Clinical Advances in
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A SPECIAL MEETING REVIEW EDITION

Year-End Highlights in Metastatic Triple-Negative Breast Cancer from the 2022 American Society of Clinical Oncology Annual Meeting, and the European Society for Medical Oncology Congress and Breast Cancer Congress

A Review of Selected Presentations from ASCO 2022, Chicago, IL, June 3-7, 2022; ESMO Breast Cancer Congress 2022, Berlin, Germany, May 3-5 2022; and ESMO Congress 2022, Paris, France, September 9-13, 2022

Special Reporting on:

- Sacituzumab Govitecan Versus Treatment of Physician's Choice in Patients With Previously Treated Metastatic Triple-Negative Breast Cancer: Final Results from the Phase 3 ASCENT Study
- Neoadjuvant Pembrolizumab + Chemotherapy Followed by Adjuvant Pembrolizumab for Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer — A Network Meta-Analysis
- Sacituzumab Govitecan Efficacy in Patients With Metastatic Triple-Negative Breast Cancer by HER2 Immunohistochemistry Status: Findings From the Phase 3 ASCENT Study
- Evaluation of Event-Free Survival as a Surrogate for Overall Survival in Early-Stage Triple-Negative Breast Cancer Following Neoadjuvant Therapy
- Phase 2 Study of Camrelizumab Plus Chemotherapy as Neoadjuvant Therapy in Patients With Early Triple-Negative Breast Cancer

PLUS Additional 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]

Survival Elevated

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

Nearly 3x LONGER median PFS vs 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]

~1 YEAR median OS[1]

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 trial (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** for 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. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late 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 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7%. 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.

Diarrhea: Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of patients. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.5% of 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 37% of patients. Grade 3-4 hypersensitivity occurred in 2% of patients. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.3%. The incidence of anaphylactic reactions was 0.3%. Pre-infusion medication is recommended. Observe patients closely for hypersensitivity and infusion-related reactions during each infusion and for at least 30 minutes after completion of each infusion. Medication to treat such reactions, as well as emergency equipment, should be available for immediate use. Permanently discontinue TRODELVY for Grade 4 infusion-related reactions.

Nausea and Vomiting: Nausea occurred in 66% of all patients treated with TRODELVY and Grade 3 nausea occurred in 4% of these patients. Vomiting occurred in 39% of patients and Grade 3-4 vomiting occurred in 3% 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 67% in patients homozygous for the UGT1A1*28, 46% in patients heterozygous for the UGT1A1*28 allele and 46% in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 11% 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 ASCENT study (IMMU-132-05), the most common adverse reactions (incidence ≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, 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 substantially 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 [package insert]. Foster City, CA: Gilead Sciences, Inc.; June 2022. **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.

GILEAD | Oncology

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/mm³ 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. Administer atropine, if not contraindicated, for early diarrhea of any severity. At the onset of late 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.
- 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 dose 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 febrile neutropenia (absolute neutrophil count or ANC <1000/mm³ and fever ≥38.5°C), 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. At third occurrence, discontinue TRODELVY.
- At time of scheduled treatment, if Grade 3-4 neutropenia occurs which delays dosing beyond 3 weeks for recovery to ≤Grade 1, discontinue TRODELVY 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 61% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 47% of patients. Febrile neutropenia occurred in 7% of patients. Withhold TRODELVY for ANC below 1500/mm³ on Day 1 of any cycle or neutrophil count below 1000/mm³ on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia.

Diarrhea: TRODELVY can cause severe diarrhea. Diarrhea occurred in 65% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 12% of all patients treated with TRODELVY. One patient had intestinal perforation following diarrhea. Neutropenic colitis occurred in 0.5% of 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 37% 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 0.3%. The incidence of anaphylactic reactions was 0.3%. 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 66% of all patients treated with TRODELVY. Grade 3 nausea occurred in 4% of patients. Vomiting occurred in 39% of patients. Grade 3-4 vomiting occurred in 3% 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 ≤Grade1. 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 701 patients who received TRODELVY and had UGT1A1 genotype results. The incidence of Grade 3-4 neutropenia was 67% in patients homozygous for the UGT1A1*28 (n=87), 46% in patients heterozygous for the UGT1A1*28 allele (n=301), and 46% in patients homozygous for the wild-type allele (n=313). The incidence of Grade 3-4 anemia was 25% in patients homozygous for the UGT1A1*28 allele, 10% in patients heterozygous for the UGT1A1*28 allele, and 11% 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 as a single agent in 795 patients from three studies, IMMU-132-01, IMMU-132-05 and IMMU-132-06 which included 366 patients with mTNBC who had received prior systemic chemotherapy for advanced disease and 180 patients with mUC. Among the 795 patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 59 months). The most common (≥ 25%) adverse reactions were nausea (66%), diarrhea (65%), fatigue (62%), neutropenia (61%), alopecia (45%), anemia (42%), vomiting (39%), constipation (37%), decreased appetite (34%), rash (32%) and abdominal pain (28%).

Metastatic Triple-Negative Breast Cancer

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label trial (ASCENT, IMMU-132-05) in patients with mTNBC who had previously received a taxane and at least two prior therapies. 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 adverse reactions (≥25%) were fatigue, neutropenia, diarrhea, nausea, alopecia, anemia, constipation, vomiting, abdominal pain, and decreased appetite. The most common Grade 3-4 lab abnormalities (≥25%) were decreased neutrophils (49%), decreased leukocytes (41%), and decreased lymphocytes (31%).

Locally Advanced or Metastatic Urothelial Cancer

The safety of TRODELVY was evaluated in a single-arm, open-label study (TROPHY, IMMU-132-06) 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 adverse reactions (incidence ≥25%) were diarrhea, fatigue, neutropenia, nausea, any infection, alopecia, anemia, decreased appetite, constipation, vomiting, rash, and abdominal pain. The most common Grade 3-4 lab abnormalities (≥25%) were decreased neutrophils (43%), decreased leukocytes (38%), and decreased lymphocytes (35%). 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 substantially 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 patients who received TRODELVY, 264/795 (33%) of all patients were ≥ 65 years old, and 11% were ≥75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

Hepatic Impairment: No adjustment to the starting dose is required when administering TRODELVY to patients with mild hepatic impairment (bilirubin ≤ 1.5 ULN and AST/ALT < 3 ULN). 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.

See PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

GILEAD

TRODELVY™
sacituzumab govitecan-hziy
180 mg for injection

Sacituzumb Govitecan Versus Treatment of Physician's Choice in Patients With Previously Treated Metastatic Triple-Negative Breast Cancer: Final Results From the Phase 3 ASCENT Study

Sacituzumab govitecan is an antibody-drug conjugate (ADC) that is under investigation for the treatment of breast cancer and other tumor types. This ADC binds to human trophoblast cell-surface antigen 2 (Trop-2) and contains an SN-38 moiety that is covalently bound by means of a hydrolyzable linker.[1] Sacitizumab govitecan is approved for the treatment of patients with unresectable, locally advanced or metastatic triple-negative breast cancer (TNBC) who have received 2 or more prior systemic therapies, including at least 1 in the metastatic setting.[2] The phase 3 ASCENT trial evaluated sacituzumab govitecan vs chemotherapy in 468 evenly randomized patients with metastatic TNBC and no evidence of brain metastasis at baseline.[3] Sacituzumab govitecan was administered at 10 mg/kg on days 1 and 8 in 21-day cycles. Chemotherapy regimens could include capecitabine, eribulin, vinorelbine, or gemcitabine, according to the physician's choice. Patients were treated until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[4] Patients had a median age of 54 years (range, 27-82 years). The trial demonstrated a median PFS of 5.6 months among patients treated with sacituzumab govitecan vs 1.7 months among patients treated with chemotherapy (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.32-0.52; *P*<.0001). The median overall survival (OS) was also superior among patients treated with sacituzumab govitecan (12.1 vs 6.7 months; HR, 0.48; 95% CI, 0.38-0.59; *P*<.0001; Figure 1).

Final data from the ASCENT trial were further examined to evaluate efficacy, safety, and quality of life.[5] The median follow-up for survival was 11.7 months for patients in the sacituzumab govitecan arm vs 6.2 months for patients in the chemotherapy arm. The most common reason for treatment discontinuation was disease progression (86% with sacituzumab govitecan vs 71% with chemotherapy). The 24-month OS rate was 20.5% with sacituzumab govitecan vs 5.5% with chemotherapy. Key treatment-related adverse events (AEs) of grade 3 or greater with sacituzumab govitecan vs chemotherapy, respectively, included neutropenia (52% vs 33%), febrile neutropenia (6% vs 2%) anemia (8% vs 5%), and diarrhea (11% vs 0.5%). Among patients treated with sacituzumab govitecan, there was no treatment-related death and no neuropathy of grade 3 or greater; however, 1 patient experienced grade 3 interstitial lung disease. In the chemotherapy arm, treatment-related death occurred in 1 patient owing to neutropenic sepsis. In both arms, fewer than 3% of patients discontinued study therapy owing to an AE. The median duration of treatment was longer for patients in the sacituzumab govitecan arm (4.4 months)

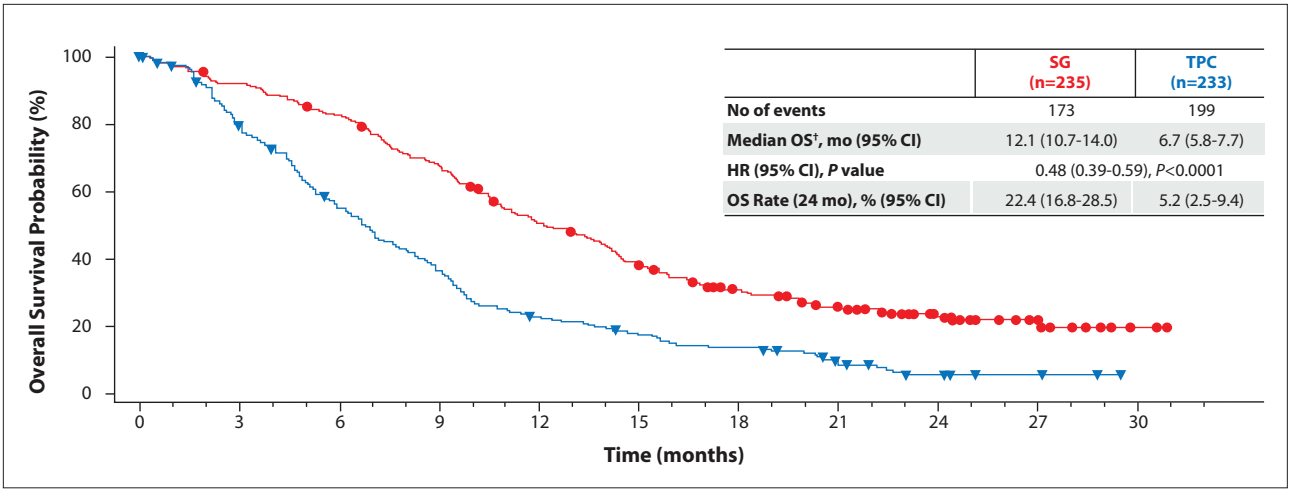

Figure 1. Sacituzumab govitecan versus treatment of choice: overall survival in patients without brain metastases. CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice. Presented at the American Society for Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, IL.[5]

than for patients in the chemotherapy arm (range, 1.0-1.6 months). Regarding the primary health-related quality of life domains, patients in the sacituzumab govitecan arm experienced a greater increase in clinically meaningful improvements from baseline than patients in the chemotherapy arm.

References

1. Goldenberg DM, Sharkey RM. Sacituzumab govitecan, a novel, third-generation, antibody-drug conjugate (ADC) for cancer therapy. *Expert Opin Biol Ther*. 2020;20(8):871-885.
2. Trodelvy [sacituzumab govitecan] prescribing information. Gilead Sciences, Inc.; Foster City, CA; 2022.
3. 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.
4. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247.
5. Bardia A, Tolaney SM, Loirat D, et al. Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated, metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study [ASCO abstract 1071]. *J Clin Oncol*. 2022;40(suppl 16).

Phase 1b/2 Study of GX-17 Plus Pembrolizumab in Patients With Refractory or Recurrent Metastatic Triple-Negative Breast Cancer: The KEYNOTE-899 Study

GX-17 (efineptakin alfa) is a hybrid protein consisting of human interleukin-17 fused with an antibody fragment crystallizable domain. The open-label phase 1b/2 KEYNOTE-899 study evaluated GX-17 plus pembrolizumab in women with recurrent or refractory metastatic TNBC (ASCO Abstract 1081). Pembrolizumab was administered at 200 mg every 3 weeks. The dosage of GX-17 ranged from 360 µg/kg to 1440 µg/kg every 9 or 12 weeks during phase 1b and was fixed at 1200 µg/kg every 9 weeks for phase 2. The study enrolled 51 patients in the phase 1b and 33 patients in the phase 2 portions of the study. Patients had a median age of 50.0 years (range, 29.0-75.0 years). The majority of patients (91.7%) had visceral metastases and 13.1% had 4 or more metastatic organ sites. After a median follow-up of 10.4 months, the ORR was 15.7% (8/51) for phase 1b and 21.2% (7/33) for phase 2, with no CRs observed. The ORR was 60% (6/10) among PD-L1–positive patients vs 0% (0/15) among PD-L1–negative patients. In the phase 2 portion of the study, the median duration of response was 3.9 months, the median PFS was 2.6 months, and the median OS was 16.0 months.

The combination of pembrolizumab plus GX-17 demonstrated a manageable safety profile in this patient setting. Every patient (84/84) experienced a treatment-related AE of any grade, and grade 3/4 treatment-related AEs were observed in 31% of patients. The most common treatment-related AEs of any grade included injection-site reaction (64%), rash (54%), and increased alanine transaminase (49%). Immune-related AEs of any grade were reported in 71% of patients. The most common immune-mediated AEs were rash (52%) and pruritus (23%), and the most common grade 3/4 immune-mediated AE was rash (6%).

Safety Interim Analysis of ATRACTIB: A Phase 2 Trial of First-Line Atezolizumab in Combination With Paclitaxel and Bevacizumab in Metastatic Triple-Negative Breast Cancer

Atezolizumab is an anti–PD-L1 antibody. The open-label, single-arm, phase 2 ATRACTIB trial evaluated the addition of atezolizumab to paclitaxel plus bevacizumab in patients with unresectable, locally advanced or metastatic TNBC (ASCO Abstract 1084). Eligible patients had not received prior systemic therapy or had received adjuvant or neoadjuvant, taxane-based chemotherapy at least 12 months prior to enrollment. PD-L1 status was not considered for eligibility. All patients received atezolizumab (840 mg, days 1 and 15), paclitaxel (90 mg/m^2, days 1, 8, and 15), and bevacizumab (10 mg/kg, days 1 and 15). The primary objective was investigator-assessed PFS based on RECIST version 1.1. A planned interim safety analysis was included in the protocol based on the first 20 patients who completed a

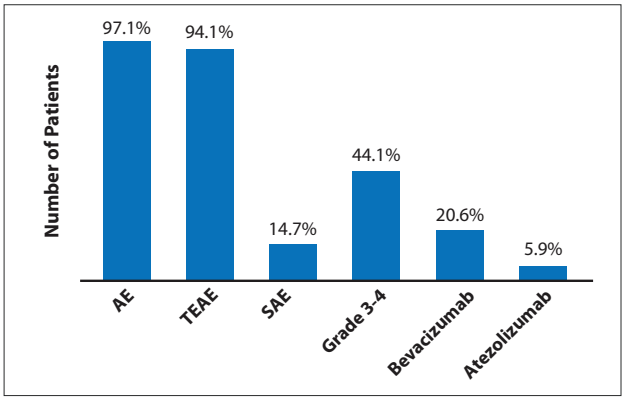

Figure 2. Total adverse events summary. AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event. Presented at the American Society for Clinical Oncology Annual Meeting; June 3-7, 2022; Chicago, IL.

3-month follow-up or completed the study.

At the time of data cutoff, 25 patients (71.4%) were continuing to receive study therapy and 9 patients (28.6%) had discontinued. At baseline, 34 patients had a median age of 57.5 years (range, 40.0-84.0 years) and 85.3% had measurable disease. One-half of patients had 3 or more metastatic sites and 55.9% of patients had visceral disease. The mean relative dose intensity was 90.2% for atezolizumab, 95.7% for bevacizumab, and 96.5% for paclitaxel. There was no evidence of synergistic toxicity with the 3-drug combination. AEs of any grade were observed in 97.1% of patients and treatment-emergent AEs in 94.1% of patients (Figure 2). The most common treatment-emergent grade 3/4 AEs were fatigue, neurotoxicity, and neutropenia, at 8% each. Serious AEs and grade 3/4 AEs were reported in 1.47% and 44.1% of patients, respectively. Serious AEs related to atezolizumab treatment included grade 3 fatigue (2.9%) and grade 3 autoimmune hepatitis (2.9%). The single AE of autoimmune hepatitis was also considered an event of clinical interest related to treatment with atezolizumab.

Mechanisms of Action and Acquired Resistance to Atezolizumab Plus Nab-paclitaxel in Metastatic Triple-Negative Breast Cancer

Atezolizumab selectively binds to programmed death-ligand 1 (PD-L1), thus inhibiting the interaction between PD-1 and B7 and releasing the immune checkpoint. The phase 3 IMpassion130 study evaluated the combination of nab-paclitaxel plus atezolizumab vs placebo in treatment-naive patients with metastatic TNBC (Schmid P et al. *N Engl J Med* 2018;379[22]:2108). Prior to 1:1 randomization, patients were stratified based on adjuvant or neoadjuvant taxane therapy, liver metastases at baseline, and PD-L1 expression at baseline. The primary endpoints were PFS in the intent-to-treat (ITT) population, PFS in the PD-L1–positive subgroup, and OS. The IMpassion130 study randomized 451 patients into each arm. After a median follow-up of 12.9 months, median PFS was 7.2 months with atezolizumab plus nab-paclitaxel vs 5.5 months with placebo plus nab-paclitaxel (HR, 0.80; 95% CI, 0.69-0.92; *P*=.002). In the subgroup of patients with PD-L1–positive tumors, the median PFS was 7.5 months vs 5.0 months, respectively (HR, 0.62; 95% CI, 0.49-0.78; *P*<.001). Median OS in the ITT population was 21.3 months with the atezolizumab combination vs 17.6 months with placebo plus nab-paclitaxel (HR, 0.84; 95% CI, 0.69-1.02; *P*=.08).

Paired tumor samples from baseline and 4 weeks after treatment were evaluated to provide insights into the mechanism of action of atezolizumab plus nab-paclitaxel and the mechanism of acquired resistance (ASCO Abstract 1078). Samples were collected from every patient at baseline, plus 42 samples after 4 weeks of treatment and 114 samples at disease progression. After 4 weeks on treatment, significant increases in PD-L1 expression were observed in both immune cells (*P*<.01) and tumor cells (*P*<.01). Among patients who experienced a complete response (CR) or partial response (PR) while on atezolizumab plus nab-paclitaxel, expression of PD-L1 increased from baseline to 4 weeks on treatment (*P*<.05). Compared with samples in the control arm, atezolizumab plus nab-paclitaxel increased the shift toward the immune inflamed phenotype (*P*<.05). Based on RNA sequencing, the expression of molecules involved in immune pathways was increased in the atezolizumab-containing arm vs the placebo arm, including interferon-α and interferon-γ, and the increase in expression was most pronounced in patients who exhibited a CR, a PR, or stable disease. From baseline to 4 weeks, expression of PD-L1 increased in the immune cells of patients treated with the atezolizumab combination (*P*<.01). In contrast, among patients in the placebo arm, PD-L1 expression decreased in tumor samples (*P*<.05).

A Phase 3, Multicenter, Open, Randomized Controlled Clinical Study of Gemcitabine Plus Capecitabine Versus Gemcitabine Plus Carboplatin in the First-Line Treatment for Advanced Triple-Negative Breast Cancer

Notable progress is being made in the development of new therapies for TNBC; however, chemotherapy regimens remain a reasonable treatment option for patients with this aggressive form of breast cancer.[1,2] A phase 3 trial evaluated the efficacy and safety of gemcitabine plus capecitabine vs gemcitabine plus carboplatin in patients with advanced TNBC.[3] Patients were evenly randomized to receive gemcitabine (1000 mg/m^2, days 1 and 8) plus oral capecitabine (1000 mg/m^2, twice daily, days 1-14) vs gemcitabine (1000 mg/m^2, days 1 and 8) plus carboplatin (area under the curve 2, days 1 and 8). The primary endpoint was PFS. The presence of

tumor-infiltrating lymphocytes was determined by immunohistochemistry (IHC), using antibodies against CD3, CD4, CD8, and CD19.

The open-label, multicenter study randomized 93 patients to gemcitabine plus capecitabine and 94 patients to gemcitabine plus carboplatin. The trial failed to meet its primary endpoint, demonstrating a median PFS of 6.1 months with gemcitabine plus capecitabine vs 6.3 months with gemcitabine plus carboplatin (HR, 1.002; 95% CI, 0.717-1.148; *P*=.992). The objective response rates (ORRs) were 37.6% with the capecitabine combination vs 39.4% with the carboplatin combination (*P*=.808), and both arms demonstrated similar rates of clinical benefit (78.5% vs 79.8%, respectively; *P*=.828). The median OS was 21.01 months in the gemcitabine plus capecitabine arm vs 21.5 months in the gemcitabine plus carboplatin arm (HR, 1.002; 95% CI, 0.717-1.400; *P*=.992). Subgroup analysis showed similar outcomes for all groups examined, based on age, Eastern Cooperative Oncology Group (ECOG) performance status, tumor pathology, and the number or type of metastatic sites.

The combination of gemcitabine plus capecitabine demonstrated more favorable toxicity than gemcitabine plus carboplatin. Patients in both arms experienced high rates of hematologic AEs. Nonhematologic AEs that were more common in the capecitabine-containing arm included hand-foot syndrome, diarrhea, and peripheral sensory neuropathy. Nonhematologic AEs that were more common in the carboplatin-containing arm included alopecia, nausea, vomiting, fatigue, decreased appetite, infusion-related reaction, and hyperglycemia. Tumors from 52 patients were available for the analysis of tumor-infiltrating lymphocytes. Compared with patients who had low levels of CD8-positive cells, patients with high levels of CD8-positive cells had a significantly longer median PFS (HR, 0.559; 95% CI, 0.314-0.993; *P*=.047) and median OS (HR, 0.436; 95% CI, 0.226-0.843; *P*=.014).

References

1. Cipriano É, Mesquita A. Emerging therapeutic drugs in metastatic triple-negative breast cancer. *Breast Cancer (Auckl)*. 2021;15:11782234211002491.
2. National Comprehensive Cancer Network. NCCN Guidelines: Invasive Breast Cancer. Version 4.2022.
3. Liu XD, Zhao WP, Jia YS, et al. A phase 3, multicenter, open, randomized controlled clinical study of gemcitabine plus capecitabine versus gemcitabine plus carboplatin in the first-line treatment for advanced triple-negative breast cancer [ASCO abstract 1077]. *J Clin Oncol*. 2022;40(suppl 16).

Sacituzumab Govitecan Efficacy in Patients With Metastatic Triple-Negative Breast Cancer by HER2 Immunohistochemistry Status: Findings From the Phase 3 ASCENT Study

Treatment guidelines from ASCO and the College of American Pathologists categorize breast cancer patients as human epidermal growth factor receptor 2 (HER2)-negative or HER2-positive, based on tumor testing.[1] To enable more personalized treatment, a new category of HER2-low has been proposed, comprising approximately 37% of TNBC patients. The subgroup includes breast cancer patients with HER2 IHC expression scores of +1 or +2, combined with a negative result from in situ hybridization, as well as no expression of the estrogen and progesterone receptors. Trop-2, the target of sacituzumab govitecan, is expressed in all breast cancer tumors, making it an attractive target for the treatment of patients with TNBC. The phase 3 ASCENT trial yielded a significant improvement in survival with sacituzumab govitecan compared with single-agent chemotherapy, along

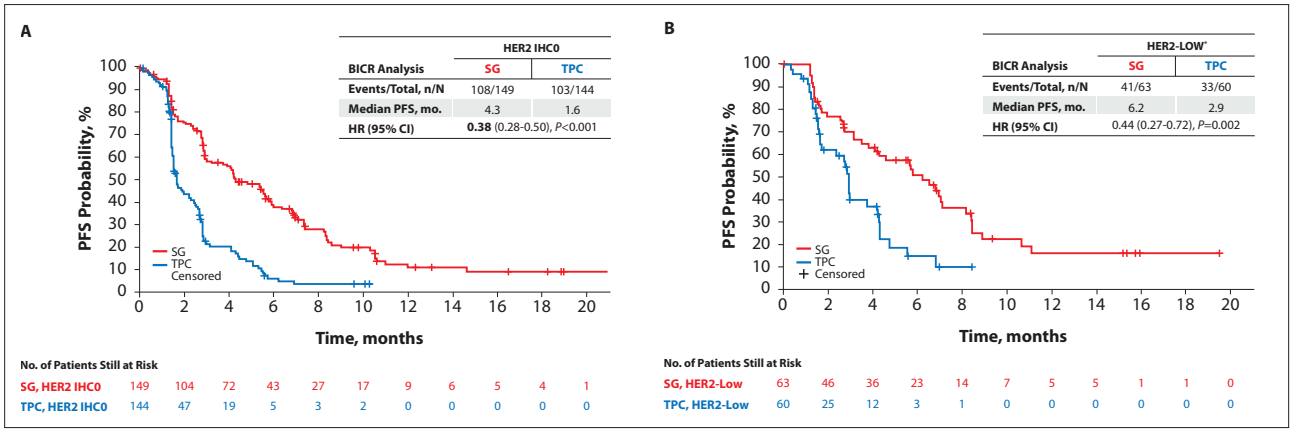

Figure 3. Progression-free survival. BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; ISH, in situ hybridization; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice. *HER2-low defined as IHC1+, or IHC2+ and ISH-negative esented at the European Society for Medical Oncology Breast Cancer Congress; May 3-5, 2022, Berlin, Germany.[4]

Table 1. Overall Responses

	HER2 IHC0		HER2-Low*		ITT	
	SG (n=149)	TPC (n=144)	SG (n=63)	TPC (n=60)	SG (n=267)	TPC (n=262)
ORR,n (%)	46 (31)	5 (3)	20 (32)	5 (8)	83 (31)	11 (4)
Best overall response, n (%)						
CR	3 (2)	0	3 (5)	1 (2)	10 (4)	2 (1)
PR	43 (29)	5 (3)	17 (27)	4 (7)	73 (27)	9 (3)
SD	55 (37)	33 (23)	23 (37)	22 (40)	96 (36)	71 (27)
PD	32 (21)	57 (40)	17 (27)	15 (25)	65 (24)	100 (38)
NE	16 (11)	49 (34)	3 (5)	18 (30)	23 (9)	80 (31)
CBR, n (%)	101 (68)	38 (26)	43 (68)	27 (45)	179 (67)	82 (31)
Median DOR, mo. (95% CI)	6.9 (5.4-9.0)	2.9 (2.8-NE)	5.6 (4.3-NE)	3.6 (2.9-NE)	6.3 (5.5-9.0)	3.6 (2.8-NE)

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in-situ hybridization; ITT, intention-to-treat; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SG, sacituzumab govitecan; TPC, treatment of physician's choice. *HER2-low = IHC1+, or IHC2+ and ISH-negative. Presented at the European Society for Medical Oncology Breast Cancer Congress; May 3-5, 2022; Berlin, Germany.[4]

with a manageable safety profile, in previously treated patients with metastatic TNBC.[2,3]

A retrospective analysis evaluated the efficacy of sacituzumab govitecan in patients with metastatic TNBC as a function of HER2 expression level.[4] HER2 IHC data were available from 416 patients (79%) who participated in the ASCENT trial. Among patients who were randomized to treatment with sacituzumab govitecan, 149 had no HER2 IHC expression (HER2-IHC0) and 63 had low HER2 IHC expression (HER2-low). Among patients randomized to the control arm, 55 patients had HER2 IHC0 expression and 60 had HER2-low expression. In both the HER2-IHC0 and HER-low populations, treatment with sacituzumab govitecan yielded a significant improvement in PFS and OS compared with single-agent chemotherapy. Median PFS was 4.3 months vs 1.6 months in the HER2-IHC0 group (P<.001) and was 6.2 months vs 2.9 months in the HER2-low population (P=.002) with sacituzumab govitecan vs chemotherapy, respectively (Figure 3). Median OS was 11.3 months vs 5.9 months in the HER2-IHC0 group (P<.001) and was 14.0 months vs 8.7 months in the HER2-low group (P<.001) with sacituzumab govitecan vs chemotherapy, respectively. Among patients in the HER2-ICH0 subgroup, the ORR was 31% with sacituzumab govitecan vs 3% with single-agent chemotherapy. In the HER-low subgroup, the ORR was 32% with sacituzumab govitecan vs 8% with single-agent chemotherapy. Overall, treatment with sacituzumab govitecan yielded superior outcomes compared with the physician's choice of single-agent chemotherapy in both the HER2-IHC0 and the HER-low subgroups, similar to the outcomes observed from the ITT population in the ASCENT trial (Table 1).

References

1. Wolff AC, Hammond MEH, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *Arch Pathol Lab Med*. 2018;142(11):1364-1382.
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.
3. Bardia A, Tolaney SM, Loirat D, et al. Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated, metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study [ASCO abstract 1071]. *J Clin Oncol*. 2022;40(suppl 16).
4. Hurvitz SA, Bardia A, Punie K, et al. Sacituzumab govitecan efficacy in patients with metastatic triple-negative breast cancer by HER2 immunohistochemistry status: findings from the phase 3 ASCENT study [ESMO abtract 168P]. *Ann Oncol*. 2022:33(Suppl 3).

Post-Progression Therapy Outcomes in Patients From the Phase 3 ASCENT Study of Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer

The phase 3 ASCENT trial met its primary endpoint, demonstrating a PFS of 5.6 months with sacituzumab govitecan vs 1.7 months in patients treated with single-agent chemotherapy (ASCO abstract 1071; ESMO abstract 168P). Although a full review of presentations on TNBC from the 2021 San Antonio

Breast Cancer Symposium is beyond the scope of this summary, a companion analysis from the phase 3 ASCENT trial provides insights on treatment following progressive disease. A post hoc subgroup analysis investigated the survival of patients in the ASCENT trial who received treatment with sacituzumab govitecan, progressed on study treatment, and then received further treatment after disease progression (SABCS 2021 Abstract P5-16-15). Among 267 patients who were randomized to treatment with sacituzumab govitecan, 222 patients (83%) discontinued owing to disease progression. Prior to discontinuation, patients received treatment with sacituzumab govitecan for a median 4.2 months (range, 0.0-18.7 months). After discontinuation of sacituzumab govitecan therapy, 163 patients (73%) received post-progression therapy, including eribulin (32%), carboplatin (15%), capecitabine (15%), and atezolizumab (7%). The remaining patients (n=59; 27%) received no further therapy after disease progression.

Patient baseline characteristics were generally well balanced between the 2 cohorts. Patients had a median age of 53 years (range, 27-82 years), 32% had received more than 3 prior chemotherapy regimens, and the median number of prior anticancer regimens was 4 (range, 2-17 prior regimens). However, the proportion of patients with an ECOG performance status of 0 was 50% in patients who did receive postprogression therapy vs 31% in patients who did not. All other patients had an ECOG performance status of 1 (50% in patients who did receive postprogression therapy vs 69% in patients who did not). The median OS was significantly longer in patients who received postprogression therapy, as calculated both from the time of randomization (13.4 vs 7.3 months; HR, 0.46; 95% CI, 0.32-0.67; *P*<.0001) and from the end of treatment with sacituzumab govitecan (7.9 vs 2.0 months; HR, 0.14; 95% CI, 0.09-0.22; *P*<.0001).

Evaluation of Event-Free Survival as a Surrogate for Overall Survival in Early-Stage Triple-Negative Breast Cancer Following Neoadjuvant Therapy

A literature meta-analysis evaluated the validity of EFS as a surrogate endpoint for OS in early-stage TNBC (ESMO Abstract 186P). Data were taken from publications in the English language available in March 2022. Databases included Cochrane Central Register of Controlled Trials, MEDLINE, Excerpta Medica Database, and Northern Light Life Sciences Conference Abstracts. Keywords included breast cancer, neoadjuvant treatment, and survival. Included studies had enrolled patients with TNBC and the treatment intervention was neoadjuvant therapy. For analysis at the individual level, randomized controlled trials (RCTs), single-arm trials, and real-world studies were included. For analysis at the trial level, only RCTs were included. Weighted linear regression was performed using data based on the TNBC patient sample size.

For individual-level analysis, the association between event-free survival (EFS) and OS was performed with data from 45 studies representing 7522 patients. The studies included 12 RCTs, 2 single-arm studies, and 31 real-world studies. Patients had a median age of 49 years (range, 42.6-53 years) and the median follow-up was 43.7 months (range, 18.6-100.6 months). At the individual level of analysis, 3-year EFS was a significant predictor of 5-year OS, with an estimated coefficient of 1.13 (*P*<.01) and a coefficient of determination (R^2) of 0.82 (95% CI, 0.68-0.91). The correlation between 5-year EFS and 5-year OS was also strong (R^2, 0.80; 95% CI, 0.65-0.89), as was the correlation between 3-year EFS and 3-year OS (R^2, 0.74; 95% CI, 0.64-0.83).

Analysis at the trial level was conducted with data from 15 RCTs representing 19 comparisons and 6469 TNBC patients. Patient populations had a median age ranging from 47 to 52 years and a median follow-up ranging from 19.8 to 94.8 months. Neoadjuvant interventions included carboplatin (8 studies), bevacizumab (5 studies), nab-paclitaxel (4 studies), anthracycline (3 studies), and pembrolizumab, atezolizumab, durvalumab, or everolimus, each evaluated in 1 study. A significant correlation was observed between EFS and OS, with an estimated coefficient of 1.03 (*P*<.01) and an R^2 of 0.64 (95% CI, 0.45-0.83). The results support the use of EFS as a clinical trial endpoint in studies of patients with TNBC.

Phase 2 Study of Camrelizumab Plus Chemotherapy As Neoadjuvant Therapy in Patients With Early Triple-Negative Breast Cancer

A single-arm phase 2 study evaluated camrelizumab—a PD-1 inhibitor—plus chemotherapy as neoadjuvant treatment in patients with treatment-naive stage II/III TNBC (ESMO Abstract 170P). Therapy consisted of camrelizumab (200 mg, days 1 and 15) plus nab-paclitaxel (125 mg/m^2, days 1, 8, and 15) for cycles 1 to 4, in 28-day cycles, followed by camrelizumab (200 mg, day 1), cyclophosphamide (600 mg/m^2, day 1), and

epirubicin (90 mg/m^2, day 1) for cycles 5 to 8, in 14-day cycles. Twenty-three enrolled patients had a median age of 52 years (range, 29-65 years). The primary endpoint was total pathological CR (tpCR), with secondary endpoints of breast pathological CR (bpCR), ORR, EFS, and safety.

Node-positive disease was observed in 69.6% of patients, and 73.9% of patients had stage II disease. The majority of patients tested had a human epidermal growth factor receptor 2 (HER2) score of 0 or 1+ (21/23; 91.3%) and Ki-67 status was 30% or greater in 91.3% of patients (21/23). Among 20 evaluable patients, including 16 (80%) who were node-positive, the tpCR rate was 65% and the bpCR rate was 70%. At the end of neoadjuvant treatment, the ORR was 95%. Grade 4 AEs included neutropenia (26.1%), leucopenia (8.7%), and lymphocyte count decreased (4.3%). The most common grade 3 AEs were leukopenia (43.5%) and neutropenia (39.1%), followed by increased alanine transaminase, increased aspartate transaminase, and decreased lymphocyte count, at 13.0% each. AEs led to treatment discontinuation in 2 patients (8.7%), and 4 patients (17.4%) experienced treatment-related serious AEs.

Neoadjuvant Pembrolizumab + Chemotherapy Followed by Adjuvant Pembrolizumab for Treatment of High-Risk, Early-Stage Triple-Negative Breast Cancer — A Network Meta-Analysis

The phase 3 KEYNOTE-522 trial evaluated neoadjuvant chemotherapy plus pembrolizumab followed by adjuvant pembrolizumab in patients with early-stage TNBC.[1] Patients in the comparator arm received placebo rather than pembrolizumab. The study enrolled 1174 patients with treatment-naive, nonmetastatic, centrally confirmed TNBC and showed a significant benefit in EFS for patients in the pembrolizumab arm compared with the placebo arm (HR, 0.63; 95% CI, 0.48-0.82; *P*=.0003).

Based on a prespecified study protocol, a systematic literature review and network meta-analysis was conducted to evaluate the relative efficacy of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab vs alternative interventions that have not been directly compared for the treatment of early-stage and locally advanced, nonmetastatic TNBC.[2] Eligible RCTs were identified in the Excerpta Medica Database, MEDLINE, and the Cochrane Central Register of Controlled Trials in July 2021. The endpoint of pathological CR was reported in 5 trials, representing 8 unique therapies, and these 5 publications were included in the network meta-analysis. Only the KEYNOTE-522 study included treatments in both the neoadjuvant and adjuvant settings.

The combination of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab yielded a superior rate of pathological CR vs alternative therapies. In terms of EFS, neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab was numerically superior to all comparator therapies (Table 2); moreover, the pembrolizumab-containing regimen was statistically superior to several regimens. The results suggest that the combination of neoad-

Table 2. Results of Fixed-Effects NMA for Event-Free Survival Based on Constant HR Assumption

Pac→anthra+cyclo	**1.75 (1.11, 2.80)**	1.51 (0.39,6.02)	**1.61 (1.01, 2.58)**	**1.59 (1.08, 2.33)**	**2.78 (1.64, 4.78)**
0.57 (0.36, 0.90)	**Pac+carb→ anthra+cyclo**	0.86 (0.23, 3.17)	0.92 (0.47, 1.78)	0.91 (0.59, 1.41)	**1.59 (1.22, 2.08)**
0.66 (0.17, 2.59)	1.16 (0.32, 4.26)	**Doc+carb→ anthra+cyclo**	1.07 (0.25, 4.51)	1.05 (0.27, 4.17)	1.85 (0.48, 6.99)
0.62 (0.39, 0.99)	1.09 (0.56, 2.13)	0.94 (0.22, 4.06)	**Nab-pac→ anthra+cyclo**	0.99 (0.53, 1.80)	1.73 (0.85, 3.54)
0.63 (0.43, 0.93)	1.10 (0.71, 1.71)	0.95 (0.24, 3.77)	1.01 (0.56, 1.88)	**Pac+carb+veli→ anthra+cyclo**	**1.75 (1.05, 2.93)**
0.36 (0.21, 0.61)	**0.63 (0.48, 0.82)**	0.54 (0.14, 2.09)	0.58 (0.28, 1.17)	**0.57 (0.34, 0.95)**	**Pembro+pac+carb→ anthra+cyclo**

Anthra, anthracycline; Carb, carboplatin; Crl, credible interval; Cyclo, cyclophosphamide; DIC, deviance information criterion; Doc, docetaxel; HR, hazard ratio; Nab-pac, nab-paclitaxel; NMA, network meta-analysis; Pac, paclitaxel; Pembro, pembrollizumab; Veli, veliparib. Each cell represents the comparison (HR and 95% Col) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC: 9.23; deviance: 4.26. Presented at the European Society for Medical Oncology; 9-13, 2022; Paris, France.[2]

juvant pembrolizumab plus chemotherapy followed by adjuvant chemotherapy is effective compared with alternative systemic interventions for the treatment of patients with treatment-naive, early-stage TNBC.

References

1. Schmid P, Cortes J, Dent R, et al. KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early-stage TNBC [ESMO abstract VP7-2021]. *Ann Oncol*. 2021;32:1198-2000.

2. Cortes J, Haiderali A, Huang M, et al. Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab for treatment of high-risk, early-stage triple-negative breast cancer — a network meta-analysis [ESMO abstract 169P]. *Ann Oncol*. 2022;33(suppl 4).

Nivolumab and Ipilimumab in Early-Stage Triple-Negative Breast Cancer With Tumor-Infiltrating Lymphocytes: First Results From the BELLINI Trial

The adaptive phase 2 BELLINI trial evaluated the safety and efficacy of nivolumab with or without ipilimumab prior to neoadjuvant chemotherapy or surgery in patients with early-stage TNBC (ESMO Abstract LBA13). Enrolled patients had stage I to III TNBC. Tumors were required to have at least 5% tumor-infiltrating lymphocytes. Study treatment consisted of 2 cycles of nivolumab, with or without 1 cycle of ipilimumab. At baseline, 16 patients in the nivolumab monotherapy arm had a median age of 48.0 years (range, 27.0-71.0 years) and 15 patients in the nivolumab plus ipilimumab arm had a median age of 50.0 years (range, 34.0-67.0 years). Baseline characteristics were generally well balanced between the 2 arms, with the exception of nodal status (N0, 81.3% vs 33.3%; N1, 12.5% vs 60.0%; N3, 6.3% vs 6.7%, with nivolumab vs the combination, respectively).

The trial met its primary endpoint of immune activation in at least 30% of patients after 4 weeks of treatment. In the nivolumab monotherapy arm, 8 patients achieved a 2-fold or greater increase in CD8-positive cells, and in the nivolumab plus ipilimumab arm, 9 patients met the threshold of immune activation. Increases in the level of interferon-γ also demonstrated immune activation in both cohorts. After 4 weeks of treatment, 7 patients (23%) achieved a PR, including 3 patients in the nivolumab monotherapy arm and 4 patients in the nivolumab plus ipilimumab arm. All 7 patients with a response had a level of tumor-infiltrating lymphocytes of at least 40%. Among 3 patients who continued to surgery after study therapy, 1 patient achieved a pathological CR and 1 achieved a near-pathological CR. Toxicity was consistent with the known safety profiles of the 2 immune checkpoint blockade drugs. Grade 3/4 AEs were observed in 6% of patients and included 1 event of hyperthyroidism and 1 event of insulin-resistant diabetes.

Primary Endpoint Results of SYNERGY, a Randomized Phase II Trial, First-Line Chemo-Immunotherapy Trial of Durvalumab, Paclitaxel and Carboplatin With or Without the Anti-CD73 Antibody Oleclumab in Patients With Advanced or Metastatic Triple-Negative Breast Cancer

Oleclumab is a human monoclonal antibody that binds to CD73, thus reducing the production of immunosuppressive adenosine. The multicenter, open-label, randomized phase 2 SYNERGY trial investigated first-line paclitaxel, carboplatin, and durvalumab, with or without oleclumab, for the treatment of locally advanced or metastatic TNBC (ESMO Abstract LBA17). Prior to randomization, patients were stratified based on expression of PD-L1 and CD73. The primary endpoint was the clinical benefit at week 24, defined as the proportion of patients with a CR, a PR, or stable disease.

Baseline characteristics were well balanced between the 2 arms. In the oleclumab-containing arm (n=63), PD-L1 status was negative in 47.6% of tumors and positive in 52.4% of tumors, and CD73 status was negative in 73.0% of tumors and positive in 27.0% of tumors. In the comparator arm (n=64), PD-L1 status was negative in 43.8% of tumors and positive in 56.3% of tumors, and CD73 status was negative in 67.2% of tumors and positive in 32.8% of tumors. The median follow-up was 13.2 months (range, 1-39 months). The trial failed to meet its primary endpoint (Figure 4). The clinical benefit rate was 43% in the oleclumab-containing arm vs 44% in the comparator arm (P=.61). Similar rates of clinical benefit were observed in subgroups based on PD-L1–positive expression (P=.29), PD-L1–negative expression (P=.90), CD73-positive expression (P=.98), and CD73-negative expression (P=.22). Median PFS was 7.7 months with oleclumab vs 6.0 months without oleclumab (P=.88). A formal interim analysis showed that the futility boundary had been crossed. The safety profile was similar for both arms.

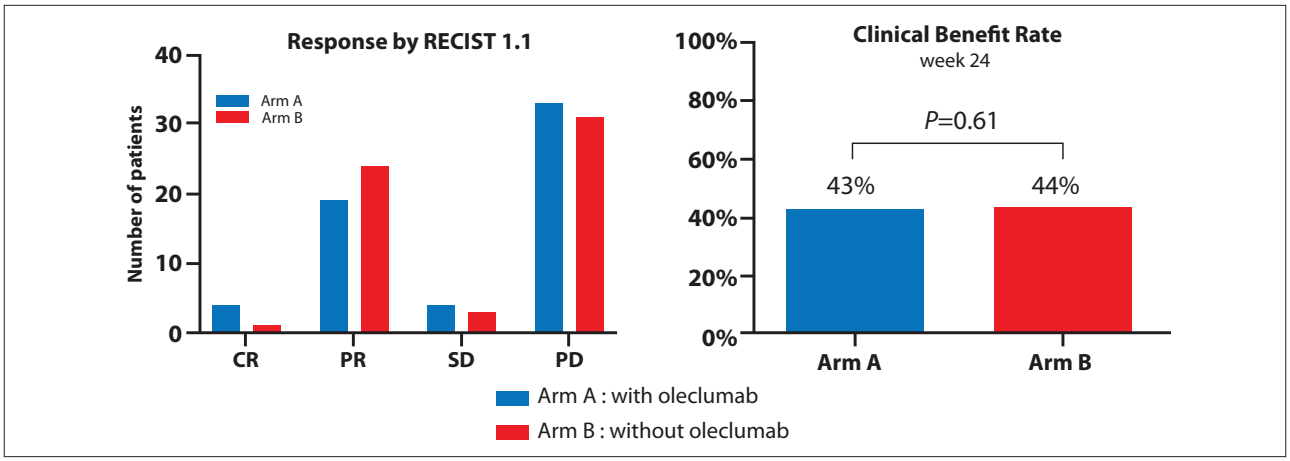

Figure 4. Clinical Benefit Rate at Week 24. CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease. Presented at the European Society for Medical Oncology; 9-13, 2022; Paris, France.[1]

Commentary

Joyce A. O'Shaughnessy, MD

Both the 2022 Annual Meeting of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) 2022 Congress included important updates on the treatment of metastatic triple-negative breast cancer (mTNBC). Key presentations provided crucial findings on the benefits of the antibody-drug conjugate sacituzumab govitecan following the completion of the phase 3 ASCENT trial; PD-1 inhibitors including pembrolizumab, camrelizumab and atezolizumab; and other experimental monoclonal antibodies. Other important work looked at how we evaluate survival as well as the mechanisms of action at play with certain therapies.

Approximately 15 percent of all breast cancer diagnoses worldwide — nearly 200,000 cases per year — are categorized as triple-negative.[1] TNBC is more commonly diagnosed in women under 40 compared to women over 50, and tends to be more aggressive than other types of breast cancer. For metastatic mTNBC, the five-year survival rate is about 12 percent.[3]

The current guidelines from the American Society for Clinical Oncology (ASCO) College of American Pathology (CAP) define TNBC as less than one percent positive for nuclear staining for estrogen receptor (ER) and progesterone receptor (PR), and either 0 to 1+ for human epidermal growth factor receptor 2 (HER2) according to immunohistochemistry (IHC).[2]

Recent data indicate that patients with HER2-low expression also benefit from treatments that have shown efficacy in mTNBC. Thus the ASCO CAP guidelines recommend in situ hybridization (ISH) testing for patients with an IHC of 1+ or 2+ for HER2 expression. For these patients, if ISH is negative, then HER2 expression is considered low.[4] An estimated one out of three patients with TNBC has HER2-low expression, so it's important to consider which therapies for MTNBC have been studied in both HER2-negative and HER2-low.[5,6]

MTNBC has constituted a major unmet need in our therapeutic armamentarium. Although more progress is needed, important strides have been made. Presentations at ASCO and ESMO in 2022 reflect that progress and point to future directions that research should continue to pursue.

Sacituzumab Govitecan

In 2021, Dr Aditya Bardia and colleagues reported the results of a phase 3 trial on sacituzumab govitecan in mTNBC.[7] This study, known as ASCENT, compared this antibody-drug conjugate with single-agent chemotherapy as chosen by the physician. The median overall survival (OS) time among the 235 patients randomized to the experimental treatment was 12.1 months, versus 6.7 months for the 233 patients randomized to chemotherapy.

At the 2022 ASCO annual meeting, Dr Bardia presented the final results from the ASCENT study. The most important finding here is that the median survival time was 11.7 months for patients who received sacituzumab govitecan versus 6.2 months for patients on the chemotherapy arm. That is a large improvement in survival time. At 24 months, the survival rate was 20.5 percent versus 5.5 percent, respectively, which again is a substantial increase. The efficacy of sacituzumab govitecan in the treatment of mTNBC is not in doubt and compared to single-agent chemotherapy, which was all we had up until now, the improvement is noteworthy.

The main toxicities reported in the ASCO follow-up were neutropenia — though the incidence of febrile neutropenia was low — anemia, diarrhea, and also fatigue. However, all of these

were manageable. Some patients treated with sacituzumab govitecan will require a dose reduction from 10 mg/kg to 7.5 mg/kg; this switch reduces dose-limited toxicity and enables patients to feel better. This option is important because the use of this helpful drug should not be discontinued due to toxicity. One patient experienced interstitial lung disease but this problem is extremely uncommon with sacituzumab govitecan. Ultimately, less than three percent of patients stopped treatment due to an adverse event. The drug appeared to improve quality of life, with a reduction in many of the symptoms associated with mTNBC.

At the ESMO Breast Cancer Congress 2022, Dr Sarah Hurvitz and colleagues presented an additional analysis of the ASCENT trial findings.[9] They wanted to know whether the benefits seen with sacituzumab govitecan applied across HER2 immunohistochemistry status including those patients with IHC 0, IHC 1+, IHC 2+. ASCO/CAP guidelines define triple-negative breast cancer as <1% expression of ER and PR, as well as HER2-negative expression, including IHC 0, IHC 1+, or IHC 2+ with negative ISH. Just under a third of patients in the ASCENT study were classified as HER2-low (IHC 1+ or 2+ and ISH negative). The study concluded clinical benefit with sacituzumab govitecan in IHC0 and HER2-low patients that was consistent with the overall study population.

Although a complete review of presentations from the San Antonio Breast Cancer Symposium is beyond the scope of this summary, an additional report from the 2021 symposium provides additional important insights from the ASCENT study. Dr Javier Cortés and colleagues analyzed post-progression therapy and found that 73 percent of patients who discontinued treatment with sacituzumab govitecan due to disease progression were able to move to chemotherapy. The most common drug following completion of the study was eribulin, followed by carboplatin, capecitabine and the checkpoint inhibitor atezolizumab. The key take-home message from this analysis was that treatment with sacituzumab govitecan does not preclude a further line of treatment for patients with relapsed/refractory mTNBC.

Pembrolizumab

The KEYNOTE-522 study led to the regulatory approval of neoadjuvant pembrolizumab plus chemotherapy, followed by pembrolizumab, for the treatment of early-stage TNBC.[11] At the ESMO 2022 Congress, Dr Javier Cortes and colleagues presented a network meta-analysis of this study. The goal of this literature analysis was to examine the efficacy of preoperative pembrolizumab in the context of other studies that have been done in that setting.

The alternative treatments with which the KEYNOTE-522 regimen was compared included paclitaxel plus carboplatin followed by anthracycline plus cyclophosphamide; paclitaxel plus bevacizumab followed by anthracycline plus cyclophosphamide plus bevacizumab; paclitaxel plus carboplatin followed by anthracycline plus cyclophosphamide, among others. According to the ESMO presentation, the pathological complete response (CR) rate associated with neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab was higher than the CR rate seen with all the alternative therapies included in the analysis.

GX-17

GX-17 is a hybrid protein in which human interleukin-17 is fused with an antibody fragment crystallizable domain. Dr. Joohyuk Sun and colleagues presented the results of the phase 1b/2 KEYNOTE-899 study of GX-17 plus pembrolizumab for refractory or recurrent mTNBC.[12] In this open-label study, patients received pembrolizumab every three weeks and GX-17 at a dose ranging from 360 µg/kg to 1440 µg/kg every nine or 12 weeks during the initial phase and then at a fixed dose of 1200 µg/kg every nine weeks for the second phase. The overall response rate was 15.7 percent (8 of 51 patients) for the first phase and 21.2 percent (7 of 33 patients) for the second phase. These are early findings from a small study, but it's interesting to note that GX-17 appeared to be fairly safe. Although all patients experienced a treatment-related adverse event, the percentage of immune-related adverse events was low.

Nivolumab

Nivolumab is a PD-1 inhibitor that is used to treat several types of cancer and is now being investigated for TNBC. The BELLINI trial is a pilot study of nivolumab plus ipilimumab in early-stage TNBC with tumor-infiltrating leukocyctes. Dr Iris Nederlof and colleagues presented the initial results from this study at the 2022 ESMO Congress.[14] This was a small study, with just 31 patients, mostly with stage 1 disease, though some had stage 2 or 3. The endpoint of the study was immune activation, which is not relevant to clinical practice.

However, the results do offer important indications for practice. Seven patients experienced a partial response, and all of these patients had a high level of tumor-infiltrating lymphocytes (TILs), with all east 40 percent of the tumor occupied by TILs. Three of these patients continued to surgery after the two cycles of therapy included in the study, with one of these patients achieving a pathological CR and a second achieving a near-pathological CR. This result indicates that tumors with a high percentage of TILs are the most likely to benefit from immune therapy, including a regimen that does not include chemotherapy.

Event-Free Survival as a Surrogate Endpoint

At the 2022 ESMO Congress, a group of researchers ,including myself, reported a study looking at the evaluation of event-free survival (EFS) as a surrogate for overall survival in early-stage TNBC following neoadjuvant therapy.[15] The rationale behind this analysis is that

EFS is often used as an endpoint in studies of neoadjuvant treatment of TNBC because OS requires extensive follow-up time and can be a burden on patient resources. However, although regulatory authorities in both the US and Europe consider EFS in evaluating novel neoadjuvant therapies, whether EFS can actually serve as a litmus test for OS was not established.

Our analysis of an individual-level association between EFS and OS was based on 45 studies including 7522 patients. Among these studies, 12 were randomized, controlled trials. The data spanned multiple geographic regions and included a median follow-up of 43.7 months.

We found that EFS is statistically likely to translate to improved survival time. The results support the use of EFS by regulatory authorities considering new neoadjuvant treatments and also indicate this outcome as a legitimate basis for approving reimbursement of these treatments as well.

Other Findings and Future Outlooks

Several studies on mTNBC presented at ASCO and ESMO 2022 were small, not clinical relevant, or not applicable to US clinicians, underscoring the unmet need of this patient population. Some of these studies do yield useful insights. For example, the phase 3 study comparing gemcitabine plus capecitabine with the standard combination of gemcitabine plus carboplatin provides useful data for the treatment of patients who have an allergic reaction to carboplatin. In addition, atezolizumab is not available in the US and is not part of our treatment guidelines here, and of course neither is bevacizumab. Still, it is informative to understand ongoing research in other countries. Taken as a whole, the research presented on mTNBC at these conferences sharpens the focus on validated therapeutic targets and where improvement is still needed. Sacituzumab govitecan is now well-established as an important cornerstone of therapy for mTNBC. Pembrolizumab is effective for PD-L1–positive patients in combination with chemotherapy for first-line treatment. We are awaiting additional data on trastuzumab deruxtecan and on datopamab deruxtecan, a humanized anti-Trop2 IgG1 monoclonal antibody. Other studies are looking at alpelisib, a PI3 kinase inhibitor approved for hormone-positive, HER2-negative breast cancer, that is being evaluated in combination with nab paclitaxel for TNBC, and capivaertib, an AKT inhibitor. Trilaciclib is a CDK4/6 inhibitor being evaluating in combination with gemcitabine and carboplatin for mTNBC.

With regard to biomarker testing, research has clarified that Trop2 is a ubiquitously expressed plasma membrane antigen in TNBC. Whether a tumor is categorized as low-, intermediate- or high-expressing Trop2 does not need to be a factor when considering treatment with Trop2 inhibitors like sacituzumab govitecan. When this antibody binds to cells with Trop2 expression, it becomes internalized inside the cell. SN38 is then cleaved off the antibody inside the cell and this cytotoxic agent goes inside the nucleus to kill the cell. Because SN38 can cross the nuclear and plasma membrane, it is able to permeate neighboring cells that do not have any Trop2 expression. This bystander effect has emerged as an important mechanism in the treatment of TNBC that will continue to play a role as research of Trop inhibitors continues.

Disclosure

Dr O'Shaughnessy has received honoraria for consulting and advisory boards from Abbvie, Agendia, Amgen Biotechnology, AstraZeneca, Athenex, Bayer, Bristol Myers Squibb, Caris, Carrick Therapeutics, Celgene, Daiichi Sankyo, Esai, Exact Sciences, G1 Therapeutics, Genetech, Genzyme, Gilead Sciences, GRAIL, Halozyme Therapeutics, Heron Therapeutics, Immunomedics, Ipsen Biopharmaceuticals, Lilly, Merck, Myriad, Nektar Therapeutics, Novartis, Ontada, Pfizer, Pharmacyclics, Pierre Fabre Pharmaceuticals, Puma Biotechnology, Prime Oncology, Roche, Samsung Bioepis, Sandoz, Sanofi, Seagen, Syndax Pharmaceuticals, Synthon, Taiho Oncology, Takeda, and Theralink.

References

1. Anders CK, Carey LA. ER/PR negative, HER2-negative (triple negative) breast cancer. UpToDate. Available online at https://www.uptodate.com/contents/er-pr-negative-her2-negative-triple-negative-breast-cancer. Accessed December 16, 2022.
2. National Cancer Institute Surveillance Epidemiology, and End Results Program. Cancer Stat Facts: Female Breast Cancer. Available online at https://seer.cancer.gov/statfacts/html/breast.html. Accessed December 16, 2022.
3. Allison KH, Hammond EH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline update. *J Clin Oncol.* 2020; 38:1346-1366.
4. Tarantino P, Hamilton E, Tolaney SM, et al. HER2-low breast cancer: pathological and clinical landscape. *J Clin Oncol.* 2022;38:1951-1962.
5. Schettini F, Chic N, Brasó-Maristany et al. Clinical, pathological, and PAM50 gene expression features of HER2-low breast cancer. *NPJ Breast Cancer.* 2021;7:1.
6. Tarantino P, Jin Q, Tayob N, et al. Prognostic and biologic significance of ERBB2-low expression in early-stage breast cancer. *JAMA Oncol.* 2022;8:1177-1183.
7. Bardia A, Hurvitz SA, Tolaney SM, et al; for the ASCENT Clinical Trial Investigators. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med.* 2021;384:1529-1541.
8. Baria A, Tolaney SM, Loirat D, et al. Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated, metastatic triple-negative breast cancer (mTNBC): final results from the phase 3 ASCENT study [ASCO abstract 1071]. *J Clin Oncol.* 2022;40(suppl 16).
9. Hurvitz SA, Bardia A, Punie K, et al. Sacituzumab govitecan efficacy in patients with metastatic triple-negative breast cancer by HER2 immunohistochemistry status: findings from the phase 3 ASCENT study [ESMO abstract 168P]. *Ann Oncol.* 2022;33(Suppl 3).
10. Cortés J, Bardia A, Loirat D, et al. Post-progression therapy outcomes in patients from the phase 3 ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer. Poster presented at the San Antonio Breast Cancer Symposium 2021 Annual Meeting. December 7-10, 2021; San Antonio, TX. Abstract P5-16-15.
11. Schmid P, Cortes J, Dent R, et al. KEYNOTE-522: Phase III study of neoadjuvant pembrolizumab + chemotherapy vs. placebo + chemotherapy, followed by adjuvant pembrolizumab vs. placebo for early-stage TNBC. *Ann Oncol.* 2021;32(9):1198-1200.
12. Cortes J, Haiderali A, Huang M, et al. Neoadjuvant pembrolizumab + chemotherapy followed by adjuvant pembrolizumab for treatment of high-risk, early-stage triple-negative breast cancer — a network meta-analysis [ESMO abstract 169P]. *Ann Oncol.* 2022;33(suppl 4).
13. Sohn J, Kim GM, Lee KS, et al. Phase 1b/2 study of GX-17 plus pembrolizumab in patients with refractory or recurrent (R/R) metastatic triple negative breast cancer (mTNBC): the KEYNOTE-899 study [ASCO abstract 1081]. *J Clin Oncol.* 2022;40(suppl 16).
14. Nederlof I, Isaeva O, Bakker N, et al. Nivolumab and ipilimumab in early stage TNBC with tumor-infiltrating lymphocytes (TILs) [ESMO LBA 13]. *Ann Oncol.* 2022;33(Suppl 7).
15. Fasching PA, Huang M, Haiderall A, et al. Evaluation of event-free survival as a surrogate for overall survival in early-stage triple-negative breast cancer following neoadjuvant therapy [ESMO 186P]. *Ann Oncol.* 2022;33(Suppl 7).