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A SPECIAL MEETING REVIEW EDITION

Highlights in Metastatic Breast Cancer From the 2023 San Antonio Breast Cancer Symposium

A Review of Selected Presentations From SABCS 2023 • December 5-9, 2023 • San Antonio, Texas

Special Reporting on:

- Clinical Outcomes by Age Subgroups in the Phase 3 TROPiCS-02 Study of Sacituzumab Govitecan vs Treatment of Physician's Choice in HR+/HER2– Metastatic Breast Cancer
- Multicenter Retrospective Cohort Study of the Sequential Use of the Antibody-Drug Conjugates (ADCs) Trastuzumab Deruxtecan (T-DXd) and Sacituzumab Govitecan (SG) in Patients With HER2-Low Metastatic Breast Cancer (MBC)
- Efficacy of Sacituzumab-Govitecan (SG) Post Trastuzumab-Deruxtecan (T-DXd) and Vice Versa for HER2low Advanced or Metastatic Breast Cancer (MBC): A French Multicentre Retrospective Study
- Randomized Phase 3 Study of Datopotamab Deruxtecan vs Chemotherapy for Patients With Previously-Treated Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer: Results From TROPION-Breast01
- HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer
- Sequencing Antibody-Drug Conjugate After Antibody-Drug Conjugate in Metastatic Breast Cancer (A3 Study): Multi-institution Experience and Biomarker Analysis
- Elacestrant vs Standard-of-Care in ER+/HER2– Advanced or Metastatic Breast Cancer (mBC) With ESR1 Mutation: Key Biomarkers and Clinical Subgroup Analyses From the Phase 3 EMERALD Trial

PLUS Meeting Abstract Summaries

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TRODELVY® (sacituzumab govitecan-hziy) is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

TRODELVY®
sacituzumab govitecan-hziy
180 mg for injection

Only ADC to provide statistically significant OS improvement in mTNBC[1]

In the Phase 3 ASCENT study, TRODELVY demonstrated statistically significant survival in **2L and later mTNBC[1,2,*]**

Survival Elevated

Nearly 3x LONGER median PFS versus single-agent chemotherapy[1]

4.8 months with TRODELVY (95% CI: 4.1–5.8) (n=267) vs **1.7 months** with TPC single-agent chemotherapy (95% CI: 1.5–2.5) (n=262); HR=0.43 (95% CI: 0.35–0.54); *P*<0.0001[1]

Help give your patients more time:
~5 more months of overall survival versus chemotherapy

11.8 months with TRODELVY (95% CI: 10.5–13.8) (n=267) vs **6.9 months** with TPC single-agent chemotherapy (95% CI: 5.9–7.6) (n=262); HR=0.51 (95% CI: 0.41–0.62); *P*<0.0001[1]

***TRODELVY was studied in ASCENT, a Phase 3, randomized, active-controlled, open-label study (N=529). The efficacy analysis included PFS in brain-met–negative patients by BICR based on RECIST 1.1 criteria (primary endpoint), PFS for the full population (all patients with and without brain metastases) and OS as secondary endpoints. Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an IV infusion on Days 1 and 8 of a 21-day cycle (n=267) or physician's choice of single-agent chemotherapy (n=262), which included eribulin, vinorelbine, gemcitabine, or capecitabine. Patients were treated until disease progression or unacceptable toxicity.[1,2]**

- 88% of patients in the full population were brain-met negative (primary analysis population), and results were similar across both groups[1,2]
  - **Primary endpoint:** Median PFS was **5.6 months** with TRODELVY (95% CI: 4.3–6.3) (n=235) vs **1.7 months** with single-agent chemotherapy (95% CI: 1.5–2.6) (n=233); HR: 0.41 (95% CI: 0.32–0.52) *P*<0.001[2]
- 13% of patients in the TRODELVY group received only 1 prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy) and efficacy results were consistent with those who received at least 2 prior lines in the metastatic setting[1]

IMPORTANT SAFETY INFORMATION

BOXED WARNING: NEUTROPENIA AND DIARRHEA

- **Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤Grade 1 and reduce subsequent doses.**

CONTRAINDICATIONS

- Severe hypersensitivity reaction to TRODELVY.

Please see additional Important Safety Information on the next page.

INDICATION

TRODELVY® (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

IMPORTANT SAFETY INFORMATION *(cont'd)*

WARNINGS AND PRECAUTIONS

Neutropenia: Severe, life-threatening, or fatal neutropenia can occur and may require dose modification. Neutropenia occurred in 64% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 49% of patients. Febrile neutropenia occurred in 6%. Neutropenic colitis occurred in 1.4%. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Administer G-CSF as clinically indicated or indicated in Table 1 of USPI.

Diarrhea: Diarrhea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 11% of patients. One patient had intestinal perforation following diarrhea. Diarrhea that led to dehydration and subsequent acute kidney injury occurred in 0.7% of all patients. Withhold TRODELVY for Grade 3-4 diarrhea and resume when resolved to ≤Grade 1. At onset, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 35% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.2%. The incidence of anaphylactic reactions was 0.2%. Pre-infusion medication is recommended. Have medications and emergency equipment to treat such reactions available for immediate use. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

Nausea and Vomiting: Nausea occurred in 64% of all patients treated with TRODELVY and Grade 3-4 nausea occurred in 3% of these patients. Vomiting occurred in 35% of patients and Grade 3-4 vomiting occurred in 2% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV). Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to Grade ≤1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of Grade 3-4 neutropenia was 58% in patients homozygous for the UGT1A1*28, 49% in patients heterozygous for the UGT1A1*28 allele, and 43% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anemia was 21% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 9% in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 function.

Embryo-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

ADVERSE REACTIONS

In the pooled safety population, the most common (≥25%) adverse reactions including laboratory abnormalities were decreased leukocyte count (84%), decreased neutrophil count (75%), decreased hemoglobin (69%), diarrhea (64%), nausea (64%), decreased lymphocyte count (63%), fatigue (51%), alopecia (45%), constipation (37%), increased glucose (37%), decreased albumin (35%), vomiting (35%), decreased appetite (30%), decreased creatinine clearance (28%), increased alkaline phosphatase (28%), decreased magnesium (27%), decreased potassium (26%), and decreased sodium (26%).

In the ASCENT study, the most common adverse reactions (incidence ≥25%) were fatigue, diarrhea, nausea, alopecia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (>1%) were neutropenia (7%), diarrhea (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

DRUG INTERACTIONS

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY.

Please see Brief Summary of full Prescribing Information, including BOXED WARNING, on the next page.

2L=second line; ADC=antibody-drug conjugate; BICR=blinded independent central review; CI=confidence interval; HR=hazard ratio; IV=intravenous; met=metastases; mTNBC=metastatic triple-negative breast cancer; OS=overall survival; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors; TPC=treatment of physician's choice.

References: 1. TRODELVY. Prescribing information. Gilead Sciences, Inc.; February 2023. **2.** Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med.* 2021;384(16):1529-1541.

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Learn more at **TRODELVYHCP.com**

TRODELVY® (sacituzumab govitecan-hziy) for injection, for intravenous use
Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

WARNING: NEUTROPENIA AND DIARRHEA

- **Severe or life-threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses.**

[See Warnings and Precautions and Dosage and Administration]

INDICATIONS AND USAGE

*Also see **Clinical Studies***

TRODELVY (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.
- Unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.
- Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

DOSAGE AND ADMINISTRATION

*Also see **Warnings and Precautions***

Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38.

The recommended dosage of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg. Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

- First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions
- Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.
- Premedication: Prior to each dose of TRODELVY, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended. Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist, as well as other drugs as indicated).

Dose Modifications for Infusion-related Reactions: Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions.

Dose Modifications for Adverse Reactions: Withhold or discontinue TRODELVY to manage adverse reactions as described below. Do not re-escalate the TRODELVY dose after a dose reduction for adverse reactions has been made.

Severe Neutropenia, defined as Grade 4 neutropenia ≥7 days, OR Grade 3-4 febrile neutropenia, OR at time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1:

- At first occurrence, 25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF). At second occurrence, 50% dose reduction and administer G-CSF. At third occurrence, discontinue TRODELVY and administer G-CSF.
- At time of scheduled treatment, if Grade 3-4 neutropenia occurs which delays dosing beyond 3 weeks for recovery to ≤ Grade 1, discontinue TRODELVY and administer G-CSF at first occurrence.

Severe Non-Neutropenic Toxicity, defined as Grade 4 non-hematologic toxicity of any duration, OR any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents, OR other Grade 3-4 non-hematologic toxicity persisting >48 hours despite optimal medical management, OR at time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤Grade 1:

- At first occurrence, 25% dose reduction. At second occurrence, 50% dose reduction. At third occurrence, discontinue TRODELVY.
- In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤Grade 1 within 3 weeks, discontinue TRODELVY at first occurrence.

CONTRAINDICATIONS

*Also see **Warnings and Precautions***

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY.

WARNINGS AND PRECAUTIONS

*Also see **BOXED WARNING, Dosage and Administration, Contraindications, Clinical Pharmacology, Nonclinical Toxicology,** and **Use in Specific Populations***

Neutropenia: Severe, life-threatening, or fatal neutropenia can occur in patients treated with TRODELVY. Neutropenia occurred in 64% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 49% of patients. Febrile neutropenia occurred in 6% of patients. The median time to first onset of neutropenia (including febrile neutropenia) was 16 days and has occurred earlier in some patient populations. Neutropenic colitis occurred in 1.4% of patients. Withhold TRODELVY for ANC below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia. Administer G-CSF as clinically indicated or indicated in Table 1 of full Prescribing Information.

Diarrhea: TRODELVY can cause severe diarrhea. Diarrhea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 11% of all patients treated with TRODELVY. One patient had intestinal perforation following diarrhea. Diarrhea that led to dehydration and subsequent acute kidney injury occurred in 0.7% of all patients. Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤ Grade 1. At the onset of diarrhea, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated. Patients who exhibit an excessive cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

Hypersensitivity and Infusion-Related Reactions: Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY treatment. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions. Hypersensitivity reactions within 24 hours of dosing occurred in 35% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.2%. The incidence of anaphylactic reactions was 0.2%. Premedication for infusion reactions in patients receiving TRODELVY is recommended. Have medications and emergency equipment to treat infusion-related reactions, including anaphylaxis, available for immediate use when administering TRODELVY. Closely monitor patients for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

Nausea and Vomiting: TRODELVY is emetogenic. Nausea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 nausea occurred in 3% of patients. Vomiting occurred in 35% of patients. Grade 3-4 vomiting occurred in 2% of these patients. Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist as well as other drugs as indicated) for prevention of CINV. Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting and resume with additional supportive measures when resolved to ≤Grade 1. Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity: Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia and may be at increased risk for other adverse reactions with TRODELVY. The incidence of neutropenia and anemia was analyzed in 948 patients who received TRODELVY and had UGT1A1 genotype results. The incidence of Grade 3-4 neutropenia was 58% in patients homozygous for the UGT1A1*28 allele (n=112), 49% in patients heterozygous for the UGT1A1*28 allele (n=420), and 43% in patients homozygous for the wild-type allele (n=416). The incidence of Grade 3-4 anemia was 21% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 9% in patients homozygous for the wild-type allele. The median time to first neutropenia including febrile neutropenia was 9 days in patients homozygous for the UGT1A1*28 allele, 15 days in patients heterozygous for the UGT1A1*28 allele, and 20 days in patients homozygous for the wild-type allele. The median time to first anemia was 21 days in patients homozygous for the UGT1A1*28 allele, 25 days in patients heterozygous for the UGT1A1*28 allele, and 28 days in patients homozygous for the wild-type allele. Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on onset, duration, and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity.

Embryo-Fetal Toxicity: Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

ADVERSE REACTIONS

*Also see **BOXED WARNING, Warnings and Precautions,** and **Clinical Studies***

The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY in 1063 patients from four studies, IMMU-132-01, ASCENT, TROPiCS-02, and TROPHY which included 366 patients with mTNBC, 322 patients with HR+/HER2- breast cancer, and 180 patients with mUC. Among the 1063 patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 63 months). The most common (≥ 25%) adverse reactions including laboratory abnormalities were decreased leukocyte count (84%), decreased neutrophil count (75%), decreased hemoglobin (69%), diarrhea (64%), nausea (64%), decreased lymphocyte count (63%), fatigue (51%), alopecia (45%), constipation (37%), increased glucose (37%), decreased albumin (35%), vomiting (35%), decreased appetite (30%), decreased creatinine clearance (28%), increased alkaline phosphatase (28%), decreased magnesium (27%), decreased potassium (26%), and decreased sodium (26%).

Locally Advanced or Metastatic Triple-Negative Breast Cancer

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label study (ASCENT) in patients with mTNBC who had previously received a taxane and at least two prior chemotherapies. Patients were randomized (1:1) to receive either TRODELVY (n=258) or single agent chemotherapy (n=224) and were treated until disease progression or unacceptable toxicity. For patients treated with TRODELVY, the median duration of treatment was 4.4 months (range: 0 to 23 months). Serious adverse reactions occurred in 27% of patients, and those in > 1% included neutropenia (7%), diarrhea (4%), and pneumonia (3%). Fatal adverse reactions occurred in 1.2% of patients, including respiratory failure (0.8%) and pneumonia (0.4%). TRODELVY was permanently discontinued for adverse reactions in 5% of patients. These adverse reactions (≥1%) were pneumonia (1%) and fatigue (1%). The most frequent (≥5%) adverse reactions leading to a treatment interruption in 63% of patients were neutropenia (47%), diarrhea (5%), respiratory infection (5%), and leukopenia (5%). The most frequent (>4%) adverse reactions leading to a dose reduction in 22% of patients were neutropenia (11%) and diarrhea (5%). G-CSF was used in 44% of patients who received TRODELVY. The most common (≥25%) adverse reactions including lab abnormalities were decreased hemoglobin (94%), decreased lymphocyte count (88%), decreased leukocyte count (86%), decreased neutrophil count (78%), fatigue (65%), diarrhea (59%), nausea (57%), increased glucose (49%), alopecia (47%), constipation (37%), decreased calcium (36%), vomiting (33%), decreased magnesium (33%), decreased potassium (33%), increased albumin (32%), abdominal pain (30%), decreased appetite (28%), increased aspartate aminotransferase (27%), increased alanine aminotransferase (26%), increased alkaline phosphatase (26%), and decreased phosphate (26%).

Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label study (TROPiCS-02) in patients with unresectable locally advanced or metastatic HR+/HER2- breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression occurred within 12 months). Patients were randomized (1:1) to receive either TRODELVY (n=268) or single agent chemotherapy (n=249) and were treated until disease progression or unacceptable toxicity. For patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 63 months). Serious adverse reactions occurred in 28% of patients, and those in >1% of patients included diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), abdominal pain, colitis, neutropenic colitis, pneumonia, and vomiting (each 2%). Fatal adverse reactions occurred in 2% of patients, including arrhythmia, COVID-19, nervous system disorder, pulmonary embolism, and septic shock (each 0.4%). TRODELVY was permanently discontinued for adverse reactions in 6% of patients. The most frequent (≥0.5%) of these adverse reactions were asthenia, general physical health deterioration, and neutropenia (each 0.7%). The most frequent (≥5%) adverse reaction leading to treatment interruption in 66% of patients was neutropenia (50%). The most frequent (>5%) adverse reactions leading to dose reduction in 33% of patients were neutropenia (16%) and diarrhea (8%). G-CSF was used in 54% of patients who received TRODELVY. The most common (≥25%) adverse reactions including lab abnormalities were decreased leukocyte count (88%), decreased neutrophil count (83%), decreased hemoglobin (73%), and decreased lymphocyte count (65%); diarrhea (62%), fatigue (60%), nausea (59%), alopecia (48%), increased glucose (37%), constipation (34%), and decreased albumin (32%). Other clinically significant adverse reactions in TROPiCS-02 (≤ 10%) include: hypotension (5%), pain (5%), rhinorrhea (5%), hypocalcemia (3%), nasal congestion (3%), skin hyperpigmentation (3%), colitis or neutropenic colitis (2%), hyponatremia (2%), pneumonia (2%), proteinuria (1%), enteritis (0.4%).

Locally Advanced or Metastatic Urothelial Cancer

The safety of TRODELVY was evaluated in a single-arm, open-label study (TROPHY) in patients (n=113) with mUC who had received previous platinum-based and anti-PD-1/PD-L1 therapy. Serious adverse reactions occurred in 44% of patients, and those in >1% included infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), sepsis or bacteremia (5%), diarrhea (4%), anemia, venous thromboembolism, and small intestinal obstruction (3% each), pneumonia, abdominal pain, pyrexia, and thrombocytopenia (2% each). Fatal adverse reactions occurred in 3.6% of patients, including sepsis, respiratory failure, epistaxis, and completed suicide. TRODELVY was permanently discontinued for adverse reactions in 10% of patients. The most frequent of these adverse reactions was neutropenia (4%, including febrile neutropenia in 2%). The most common adverse reactions leading to dose interruption in 52% of patients were neutropenia (27%, including febrile neutropenia in 2%), infection (12%), and acute kidney injury (8%). The most common (>4%) adverse reactions leading to a dose reduction in 42% of patients were neutropenia (13%, including febrile neutropenia in 3%), diarrhea (11%), fatigue (8%), and infection (4%). G-CSF was used in 47% of patients who received TRODELVY. The most common (≥25%) adverse reactions including lab abnormalities were decreased leukocyte count (78%), diarrhea (72%), decreased hemoglobin (71%), decreased lymphocyte count (71%), fatigue (68%), decreased neutrophil count (67%), nausea (66%), increased glucose (59%), decreased albumin (51%), any infection (50%), alopecia (49%), decreased calcium (46%), decreased sodium (43%), decreased appetite (41%), decreased phosphate (41%), increased alkaline phosphatase (36%), constipation (34%), vomiting (34%), increased activated partial thromboplastin time (33%), increased creatinine (32%), rash (32%), decreased magnesium (31%), abdominal pain (31%), increased alanine aminotransferase (28%), increased lactate dehydrogenase (28%), decreased potassium (27%), increased aspartate aminotransferase (26%), and decreased platelet count (25%). Other clinically significant adverse reactions (≤15%) include: peripheral neuropathy (12%), sepsis or bacteremia (9%), and pneumonia (4%).

DRUG INTERACTIONS

*Also see **Warnings and Precautions** and **Clinical Pharmacology***

UGT1A1 Inhibitors: Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers: Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Avoid administering UGT1A1 inducers with TRODELVY

USE IN SPECIFIC POPULATIONS

*Also see **Warnings and Precautions, Clinical Pharmacology,** and **Nonclinical Toxicology***

Pregnancy: TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

Lactation: There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

Females and Males of Reproductive Potential: Verify the pregnancy status of females of reproductive potential prior to initiation. TRODELVY can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males: Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Infertility: Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential.

Pediatric Use: Safety and effectiveness of TRODELVY have not been established in pediatric patients.

Geriatric Use:

Of the 366 patients with TNBC who were treated with TRODELVY, 19% of patients were 65 years and 3% were 75 years and older. No overall differences in safety and effectiveness were observed between patients ≥ 65 years of age and younger patients.

Of the 322 patients with HR+/HER2- breast cancer who were treated with TRODELVY, 26% of patients were ≥ 65 years and 6% were ≥ 75 years. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (3%).

Of the 180 patients with UC who were treated with TRODELVY, 59% of patients were ≥ 65 years and 27% were ≥ 75 years. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (8%).

Hepatic Impairment: No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment. The safety of TRODELVY in patients with moderate or severe hepatic impairment has not been established, and no recommendations can be made for the starting dose in these patients.

761115-GS-007 Feb 2023

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180 mg for injection

Clinical Outcomes by Age Subgroups in the Phase 3 TROPiCS-02 Study of Sacituzumab Govitecan vs Treatment of Physician's Choice in HR+/HER2– Metastatic Breast Cancer

The open-label, phase 3 TROPiCS-02 trial evaluated sacituzumab govitecan vs the physician's treatment of choice in patients with previously treated, endocrine-resistant, hormone receptor–positive/human epidermal growth factor–negative (HR+/HER2–) metastatic breast cancer.[1-3] Enrolled patients had either inoperable locally recurrent breast cancer or metastatic breast cancer that had progressed after prior therapy with 1 or more regimens of endocrine therapy, a taxane, and a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, or with 2 to 4 lines of chemotherapy. Stratification factors included visceral metastasis, 6 or more months of endocrine therapy in the metastatic setting, and prior lines of chemotherapy. In the experimental arm, patients received sacituzumab govitecan (10 mg/kg, days 1 and 8, in 21-day cycles); patients in the control arm received the physician's choice of chemotherapy agent from among capecitabine, vinorelbine, gemcitabine, and eribulin. The

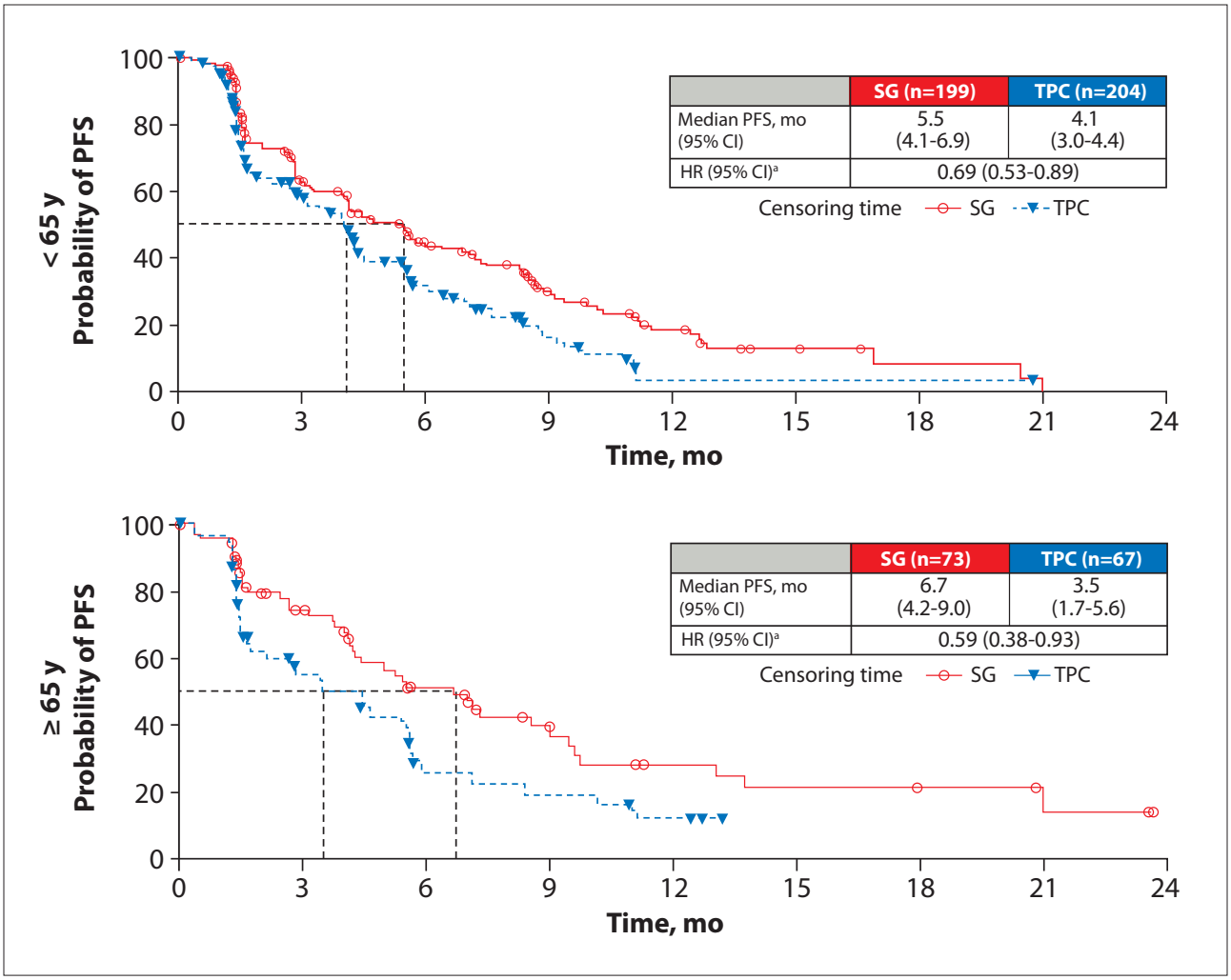

Figure 1. The median PFS per BICR across all age subgroups in patients with HR+/HER2– metastatic breast cancer from the phase 3 TROPiCS-02 study.

[a]HR and 95% CI are based on unstratified Cox regression.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; mo, months; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice; y, years.

Adapted from Bardia et al. Abstract P05-21-09. Presented at: the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, Texas.[3]

primary endpoint was progression-free survival (PFS) according to blinded independent review.

The TROPiCS-02 study randomized 272 patients to an experimental arm and 271 to a control arm. The study yielded a superior median PFS with sacituzumab govitecan vs physician's treatment of choice (5.5 vs 4.0 months; hazard ratio [HR], 0.66; *P*=.003), as well as a significant improvement in median overall survival (OS; 14.4 vs 11.2 months; HR, 0.79; *P*=.020).[1,2] A post hoc study evaluated the efficacy, safety, and quality of life of patients from the TROPiCS-02 study on the basis of age subgroups.[3] Because the incidence of HR+/HER2– metastatic breast cancer increases with age, the study compared patients who were younger than 65 years vs patients who were 65 years old or older. Median PFS was superior with sacituzumab govitecan vs physician's treatment of choice, both among patients who were younger than 65 years (5.5 vs 4.1 months; HR, 0.69; 95% CI, 0.53-0.89) and among patients who were 65 years old or older (6.7 vs 3.5 months; HR, 0.59; 95% CI, 0.38-0.93) (Figure 1). The median OS was also superior with sacituzumab govitecan vs chemotherapy, both in the younger patient subgroup (14.1 vs 11.5 months; HR, 0.81; 95% CI, 0.64-1.02) and in the older patient subgroup (14.9 vs 10.1 months; HR, 0.80; 95% CI, 0.54-1.19). In both the younger and older patient subgroups, treatment-emergent adverse events (AEs) of grade 3 or higher were more common with sacituzumab govitecan than with chemotherapy, as were treatment-emergent AEs leading to dose interruption. Sacituzumab govitecan was generally associated with a superior quality of life, and in the subgroup of patients younger than 65 years, the time to deterioration owing to fatigue was significantly longer with the antibody-drug conjugate (ADC) than with chemotherapy (*P*=.021).

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Multicenter Retrospective Cohort Study of the Sequential Use of the Antibody-Drug Conjugates (ADCs) Trastuzumab Deruxtecan (T-DXd) and Sacituzumab Govitecan (SG) in Patients With HER2-Low Metastatic Breast Cancer (MBC)

Trastuzumab deruxtecan (T-DXd) is an ADC comprising an anti-HER2 antibody that is chemically bound by a tumor-selective, cleavable linker to an agent that blocks the activity of topoisomerase I.[1] T-DXd is approved for the treatment of unresectable or metastatic HER2-positive (HER2+) breast cancer in patients who have received a prior anti-HER2–based regimen and for the treatment of unresectable or metastatic HER2-low breast cancer.[2,3] Sacituzumab govitecan is an ADC comprising an antibody against TROP2 and the SN-38 payload, which is an active metabolite of irinotecan; the antibody and payload are linked together by a pH-sensitive, cleavable linker. Sacituzumab govitecan is approved for the treatment of unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) and for the treatment of unresectable locally advanced or metastatic HR+/HER2– breast cancer.[4-6]

A retrospective cohort study investigated the safety and efficacy as well as the effect of sequencing of these 2 ADCs in the real-world setting at 5 cancer treatment centers among patients with HER2-low metastatic

ABSTRACT SUMMARY: ASCENT-07: A Phase 3, Randomized, Open-Label Study of Sacituzumab Govitecan vs Treatment of Physician's Choice in Patients With HR+/HER2– Inoperable Locally Advanced or Metastatic Breast Cancer Post Endocrine Therapy

The open-label phase 3 ASCENT-07 trial will investigate sacituzumab govitecan vs the physician's treatment of choice as first-line therapy in patients with inoperable locally advanced or metastatic HR+/HER2– breast cancer that is resistant to endocrine therapy (Abstract PO1-05-09). Stratification factors include prior therapy with a CDK4/6 inhibitor for metastatic disease, HER2 status, and geographic region. The study will randomize 654 patients 2:1 to receive the ADC (10 mg/kg, days 1 and 8, every 21 days) vs capecitabine, paclitaxel, or nab-paclitaxel. The primary endpoint is PFS assessed by blinded independent review. Key secondary endpoints include OS, ORR, safety, and quality of life. The study is currently recruiting patients.

Table. Efficacy Data for Patients With HR+/HER2-Low Metastatic Breast Cancer Treated Sequentially With T-DXd and SG

SG → T-DXd (n=24, 42.9%)		
	ADC1 (SG)	**ADC2 (T-DXd)**
ORR by investigator assessment, %	77.3	34.8
CBR by investigator assessment, %	86.4	60.9
Median rwPFS, mo	8.0	3.7
Median rwOS from time of each ADC start, mo	22.8	7.8

T-DXd → SG (n=32, 51.7%)		
	ADC1 (T-DXd)	**ADC2 (SG)**
ORR by investigator assessment, %	46.9	18.5
CBR by investigator assessment, %	78.1	37.0
Median rwPFS, months	5.5	2.6
Median rwOS from time of each ADC start, mo	19.8	10.1

ADC, antibody-drug conjugate; ADC1, first ADC; ADC2, second ADC; CBR, clinical benefit response; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor–positive; mo, months; ORR, overall response rate; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.
Adapted from Huppert et al. Abstract PS08-04. Presented at: the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, Texas.[7]

breast cancer.[7] The study included 84 patients with HER2-low metastatic breast cancer who had received therapy with both ADCs in either order or who had received monotherapy with 1 of the ADCs while participating in a clinical trial. Most of the 84 patients had visceral disease before receiving ADC therapy and were heavily pretreated. Among 56 patients with HR+/HER2-low disease, 24 had received sacituzumab govitecan followed by T-DXd and 32 had received T-DXd followed by sacituzumab govitecan.

Among 56 patients who received sacituzumab govitecan as their first ADC, the median PFS was 8.0 months with sacituzumab govitecan and 3.7 months with T-DXd. Among patients who received T-DXd as their first ADC, the median PFS was 5.5 months with T-DXd and 2.6 months with sacituzumab govitecan (Table). There were 28 patients who had HR–/HER2-low disease, including 25 who received sacituzumab govitecan as their first ADC. Among this group, the median PFS was 7.8 months with sacituzumab govitecan and 2.8 months with T-DXd. Among 3 patients who received T-DXd as their first ADC, the median PFS was undetermined for both ADCs. In all subgroups, the median objective response rate (ORR) was higher and the median PFS was longer with the first ADC treatment than with the second ADC treatment.

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Efficacy of Sacituzumab-Govitecan (SG) Post Trastuzumab-Deruxtecan (T-DXd) and Vice Versa for HER2low Advanced or Metastatic Breast Cancer (MBC): A French Multicentre Retrospective Study

T-DXd and sacituzumab govitecan were approved for the treatment of HER2-low metastatic breast cancer on the basis of the ASCENT, TROPiCS-02, and DESTINY-Breast04 trials.[1] The multicenter ADC Low study retrospectively evaluated the efficacy and safety of the 2 ADCs when administered sequentially as monotherapy in patients with HER2-low metastatic breast cancer.[2] The primary endpoint was the PFS on the basis of treatment with the second ADC. The study included 179 patients, 115 of whom

Table 2. Median PFI for ADC1 and Median PFS for ADC2

Population and Sequential Regimen	Median PFI ADC1, mo	Median PFS ADC2, mo
Whole population (n=179) SG → T-DXd (n=115) T-DXd → SG (n=64)	4.5 (95% CI, 3.4-5.1)	2.7 (95% CI, 2.4-3.3)
HR–/HER2-low (n=100) having received SG as ADC1 then T-DXd as ADC2	4.9 (95% CI, 3.9-5.5)	2.2 (95% CI, 1.9-2.7)
HR+/HER2-low (n=56) having received T-DXd as ADC1 then SG as ADC2	2.7 (95% CI, 2.3-3.5)	3.1 (95% CI, 2.6-3.6)

ADC, antibody-drug conjugate; ADC1, first antibody-drug conjugate; ADC2, second antibody-drug conjugate; CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PFI, progression-free interval; PFS, progression-free survival; SG, sacituzumab govitecan; T-DXd, trastuzumab deruxtecan.
Adapted from Poumeaud et al. Abstract PS08-02. Presented at: the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, Texas.[2]

received sacituzumab govitecan as their first ADC and 64 of whom received T-DXd as their first ADC. The first ADC was the median third line of therapy, and the second ADC was the median fifth line of therapy. At the time of data analysis, 32% of patients were still receiving therapy with the second ADC.

After treatment with the first ADC, the median PFS was 2.7 months for the patients with HR+ disease and 4.9 months for the patients with HR– disease. (Table 2) The low median PFS among the patients with HR+ disease was considered to stem from the fact that T-DXd was the median fourth line of treatment in that patient group. After treatment with the second ADC, the median PFS was 2.7 months for the entire study population (95% CI, 2.4-3.3 months); the median PFS after treatment with the second ADC was short regardless of ADC sequencing (95% CI, 2.2-3.1 months). Multivariate analysis suggested a trend toward benefit with sacituzumab govitecan as the first ADC, but in the comparison with T-DXd as the first ADC, the difference did not reach statistical significance (*P*=.063).

To identify a subgroup of patients who were more likely to benefit from treatment with a second ADC, patients were categorized according to their response to ADC therapy. Those with primary resistance had progressive disease as their best response, and those with secondary resistance had an objective response or stable disease. On the basis of these concepts, 40.4% of the patients had primary resistance and 59.6% had secondary resistance to the first ADC. In the patients who were also resistant to the second ADC, payload cross-resistance may have developed at progression with the first ADC. Among the patients who exhibited primary resistance at progression with the first ADC, a short time of efficacy with the second ADC was noted in 39%. The study suggests that sequencing 2 ADCs with the same payload may limit efficacy, particularly in heavily pretreated patients.

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Randomized Phase 3 Study of Datopotamab Deruxtecan vs Chemotherapy for Patients With Previously-Treated Inoperable or Metastatic Hormone Receptor-Positive, HER2-Negative Breast Cancer: Results From TROPION-Breast01

Datopotamab deruxtecan (Dato-DXd) is an ADC comprising a TROP2-directed antibody linked to deruxtecan, a topoisomerase I inhibitor.[1] The open-label, international, phase 3 TROPION-Breast01 trial evaluated Dato-DXd vs chemotherapy in patients with HR+/HER2– breast cancer.[2-4] The study included patients who had previously received 1 or 2 lines of chemotherapy for inoperable or metastatic disease. Patients had experienced disease progression on endocrine therapy or for whom endocrine therapy was unsuitable. Stratification factors included the number of prior lines of chemotherapy, geographic location,

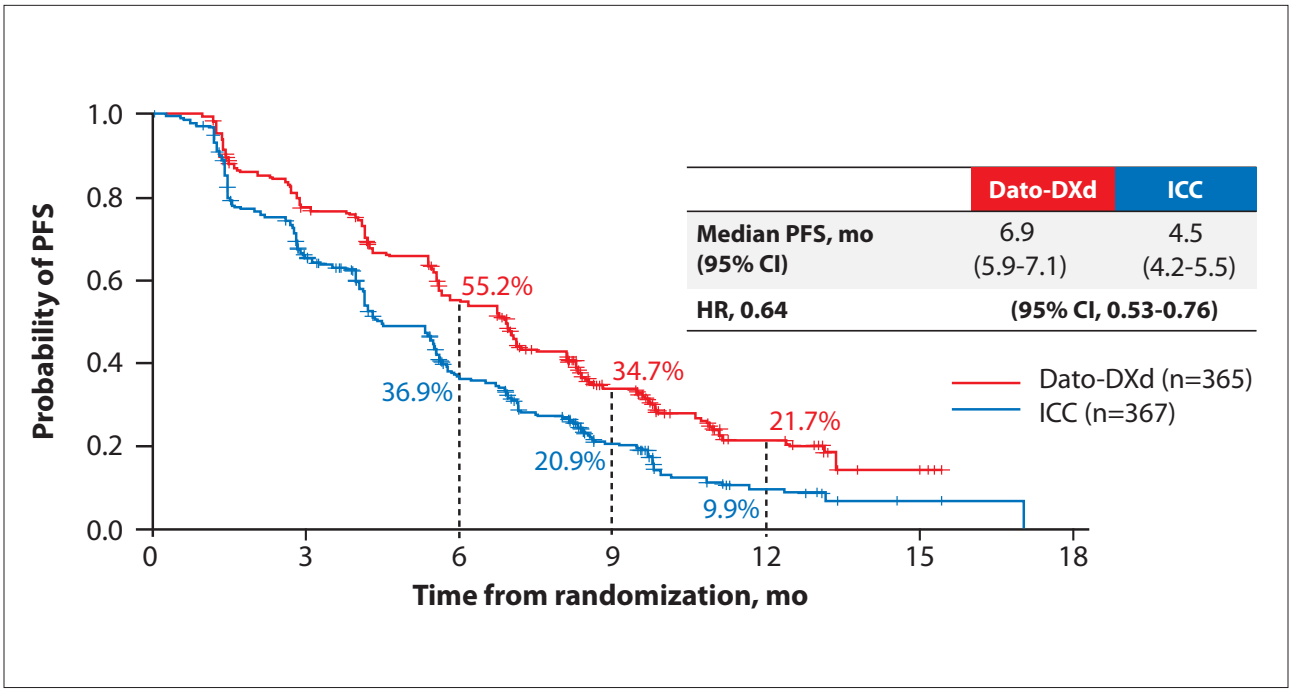

Figure 2. The PFS by BICR per RECIST v1.1 in patients with HR+/HER2– breast cancer from the TROPION-Breast01 study.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ICC, investigator's choice of chemotherapy; mo, months; PFS, progression-free survival.
Adapted from Bardia et al. Abstract GS02-01. Presented at: the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, Texas.[2]

and prior exposure to a CDK4/6 inhibitor. Patients were evenly randomized to receive Dato-DXd (6 mg/kg, day 1) or the investigator's choice of chemotherapy on a 21-day schedule. The study's 2 primary endpoints were PFS and OS according to a blinded independent review.

The TROPION-Breast01 study included 732 patients and showed a significant improvement in median PFS when Dato-DXd was compared with chemotherapy (6.9 vs 4.5 months; HR, 0.64; 95% CI, 0.53-0.76; *P*<.0001) (Figure 2), thus meeting the primary endpoint of PFS. Among 317 patients with more than 12 months of prior treatment with a CDK4/6 inhibitor, the median PFS was 7.1 months with Dato-DXd vs 5.0 months with chemotherapy (HR, 0.61; 95% CI, 0.45-0.82). Patients who received the ADC also had a longer time until the first subsequent therapy vs those who received chemotherapy (8.2 vs 5.0 months; HR, 0.53; 95% CI, 0.45-0.64). Therapy with Dato-DXd was also superior to the investigator's choice of chemotherapy among patient subgroups, including patients with prior exposure to a CDK4/6 inhibitor (≤12 months or >12 months) and patients with or without brain metastasis at baseline.

Among the patients who received treatment with the ADC, the rate of treatment-related AEs of at least grade 3 was 21%, which was less than half the rate observed in the chemotherapy arm (45%). In the Dato-DXd arm, treatment-related AEs led to treatment discontinuation in 3% of patients, and serious treatment-related AEs were observed in 6% of patients. Grade 3 or higher AEs of clinical interest in the Dato-DXd arm included neutropenia (1%) and stomatitis (6%). On the basis of measures of time to deterioration in quality of life, overall quality of life was superior with Dato-DXd in comparison with chemotherapy, as were more specific measures of physical functioning and pain.

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HER2CLIMB-02: Randomized, Double-Blind Phase 3 Trial of Tucatinib and Trastuzumab Emtansine for Previously Treated HER2-Positive Metastatic Breast Cancer

Tucatinib is a HER2-directed tyrosine kinase inhibitor (TKI) that is approved for the treatment of patients with locally advanced or metastatic breast cancer, including those with brain metastasis.[1,2] Trastuzumab emtansine (T-DM1) is a HER2-directed ADC that delivers a microtubule-disrupting agent, emtansine, to the targeted cell.[3] The double-blind, phase 3 HER2CLIMB-02 study evaluated T-DM1 combined with tucatinib or placebo in patients with unresectable locally advanced or metastatic breast cancer.[4] The study enrolled patients with HER2+ disease who had experienced disease progression after treatment with trastuzumab and a taxane in any setting. Patients with previously treated brain metastases that did not require immediate local therapy were allowed. Stratification factors included the number of prior lines of therapy for metastatic disease, HR status, brain metastasis, and Eastern Cooperative Oncology Group performance status. The primary endpoint was PFS by investigator assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[5]

The HER2CLIMB-02 study randomized 228 patients to T-DM1 plus tucatinib and 235 to T-DM1 plus placebo (Figure 3). Baseline characteristics were well balanced between the 2 arms. Patients had a median age of 53 to 55 years and 60% had HR+ disease. Current or prior brain metastases were noted in 43% to 45% of patients, including active (22%-24%) and treated stable (20%-21%) masses. Patients had received a median of 1 prior line of systemic therapy in the metastatic setting (range, 0-8), and nearly all the patients had received prior treatment with pertuzumab (89%-91%). The trial met its primary endpoint, demonstrating a median PFS of 9.5 months with T-DM1 plus tucatinib vs 7.4 months with T-DM1 plus placebo (HR, 0.76; 95% CI, 0.61-0.95; *P*=.0163). Analysis of prespecified subgroups showed a consistent improvement in median PFS with T-DM1 plus tucatinib vs T-DM1 plus placebo. Among patients with brain metastasis, the median PFS was again superior with T-DM1 plus tucatinib (n=99) vs T-DM1 plus placebo (n=105; 7.8 vs 5.7 months; HR, 0.64; 95% CI, 0.46-0.89); statistical significance was not evaluated because of the hierarchical testing strategy. Among evaluable patients in the overall study population, the confirmed ORR was

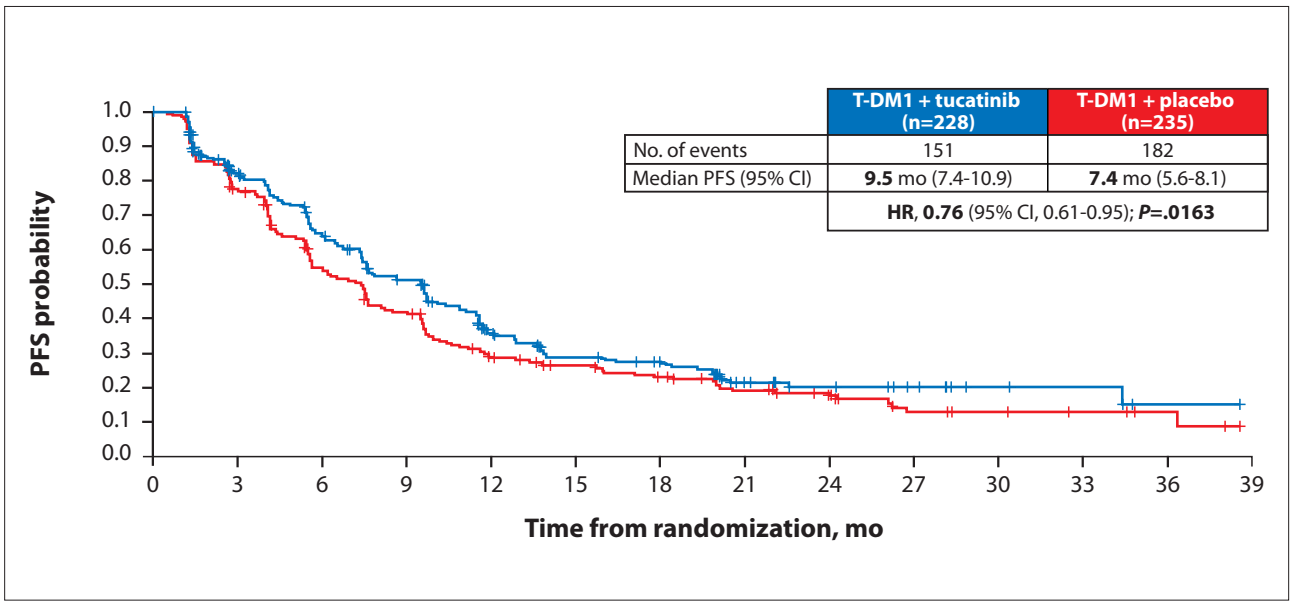

Figure 3. The PFS by investigator assessment per RECIST v.1.1 in patients with HER2+ LA/MBC from the HER2CLIMB-02 study.
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; LA/MBC, locally advanced or metastatic breast cancer; PFS, progression-free survival; T-DM1, trastuzumab emtansine.
Adapted from Hurvitz et al. Abstract GS01-10. Presented at: the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, Texas.[4]

42.0% with the tucatinib combination vs 36.1% with the placebo combination, with a complete response rate of approximately 4% in both arms. After a median follow-up of 24.4 months, the median OS was similar for the 2 arms (HR, 1.23; 95% CI, 0.87-1.74). Interim OS results did not meet the prespecified crossing boundary of $P \leq .0041$.

In the arm that received T-DM1 plus tucatinib, 68.8% of patients experienced a treatment-emergent AE of grade 3 or higher vs 41.2% in the placebo arm, and 1.3% of patients in the arm that received T-DM1 plus tucatinib had a fatal treatment-emergent AE vs 0.9% in the placebo arm. The most common treatment-emergent AEs of grade 3 or higher in the T-DM1-plus-tucatinib arm vs the T-DM1-plus-placebo arm were increased alanine transaminase (16.5% vs 2.6%), increased aspartate transaminase (16.5% vs 2.6%), and anemia (8.2% vs 4.7%). Hepatic events in the T-DM1-plus-tucatinib arm were generally transient, manageable, and reversible.

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Sequencing Antibody-Drug Conjugate After Antibody-Drug Conjugate in Metastatic Breast Cancer (A3 Study): Multi-institution Experience and Biomarker Analysis

To provide insights regarding best practices for sequencing the administration of ADCs, a study conducted at 3 academic medical institutions evaluated outcomes in patients with metastatic HR+/HER2– breast cancer or TNBC who were treated with 2 or more ADCs in sequence.[1] Clinical data were extracted by chart review. Cross-resistance to the second ADC was defined as disease progression at the first restaging assessment or progression within 60 days after initiating treatment. The study identified 68 patients with metastatic HR+/HER2– breast cancer or TNBC who received therapy with 2 ADCs between August 2014 and June 2023. The study included 30 patients (44%) with HR+/HER2– disease and 38 patients (56%) with TNBC. There were 50 patients (74%) who had HER2-low disease. At the time of initiation of treatment with the second ADC, the patients had a median age of 59.6 years (range, 29.9-88.6). Before the start of therapy with the second ADC, patients had received a median of 4 lines of prior therapy in the metastatic setting.

The median time to progression with the first ADC was 161 days (95% CI, 131-224) and with the second ADC was 77 days (95% CI, 51-112; $P < .01$). Of 47 patients who were treated with a second ADC that had a change in antibody target and a change in payload, cross-resistance was observed in 23 patients (49%) (Figure 4). Of 10 patients who were treated with a second ADC that had the same payload but a different antibody target, cross-resistance was observed in 3 (30%). Of 14 patients who were treated with a second ADC that had the same antibody target but a different payload, 8 (57%) exhibited

ABSTRACT SUMMARY: OPERA-01: A Randomized, Open-Label, Phase 3 Study of Palazestrant (OP-1250) vs Standard-of-Care Treatment for ER+, HER2– Advanced or Metastatic Breast Cancer After Endocrine and CDK4/6 Inhibitor Therapy

Palazestrant is an oral complete ER antagonist and SERD that prevents transcription of *ESR1* (Abstract PO3-18-09). The international, open-label, phase 3 OPERA-I trial will investigate palazestrant vs SOC in patients with ER+/HER2– breast cancer whose locally advanced or metastatic disease has progressed on endocrine therapy combined with a CDK4/6 inhibitor. The study will initially test 2 dose levels of palazestrant: 90 and 120 mg daily. In all, 510 patients will be evenly randomized to receive the selected dose of palazestrant or SOC. The primary endpoints are the PFS in patients with *ESR1* mutation and the PFS in patients without *ESR1* mutation, both according to blinded independent review.

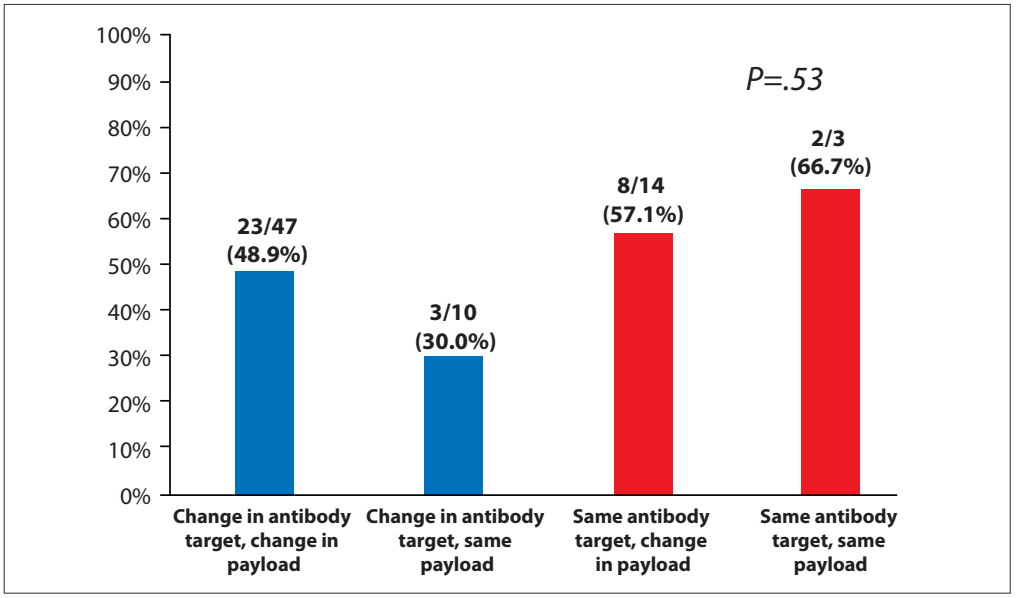

Figure 4. Cross-resistance to later ADC on the basis of ADC-to-ADC characteristics in patients with metastatic breast cancer from the A3 study.
ADC, antibody-drug conjugate.
Adapted from Abelman et al. Abstract PS08-03. Presented at: the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, Texas.[1]

cross-resistance. Only 3 patients were treated with a second ADC that had the same target and payload as the first ADC, and 2 of these patients (67%) showed cross-resistance. Tumor DNA sequencing data were available for 20 patients who had received therapy with more than 1 ADC. Mutations in genes associated with topoisomerase I, including *TOP1*, *TOP2A*, *TOP3A*, and *TOP3B*, were identified in 7 patients who exhibited cross-resistance to the second ADC, which carried a payload that inhibited topoisomerase I activity.

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Elacestrant vs Standard-of-Care in ER+/HER2– Advanced or Metastatic Breast Cancer (mBC) With ESR1 Mutation: Key Biomarkers and Clinical Subgroup Analyses From the Phase 3 EMERALD Trial

Endocrine therapy plus a CDK4/6 inhibitor is the preferred first-line therapy for patients with estrogen receptor–positive (ER+)/HER2– metastatic breast cancer.[1] The open-label, phase 3 EMERALD trial compared elacestrant, a selective estrogen receptor degrader (SERD), vs standard-of-care therapy (SOC) in patients with ER+/HER2– metastatic breast cancer.[2,3] Enrolled patients were required to have had 1 or 2 prior lines of endocrine therapy as well as prior therapy with a CDK4/6 inhibitor. Patients in the SOC arm were treated with an aromatase inhibitor or fulvestrant. The study included 239 patients who were randomized to elacestrant and 239 who were randomized to SOC. The trial led to the approval of elacestrant for patients with ER+/HER2– metastatic breast cancer harboring mutations in the *ESR1* gene following 1 or more lines of endocrine therapy.[4] Thus, elacestrant became the first SERD to be approved for the treatment of patients with ER+/HER2– breast cancer harboring an *ESR1* mutation.

In the EMERALD trial, the duration of prior therapy with a CDK4/6 inhibitor correlated with elacestrant efficacy. Among all patients with an *ESR1* mutation who had at least 12 months of prior exposure to a CDK4/6 inhibitor (n=159), the median PFS was 8.61 months with elacestrant vs 1.91 months with SOC (HR, 0.410; 95% CI, 0.262-0.634) (Table 3). Subgroup analysis was performed to evaluate the efficacy of elacestrant vs SOC in subgroups of patients with important biomarkers and clinical characteristics, such as resistance mutations and bone or visceral metastasis. The analysis showed a consistent benefit with elacestrant vs SOC among subgroups of patients with *ESR1* mutation who had received at least 12 months of prior CDK4/6 inhibitor therapy, including those with bone metastasis (HR, 0.381; 95% CI, 0.230-0.623), liver and/or lung metastasis (HR, 0.354; 95% CI, 0.209-0.589), *PIK3CA* mutation (HR, 0.423; 95% CI, 0.176-0.941), HER2-low expression (HR, 0.301; 95% CI, 0.142-0.604), or *TP53* mutation (HR, 0.300; 95% CI, 0.132-0.643).[3] Safety analysis showed that the toxicity profile

Table 3. Patient Population With Exposure to CDK4/6 Inhibitors for ≥12 Months From EMERALD Trial

	Patients, % (No.)	Median PFS, mo (95% CI)		HR (95% CI)
		Elacestrant	SOC	
All *ESR1*-mutated patients	**100** (159)	**8.61** (4.14-10.84)	**1.91** (1.87-3.68)	0.410 (0.262-0.634)
ESR1-mutated and liver and/or lung metastases	**71** (133)	**7.26** (2.20-10.84)	**1.87** (1.84-1.94)	0.354 (0.209-0.589)
ESR1-mutated and *PIK3CA* mutations[a]	**39** (62)	**5.45** (2.14-10.84)	**1.94** (1.84-3.94)	0.423 (0.176-0.941)
ESR1-mutated and *TP53* mutations	**38** (61)	**8.61** (3.65-24.25)	**1.87** (1.84-3.52)	0.300 (0.132-0.643)
ESR1-mutated and *HER2*-low expression[b]	**48** (77)	**9.03** (5.49-16.89)	**1.87** (1.84-3.75)	0.301 (0.142-0.604)

[a]Includes E545K, H1047R, and E542K, among others
[b]HER2 IHC 1+ and 2+ with no ISH amplification
CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; ISH, in situ hybridization; HER2, human epidermal growth factor receptor 2; PFS, progression-free survival; SOC, standard of care.
Adapted from Bardia et al. Abstract: PS17-02. Presented at: the 2023 San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, Texas.[3]

for each subgroup was similar to that of the overall population of patients with *ESR1* mutation and at least 12 months of prior CDK4/6 inhibitor therapy.

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Highlights in Metastatic Breast Cancer from the 2023 San Antonio Breast Cancer Symposium: Commentary

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The San Antonio Breast Cancer Symposium (SABCS), which was held in San Antonio, Texas, in December 2023, provided valuable insights into the management of metastatic breast cancer. Data focused on the efficacy, safety, and utilization as treatment options of several single-agent and combination therapies, including sacituzumab govitecan, datopotamab deruxtecan, elacestrant, and trastuzumab emtansine plus tucatinib.

Sacituzumab Govitecan

The phase 3 TROPiCS-02 study demonstrated a similar efficacy benefit with sacituzumab govitecan vs treatment of physician's choice in patients with pretreated, endocrine-resistant, hormone receptor-positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) metastatic breast cancer, regardless of age subgroup, with manageable safety.[1] As expected, the older patients had higher Eastern Cooperative Oncology Group performance status scores and more preexisting comorbidities. Similar rates of treatment-emergent adverse events (AEs) were observed regardless of age subgroup, and efficacy was improved at higher vs lower relative dose intensity in patients older than 65 years. Time to deterioration owing to fatigue was significantly longer with sacituzumab govitecan vs physician's choice in patients older than 65 years. Sacituzumab govitecan also demonstrated a favorable benefit-to-risk profile in older patients, a finding that supports its use vs physician's choice in this patient population, which is known for experiencing increased toxicity and decreased efficacy with chemotherapy.

Antibody-Drug Conjugate Sequencing

Several abstracts looking at the sequential use of antibody-drug conjugates (ADCs) were presented at the

poster spotlight session, including institutional experience from the University of California San Francisco, MD Anderson, French sites, and the Massachusetts General Cancer Center.[2-6]

Remarkably, all studies reported somewhat similar results, indicating that progression-free survival (PFS) was longer in patients who received a first ADC (ADC1) than in those who received a second ADC (ADC2) after ADC1. Regardless of which agent was used as ADC2, the PFS was shorter. It appears that cross-resistance between ADC1 and ADC2 developed in a subset of patients. However, other patients still derived benefit from the sequential use of ADC1 followed by ADC2. This finding raises pertinent questions for the field: How can we identify patients who continue to benefit from ADC2 after receiving ADC1? Can we identify biomarkers of resistance to avoid the use of ADC2 after ADC1?

Digging deeper into the specifics of ADC1 and ADC2, the abstracts looked at the question of trastuzumab deruxtecan after sacituzumab govitecan or vice versa. The group from MD Anderson demonstrated that using trastuzumab deruxtecan first, followed by sacituzumab govitecan, resulted in an overall survival benefit. Of note, this was not a randomized trial, so the results need to be viewed with caution. However, the findings are consistent with the current practice of considering trastuzumab deruxtecan for patients with HER2-low metastatic breast cancer, followed by the potential consideration of sacituzumab govitecan, the other ADC approved in this space.

Datopotamab Deruxtecan

TROPION-Breast01 is a global, randomized, phase 3 trial that looked at datopotamab deruxtecan vs investigator's choice of chemotherapy for patients with metastatic HR+ breast cancer who had received at least 1 prior line of chemotherapy.[7] Patients were randomized 1:1 to datopotamab deruxtecan, given every 3 weeks, or the investigator's choice of chemotherapy: eribulin, mesylate, vinorelbine, gemcitabine, or capecitabine. The primary endpoint of the trial was PFS by independent review. In addition, several secondary endpoints included PFS by investigator assessment, quality-of-life results, and safety.

The first results from TROPION-Breast01 were presented at the European Society for Medical Oncology (ESMO) Congress 2023. The study met its primary endpoint, demonstrating improvement in PFS with datopotamab deruxtecan vs physician's choice of chemotherapy (hazard ratio, 0.63).[8] At SABCS 2023, we saw results by subgroups, investigator-assessed PFS, quality of life, and safety.[9] Per investigator assessment, an improvement in PFS was noted; the median PFS was approximately 7 months with datopotamab deruxtecan vs 4.5 months with standard chemotherapy. The benefit was maintained in patients who had baseline brain metastases vs those who did not, as well as in patients who had a prior duration of cyclin-dependent kinase 4/6 (CDK4/6) inhibitor treatment of more than 12 months vs those who did not.

In terms of safety, the patients who received datopotamab deruxtecan had fewer grade 3 AEs in comparison with those who received the investigator's choice of chemotherapy. The most common AEs with chemotherapy were side effects like myelosuppression and neutropenia. Neutropenic fever was the cause of death in 1 patient. With datopotamab deruxtecan, common AEs included mucositis, although generally grade 1 or 2. The rate of grade 3 mucositis was low, and the rate of discontinuation because of mucositis was also low. Finally, in terms of quality of life, the patients who received datopotamab deruxtecan had a delayed time to deterioration in quality of life, global health-related quality of life, pain domain, and physical functioning domain. Generally, the patients receiving datopotamab deruxtecan had a delayed time to deterioration or a better quality of life in comparison with those receiving standard chemotherapy.

After all these factors of efficacy, safety, and quality of life were considered, datopotamab deruxtecan was superior to standard chemotherapy, and if approved, it would be the third ADC approved for patients with HR+ metastatic breast cancer.

Elacestrant

The EMERALD trial looked at elaces-

ABSTRACT SUMMARY: Exposure-Efficacy and Exposure-Safety Analysis of Trastuzumab Deruxtecan in Patients With Advanced/Metastatic HER2+ Breast Cancer: Analyses From Phase 3 Studies DESTINY-Breast02 and DESTINY-Breast03

A post hoc study investigated exposure-efficacy relationships in 648 patients with previously treated HER2+ breast cancer from the phase 3 DESTINY-Breast02 (DB-02) and DESTINY-Breast03 (DB-03) trials who were treated with T-DXd (Abstract PO3-04-02). In data from both trials, a flat exposure-response relationship was observed for PFS because of the narrow exposure range resulting from the administration of T-DXd (5.4 mg/kg, every 3 weeks). A significant relationship was observed between T-DXd exposure and OS in patients from DB-02 ($P<.01$) but not in patients from DB-03. A significant relationship was observed between increasing exposure to T-DXd and increasing likelihood of interstitial lung disease of grade 3 or higher at dose levels ranging from 0.8 to 8 mg/kg ($P<.001$).

trant vs fulvestrant or endocrine monotherapy with an aromatase inhibitor for patients with estrogen receptor–positive (ER+) metastatic breast cancer after second-line or higher CDK4/6 inhibitor treatment. We saw improvement in PFS with elacestrant, particularly in patients who had detectable estrogen receptor 1 (*ESR1)* mutations and had received CDK4/6 inhibitors for more than 12 months.[10] In that setting, PFS was about 8.5 months with elacestrant vs about 2 months with standard endocrine therapy. At SABCS 2023, we saw biomarker results from the EMERALD trial, which included patients with coexisting *ESR1* and *PIK3C* mutations, with *ESR1* and *TP53* mutations, and with HER2-low breast cancer. [11] In all these subgroups, the benefit with elacestrant was maintained in comparison with standard-of-care endocrine therapy. The drug can be used regardless of these coexisting alterations so long as a patient has a detectable *ESR1* mutation, which is consistent with the US Food and Drug Administration label for elacestrant in patients with metastatic ER+ breast cancer.[12]

Trastuzumab Emtansine Plus Tucatinib

The HER2CLIMB-02 study investigated trastuzumab emtansine plus tucatinib and found a notably improved PFS for this combination in comparison with a single agent.[13] On average, the median enhancement in PFS was approximately 2 months. However, further data and extended follow-up, particularly evaluating the effect on overall survival, are necessary before integration of this approach into routine clinical practice can be considered. The study provided encouraging results supporting the concept that a combination therapy regimen involving an antibody-based treatment and a tyrosine kinase inhibitor can yield outcomes superior to those of single-agent treatment.

Disclosures

Dr Bardia is a consultant/serves on the advisory board for Pfizer, Novartis, Genentech, Merck, Radius Health, Immunomedics/Gilead, Sanofi, Daiichi Pharma/AstraZeneca, Phillips, Eli Lilly, and Foundation Medicine; and has received research/grants (to institution) from Genentech, Novartis, Pfizer, Merck, Sanofi, Radius Health, Immunomedics/Gilead, Daiichi Pharma/AstraZeneca, and Eli Lilly.

ABSTRACT SUMMARY: INAVO121: Phase III Study of Inavolisib + Fulvestrant vs Alpelisib + Fulvestrant in Patients With Hormone Receptor-Positive, HER2-Negative, *PIK3CA*-Mutated Locally Advanced or Metastatic Breast Cancer

The open-label, phase 3 INAVO121 trial will investigate inavolisib, a PI3Kα inhibitor, plus fulvestrant vs alpelisib plus fulvestrant in patients with HR+/HER2–/*PIK3CA*-mutated locally advanced or metastatic breast cancer (Abstract PO2-19-08). Eligible patients have experienced disease progression during or after treatment with endocrine therapy plus a CDK4/6 inhibitor. Stratification factors include visceral disease and the disease setting of prior CDK4/6 inhibitor therapy. Patients will be evenly randomized to receive inavolisib (9 mg, daily) or alpelisib (300 mg, daily), plus fulvestrant (500 mg, days 1 and 15 of cycle 1, then only on day 1). The trial has a planned enrollment of 400 patients. The primary endpoint is PFS by blinded independent review.

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