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Advancements in Pretreated Metastatic Triple-Negative Breast Cancer

Announcer:
Welcome to ReachMD.

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

The speakers have been compensated for their participation in this program. The information in this program does not constitute the provision of medical advice and should not be substituted for clinical decision-making. The information in this presentation is intended for healthcare professionals in the United States and its territories, including Puerto Rico.

Here is your host, Dr Sanjay Juneja.

Dr Juneja:
Hello, and welcome to ReachMD. I'm Dr Sanjay Juneja, and today we are focusing on TRODELVY, sacituzumab govitecan. I'm also known as the Onc Doc, and I'm a triple board–certified hematologist and medical oncologist known for simplifying cancer concepts on social media. I'm part of the editorial board for the *AI in Precision* Oncology journal, and I'm the host of *Target: Cancer Podcast*.

With me today to talk about TRODELVY 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 the ASCENT study, including the study design and the efficacy and safety findings. We will also discuss how the National Comprehensive Cancer Network®, NCCN®, recommends using TRODELVY in the published guidelines. So with that said, welcome, Dr Gadi. We’re very happy to have you.

Dr Gadi:
Thank you. I’m so excited to be here.

Dr Juneja:
Let’s start with the indication and 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 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
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:
Dr Gadi, what is the outlook for patients with metastatic triple-negative breast cancer? What does the median overall survival look like?

Dr Gadi:
Survival for patients with metastatic TNBC is low, with metastatic TNBC patients experiencing a median overall survival of just 15.2 months.[2]

Dr Juneja:
When a patient progresses after first-line treatment, how do you go about deciding what to do next or possibly target?

Dr Gadi:
When a patient progresses in this challenging disease state, there's a need for additional options that are differentiated from traditional chemotherapy that may extend survival and may support quality of life.[3]

Consider actionable targets like Trop-2, which is overexpressed in breast cancer, as well as immunohistochemistry status.[4-6]

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:
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]

Trop-2 is overexpressed in more than 80 percent of breast cancer as compared with normal breast tissue and overexpressed in many other solid tumors.[4-6]

So a few key characteristics about this molecule.

The humanized monoclonal antibody piece is the piece that binds to Trop-2, the trophoblast cell-surface antigen-2.[1]

The cytotoxic payload, the payload of TRODELVY is SN-38, a topoisomerase I 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.[1,7]

Then there's this bystander effect. So the preclinical data suggests that topoisomerase inhibitor payload can act both on the target Trop-2–overexpressing cells and on surrounding cells following intracellular release.[1,7-10]

Trop-2 biomarker testing is not necessary for TRODELVY.

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

Dr Gadi, let's dive in. Would you mind walking us through the ASCENT study design?

What makes this study design interesting? And what really kind of stood out to you?

Dr Gadi:
ASCENT is the landmark Phase 3 study evaluating TRODELVY versus chemotherapy in 529 patients with unresectable, locally advanced or metastatic triple-negative breast cancer, which is HR-negative, HER2-negative, immunohistochemistry zero, 1+, 2+/ISH-negative. These patients had relapsed after at least two prior chemotherapies, at least one of them for metastatic disease. While all patients previously received taxane treatment, it could have been received in either the adjuvant, neoadjuvant, or advanced stage.[1,11-13]

Patients were randomized one-to-one to receive either TRODELVY, n equals 267 patients, or physician's choice of single-agent chemotherapy; here we have 262 patients. These included eribulin, vinorelbine, gemcitabine, or capecitabine. Patients on TRODELVY were given 10 milligrams per kilogram IV on day one and day eight of a 21-day cycle and continued until disease progression or unacceptable toxicity.[1]

The primary endpoint was progression-free survival, or PFS, in the brain metastasis–negative population as assessed by blinded independent central review, per the RECIST 1.1 criteria. Secondary endpoints included an investigator's assessment of progression-free survival, or PFS, overall survival, objective response rate, and safety.[11]

So for our audience, think about what this data could mean for everyday patients in your practice.

Dr Juneja:
So the primary endpoint of ASCENT was progression-free survival in metastatic TNBC. Dr Gadi, did TRODELVY provide a PFS benefit versus single-agent chemotherapy?

Dr Gadi:
In the primary analysis of the brain-met–negative population, median PFS was 5.6 months with TRODELVY versus 1.7 months with single-agent chemotherapy, respectively, with 95 percent confidence intervals of 4.3 to 6.3 for the 235 patients receiving TRODELVY, and 1.5 to 2.6 for the 233 patients receiving single-agent chemotherapy.[11]

The hazard ratio was 0.41 with a 95 percent confidence interval of 0.32 to 0.52 and a *P* value of less than 0.001.[11]

Dr Juneja:
What were the results in the full population compared to the brain-met–negative population?

Dr Gadi:
In the TRODELVY arm of the full population, median PFS was 4.8 months with a 95 percent confidence interval of 4.1 to 5.8 for the n of 267 patients, versus 1.7 months with single-agent chemotherapy with 95 percent confidence interval of 1.5 to 2.5. Here we have 262 patients.[1]

The hazard ratio was 0.43 with a 95 percent confidence interval of 0.35 to 0.54 and a *P* value of less than 0.0001.[1]

Please note that the median PFS for the full population was not part of the primary endpoint.

Median PFS was nearly three times longer with TRODELVY.[1]

Dr Juneja:
So one of the secondary endpoints was overall survival. Dr Gadi, what did that look like in ASCENT when you looked at the full population?

Dr Gadi:
TRODELVY significantly extended survival with approximately five more months of overall survival versus single-agent chemotherapy.[1]

In the full population, in the TRODELVY arm, median overall survival was 11.8 months versus 6.9 months with single-agent chemotherapy, the 95 percent confidence intervals of 10.5 to 13.8 for the TRODELVY 267 patients, and 5.9 to 7.6 for the 262 patients receiving single-agent chemotherapy, respectively.[1]

Hazard ratio is 0.51. Here are the confidence intervals of 0.41 to 0.62. And when you calculate a *P* value less than 0.0001.[1]

Dr Juneja:
What was the overall survival in the brain-met–negative population?

Dr Gadi:
In the primary analysis as a brain-met–negative population, the median overall survival was 12.1 months with TRODELVY, the 95 percent confidence interval of 10.7 to 14.0 for 235 patients, versus 6.7 months with single-agent chemotherapy. Here, the 95 percent confidence interval of 5.8 to 7.7 with 233 patients.[11]

The hazard ratio was 0.48, 95 percent confidence interval of 0.38 to 0.59. And when you calculate the *P* value, it was less than 0.001.[11]

Dr Juneja:
What about the two-year follow-up analysis of the brain-met–negative population?

Dr Gadi:
In a follow-up analysis of the brain-met–negative population with a data cut-off of February 25, 2021, the two-year overall survival rate was 22.4 percent with TRODELVY, versus 5.2 percent with single-agent chemotherapy. Respectively, the 95 percent confidence intervals of 16.8 to 28.5 versus 2.5 to 9.4.[14]

Dr Juneja:
In the follow-up analysis of the brain-met–negative population, this analysis was not powered for significance as part of the pivotal study and should be considered descriptive only. Therefore, the results require cautious interpretation and could represent chance findings.

Dr Juneja:
What did the overall survival look like when it was categorized by IHC status?

Dr Gadi:
In a post hoc subgroup analysis of HER2-negative status by IHC score, overall survival results were consistent across HER2-negative IHC status compared to the full population.[13]

In the HER2-low subgroup, in the TRODELVY arm, 63 patients, median overall survival was 14.0 months versus 8.7 months with single-agent chemotherapy. Here we have 60 patients. The hazard ratio when it was calculated was 0.43, a 95 percent confidence interval from 0.28 to 0.67.[13]

In the IHC zero subgroup in the TRODELVY arm, 149 patients, median overall survival was 11.3 months versus 5.9 months with single-agent chemotherapy for those 144 patients. The hazard ratio was 0.51 with a 95 percent confidence interval from 0.39 to 0.66.[13]

Dr Juneja:
Results from the post hoc subgroup analysis of HER2-negative status by IHC score include the following limitations: these results are from a post hoc subgroup analysis of the Phase 3 ASCENT study, were not powered for statistical analysis, and should be considered descriptive only. The lack of central assessment for HER2 expression and the 21 percent of patients in the ASCENT full population with missing specific HER2 IHC results are known limitations of this study. Therefore, these results require cautious interpretation and could represent chance findings.[13]

For those who are just joining us, 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 ASCENT study, and the efficacy and safety findings.

How do you talk with patients about potential adverse events that may occur, or they may experience with TRODELVY?

What strategies may be used to manage neutropenia?

How may healthcare professionals plan and prepare for the management of diarrhea, should it occur?

Dr Gadi:
TRODELVY has a well-characterized safety profile. In the ASCENT study, serious adverse reactions, or SAR, were reported in 27 percent of patients receiving TRODELVY.[1]

The most frequent SAR greater than one percent were neutropenia in seven percent, diarrhea in four percent, and pneumonia in three percent.[1]

Adverse reactions that led to discontinuation of TRODELVY occurred in five percent of patients. Adverse reactions leading to permanent discontinuation in one percent or more of patients who received TRODELVY were pneumonia for one percent, and fatigue for one percent.[1]

The most common adverse reactions, including lab abnormalities, that were greater than or equal to 25 percent with TRODELVY were

decreased hemoglobin, 94 percent, decreased lymphocyte count, 88 percent, decreased leukocyte count, 86 percent, decreased neutrophil count, 78 percent, fatigue in 65 percent, diarrhea, 59 percent, nausea, 57 percent, increased glucose, 49 percent, alopecia, 47 percent, constipation, 37 percent, decreased calcium, 36 percent, vomiting, 33 percent, decreased magnesium, 33 percent, decreased potassium, 33 percent, increased albumin, 32 percent, abdominal pain, 30 percent, decreased appetite, 28 percent, increased aspartate aminotransferase, 27 percent, increased alanine aminotransferase, 26 percent, increased alkaline phosphatase, 26 percent, and decreased phosphate, 26 percent.[1]

In ASCENT, out of 258 patients treated with TRODELVY, one, less than 0.5 percent, experienced pneumonitis, and no other cases of ILD were observed.[15]

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.[1]

Neutropenia occurred in 64 percent of patients treated with TRODELVY. Grade 3 to 4 neutropenia occurred in 49 percent of patients. 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. 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. 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 1,500 per cubic millimeter on day one of any cycle, or an ANC below 1,000 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?

Dr Gadi:
TRODELVY is recommended as a Category 1 preferred treatment option for adult patients with unresectable, locally advanced, or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease. It may be considered for later line if not used as a second-line therapy.[16]

So for our audience, think about how this might influence your practice.

Dr Juneja:
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.[16]

So, Dr Gadi, if I may, how do the NCCN recommendations regarding TRODELVY kind of align with how you treat your metastatic triple-negative breast cancer patients in your own clinic?

Dr Gadi:
I've actually reached for this therapy based on those NCCN recommendations and the availability of this agent for patients who fall into this situation where they've received that first line of therapy with a taxane, often plus a drug like a checkpoint inhibitor. Historically, we've been searching for what that next thing is, and it's generally been single-agent chemotherapy. So having this data showing this improvement in PFS and overall survival with TRODELVY makes it an attractive option. It aligns with the NCCN. So when I sit down with a patient and say, 'Look at my colleagues who have made these expert guideline recommendations, look at this data,' it becomes a good way for me to build trust and engagement around an option for patients. That's really exciting.

Dr Juneja:
I hope you found this to be an informative discussion. And I sincerely want to thank my guest, Dr Gadi, for joining us today and providing his knowledge.

Dr Gadi:
Thank you. It was my sincere pleasure to discuss TRODELVY for the treatment of patients with metastatic triple-negative 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.

Dr Gadi and I will also be having a separate conversation discussing TRODELVY in another patient population right here on ReachMD. To access this and other episodes in the series, please visit reachmd.com/industry feature, 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 ASCENT study, the most common adverse reactions (incidence ≥25%) were fatigue, diarrhea, nausea, alopecia, constipation, vomiting, abdominal pain, and decreased appetite. The most frequent serious adverse reactions (SAR) (>1%) were neutropenia (7%), diarrhea (4%), and pneumonia (3%). SAR were reported in 27% of patients, and 5% discontinued therapy due to adverse reactions. The most common Grade 3-4 lab abnormalities (incidence ≥25%) in the ASCENT study were reduced neutrophils, leukocytes, and lymphocytes.

DRUG INTERACTIONS

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

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

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

Announcer:
This program was sponsored by Gilead Oncology. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be Part of the Knowledge.

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