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A SPECIAL MEETING REVIEW EDITION

Progress in the Treatment of Breast Cancer: Increased Survival, Improved Patient Experience, and Advances in Drug Formulation

A Review of Selected Presentations From the 2022 San Antonio Breast Cancer Symposium® • December 6-11, 2022 • San Antonio, Texas

Special Reporting on:

- 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
- Effect of Sacituzumab Govitecan vs Chemotherapy in HR+/HER2– Metastatic Breast Cancer: Patient-Reported Outcomes From the TROPiCS-02 Trial
- 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
- EMERALD Phase 3 Trial of Elacestrant vs Standard-of-Care Endocrine Therapy in Patients With ER+/HER2– Metastatic Breast Cancer: Updated Results by Duration of Prior CDK4/6i in Metastatic Setting
- 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
- Trastuzumab Deruxtecan vs Treatment of Physician's Choice in Patients With HER2-Low Unresectable and/or Metastatic Breast Cancer: Subgroup Analyses From DESTINY-Breast04

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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In HR+/HER2- metastatic breast cancer

following resistance to endocrine-based therapy

what's next

Outcomes for heavily pretreated patients with HR+/HER2- metastatic breast cancer (mBC) after endocrine resistance are poor.

The median overall survival after single-agent chemotherapies is ~12-18 months.[1-5]

Gilead Oncology is working tirelessly to ignite innovation after endocrine resistance in HR+/HER2- mBC.

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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

Metastatic breast cancer (mBC) continues to present treatment challenges in part because various subtypes express different markers, thus requiring different targeted drugs. Hormone receptor–positive/human epidermal growth factor 2–negative (HR+/HER2–) breast cancer is the most common type of this disease, accounting for approximately 70% of all cases.[1,2] Resistance to endocrine therapy typically develops, and oncologists have vigorously sought alternatives.

Expression of trophoblast cell surface antigen 2 (Trop-2) has been observed across all breast cancer subtypes, and Trop-2 is an attractive target for the treatment of patients who have received multiple lines of therapy for HR+/HER2– mBC.[3,4]

Sacituzumab govitecan (SG) is a novel antibody-drug conjugate (ADC) that comprises a humanized anti–Trop-2 antibody with an SN-38 payload covalently attached by means of a pH-sensitive, hydrolyzable linker.[5] The SN-38 moiety is a topoisomerase I inhibitor that is more potent than its predecessors. SG is approved for the treatment of patients with metastatic triple-negative breast cancer who have received 2 or more prior therapies, including 1 or more treatments for mBC.[6]

TROPiCS-02 Trial

The phase 3 TROPiCS-02 trial evaluated the safety and efficacy of SG vs that of the physician's choice of therapy in patients with unresectable locally advanced or metastatic HR+/HER2– disease.[7,8] Patients had had disease progression after treatment with 1 or more endocrine therapies, a taxane, and a CDK4/6 inhibitor. Enrolled patients had received 2, 3, or 4 prior lines of chemotherapy for metastatic disease and had measurable disease by Response Evaluation in Solid Tumors (RECIST) 1.1.[9]

Patients were stratified on the basis of visceral metastases, endocrine therapy in the metastatic setting, and number of prior lines of therapy. The study included 543 participants, who were randomly assigned to receive SG (10 mg/kg on days 1 and 8 of 21-day cycles) or the physician's choice of therapy (capecitabine, vinorelbine, gemcitabine, or eribulin).

The primary endpoint was progression-free survival (PFS) by blinded independent central review. Patients in the TROPiCS-02 trial had received a median of 3 prior chemotherapy regimens for mBC, and 95% had visceral metastasis. After a median follow-up of 10.2 months, the trial met its primary endpoint, demonstrating a median PFS of 5.5 months (95% CI, 4.2-7.0 months) with SG vs 4.0 months (95% CI, 3.1-4.4 months) with the physician's choice of treatment (hazard ratio [HR], 0.66; 95% CI, 0.53-0.83; *P*=.0003). The trial also showed superior overall survival (OS) with the ADC vs the comparator (14.4 vs 11.2 months, respectively; HR, 0.79; 95% CI, 0.65-0.96; *P*=.020).

Table 1a. Median Progression-Free Survival Outcomes with Sacituzumab Govitecan vs Physician's Choice of Treatment in the TROPiCS-02 Trial

Treatment	Trop-2 H-score Cutoff	Median PFS (Range, mo)	HR (95% CI)
Sacituzumab govitecan	<100	5.5 (2.9–9.5)	0.89 (0.51–1.57)
Physician's choice of treatment	<100	4.3 (1.7–6.4)	
Sacituzumab govitecan	≥100	5.0 (4.1–7.1)	0.67 (0.42–1.07)
Physician's choice of treatment	≥100	3.5 (1.6–5.6)	
Sacituzumab govitecan	≤10	5.5 (2.9–9.5)	0.89 (0.51–1.57)
Physician's choice of treatment	≤10	4.3 (1.7–6.4)	
Sacituzumab govitecan	>10 to <100	5.0 (4.1–7.1)	0.67 (0.42–1.07)
Physician's choice of treatment	>10 to <100	3.5 (1.6–5.6)	

Post Hoc Analysis

A post hoc analysis of the TROPiCS-02 study was conducted to evaluate efficacy outcomes with SG vs outcomes with the physician's choice of treatment according to levels of expression of Trop-2.[10] Tissue samples were collected from primary or metastatic tumors at study entry; however, levels of Trop-2 expression were not used to determine patient eligibility

Table 1b. Median Overall Survival With Sacituzumab Govitecan vs Physician's Choice of Treatment in the TROPiCS-02 Trial

Treatment	Trop-2 H-score Cutoff	Median PFS (Range, mo)	HR
Sacituzumab govitecan	<100	14.6 (12.7–18.1)	0.75 (0.54–1.04)
Physician's choice of treatment	<100	11.3 (10.0–13.3)	
Sacituzumab govitecan	≥100	14.4 (12.7–16.4)	0.83 (0.62–1.11)
Physician's choice of treatment	≥100	11.2 (9.9–12.9)	
Sacituzumab govitecan	≤10	17.6 (11.5–NE)	0.61 (0.34–1.08)
Physician's choice of treatment	≤10	12.3 (8.0–15.3)	
Sacituzumab govitecan	>10 to <100	13.7 (10.9–16.3)	0.81 (0.43–1.23)
Physician's choice of treatment	>10 to <100	11.0 (9.0–13.5)	

HR, hazard ratio; NE, not estimable; OS, overall survival;
PFS, progression-free survival; Trop-2, trophoblast cell surface antigen 2.

for the trial.

The median time from tumor tissue collection to study entry was 7.7 months (range, 0.03-177.9). Levels of Trop-2 expression were centrally determined by a validated research immunohistochemistry (IHC) assay. Samples were available from 238 patients (88%) in the ADC arm and 224 patients (83%) in the comparator arm. Trop-2 expression was observed in approximately 95% of tumors. Most patients (58%) had a histochemistry score (H-score) of 100 or greater.

Results from the retrospective analysis consistently suggested a trend of improved efficacy with SG vs the physician's choice of treatment across all levels of Trop-2 expression examined (Table 1a, b; Figure 1). It is important to note the relatively small sizes of the patient groups and to interpret the results accordingly. Treatment with the ADC was associated with a manageable safety profile, and safety was not affected by levels of Trop-2 expression.

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Effect of Sacituzumab Govitecan vs Chemotherapy in HR+/HER2– Metastatic Breast Cancer: Patient-Reported Outcomes From the TROPiCS-02 Trial

Although therapies may improve longevity for patients with HR+/HER2– mBC, their quality of life is also an important consideration. The TROPiCS-02 study assessed patient-reported outcomes (PROs) by means of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) health utility index and the EuroQol 5 Dimension 5 level (EQ-5D-5L) descriptive system and the EQ visual analogue pain scale (EQ VAS).[1-3]

The Patient Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-

CTCAE) measurement system was used to capture patient-reported toxicity symptoms. The frequency of PROs in patients treated with SG was compared with the frequency in those who received the physician's choice of treatment. Baseline demographics and characteristics were similar in the compared patient groups.

In all, 543 patients participated in the randomized TROPiCS-02 trial, and between 82% and 95% of patients were available for PRO analysis. In the primary domains of the EORTC QLQ-C30, the outcomes of role functioning (HR, 0.92; 95% CI, 0.75-1.14) and pain (HR, 0.92; 95% CI, 0.74–1.14) were similar; however, treatment with SG significantly prolonged the time to deterioration in comparison with the physician's choice of treatment in terms of global health status/quality of life (HR, 0.74; 95% CI, 0.59-0.91), physical functioning (HR, 0.77; 95% CI, 0.62-0.96), and fatigue (HR, 0.76; 95% CI, 0.62-0.93) (Figure 2).

SG was also associated with a longer time to deterioration in comparison with the physician's choice of treatment in terms of emotional functioning (HR, 0.67; 95% CI, 0.54-0.84), dyspnea (HR, 0.75; 95% CI, 0.61-0.94), insomnia (HR, 0.77; 95% CI, 0.62-0.97), and financial difficulties (HR, 0.79; 95% CI, 0.62-0.99).

On the EQ VAS, time to deterioration was also significantly longer with the ADC than with the physician's choice of treatment (HR, 0.79; 95% CI, 0.64-0.98). Results from the PRO-CTCAE questionnaire showed that the proportions of patients with symptom worsening to a score of 3 or 4 were similar in the SG and the physician's choice of treatment cohorts for decreased appetite, nausea, vomiting, constipation, abdominal pain, shortness of breath, and fatigue. However, study treatment with SG was superior to the physician's choice of treatment in terms of the frequency of diarrhea (35% vs 11%) and hair loss (71% vs 24%).

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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 comprising a humanized anti-HER2 antibody covalently linked to a topoisomerase I inhibitor by a tetrapeptide-based cleavable linker.[1-3] Destiny-Breast01, a previously conducted open-label, single-arm, multicenter phase 2 study, evaluated the efficacy of T-DXd in 184 patients with HER2+ mBC who had previously received a median of 6 treatments with trastuzumab emtansine.[4,5] The median duration of response was 20.8 months and the median PFS was 19.4 months, results that led to regulatory approvals of the ADC in several countries.

DESTINY-Breast02

Destiny-Breast02 was an open-label, multicenter phase 3 trial designed to evaluate T-DXd vs the physician's choice of treatment in patients with centrally confirmed HER2+ unresectable or metastatic breast cancer previously treated with trastuzumab emtansine.[6] Eligible patients had radiographic evidence of progression after their most recent treatment.

Patients were stratified according to hormone receptor status, prior treatment with pertuzumab, and history of visceral disease. They were then randomly assigned in a 2:1 ratio to receive T-DXd (5.4 mg/kg every 3 weeks) or the physician's choice of treatment (trastuzumab plus capecitabine or lapatinib plus capecitabine). The primary endpoint was PFS according to blinded independent central review.

In all, 406 patients were assigned to the T-DXd arm and 202 to the comparator arm. The median duration of follow-up was 21.5 months (range, 0.1-45.6) in the T-DXd arm vs 18.6 months (range, 0-45.7) in the physician's choice of treatment arm. Treatment was ongoing in 94 patients (23.3%) in the T-DXd arm vs 5 patients (2.6%) in the physician's choice of treatment arm.

In the T-DXd and comparator arms, the primary reasons for discontinuation were disease progression (43.1% vs 72.3%, respectively) and adverse events (AEs; 18.3% vs 7.2%, respectively). Baseline characteristics were well balanced: The patients' median age was 54.2 to 54.7 years (range, 22.4-88.5). The HER2 status

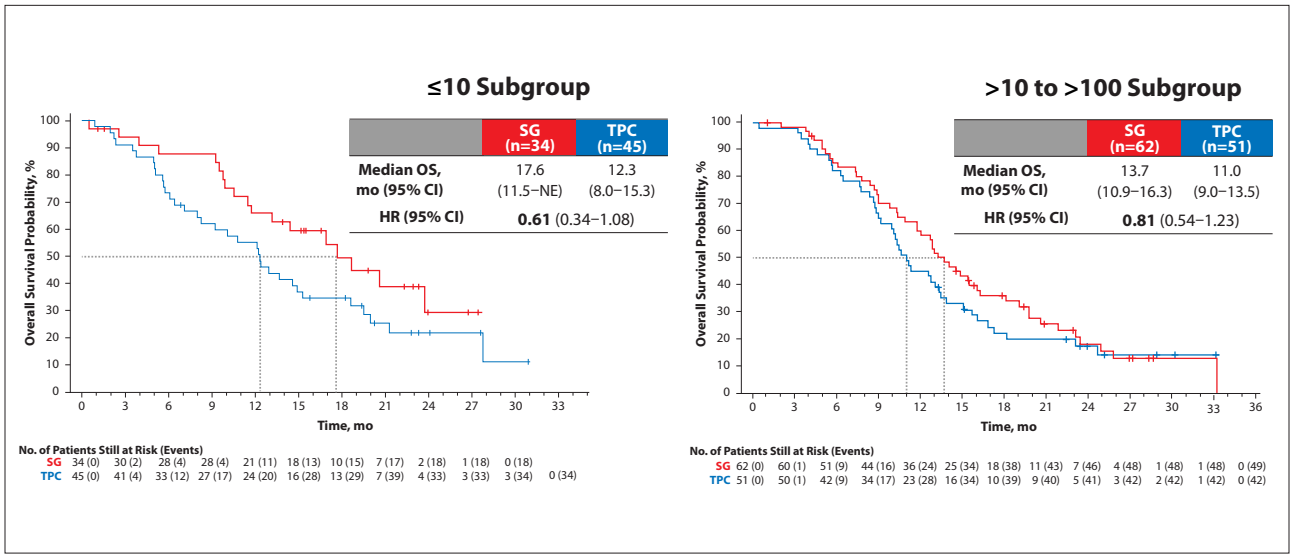

Figure 1. OS benefit with SG over TPC was consistently observed across all Trop-2 H-score subgroups, including those with very low Trop-2 expression {H-score ≤10), though caution should be exercised in data interpretation given the small sample size. Overall survival: Trop-2 H-score cutoff of 10. Hazard ratio is from an unstratified Cox regression analysis.

H-score, histochemical score; NE, not evaluable; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2.

was IHC3+ in the majority of the patients (79%-80%), and 58.4% to 58.6% of the patients had HR+ disease. Visceral metastases were observed in 20.8% to 22.2% of the patients. Patients in both arms had received a median of 2 prior lines of therapy (range, 0-10).

T-DXd therapy was superior to the physician's choice of treatment in all subgroups examined.

Progression-Free Survival

The trial achieved its primary endpoint, demonstrating a median PFS of 17.8 months (range, 14.3-20.8) with T-DXd vs 6.9 months (range, 5.5-8.4) with the physician's choice of treatment (HR, 0.3589; 95% CI, 0.2840-0.4535; *P*<.000001). T-DXd therapy was superior to the physician's choice of treatment in all subgroups examined (age, hormone receptor status, prior pertuzumab exposure, visceral disease, brain metastases at baseline, number of prior lines of therapy, and performance status) (Figures 3 and 4). Treatment with T-DXd also yielded a superior median OS in comparison with the physician's choice of treatment (39.2 vs 26.5 months; HR, 0.6575; 95% CI, 0.5023-0.8605; *P*=.0021). The confirmed objective response rate (ORR) was 69.7% with T-DXd vs 29.2% with the physician's choice of treatment (*P*<.0001), with complete response (CR) rates of 14.0% vs 5.0%, respectively.

The median duration of treatment was 11.3 months in the patients who received T-DXd vs approximately 4.5 months in those who received the physician's choice of treatment. Treatment-emergent AEs of grade 3 or higher were observed in 52.7% of the patients in the T-DXd arm vs 44.1% of those in the comparator arm and were considered drug-related in 41.3% vs 30.8% of patients, respectively. Treatment-emergent AEs were associated with discontinuation of study therapy in 19.8% of patients in the T-DXd arm vs 9.7% in the comparator arm. In the T-DXd arm, AEs of special interest included interstitial lung disease (ILD) and left ventricular dysfunction. Among 404 patients evaluable for safety in the T-DXd arm, 3 patients (0.7%) experienced grade 3 ILD and 2 patients (0.5%) experienced grade 5 ILD. Also in the T-DXd arm, 2 patients (0.5%) experienced a left ventricular dysfunction event of grade 3 or higher.

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

Breast tumors that express the estrogen receptor (ER) are dependent on estrogen-mediated signaling for growth. The standard first-line therapy for ER+/HER2– mBC is endocrine therapy plus a CDK4/6 inhibitor.[1] However, it is common for such tumors to become resistant to this therapy, such as with estrogen receptor 1 (ESR1). Available alternative treatments for hormone-resistant tumors are limited by poor efficacy and significant toxicity.

Elacestrant

Elacestrant is a next-generation selective estrogen receptor disruptor (SERD) that causes degradation of the ER. The EMERALD trial, an open-label, international phase 3 trial, evaluated elacestrant vs standard of care (SOC) in patients with ER+/HER2– advanced breast cancer.[2] Eligible patients were men or postmenopausal women who had received prior treatment with a CDK4/6 inhibitor within 1 year before initiation of the chemotherapy regimen. Prior treatment with fulvestrant was allowed.

Patients were randomly assigned

Table 2a, b. Median Progression-Free Survival with Elacestrant vs Standard of Care Based on Prior Exposure to CDK4/6 Inhibitor Therapy in the EMERALD Trial

A. All Study Participants						
Duration of Prior CDK4/6; Therapy	**≥6 Months (87.5%)**		**≥12 Months (66.7%)**		**≥18 Months (46.7%)**	
	Elacestrant (n=202)	**SOC (n=205)**	**Elacestrant (n=150)**	**SOC (n=160)**	**Elacestrant (n=98)**	**SOC (n=119)**
Median PFS, mo (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)
HR (95% CI)	0.688 (0.535–0.884)		0.613 (0.453–0.828)		0.703 (0.482–1.019)	

B. Patients With *ESR1* Mutation Only						
Duration of Prior CDK4/6; Therapy	**≥6 Months (92.3%)**		**≥12 Months (71.6%)**		**≥18 Months (50.0%)**	
	Elacestrant (n=103)	**SOC (n=102)**	**Elacestrant (n=78)**	**SOC (n=81)**	**Elacestrant (n=55)**	**SOC (n=56)**
Median PFS, mo (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)
HR (95% CI)	0.517 (0.361–0.738)		0.410 (0.262–0.634)		0.466 (0.270–0.791)	

ESR1, estrogen receptor alpha gene; HR, hazard ratio; PFS, progression-free survival; SOC, standard of care.

to receive oral elacestrant (400 mg daily) or standard endocrine therapy (fulvestrant, anastrozole, letrozole, or exemestane). The researchers sought 2 primary endpoints: PFS in all patients and PFS in patients who had an *ESR1* mutation.

> Treatment with elacestrant significantly improved median PFS in comparison with SOC.

Among the 478 randomized patients, 228 had tumors with an *ESR1* mutation. Patient baseline characteristics were well balanced between the 2 arms.

Visceral metastasis was noted in 68.2% of patients in the elacestrant arm vs 71.1% of patients in the SOC arm. The percentages of patients who had received prior treatment with fulvestrant were 29.3% in the elacestrant arm vs 31.4% in the SOC arm. The percentages of patients who had received 2 prior lines of endocrine therapy were 46.0% in the elacestrant arm vs 40.6% in the SOC arm; 81% of patients in each arm had received prior treatment with an aromatase inhibitor.

Elacestrant Was Found to Be Significantly More Effective

The researchers found that treatment with elacestrant significantly improved median PFS in comparison with SOC (HR, 0.70; 95% CI, 0.55-0.88; *P*=.002). Updated results continued to demonstrate superior outcomes with elacestrant vs SOC.[3]

Median PFS, determined for patient groups based on the duration of prior CDK4/6 inhibitor therapy, showed consistent benefit regardless of the duration of prior CDK4/6 inhibitor therapy (Table 2a, b).

Updated safety data were consistent with prior findings. Most AEs were mild, with no grade-4 treatment-related AEs reported. Treatment discontinuation due to an AE was reported in 3.4% of patients in the elacestrant arm and 0.9% in the SOC arm. No treatment-related death occurred in either arm. No hematologic safety signals arose, and no patient in either arm experienced sinus bradycardia.

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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

Tumors with alterations in the phosphatidylinositol-3-kinase (PI3K)/AKT/PTEN pathway are common in patients with advanced HR+/HER2– breast cancer.[1] Mutations in this pathway can promote cell proliferation, prevent apoptosis, and confer resistance to treatment.

CAPItello-291 Phase 2

Mutations in AKT are associated with resistance to endocrine therapy. Capivasertib is a potent, selective inhibitor of the 3 AKT isoforms: AKT1, AKT2, and AKT3. CAPItello-291, a double-blind phase 2 trial, evaluated fulvestrant plus capivasertib vs fulvestrant plus placebo in 140 postmenopausal women with HR+/HER2– metastatic or inoperable locally advanced breast cancer that was resistant to aromatase inhibitor therapy.[2]

Prior therapy with a CDK4/6 inhibitor was not allowed. Median PFS with fulvestrant plus capivasertib was superior to median PFS with fulvestrant plus placebo (10.3 vs 4.8 months; HR, 0.56; 95% CI, 0.38-0.81; *P*=.0023).[3] Median OS was also superior with the capivasertib combination (29.3 vs 23.4 months; HR, 0.66; 95% CI, 0.45-0.97; *P*=.035). The superiority of the capivasertib combination was more pronounced among patients with alterations in the PI3K/AKT/PTEN pathway.

CAPItello-291 Phase 3

The double-blind phase 3 CAPItello-291 study evaluated fulvestrant plus capivasertib vs fulvestrant plus placebo in patients with HR+/HER2–

n (%)[a]	SG (n=268)		TPC (n=249)	
	H-score <100 (n=96)	H-score ≥100 (n=140)	H-score <100 (n=94)	H-score ≥100 (n=123)
Grade >3 TEAEs	76 (79)	103 (74)	58 (62)	78 (63)
TEAEs leading to treatment discontinuation	2 (2)	11 (8)	5 (5)	5 (4)
TEAEs leading to dose delay	68 (71)	93 (66)	43 (46)	52 (42)
TEAEs leading to dose reductions	32 (33)	51 (36)	37 (39)	35 (28)
TE SAEs	25 (26)	42 (30)	18 (19)	27 (22)
TEAEs leading to death[b]	1 (1)	4 (3)	0	0
Treatment-related	1 (1)	0	0	0
Selected TEAEs (grade ≥3)				
Neutropenia[c]	56 (58)	76 (54)	43 (46)	43 (35)
Febrile neutropenia	7 (7)	9 (6)	4 (4)	6 (5)
Diarrhea	10 (10)	13 (9)	1(1)	1 (1)

Figure 2. TROPiCS-02 safety summary. The safety profile for SG was not affected by Trop-2 expression. [a]The denominator for percentages is the number of patients in the safety population for each subgroup and each treatment group. Treatment-emergent adverse events (AEs) are defined as any AEs that started on or after the first dose date and up to 30 days after the last dose date. [b]Of the 6 participants who died as a result of a TEAE, 5 had a known H-score. Of 6 TEAEs leading to death, 1 was considered by the investigator to be treatment-related (septic shock due to neutropenic colitis). Five deaths were caused by COVID-19 pneumonia, pulmonary embolism, pneumonia, nervous system disorder, and arrhythmia. Detailed review of the TEAEs leading to death revealed no pattern. [c]Neutropenia includes combined terms of neutropenia, neutrophil count decreased, and febrile neutropenia. H-score, histochemical score; SAE, serious adverse event; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice; Trop-2, trophoblast cell surface antigen 2. Source: Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-3376.

advanced breast cancer.[4] Eligible patients had experienced recurrence during or within 12 months after treatment with an aromatase inhibitor. Participants were allowed to have had 2 or fewer prior lines of endocrine therapy and no or 1 prior line of chemotherapy for advanced breast cancer. Prior treatment with a CDK4/6 inhibitor was allowed. No prior treatment with a SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor was allowed. Patients were stratified on the basis of liver metastases, prior exposure to a CDK4/6 inhibitor, and geographic location, then randomized in a 1:1 ratio.

Patients in both arms received fulvestrant (500 mg on days 1 and 15 of cycle 15, then every 4 weeks). Patients in the experimental arm received capivasertib (400 mg twice daily, 4 days on then 3 days off), and patients in the control arm received matching placebo. Alterations in the PI3K/AKT1/PTEN pathway were determined by next-generation sequencing. The 2 primary endpoints were PFS by investigator assessment in the overall study population and in the subpopulation of patients with at least 1 alteration in PI3K, AKT1, or PTEN.

> The vast majority of subgroups benefited from the addition of capivasertib to fulvestrant, including patients with liver metastasis.

The CAPItello-291 trial randomly assigned 355 patients to capivasertib plus fulvestrant and 353 patients to placebo plus fulvestrant. The median age of patients the 2 arms was 58 to 59 years (range, 26-90), 99% were female, and the majority (74%-81%) were postmenopausal.

Approximately two-thirds of the patients in each arm had visceral metastases (liver metastases in 43%-44%), and 69% had received prior CDK4/6 inhibitor therapy for advanced or metastatic breast cancer. Alterations in the PI3K/AKT1/PTEN pathway were detected in 43.7% of

patients in the capivasertib combination arm vs 38.0% in the placebo control arm.

Evidence for Capivasertib

In the overall population, the median PFS was 7.2 months (95% CI, 5.5-7.4) in the capivasertib-plus-fulvestrant arm vs 3.6 months (95% CI, 2.8-3.7) in the placebo-plus-fulvestrant arm (HR, 0.60; 95% CI, 0.51-0.71; *P*<.001). Among the patients with alteration in the PI3K/AKT1/PTEN pathway, the median PFS was 7.3 months (95% CI, 5.5-9.0) in the capivasertib-plus-fulvestrant arm vs 3.1 months (95% CI, 2.0-3.7) in the placebo-plus-fulvestrant arm (HR, 0.50; 95% CI, 0.38-0.65; *P*<.001).

The vast majority of subgroups benefited more from the addition of capivasertib than of placebo to fulvestrant, including patients with liver metastasis (HR, 0.61; 95% CI, 0.48-0.78) and patients with prior exposure to a CDK4/6 inhibitor (HR, 0.62; 95% CI, 0.51-0.75). According to investigator assessment, the ORR in the overall population was 22.9% with capivasertib plus fulvestrant vs 12.2% with placebo plus fulvestrant, with partial responses predominant in both arms (19.2% vs 10.8%, respectively). At 28% maturity overall, the median OS was superior with capivasertib in the overall study population (HR, 0.74; 95% CI, 0.56-0.98) as well as in the population of patients with alteration in the PI3K/AKT1/PTEN pathway (HR, 0.69; 95% CI, 0.45-1.05).

In the capivasertib-plus-fulvestrant arm vs the placebo-plus-fulvestrant arm, serious AEs occurred in 16.1% vs 8.0% of patients, AEs leading to death occurred in 1.1% vs 0.3% of patients, and AEs leading to discontinuation of the study treatment occurred in 13.0% vs 2.3% of patients, respectively. No grade 4 AEs were reported. The most common grade 3 AEs in the capivasertib-plus-fulvestrant arm were diarrhea, rash, and hyperglycemia.

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

Breast cancer tumors with low expression of HER2 by immunohistochemistry (IHC1+), as well as those that are both IHC2+ and HER2– by in situ hybridization, are classified as HER2-low and may respond to HER2-targeted therapy.

DESTINY-Breast04

Destiny-Breast04, an open-label, multicenter phase 3 trial, evaluated the safety and efficacy of T-DXd in patients with unresectable and/or metastatic breast cancer.[1,2] Eligible patients had previously received 1 or 2 prior lines of chemotherapy for metastatic disease.

Patients were stratified according to HER2 status, number of prior lines of chemotherapy, and hormone receptor status. Patients with HR+ tumors were stratified on the basis of prior treatment with a CDK4/6 inhibitor, then randomized to receive T-DXd or the physician's choice of chemotherapy.

> Rates of objective response were consistently higher across all subgroups with T-DXd than with chemotherapy.

Progression-Free Survival Advantage

The trial met its primary endpoint, demonstrating superior median PFS with T-DXd vs chemotherapy in the HR+ cohort of 494 patients (10.1 vs 5.4 months; HR, 0.51; *P*<.001). Median OS also was superior with T-DXd vs chemotherapy among patients with HR+ disease (23.9 vs 17.5 months; HR, 0.64; *P*=.003). In the overall study population, treatment with T-DXd was superior to chemotherapy in terms of median PFS (*P*<.001) and median OS (*P*=.001).

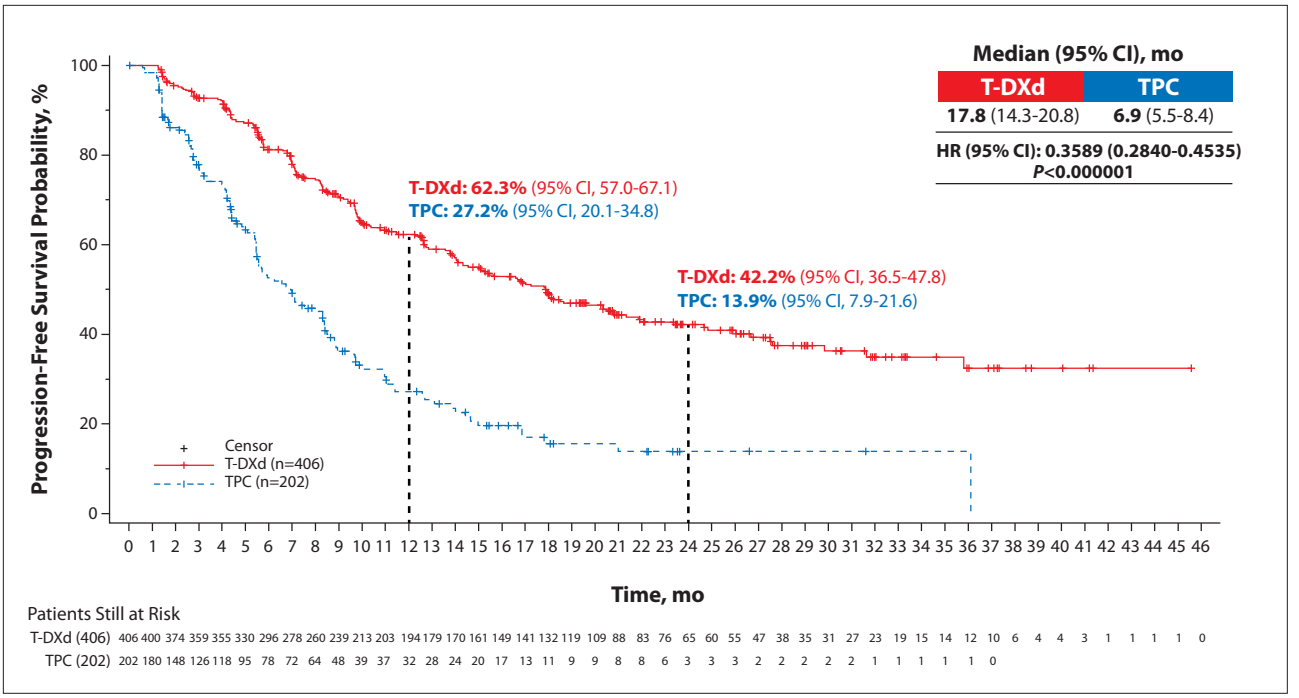

Figure 3. DESTINY-BREAST02 primary endpoint: PFS by BICR. BICR, blinded independent central review; HR, hazard ratio; mo, months; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

		Number of Events		Median PFS, mo (95% CI)		
		T-DXd	TPC	T-DXd	TPC	HR (95% CI)
All patients		200/406	125/202	17.8 (14.3-20.8)	6.9 (5.5-8.4)	0.36 (0.28-0.45
Age	<65	160/321	101/164	17.9 (14.1-20.8)	7.1 (5.5-8.6)	0.37 (0.29-0.48)
	≥65	40/85	24/38	16.8 (12.7-NE)	6.7 (4.3-8.4)	0.39 (0.23-0.65)
Hormone receptor status	Positive	115/238	71/118	18.0 (15.1-21.3)	8.5 (6.5-10.0)	0.42 (0.31-0.57)
	Negative	84/165	53/83	17.0 (12.3-24.6)	5.3 (4.3-6.7)	0.31 (0.22-0.45)
Prior pertuzumab treatment[a]	Yes	155/318	95/156	17.8 (14.0-20.8)	6.2 (5.0-8.4)	0.38 (0.29-0.49)
	No	45/88	30/46	18.0 (13.9-26.7)	8.3 (5.5-12.6)	0.37 (0.23-0.60)
Visceral disease[a]	Yes	164/316	98/160	15.6 (12.8-20.3)	5.7 (5.3-7.2)	0.36 (0.28-0.46)
	No	36/90	27/42	29.8 (16.8-NE)	9.8 (6.2-12.6)	0.39 (0.23-0.64)
Baseline brain metastases	Yes	44/74	20/36	13.9 (11.1-18.0)	5.6 (3.3-8.1)	0.35 (0.20-0.61)
	No	156/332	105/166	18.7 (15.1-24.8)	7.1 (5.5-8.6)	0.38 (0.29-0.48)
Prior lines of therapy[b]	<3	105/212	66/104	16.6 (13.8-24.6)	7.0 (4.6-8.6)	0.35 (0.26-0.49)
	≥3	95/194	59/98	18.2 (14.3-22.0)	6.9 (5.5-8.8)	0.41 (0.29-0.57)
ECOG PS	0	101/228	75/121	24.6 (15.3-31.6)	8.1 (5.7-9.7)	0.36 (0.27-0.50)
	1	98/177	50/81	15.1 (11.5-18.0)	5.4 (4.3-7.5)	0.37 (0.26-0.53)

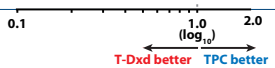

Figure 4. Progression-free survival in key subgroups in DESTINY-BREAST02. ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; mo, months; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice. [a]Subgroup values are derived from baseline. [b]Lines of prior systemic therapy not including hormone therapy.

Subgroup Analyses

The efficacy and safety of T-DXd therapy were further elucidated by the analysis of subgroups based on demographics and disease characteristics.[1] The results showed a consistent benefit across subgroups based on prior CDK4/6 exposure (among HR+ patients), disease burden, HER2 IHC status, number of prior lines of chemotherapy, age, presence of central nervous system metastases at baseline, and prior exposure to anthracycline.

Among 348 patients with HR+ disease, median PFS with T-DXd was superior to median PFS with chemotherapy (10.0 vs 5.4 months; HR, 0.55; 95% CI, 0.42-0.74); rapid disease progression, defined as progression within 6 months after completion of a prior course of chemotherapy in early breast cancer, occurred in 22 patients. Among these patients, the proportion with a response was greater in those treated with T-DXd (7/14; 50%) than with chemotherapy (0/8). ORRs were consistently higher across all subgroups with T-DXd vs chemotherapy. Safety analysis revealed similar outcomes in the subgroups of patients who did vs those who did not have prior exposure to a CDK4/6 inhibitor, as well as in the subgroups of patients with a low vs a high burden of disease.

ABSTRACT SUMMARY: Evaluation of Anti-PD-1 Cemiplimab Plus Anti-LAG-3 REGN3767 in Early-Stage, High-Risk HER2-Negative Breast Cancer: Results From the Neoadjuvant I-SPY 2 Trial

Cemiplimab is a programmed death 1 (PD-1) antibody. It has been approved by the US Food and Drug Administration for the treatment of non–small cell lung cancer and cutaneous and squamous cell carcinoma (Abstract GS5-03). Fianlimab (REGN3767) is a humanized antibody that antagonizes the lymphocyte activation gene 3, an immune checkpoint receptor.

The multicenter phase 2 I-SPY2 trial compared treatment with cemiplimab, fianlimab, and paclitaxel vs paclitaxel monotherapy in women with HER2– breast cancer and a primary tumor of 2.5 cm or larger. The trial used response-adaptive randomization within biomarker subtypes, which were defined by HER2 and hormone receptor status, as well as results from a 70-gene microarray analysis. The primary endpoint was pathologic CR (pCR). Among patients with HER2–, treatment-naive breast cancer, 76 received 12 weeks of neoadjuvant cemiplimab, fianlimab, and paclitaxel. In the control arm, 350 patients received 12 weeks of paclitaxel monotherapy.

In the overall study population, the estimated pCR rate was 21% with paclitaxel monotherapy vs 44% with cemiplimab, fianlimab, and paclitaxel. The 3-drug combination yielded a superior estimated pCR rate in patients with HR– disease (29% vs 53%) and in patients with HR+ disease (14% vs 36%). A 53-gene signature was developed to identify patients who derived the greatest benefit from cemiplimab, fianlimab, and paclitaxel and from cemiplimab plus paclitaxel. Because of safety concerns, the trial will evaluate a lower dose of fianlimab in combination with cemiplimab plus paclitaxel.

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Progress in the Treatment and of Breast Cancer: Increased Survival, Improved Patient Experience, and Advances in Drug Formulation

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Data presented at this year's San Antonio Breast Cancer Symposium® (SABCS) have already started to excite our practice community. The positive results of very large ongoing trials were updated, as were the results of studies of promising new therapies, and various researchers reported on their efforts to improve patient experience and outcomes.

The research findings presented at the SABCS will improve both our clinical practice and the quality of care we deliver to our patients. It was another rich and inspiring meeting.

SABCS 2022

At this year's meeting, the most sig-

nificant findings fell into three broad categories:

1) Researchers provided significant updates on ongoing trials, including DESTINY-Breast03, EMERALD, and monarch-E, among others.
2) Findings were presented that challenge existing dogmas. The results of the POSITIVE and RIGHT Choice trials are likely to change the culture of oncology.
3) Significant findings presented on newer agents and targeted therapy options, including camizestrant and capivasertib, demonstrated that patients and clinicians can expect to see improvements in treatment efficacy and the overall patient experience.

Updates

The DESTINY-Breast03 Trial

At last year's SABCS, preliminary results from this randomized phase 3 trial suggested significantly better progression-free survival (PFS) in patients who received trastuzumab deruxtecan (T-DXd) than in those who received trastuzumab emtansine (T-DM1). Both drug combinations were administered as second-line therapy to patients with metastatic breast cancer (mBC).

At SABCS 2022, we were able to see the significant advantage in overall survival (OS) provided by T-DXd. OS was shown to be significantly extended when this combination was compared with T-DM1 (hazard ratio [HR], 0.64; P=0.0037[a,b]).

These findings further cement the position of T-DXd as the most effective second-line therapy for patients with mBC. This is very encouraging news.

The EMERALD Trial

Fulvestrant is currently the only selective estrogen-receptor degrader (SERD) approved by the US Food and Drug Administration for patients with hormone receptor–positive mBC. However, the drug is administered as an intramuscular injection, which can be inconvenient for patients and so reduce compliance. Furthermore, fulvestrant is less effective when used as a second-line therapy. As a result, considerable interest has been shown in developing an oral SERD.

The randomized phase 3 EMERALD trial was designed to examine the safety and efficacy of an oral SERD, elacestrant, with that of standard-of-care (SOC) endocrine therapy in the second- and third-line treatment of hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) mBC. Preliminary results were presented at SACBS 2021. It was clear that elacestrant was associated with improved PFS in comparison with SOC.

Further examination of the PFS curves revealed an initial drop in the curves for both arms followed by separation in the curves in favor of elacestrant, highlighting activity in an "endocrine-sensitive" setting. At SABCS 2022, the team reported trial results by prior duration of CDK 4/6 inhibitor treatment as a surrogate marker of endocrine-sensitive disease. Elacestrant demonstrated longer PFS vs SOC that was positively associated with duration of prior treatment with a CDK4/6 inhibitor, which was more pronounced in *ESR1*-mutant mBC. (Median PFS was 7.2 months with capivasertib plus fulvestrant and 3.6 months with placebo plus fulvestrant (HR, 0.60; 95% CI, 0.51-0.71; P<0.001), highlighting a potential therapeutic role in this setting. Another oral SERD in advanced development is camizestrant, reviewed later in this summary.

ABSTRACT SUMMARY: Trastuzumab Deruxtecan Versus Trastuzumab Emtansine in Patients With HER2-Positive Metastatic Breast Cancer: Updated Survival Results of the Randomized Phase 3 Study DESTINY-Breast03

The multicenter, open-label phase 3 Destiny-Breast03 trial evaluated the efficacy of T-DXd vs that of trastuzumab emtansine in patients with unresectable or metastatic HER2+ breast cancer (Abstract GS2-02). Enrolled patients had received prior therapy with trastuzumab and a taxane. No crossover was allowed. The primary endpoint was PFS based on blinded independent central review.

Results in the 524 randomly assigned patients significantly favored T-DXd vs trastuzumab emtansine. The proportion of patients with no disease progression at 12 months was 75.8% with T-DXd vs 34.1% with trastuzumab emtansine (HR, 0.28; 95% CI, 0.22-0.37; P<.001).

The study protocol included a prespecified interim analysis of OS. For the interim OS analysis, the median follow-up was 28.4 months (range, 0.0-46.9) in the T-DXd arm and 26.5 months (range, 0.0-45.0) in the trastuzumab emtansine arm.

The risk of death was decreased by 36% with T-DXd vs trastuzumab emtansine (HR, 0.64; 95% CI, 0.47-0.87; P=.0037). Treatment with T-DXd was associated with a superior OS across all examined subgroups (based on hormone receptor status, prior exposure to pertuzumab, presence of visceral disease at baseline, number of prior lines of therapy, and presence of bone metastases at baseline).

Updated data based on blinded independent central review yielded a median PFS of 28.8 months (95% CI, 22.4-37.9) with T-DXd vs 6.8 months (95% CI, 5.6-8.2) with trastuzumab emtansine (HR, 0.33; 95% CI, 0.26-0.43; P<.000001). The confirmed ORR by blinded independent central review was 78.5% with T-DXd vs 35.0% with trastuzumab emtansine, with CR rates of 21.1% vs 9.5%, respectively. T-DXd continued to demonstrate an acceptable safety profile.

These are the types of advancements that will change the way we practice oncology, and the ways in which patients experience treatment. Instead of having to come to the office or hospital for an intramuscular injection, they will have the convenience of taking an oral medication at home. In addition, these medications appear to be more effective than fulvestrant.

The monarch-E Trial

The randomized phase 3 monarch-E trial had previously demonstrated higher rates of event-free survival (EFS) with adjuvant endocrine therapy plus abemaciclib than with endocrine therapy (ET) in patients with high-risk localized HR+ breast cancer. However, there was some concern regarding whether the EFS curves would continue to remain separate or converge.

At SABCS 2022, the monarch-E researchers reported continued positive results in their 4-year update of the phase 3 trial (PFS, 8.9 vs 1.9 months; HR, 0.41; 95% CI, 0.26-0.63). They demonstrated persistent benefit with abemaciclib plus ET over ET alone as adjuvant treatment for patients with high-risk early breast cancer.

Challenging Traditional Dogmas

Breast Conservation

Traditionally, mastectomy is considered for patients with multiple tumors, but it can be associated with significant morbidity. Researchers examined whether patients with multiple tumors in the breast could be safely treated with lumpectomy rather than mastectomy. They found that lumpectomy was safe and effective. The risk of recurrence proved to be low. Patient satisfaction was significantly improved.

Patients and clinicians can continue to become comfortable with less-radical surgeries, especially when effective adjuvant therapies are used.

The POSITIVE Trial

This study addressed an important question related to pregnancy among breast cancer survivors.

Findings from the POSITIVE study, an international single-arm trial, showed that stopping and restarting ET was safe and effective, and that patients were able to become pregnant.

Safety in the POSITIVE trial was defined as the risk of distant metastases in women who stopped therapy to conceive. The researchers found that from the perspective of distant recurrence, it was safe for these patients to cease ET for as long as 2 years, then restart ET and complete the duration of therapy.

The researchers continue to find that the following strategy is safe, at the proper time and for the proper duration: cease ET, attempt to become pregnant, become pregnant, carry a baby to term, safely deliver the baby, and then resume ET.

The researchers included nearly 10,000 women in their analysis, all of whom were being treated for stage I, II, or III breast cancer. Patients were eligible to pause ET at between month 18 and month 30. Those who chose to pause therapy were able to conceive, deliver a live birth, and resume ET without any increase in the rate of distant recurrence or decrease in survival.

This finding, of course, will come as a great relief to our patients who want to have children. They had previously been discouraged from attempting pregnancy during and after treatment. It gives clinicians greater confidence about holding adjuvant ET in the right patient.

The RIGHT Choice Trial

Traditionally, chemotherapy is recommended for patients with metastatic disease who are in visceral crisis. The RIGHT Choice trial compared ET with ribociclib vs standard chemotherapy as first-line therapy for

ABSTRACT SUMMARY: Exposure-Adjusted Incidence Rates of Adverse Events From the Phase 3 TROPiCS-02 Study of Sacituzumab Govitecan vs Treatment of Physician's Choice in HR+/HER2- Metastatic Breast Cancer

AE outcomes in clinical trials are typically reported as absolute incident rates. However, adjusting for exposure to therapy may provide a more accurate way to compare toxic effects of treatments.

A post hoc safety analysis of data from TROPiCS-02 evaluated the exposure-adjusted incidence rates (EAIRs) of AEs (Abstract P3-07-08). EAIRs were calculated as incidence rates per patient-year of exposure to therapy. According to EAIR analysis, treatment-emergent AEs leading to dose reduction were significantly more common with SG than with the physician's choice of treatment (EAIR difference, –60; 95% CI, –1.05 to –0.19), as were rates of treatment-emergent AEs leading to dose delay (EAIR difference, 0.67; 95% CI, 0.002-1.33).

Other safety incidence rates were not significantly different for SG vs the physician's choice of treatment when evaluated by EAIRs, including the rates of treatment-emergent AEs of grade 3 or higher, serious AEs, treatment-emergent AEs that led to discontinuation of study treatment, and treatment-emergent AEs that led to death.

On EAIR analysis, the incidence of grade 3 or higher diarrhea was significantly increased with SG vs the physician's choice of treatment (EAIR difference, 0.19; 95% CI, 0.08-0.30). On exposure-adjusted analysis, rates of other AEs of grade 3 or higher were similar in the 2 arms, including neutropenia, febrile neutropenia, leukopenia, anemia, and fatigue.

patients with HR+ mBC having a "visceral crisis" or symptomatic disease. The primary finding was that ET with ribociclib was superior to chemotherapy plus ET for the treatment of patients with metastatic disease. In addition, rates of toxicity were lower in patients who received ET with ribociclib than in those who received chemotherapy.

New Agents

Considerable new data were presented on advances in drug development at SABCS 2022. Here are a few of the standouts.

CAPItello-291 Trial

The randomized phase 3 CAPItello-291 trial evaluated capivasertib plus fulvestrant vs fulvestrant plus placebo as second-line therapy for patients with HR+/HER2– mBC. The study demonstrated significant improvement in PFS with combination therapy (median PFS, 7 60 months; 95% CI, 0.51-0.71; *P*=0.001.). Diarrhea was the most common adverse effect with capivasertib, and the incidence of hyperglycemia was low.

This is a promising finding from the registration trial and likely will result in regulatory approval of the agent. If approved, another option for endocrine-based combination therapy, besides alpelisib and everolimus, will be available.

Camizestrant

Camizestrant is another oral SERD in clinical development. At SABCS, we saw the results of SERENA-2, a phase 2 randomized clinical trial that compared camizestrant vs fulvestrant as second-line therapy for patients with HR+/HER2– mBC. PFS was significantly better in patients treated with camizestrant than in those who received fulvestrant (median PFS, 17.4 vs 18.6 months; HR, 0.58 [95% CI, 0.41-0.81] and 0.67 [95% CI, 0.48-0.92]; *P*=0.01), supporting further the efficacy of SERDs.

In All ...

It was another year of important news from SABCS 2022. Cancer treatment continues to become more effective for patients, and outcomes continue to improve.

Newer therapies offer more hope for improved clinical outcomes. Oncologists must maintain their efforts to accelerate meaningful research on the treatment of patients with breast cancer.

In HR+/HER2- metastatic breast cancer

following resistance to endocrine-based therapy

what's next

Outcomes for heavily pretreated patients with HR+/HER2- metastatic breast cancer (mBC) after endocrine resistance are poor.

The median overall survival after single-agent chemotherapies is ~12-18 months.[1-5]

Gilead Oncology is working tirelessly to ignite innovation after endocrine resistance in HR+/HER2- mBC.

visit **IgniteWhatsNextInmBC.com** to learn more

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