients in both arms had received a median of 2 prior lines of systemic therapy in the metastatic setting (range, 0-10 lines in the T-DXd arm and 1-8 lines in the TPC arm). Analysis of the primary endpoint yielded a median PFS of 17.8 months (range, 14.3-20.8 months) with T-DXd vs 6.9 months (range, 5.5-8.4 months) with TPC (HR, 0.3589; 95% CI, 0.2840-0.4535; *P*<.000001). Treatment with T-DXd was superior to TPC in all subgroups examined. Analysis of the median OS revealed a significant reduction in the risk of death with T-DXd compared with TPC (39.2 vs 26.5 months; HR, 0.6575; 95% CI, 0.5023-0.8605; *P*=.0021), as was the independently confirmed overall response rate (ORR) (69.7% vs 29.2%; *P*<.0001). The overall safety profile of T-DXd monotherapy was consistent with results from prior studies. Drug-related interstitial lung disease was identified in 10.4% of patients, most of which was low grade; however, 2 patients (0.5%) experienced fatal interstitial lung disease that was considered related to treatment with T-DXd.

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Capivasertib and Fulvestrant for Patients With Aromatase Inhibitor–Resistant Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: Results From the Phase III CAPItello-291 Trial

Capivasertib is a selective inhibitor of AKT1, AKT2, and AKT3 isoforms of AKT that are key elements of the PI3K/AKT signaling pathway.[1] The phase 3 CAPItello-291 trial investigated capivasertib vs placebo combined with fulvestrant in patients with HR-positive/HER2-negative advanced breast cancer.[2] The double-blind study enrolled patients who had experienced disease recurrence during or within 12 months of treatment with an aromatase inhibitor. Study participants had received up to 2 prior lines of endocrine therapy and no more than 1 prior line of chemotherapy for their advanced breast cancer. The study required at least 51% of enrolled patients to have prior exposure to a CDK4/6 inhibitor, although prior therapy with a SERD, mechanistic target of rapamycin inhibitor, phosphoinositide 3-kinase (PI3K) inhibitor, or AKT inhibitor was not allowed. Fulvestrant (500 mg) was administered on days 1 and 15 of cycle 1, then on day 1 every 4

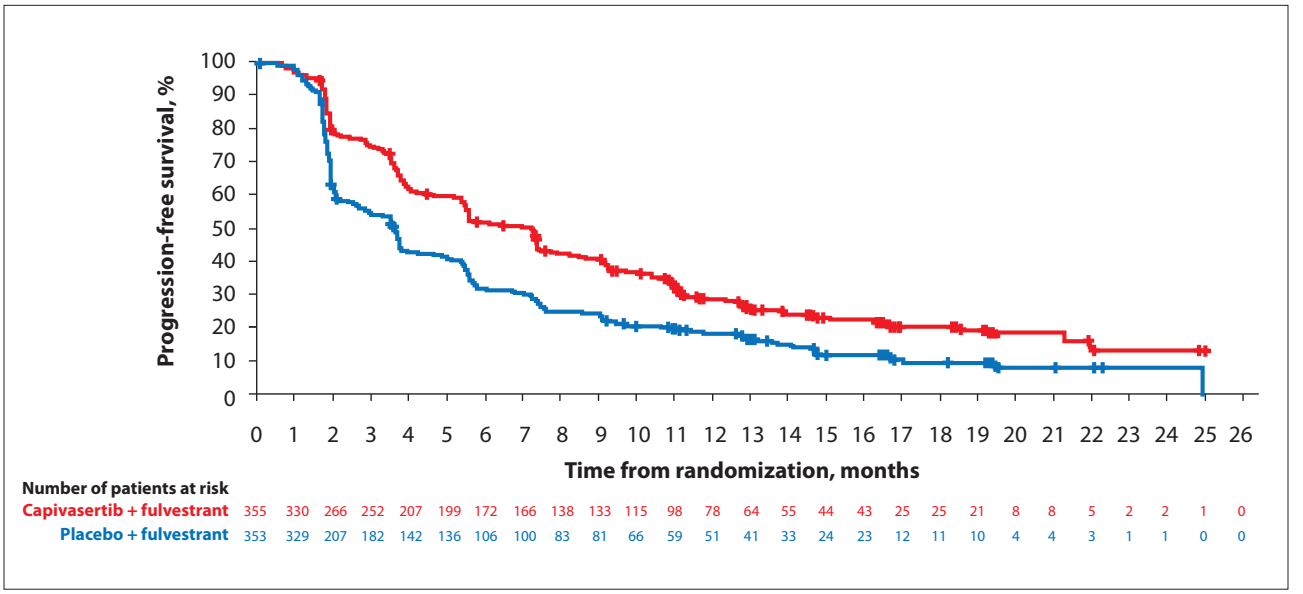

Figure 3. CAPItello trial: capivasertib + fulvestrant versus placebo + fulvestrant: investigator-assessed progression-free survival in the overall population (dual-primary endpoint). Adapted from a presentation at the 2022 San Antonio Breast Cancer Symposium, December 6-10, 2022, San Antonio, Texas.[2]

weeks. Patients in the experimental arm received capivasertib (400 mg twice daily) on a schedule of 4 days on, 3 days off, and patients in the comparator arm received matched placebo. The trial had 2 primary endpoints: PFS in the overall study population and PFS in the cohort of patients with mutation in PTEN, PI3K, or AKT1.

The trial randomized 355 patients to the capivasertib plus fulvestrant arm and 353 patients to the placebo plus fulvestrant arm. Patients had a median age of 58 to 59 years (range, 26-90 years). Key baseline characteristics in the capivasertib vs the placebo arms included visceral metastases (67% vs 68%) and primary endocrine resistance (36% vs 38%), respectively, and 69% of patients in each arm had received prior CDK4/6 inhibitor therapy. Mutation in PTEN, PI3K, or AKT1 was detected in 44% of patients in the capivasertib arm vs 38% in the placebo arm. The investigator-assessed median PFS in the overall study population was 7.2 months with capivasertib vs 3.6 months with placebo (HR, 0.60; 95% CI, 0.51-0.71; *P*<.001). Among patients with AKT pathway alterations (these subgroups included AKT1 only; PTEN only; PIK3CA only; PIK3CA and AK1; or PIK3CA and PTEN), investigator-assessed median PFS was also superior with capivasertib vs placebo (7.3 vs 3.1 months; HR, 0.50; 95% CI, 0.38-0.65; *P*<.001). In the overall population, prespecified subgroup analysis underscored the superiority of fulvestrant plus capivasertib vs fulvestrant alone, particularly in patients with visceral metastases (HR, 0.61; 95% CI, 0.48-0.78; Figure 3) and in patients with prior exposure to a CDK4/6 inhibitor (HR, 0.62; 95% CI, 0.51-0.75). The safety profile of capivasertib plus fulvestrant was consistent with results from prior studies and was comparable in patients with or without alteration in the AKT pathway.

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Determination of HER2-Low Status in Tumors of Patients With Unresectable and/or Metastatic Breast Cancer in DESTINY-Breast04

In the DESTINY-Breast04 trial, T-DXd significantly increased the median PFS and median OS compared with TPC in patients with metastatic breast cancer and a low level of HER2 expression (HER2-low). A post hoc analysis was conducted to investigate the HER2 scoring concordance between historical and central testing and to determine the efficacy of T-DXd based on tumor samples characterized by HER2-low status in

the DESTINY-Breast04 trial (Abstract HER2-18). HER2-low was defined as IHC1+ or IHC2+ and negative by in situ hybridization. Historical and central results were available for 1108 samples. Approximately one-third of tumor samples were from primary sites. Among 1060 samples deemed HER2-low by historical or local testing, 823 (78%) were confirmed as HER2-low by central testing using the investigational PATHWAY 4B5 IHC assay. The percentage scoring agreement by local vs central testing was the highest in North America (0.85; 95% CI, 0.81-0.90) and lowest in China (0.68; 95% CI, 0.59-0.76). T-DXd efficacy was superior to TPC in subgroups based on tumor location (primary vs metastatic), specimen type (biopsy vs excision/resection), collection time (archival vs new tissue), and specimen collection year (2013 or earlier; 2014-2018; 2019 or later).

Trastuzumab Deruxtecan vs Treatment of Physician's Choice in Patients With HER2-Low Unresectable and/or Metastatic Breast Cancer: Subgroup Analyses From DESTINY-Breast04

Outcomes in patients from the DESTINY-Breast04 trial were assessed in subgroups based on patient history and disease characteristics (Abstract P1-11-01). The study included 557 patients with metastatic, HER2-low breast cancer who were randomized 2:1 to therapy with T-DXd or TPC. Based on median PFS, treatment with T-DXd was consistently superior to TPC in subgroups, regardless of prior CDK4/6 inhibitor exposure, disease burden, rate of disease progression, HER2 IHC status, number of prior lines of chemotherapy, prior exposure to anthracycline, or age. PFS with T-DXd was superior to TPC in patients with central nervous system metastasis at baseline; however, the subgroup contained only 22 patients and the results were not significant (HR, 0.71; 95% CI, 0.28-1.80). Among patients with HR-positive disease, the median PFS was superior with T-DXd vs TPC among patients with prior exposure to a CDK4/6 inhibitor (HR, 0.5532; 95% CI, 0.4166-0.7347) and in patients without prior exposure to a CDK4/6 inhibitor (HR, 0.4211; 95% CI, 0.2751-0.6446). In all subgroups examined, T-DXd yielded ORRs of 50% or greater and was superior to TPC.

Results From ALICE: Atezolizumab Combined With Immunogenic Chemotherapy in Patients With Metastatic Triple Negative Breast Cancer, a Randomized Phase IIb Trial

The double-blind phase 2b ALICE trial investigated atezolizumab plus immunogenic chemotherapy in patients with metastatic triple-negative breast cancer (TNBC; Abstract PD11-11). Atezolizumab was administered at 840 mg every 2 weeks. Chemotherapy consisted of pegylated liposomal doxorubicin (20 mg/m^2 every 2 weeks) plus low-dose, metronomic cyclophosphamide (50 mg daily, 2 weeks on and 2 weeks off). The study randomized 42 patients to receive atezolizumab plus chemotherapy and 28 patients to placebo plus chemotherapy. The median PFS was superior with atezolizumab vs placebo, both in the per protocol population (36 vs 23 patients, respectively; HR, 0.57; 95% CI, 0.33-0.99; *P*=.047) and in the full analysis set of patients (40 vs 28 patients; HR, 0.56; 95% CI, 0.33-0.95; *P*=.033). The median PFS was superior with atezolizumab vs placebo among patients with programmed death-ligand 1 (PD-L1)–positive tumors (HR, 0.65; 95% CI, 0.27-1.54) and among patients with PD-L1–negative tumors (HR, 0.57; 95% CI, 0.27-1.21). The combination of atezolizumab, pegylated liposomal doxorubicin, and cyclophosphamide was tolerable, with no new safety concerns.

Palbociclib After CDK4/6i and Endocrine Therapy (PACE): A Randomized Phase II Study of Fulvestrant, Palbociclib, and Avelumab for Endocrine Pretreated ER+/HER2- Metastatic Breast Cancer

The phase 2 PACE trial investigated fulvestrant monotherapy (Arm A), fulvestrant and palbociclib (Arm B), or fulvestrant, palbociclib, and the PD-L1 inhibitor avelumab (Arm C) in patients with HR-positive/HER2-negative metastatic breast cancer (Abstract GS3-06). Dose reduction of fulvestrant or avelumab was not permitted. Eligible patients had experienced stable disease and/or disease progression while receiv-

ing at least 6 months of treatment with a CDK4/6 inhibitor plus endocrine therapy. Patients were considered endocrine resistant if their disease had recurred less than one year after adjuvant endocrine therapy (n=58). Endocrine-sensitive patients (n=160) had either progressed to metastatic disease or had a disease recurrence more than one year after prior endocrine therapy. The trial randomized 220 patients 1:2:1 into Arms A, B, and C. After a median follow-up of 23.6 months, the median PFS was not significantly different in Arm A vs Arm B (4.8 vs 4.6 months, respectively; *P*=.62). The addition of avelumab increased the median PFS to 8.1 months, but the result did not reach significance (*P*=.23). No new safety concerns were raised. There were no episodes of febrile neutropenia and no grade 5 toxicity events, and rates of immune-related toxicity events were low. The study showed that continuing treatment with palbociclib after disease progression did not provide added efficacy vs fulvestrant alone.

DORA: A Phase II, Multicenter, International, Non-Comparator Study of Olaparib +/- Durvalumab as a Chemotherapy-Free Maintenance Strategy in Platinum-Treated Advanced Triple-Negative Breast Cancer

The phase 2 DORA trial investigated olaparib (300 mg twice daily) with or without durvalumab (1500 mg every 4 weeks) as maintenance treatment in patients with TNBC who had received prior platinum therapy (Abstract PD11-12). Eligible patients had experienced a clinical benefit of stable disease, partial response (PR), or complete response (CR) after platinum-based therapy as first- or second-line treatment. The international trial randomized 23 patients to the olaparib monotherapy arm and 23 patients to the olaparib plus durvalumab arm. After a median follow-up of 9.8 months, the median PFS was 4.0 months (95% CI, 2.6-6.1; *P*=.0023 vs historical control) with olaparib alone and was 6.1 months (95% CI, 3.7-10.1; *P*<.0001 vs historical control) with olaparib plus durvalumab. Among patients who experienced a CR or PR with prior platinum therapy, the median PFS was 5.4 months (95% CI, 3.0-9.7) with olaparib and 7.6 months (95% CI, 3.8-15.1) with olaparib plus durvalumab. Grades 3 or 4 AEs were observed in 9 patients (39%) in the olaparib arm and 8 patients (36%) in the olaparib plus durvalumab arm. No new safety signals were raised. This treatment strategy is undergoing further evaluation in TNBC patients in the phase 2/3 KEYLYNK-009 trial (NCT04191135).

Long-Term and Very-Long-Term Disease Control in Patients From BYLieve Study Cohort A With PIK3CA-Mutant, Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative, Advanced Breast Cancer

The open-label phase 2 BYLieve trial investigated alpelisib plus endocrine therapy in patients with HR-positive/HER2-negative advanced breast cancer harboring *PIK3CA* mutation (Abstract PD13-06). Patients in Cohort A had received a CDK4/6 inhibitor plus an aromatase inhibitor as the most recent prior therapy, and these patients received study therapy consisting of alpelisib (300 mg daily) plus fulvestrant (500 mg). Long-term (LT) disease control was defined as a PFS of at least 12 months, and very long-term (VLT) disease control was defined as a PFS of at least 18 months. Patients in Cohort A yielded a median PFS of 7.26 months. Among 121 patients in Cohort A, 31 patients (25.6%) achieved LT disease control, with a median PFS of 24.8 months (95% CI, 18.2-30.1) and 20 patients (16.5%) achieved VLT disease control, with a median PFS of 29.4 months (95% CI, 22.1-33.1). Based on multivariate analysis, positive prognostic factors associated with LT or VLT disease control included metastasis in the bone only; longer duration of prior endocrine therapy; no detectable *PIK3CA* mutation in baseline circulating tumor DNA; longer duration from first to last progression; and radiotherapy as the last treatment. Five negative prognostic factors were also identified. Patients who had a high predicted probability of achieving LT disease control had a median PFS of 19.3 months (95% CI, 16.7-28.0), and patients with a low predicted probability of achieving LT disease control had a median PFS of 5.5 months (95% CI, 4.2-6.1).

Trastuzumab Deruxtecan + Durvalumab as First-Line Treatment for Unresectable Locally Advanced/Metastatic Hormone Receptor-Negative, HER2-Low Breast Cancer: Updated Results From BEGONIA, a Phase 1b/2 Study

The phase 1b/2 BEGONIA study investigated the efficacy and safety of durvalumab combined with other therapies as first-line treatment in patients with advanced or metastatic TNBC (Abstract PD11-08). Arm 6 of this 2-part, open-label platform study enrolled 58 patients with HR-negative tumors with HER2-low expression by local testing. Patients received treatment with T-DXd (5.4 mg) plus durvalumab (1120 mg) every 3 weeks. The PD-L1 expression level was high in 12.1%, low in 77.6%, and missing in 10.3% of patients. The most common AEs of any grade were nausea (77.6%), fatigue (51.7%), and neutropenia (31.0%). Grades 3 or 4 AEs were observed in 43.1% of patients and serious AEs in 20.7% of patients. Grades 3 or 4 AEs were mostly hematologic, and no dose-limiting toxicity was observed. The confirmed ORR was 56.9%, including a CR rate of 1.7%. The median PFS was 12.6 months (95% CI, 8.3–not calculated). Responses were durable, and responses were observed in tumors with both high and low PD-L1 expression levels. The results support further investigation of the dual antibody combination in this patient setting.

Datopotamab Deruxtecan + Durvalumab as First-Line Treatment for Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer: Updated Results From BEGONIA, a Phase 1b/2 Study

Arm 7 of the phase 1b/2 BEGONIA study enrolled 61 patients with unresectable, locally advanced or metastatic TNBC who had not received prior therapy for their stage IV disease (Abstract PD11-09). Patients in this arm received treatment with datopotamab deruxtecan (Dato-DXd; 6 mg/kg) plus durvalumab (1120 mg) every 3 weeks. The PD-L1 expression level was high in 11.5%, low in 86.9%, and missing in 1.6% of patients. The most common AEs of any grade were nausea (57.4%), stomatitis (55.7%), and alopecia (45.9%). Grades 3 or 4 AEs were reported in 41.0% of patients and serious AEs in 16.4% of patients. No dose-limiting toxicity was observed. The confirmed ORR was 73.6% (39/53), including a CR rate of 7.5%. Responses were durable, with 82% of patients remaining in response at data cutoff, and responses were observed in tumors with both high and low PD-L1 expression levels. PFS data will be forthcoming.

Datopotamab Deruxtecan in Advanced Triple Negative Breast Cancer: Updated Results From the Phase I TROPION-PanTumor01 Study

Dato-DXd is an ADC comprising a humanized anti-Trop-2 antibody covalently linked to a topoisomerase I inhibitor by means of a tumor-selective cleavable linker (Abstract P6-10-03). The phase 1 TROPION-PanTumor01 study investigated Dato-DXd monotherapy in previously treated patients with solid tumors. The multicenter, open-label, dose escalation and expansion study included 44 patients with advanced or metastatic TNBC. Patients had received a median 3 prior therapies in the metastatic setting (range, 1-10 prior therapies) and 32% of patients had de novo metastatic disease. The most common treatment-emergent AEs of any grade were stomatitis (73%), nausea (66%), and vomiting (39%). The most common grades 3 or 4 treatment-emergent AEs were stomatitis (11%), fatigue (7%), and decreased lymphocyte count (7%). Neutropenia and diarrhea were uncommon. Among all patients, the median PFS was 4.4 months (95% CI, 3.0-7.3). Among patients without prior exposure to a topoisomerase I inhibitor, the median PFS was 7.3 months (95% CI, 3.0-18.0) and the ORR was 32%, with a CR rate of 1%. The median OS among all patients was 13.5 months (95% CI, 10.1-16.3) and the ORR was 44%, with a CR rate of 4%.

Camizestrant, a Next Generation Oral SERD, vs Fulvestrant in Post-Menopausal Women With Advanced ER-Positive HER2-Negative Breast Cancer: Results of the Randomized, Multi-Dose Phase 2 SERENA-2 Trial

Camizestrant is a novel SERD with high specificity for the ER (Abstract GS3-02). The randomized, phase 2 SERENA-2 study investigated camizestrant vs fulvestrant in patients with ER-positive/HER2-negative breast cancer. Camizestrant was evaluated in 2 arms at daily doses of 75 mg or 150 mg. In the overall study population of 240 patients, 58.3% had liver metastasis and 36.7% had detectable mutation in the *ESR1* gene. After a median follow-up of approximately 17 months for each arm, the SERENA-2 trial met its primary objective, demonstrating a median PFS of 3.7 months with fulvestrant, 7.2 months with the lower dose of camizestrant (*P*=.0124), and 7.7 months with the higher dose of camizestrant (*P*=.0161). Among patients with prior exposure to a CDK4/6 inhibitor, the median PFS was 2.1 months with fulvestrant, 5.5 months (HR, 0.49; 95% CI, 0.31-0.75) with camizestrant 75 mg, and 3.8 months (HR, 0.68; 95% CI, 0.44-1.04) with camizestrant 150 mg. A meaningful PFS benefit was observed in other prespecified subgroups based on lung or liver metastasis, *ESR1* mutation, and evidence of ER-driven disease. Camizestrant was well tolerated at both dose levels.

Highlights in Metastatic Breast Cancer from SABCS 2022

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SABCS 2022 included a wealth of important data. This commentary provides some additional insights to accompany the summaries included above, as well as a brief look at some crucial findings that are not summarized further here. The treatment of metastatic breast cancer continues to improve, as the studies herein indicate, yielding options and advances that we can begin offering our patients soon if not right away.

Dr. Virginia Kaklamani presented an update on the EMERALD trial, a phase 3 study that randomized previously treated patients to receive the oral selective estrogen receptor downregulator (SERD) elacestrant versus investigator's choice of endocrine therapy, including fulvestrant or an aromatase inhibitor (patients could not receive fulvestrant if they had previously progressed on it).[1] Importantly, the eligibility requirements included prior treatment with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor. The study endpoints were progression-free survival (PFS) among all patients and among patients with an estrogen receptor 1 (*ESR1*) mutation.

Among patients treated for at least 6 months, then 12 months, then 18 months, PFS was longer among those treated with elacestrant versus treatment of physician's choice. The results were particularly striking when viewed in terms of duration of exposure to a CDK4/6 inhibitor. Here, 21% of patients on the elacestrant arm and 6% of patients on the control arm experienced a PFS of 12 months.

Earlier data showed a modest improvement in PFS among all patients and a more striking improvement in PFS among patients with *ESR1* mutations. Overall survival (OS) had been designated as a secondary endpoint but the trial did not accrue enough events, which is a valuable indicator on how patients with metastatic, hormone receptor (HR)–positive disease are faring in light of the many new treatment options now available. Instead, the EMERALD investigators focused on PFS by duration of CDK4/6 inhibitor exposure in the metastatic setting, a surrogate marker of endocrine sensitivity.

The outcomes also differed according to the presence or absence of *ESR1* mutations. For example, the media PFS among patients with *ESR1* mutations and who had been treated for at least 6 months with a CDK4/6 inhibitor was 4.14 months for those on the elacestrant arm versus 1.87 months on the standard-of-care arm. The benefit was even more apparent among *ESR1* mutation patients who had received a CDK4/6 inhibitor for at least 18 months: 8.61 months versus 2.10 months, respectively. Based on data from the EMERALD trial, the FDA-approved elacestrant in patients with HR-positive, *ESR1*-mutated

metastatic breast cancer after 1-2 lines of endocrine therapy. Future studies will investigate the safety and efficacy of elacestrant combined with other targeted drugs and in combination with abemaciclib in patients with brain metastases.

Dr. Nick Turner presented data from CAPItello-219, a phase 3, randomized, double-blind, placebo-controlled study to evaluate capivasertib, a novel AKT inhibitor, plus fulvestrant in patients with metastatic, HR-positive, human epidermal growth factor 2 (HER2)–negative, advanced disease.[2] At least 51% of the patient population had to have been treated with a CDK4/6 inhibitor at the time of enrollment. Prior treatment with a SERD, a PI3 kinase, an AKT inhibitor or an mTOR inhibitor was not permitted.

In this trial of 708 patients, 38% had primary endocrine resistance and about 68% had visceral metastases. Most patients had received 1 prior line of endocrine therapy for metastatic disease and 70% had received a prior CDK4/6 inhibitor. About 18% of patients had been treated with chemotherapy for advanced breast cancer.

The dual primary endpoints in the final trial population were PFS in the overall study population and PFS among patients with an altered AKT pathway in their tumor. AKT-altered pathway means having at least one qualifying alteration in PIK3CA, AKT1 or PTEN. Alterations in AKT1 or PTEN were present in about 10% of patients, and PIK3CA mutations were present in about 30% of patients.

As Dr. Turner noted at SABCS, patients treated with capivasertib plus fulvestrant experienced a statistically significant improvement in PFS compared to patients treated with fulvestrant alone: 7.2 months versus 3.6 months, respectively, with a hazard ratio of 0.60. In the altered AKT pathway population, PFS was roughly the same but with a hazard ratio of 0.50. And among patients with nonaltered tumors or whose alteration status was unknown, the hazard ratio for PFS was 0.70. The overall response was about 12% among patients treated with fulvestrant plus placebo versus 23% for those treated with capivasertib, and again, that rate was a bit higher among patients with an altered AKT pathway.

It's important to note that treatment with capivasertib was associated with some toxicities, including diarrhea, rash and nausea. The discontinuation rate was low, but was higher for capivasertib compared to placebo, at about 9%. About 20% of patients receiving capivasertib required dose reductions, versus 2% for the placebo arm. The rate of hyperglycemia was lower than has been observed with other agents. The side effects were generally manageable and the benefit seen with capivasertib in the CAPItello trial is very encouraging. Future studies will examine whether this drug can be combined with an oral SERD and whether outcomes may be improved by adding CDK4/6 inhibitors.

International guidelines recommend that patients receive endocrine therapy with an aromatase inhibitor with a CDK4/6 inhibitor as a first-line treatment unless the disease is life-threatening. Despite this recommendation, many clinicians, particularly outside of the U.S., have maintained that in younger women with more aggressive disease, starting with chemotherapy to debulk the tumor may lead to better outcomes.

The RIGHT Choice study, conducted in Asia and several countries in the Middle East, was an opportunity to test this belief.[3] The 222 patients enrolled in this study had visceral metastases, rapid disease progression, impending visceral compromise or markedly symptomatic nonvisceral disease. The patient population consisted of pre- or postmenopausal women with aggressive, HR-positive, HER2-negative advanced breast cancer. The median patient age was 44 years, and 67% had symptomatic visceral metastases.

Patients were randomized to treatment with either combination chemotherapy or endocrine therapy plus ribociclib. PFS, the primary endpoint, was significantly longer among patients who received ribociclib and an aromatase inhibitor compared to combination chemotherapy: 24.0 months versus 12.3 months, respectively, with a hazard ratio of 0.54. The PFS curve separated relatively early on in treatment, showing a difference starting at about 6 months. This response is very noteworthy because combination chemotherapy is typically not well tolerated over time due to hematologic and nonhematologic toxicities, leading to early discontinuation.

Patients treated with ribociclib plus a nonsteroidal aromatase inhibitor were able to continue the treatment until their disease progressed. The overall response and clinical benefit rates were similar between the two arms, but the time to treatment failure was more than twice as long among patients treated with ribociclib plus endocrine therapy versus combination chemotherapy (18.6 months versus 8.5 months, respectively, with a hazard ratio of 0.45). These results along with the other data from this study provide evidence that initial chemotherapy does not improve outcomes in this setting. Some patients will still require chemotherapy, such as those with rising liver function tests or respiratory failure. But for the vast majority of young women diagnosed with advanced disease, endocrine therapy plus a CDK4/6 inhibitor is the most effective and appropriate choice for first-line treatment.

In the DESTINY-Breast03 trial, second-line trastuzumab deruxtecan (T-DXd), the novel HER2 antibody drug conjugate (ADC), showed a markedly superior PFS compared to the prior standard of trastuzumab emtansine (T-DM1) in HER2-positive metastatic breast cancer.[4] Most of the patients in this study had visceral

disease, all patients were required to have had prior trastuzumab, and about 60% had prior pertuzumab. The median OS was significantly improved with T-DXd compared to T-DM1, although the median OS was not reached in either arm. The OS rate at 12 months was 94% for patients treated with T-DXd and 86% for those treated with T-DM1.

The results of the DESTINY-Breast02 trial further strengthen the efficacy of T-DXd in the treatment of patients with metastatic HER2-positive breast cancer.[5] In this study, patients with metastatic HER2-positive disease previously treated with T-DM1 were randomized to receive T-DXd every 3 weeks or either trastuzumab plus capecitabine or lapatinib plus capecitabine.

After about 20 months, almost 25% of patients randomized to T-DXd were still on treatment, compared to fewer than 3% of patients receiving treatment of physician's choice. PFS was significantly improved among patients receiving T-DXd: 17.8 months versus 6.9 months, respectively, with a hazard ratio of 0.36. OS was also significantly improved (39 months versus 26.5 months). It's also interesting to note that 26% of patients received T-DXd in the posttrial setting, indicating a survival benefit with this agent even among patients initially randomized to the other treatment arm.

Nausea was the primary toxicity for T-DXd. Preventing nausea upfront helps patients maintain quality of life and continue therapy for as long as possible. About 10% of patients treated with T-DXd also developed interstitial lung disease, with 2 patients (0.5%) experiencing grade-5 events. Given the lack of mortality in DESTINY-Breast03, it is possible that the severity of interstitial lung disease could depend on the extent of prior treatment before T-DXd. Early identification and treatment clearly play a critical role.

Taken together, the results from DESTINY-Breast02 and DESTINY-Breast03 illustrate that treating patients with T-DXd earlier in the second-line setting is preferable to waiting for later in the treatment course, with remarkable efficacy and possibly less toxicity. DESTINY-Breast02 showed that patients who may not have access to T-DXd at this stage of care clearly benefit even when the drug is started later. But the data are even stronger when the drug is given earlier.

A crucial question at the moment is how we determine HER2-low status. In DESTINY-Breast04, patients who had a HER2 status of 1+ or 2+ by immunohistochemistry (IHC), without gene amplification, with a median of 1 line of prior chemotherapy, were randomized to T-DXd or chemotherapy (physician's choice).[6] As previously reported, both PFS and OS were significantly improved in patients receiving T-DXd, who primarily had HR-positive disease. At SABCS, Aleix Prat and colleagues examined the concordance between the historical IHC results of the patients enrolled in DESTINY-Breast04, their central testing and tumor sample characteristics.[7]

Out of 1060 patients whose tumors were classified as HER2-low using local results, 237 were found to be either HER2-0 or HER2-positive. About 50% of the samples were from 2018 or earlier, and about 87% were archival. Of the 22% discordant samples, 12% were found to be HER2-positive, indicating that they should have received HER2-targeted treatment. Overall, the 78% concordance was quite encouraging. Several posters in this session at SABCS emphasized that formal training among pathologists can improve concordance, and a presentation by David Rimm described new testing methods that may further improve this biomarker identification.

In the phase 2 SERENA-2 trial, 240 patients with up to one line of prior chemotherapy but no prior fulvestrant or oral SERD were randomized to three different doses of camizestrant versus fulvestrant.[8] The high-dose arm of the study closed early. The two primary arms showed an advantage in PFS survival for camizestrant regardless of the dose. Interestingly, patients who had been treated with a CDK4/6 inhibitor before the study seemed to benefit less from camizestrant, though this association needs further research. Patients with visceral metastases experienced a particular benefit from camizestrant compared to fulvestrant, compared to those with nonvisceral disease. The benefit of camizestrant among patients with *ESR1* mutations was also greater than it was among patients with wild-type *ESR1*. Toxicity from camizestrant includes low-grade bradycardia and photopsia. The results from this and other studies indicate that the lower dose of camizestrant is as effective and may lead to fewer toxicities. Data from ongoing and planned phase 3 studies will yield further clarity on the efficacy of this drug in various settings. Other novel endocrine agents with different mechanisms of action are under investigation, with encouraging early results.

Another study, known as PACE, focused on patients with metastatic, hormone-receptor positive breast cancer after first-line endocrine therapy in combination with a CDK4/6 inhibitor.[9] In this investigation, 220 patients were randomized to receive fulvestrant alone, fulvestrant and palbociclib, or fulvestrant, palbociclib and avelumab, with twice as many patients enrolled on the two-drug arm versus the one- and three-drug arms. It's important to note that about 80% of the enrolled patients were postmenopausal, approximately 40% had de novo metastatic disease, and around 50% or so had visceral. There was no discernible difference in PFS among the three arms. However, it is important to note that the results showed a longer PFS from fulvestrant alone than other studies have found, suggesting that confounding variables may have impacted the results. In addition, the data suggested

an improved outcome with the triple combination, encouraging further investigation.

SABCS 2022 also included an important update of the randomized adjuvant monarchE trial investigating standard endocrine therapy alone or with 2 years of abemaciclib in patients with high-risk, node-positive, early-stage, HR-positive breast cancer.[10] The study enrolled 5637 patients and at a median follow-up of 4 years, 99% of patients had completed abemaciclib. With this longer follow-up, there is now a 6.4% improvement in invasive disease–free survival among patients treated with abemaciclib, versus a 2.8% and 4.8% improvement at a median follow-up of 2 years and 3 years, respectively. These improved outcomes held for all disease subsets regardless of age, stage, grade, tumor size and menopausal status; distant disease–free survival was also similarly improved. The updated results from monarchE are very encouraging, demonstrating a carry-over effect with increasing improvement in outcome over time and years after completing treatment with the CDK4/6 inhibitor, as well as benefit in both high and low Ki-67 disease. Abemaciclib has regulatory approval in this setting and is now a standard of care for women with high-risk, node-positive disease, regardless of tumor Ki-67. The primary toxicity of abemaciclib is diarrhea, and careful management is critical to maintain adherence and treatment benefit.

The tremendous amount of intriguing and important data were presented at SABCS 2022. In the coming months and years, numerous trials will report on new approaches to treating patients with hormone receptor positive disease associated with *ESR1* mutations and alterations in the AKT pathway.

In terms of chemotherapy for HR-positive disease, ADCs are an exciting new treatment approach, with data from TROPiCS-02 demonstrating improved PFS and OS in patients with heavily treated disease compared to standard chemotherapy, and regardless of TROP2 expression.[11] Durvalumab deruxtecan is a TROP2 ADC with encouraging early results in the first-line treatment of metastatic breast cancer,[12] and an ongoing phase 3 trial.[13] In the meantime, findings from multiple studies have delivered practice-changing results that have already impacted outcomes for our patients.[1,4,5,11]

Disclosure

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