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Advancements in Pretreated HR+/HER2- Metastatic Breast Cancer

Announcer:
Welcome to ReachMD.

This medical industry feature, titled “Advancements in Pretreated HR+/HER2-Negative Metastatic Breast Cancer,” has been created and paid for by Gilead Oncology.

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Here is your host, Dr Sanjay Juneja.

Dr Juneja:
Hello, and welcome to ReachMD.

I’m Dr Sanjay Juneja, and with me today to talk about TRODELVY, sacituzumab govitecan, is Dr VK Gadi, a medical oncologist from Chicago, Illinois.

We are looking forward to a robust discussion of TRODELVY. We will take you through the TRODELVY mechanism of action, then delve into TROPiCS-02 study, including the study design and the efficacy and safety findings. We will also discuss how the National Comprehensive Cancer Network®, or NCCN®, recommends using TRODELVY in the published guidelines.

So welcome, Dr Gadi. Let’s get started.

Dr Gadi:
Thanks. I’m happy to be here.

Dr Juneja:
Let’s start with some Important Safety Information about TRODELVY

ANNOUNCER:

INDICATION[1]

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 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.

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.

To see full Prescribing Information, including BOXED WARNING, please click on the link on the ReachMD landing page or visit TRODELVYHCP.com, and please stay tuned for continued Important Safety Information later in this podcast.

Dr Juneja:
So, Dr Gadi, when it comes to different types of breast cancer, what is the outlook for patients with hormone receptor–positive/HER2-negative metastatic breast cancer?

Maybe specifically, what is the five-year relative survival percentage?

Dr Gadi:
Relative survival for patients with HR-positive/HER2-negative metastatic breast cancer is low, with 34 percent of patients alive after five years. In this challenging disease state, targeting another receptor could potentially offer therapeutic benefits.[2]

Dr Juneja:
When a patient with hormone receptor–positive/HER2-negative metastatic breast cancer progresses after that first-line treatment, how do you decide what to target next?

Dr Gadi:
Consider actionable targets like Trop-2, which is overexpressed in breast cancer, as well as IHC status.[3]

Dr Juneja:
So TRODELVY is the first Trop-2–directed antibody-drug conjugate, or ADC.[1]

How does TRODELVY work differently than traditional chemotherapy?

Dr Gadi:
So let's focus on some of the key characteristics of TRODELVY.[1]

TRODELVY is designed to work differently than traditional chemotherapy.[1]

TRODELVY is a Trop-2–directed antibody-drug conjugate, or ADC, as you pointed out. ADCs contain a cytotoxic agent, a linker, and an antibody component that can recognize a target.[1]

It's a humanized, monoclonal antibody. It binds to Trop-2, or also known as the trophoblast cell-surface antigen-2.[1]

It has a cytotoxic payload. The payload of TRODELVY is SN-38, a topoisomerase 1 inhibitor that prevents repair of DNA damage and leads to apoptosis and cell death. TRODELVY has a high drug-to-antibody ratio of approximately eight to one.[1]

There's a hydrolyzable linker that links the humanized monoclonal antibody to the SN-38, and when you hydrolyze that linker, it releases SN-38 to kill the tumor cells.[1]

And then there's this phenomena of the bystander effect. There's preclinical data suggesting that the topoisomerase inhibitor payload can act both on the target Trop-2–expressing cells and on surrounding cells following intracellular release.[1,6-9]

The Trop-2 biomarker testing is not necessary for TRODELVY.[1]

Dr Juneja:
The proposed mechanism of action is based on preclinical data, which may not correlate with clinical outcomes.

So let's talk about TROPiCS-02 and their study design, where they looked at TRODELVY as a potential to treat patients that had been exposed to prior lines and different classes of therapy. What makes this study design interesting, and what stood out to you?

Dr Gadi:
TROPiCS-02 was a Phase 3 study of 543 patients with HR-positive/HER2-negative metastatic breast cancer, previously treated with one or more prior endocrine therapies, a CDK4/6 inhibitor, a taxane in any setting, as well as two to four lines of chemotherapy in the metastatic setting.[1,10,11]

Patients were randomized one to one to receive either TRODELVY 10 milligrams per kilogram IV on days one and eight of a 21-day treatment cycle, and there were 272 patients in that category, or investigator's choice of single-agent chemotherapy, and there were 271 patients in that category. These therapies included eribulin, vinorelbine, gemcitabine, or capecitabine.[1]

Patients were treated until progression or unacceptable toxicity.[1] The primary endpoint was progression-free survival, or PFS, as assessed by blinded independent central review per RECIST 1.1 criteria.[10,11]

Secondary endpoints included overall survival, as well as assessment of safety and quality-of-life measures.[10,11]

Dr Juneja:
I'm Dr Sanjay Juneja, and with me is Dr VK Gadi to discuss TRODELVY. Today, we're focusing on the mechanism of action, the TROPiCS-02 study, and the efficacy and safety findings.

So patients need additional options in later lines of treatment, and two of the categories we think about are how efficacious it is and tolerable.

When they looked at the primary endpoint of TROPiCS-02, what was the PFS, and was there a benefit in the TRODELVY group?

And how did it compare to those single-agent chemotherapies that you mentioned?

Dr Gadi:
In the TRODELVY arm, median PFS was 5.5 months, 95 percent confidence interval of 4.2 to 7.0, versus 4.0 months with single-agent chemotherapy, 95 percent confidence interval of 3.1 to 4.4.[1]

Hazard ratio for this Kaplan-Meier curve was 0.66. 95 percent confidence interval of 0.53 to 0.83, with a *P* value of 0.0003.[1,10]

Three times more patients on TRODELVY remained progression-free and alive at 12 months, based on Kaplan-Meier estimates of the intent-to-treat population, based on prespecified, descriptive analysis. The 12-month PFS rate was 21 percent with TRODELVY versus seven percent with single-agent chemotherapy. Here, the 95 percent confidence intervals of 15 to 28 versus three to 14, respectively.[1,10]

Dr Juneja:
12-month data are not powered for statistical analysis.[10]

So when we talk about the secondary endpoint of TROPiCS-02, the overall survival in hormone receptor–positive/HER2-negative metastatic breast cancer, how did TRODELVY compare with single-agent chemotherapy in that overall survival?

Dr Gadi:
TRODELVY provided 3.2 more months of overall survival. Hazard ratio was 0.79. 95 percent confidence interval of 0.65 to 0.96, with a *P* value of 0.02.[1]

In the TRODELVY arm, median overall survival was 14.4 months versus 11.2 months with single-agent chemotherapy. Here, the 95 percent confidence intervals of 13.0 to 15.7 and 10.1 to 12.7, respectively.[1]

61 percent of patients on TRODELVY were alive at 12 months, based on a prespecified, descriptive analysis. The 12-month OS rate was 61 percent with TRODELVY, versus 47 percent with single-agent chemotherapy. 95 percent confidence intervals of 55 to 66 and 41 to 53, respectively. Approximately six out of 10 patients were still alive at one year.[11,12]

Dr Juneja:
Should be noted these 12-month data are also not powered for statistical analysis.

Quality of life is very important to patients, their families, and of course, to their care teams.

TROPiCS-02 evaluated the time to deterioration, otherwise known as TTD, for global health status or quality of life. This may be a

confusing endpoint. How do you interpret using this data when they looked at that analysis?

Dr Gadi:
Time to deterioration of global health status and quality of life, fatigue, and pain were prespecified secondary endpoints in TROPiCS-02.[11]

Time to deterioration was defined as the time from randomization to the first date a patient achieved a greater than 10-point deterioration from baseline or died due to any cause, whichever occurred first.[11]

TRODELVY extended time to deterioration of global health status and quality of life.[13]

Looking at the specific results of the patient-reported EORTC quality of life questionnaire C-30 of evaluable patients, the median time to deterioration for global health status or quality of life was 4.3 months with TRODELVY, versus 3.0 months with single-agent chemotherapy. Respectively, 95 percent confidence intervals of 3.1 to 5.7 for the 234 patients receiving TRODELVY, and 2.2 to 3.9 months for the 207 patients receiving single-agent chemotherapy. The hazard ratio was 0.75, a range is 0.61 to 0.92, with a *P* value of 0.006. For fatigue, the median time to deterioration in the TRODELVY arm was 2.2 months versus 1.4 months for single-agent chemotherapy. Respectively, 95 percent confidence intervals of 1.6 to 2.8 for the 234 patients receiving TRODELVY, and 1.1 to 1.9 for the 205 patients receiving single-agent chemotherapy. The hazard ratio was 0.73, with a range of 0.6 to 0.89, with a *P* value of 0.002. The time to deterioration for pain was similar between TRODELVY and single-agent chemotherapy.[13]

Dr Juneja:
There are some limitations of the EORTC QLQ-C30, as it is not all-inclusive and does not include adequate assessment of additional, expected, treatment-related symptoms or overall side effect bother from the patient perspective. The results should be interpreted with caution due to the open-label design of the study, and because TTD may be confounded by events not related to the disease or treatment.

So, Dr Gadi, when it comes to adverse events, how do you talk with patients about the potential side effects they may experience?

What strategies may be used to manage some of these adverse events with TRODELVY, like neutropenia?

How may healthcare professionals plan and prepare for the management of diarrhea?

Dr Gadi:
TRODELVY has a well-characterized safety profile.[10] In the TROPiCS-02 study, serious adverse reactions, or SARs, were reported in 28 percent of patients. The most frequent SARs, greater than one percent, were diarrhea at five percent, febrile neutropenia at four percent, neutropenia at three percent, abdominal pain, colitis, neutropenic colitis, pneumonia and vomiting, each at two percent.[1]

Six percent of patients on TRODELVY discontinued therapy due to adverse reactions. The most frequent, at 0.5 percent or greater, were asthenia, general physical health deterioration, and neutropenia, each at 0.7 percent.[1]

The most common adverse reactions, including lab abnormalities with TRODELVY were decreased leukocytes, 88 percent, decreased neutrophils, 83 percent, decreased hemoglobin, 73 percent, decreased lymphocytes, 65 percent, diarrhea, 62 percent, fatigue, 60 percent, nausea, 59 percent, alopecia, 48 percent, increased glucose, 37 percent, constipation, 34 percent, and decreased albumin, 32 percent.[1]

The most common Grade 3 to 4 lab abnormalities, incidence greater than or equal to 25 percent, in the TROPiCS-02 study, were reduced neutrophils and leukocytes. There were no events of ILD with TRODELVY in TROPiCS-02.[1]

With a drug like TRODELVY, it is important to talk with patients about potential AEs. Discussing potential AEs early can help patients prepare strategies for managing certain AEs or line up additional support from family and friends. Discussing potential AEs with patients early can help address patients' fears and increase patient engagement with their treatment.

Neutropenia occurred in 64 percent of patients treated with TRODELVY. Grade 3 to 4 neutropenia occurred in 49 percent of patients.[1]

Febrile neutropenia occurred in six percent, while neutropenic colitis occurred in 1.4 percent of patients.[1]

I recommend talking to patients about the possibility of experiencing neutropenia while on TRODELVY, which can be severe, life-threatening, or fatal.[1]

I encourage my patients to tell me swiftly if they experience fever, chills, or other signs of infection. Often, I consider secondary

prophylactic use of G-CSF to manage neutropenia.[1]

Based on the US prescribing information, I will make dose reductions or discontinue treatment to manage severe neutropenia, if it is necessary for a specific patient. These dose modifications may help my patients to continue treatment if appropriate. If my patient has an absolute neutrophil count, or ANC, below 1500 per cubic millimeter on day one of any cycle, or an ANC below 1000 per cubic millimeter on day eight of any cycle, I withhold TRODELVY. I would also withhold TRODELVY if my patient has had a neutropenic fever.[1]

Diarrhea occurred in 64 percent of patients treated with TRODELVY. Grade 3 to 4 diarrhea occurred in 11 percent of patients. One patient had intestinal perforation following diarrhea. Diarrhea that led to dehydration and subsequent acute kidney injury occurred in 0.7 percent of all patients.[1]

When planning and preparing for the management of diarrhea, I first talk to patients about the possibility of experiencing diarrhea, which can be severe while on TRODELVY. At the onset of diarrhea, I will initiate loperamide unless an infectious cause is identified. The recommended starting dose of loperamide is four milligrams initially, followed by two milligrams with every episode of diarrhea, for a maximum of 16 milligrams per day. Loperamide should be discontinued 12 hours after diarrhea resolves. I will also initiate other supportive measures, such as administration of fluids or electrolytes, if clinically appropriate. If a patient experiences an excessive, cholinergic response to treatment with TRODELVY, I may premedicate with atropine or similar treatment for subsequent treatments.[1]

In certain cases of diarrhea, dose modifications or discontinuations may be required. Healthcare professionals should withhold TRODELVY for Grade 3 to 4 diarrhea at the time of scheduled treatment administration, and resume when resolved to Grade 1 or lower.[1]

There are a variety of tools available to help healthcare professionals in managing AEs.

For example, there are dose modification tables in the TRODELVY Prescribing Information.

Information about managing certain AEs in the Prescribing Information.

Ask a TRODELVY Gilead therapeutic specialist for additional materials created for healthcare professionals or patients.

These are some of the AEs to be aware of, but please stay tuned for more within the full Important Safety Information.

Dr Juneja:
So, Dr Gadi, has the National Comprehensive Cancer Network, or NCCN, made a recommendation for TRODELVY for the treatment of hormone receptor–positive/HER2-negative metastatic breast cancer?

Dr Gadi:
TRODELVY is recommended as a Category 1 preferred treatment option for adult patients with recurrent, unresectable, or metastatic HR-positive, HER2-negative breast cancer, who have received prior treatment including endocrine therapy, a CDK4/6 inhibitor, and at least two lines of chemotherapy including a taxane, at least one of which in the metastatic setting. It may be considered for later line, if not used in the second line of therapy.[14]

Dr Juneja:
What do you think when you see the disclaimer, if not a candidate for fam-trastuzumab deruxtecan in the NCCN guidelines?

Dr Gadi:
The guidelines specify that TRODELVY may be used in the second line if the patient is not a candidate for fam-trastuzumab deruxtecan.[14]

Seeing this disclaimer in the NCCN guidelines highlights the importance of individualized treatment plans.

Dr Juneja:
It‘s important to note here that the NCCN recommendation differs from the TRODELVY Prescribing Information. Category 1 indicates that based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. NCCN makes no warranties of any kind, whatsoever, regarding their content, use, or application, and disclaims any responsibility for their application or use in any way.[14]

This has been an informative discussion, and I would really like to thank my guest, Dr Gadi, for joining us today.

Dr Gadi:

Thank you, Dr Juneja. It was my pleasure to speak about TRODELVY for the treatment of patients with pretreated, HR-positive/HER2-negative metastatic breast cancer.

Dr Juneja:
To see full Prescribing Information, including BOXED WARNING, please click on the link on the ReachMD landing page, or visit TRODELVYHCP.com. Please stay tuned for continued full Important Safety Information.

In another conversation with Dr Gadi, I discuss the use of TRODELVY in another patient population, right here on ReachMD. To access this and other episodes in this series, please visit reachmd.com/industryfeature, where you can Be Part of the Knowledge.

Announcer:
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 TROPiCS-02 study, the most common adverse reactions (incidence ≥25%) were diarrhea, fatigue, nausea, alopecia, and constipation. The most frequent serious adverse reactions (SAR) (>1%) were diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), abdominal pain, colitis, neutropenic colitis, pneumonia, and vomiting (each 2%). SAR were reported in 28% of patients, and 6% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the TROPiCS-02 study were reduced neutrophils and leukocytes.

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 full Prescribing Information, including BOXED WARNING, by clicking on the link on the ReachMD landing page or visiting TRODELVYHCP.com.

Announcer:

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