Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/why-is-trop2-directed-antibody-therapy-important-in-breast-cancer/14292/

Released: 06/15/2022
Valid until: 06/30/2023
Time needed to complete: 1h 21m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Why Is TROP2-Directed Antibody Therapy Important in Breast Cancer?

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME curriculum.
Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Hurvitz:
Hello, my name is Sara Hurvitz. I'm from the University of California, Los Angeles. And I'm talking about "*Why is TROP2-Directed Antibody Therapy Important in Breast Cancer?*" Antibody-drug conjugates selectively deliver chemotherapy to cancer cells. The antibody which is linked to chemotherapy binds to the tumor antigen and becomes internalized via receptor-mediated endocytosis. it is then trafficked to the lysosome. It gets degraded and the payload is released. There are a number of tumor antigens that have been selected for targeting by ADCs.

One such tumor antigen is TROP2. TROP2 stands for trophoblast cell surface antigen 2. It is a glycoprotein that spans epithelial membrane surfaces, and it is ubiquitously expressed in epithelial cells, but is more highly expressed in a number of cancers. It has been shown to play a role in cell self-renewal, proliferation, and transformation, and it appears to have an essential role in embryonic development, placental tissue formation, implantation, stem cell proliferation, and organ development. It has been shown to be expressed in all subtypes of breast cancer and has been linked to a poor prognosis in patients with breast cancer.

As you can see here from this 2011 paper, a number of tissues normally express TROP2, as shown in the top panel, including prostate, cervix, lung, and breast, but the TROP2 is more highly expressed in carcinomas shown in the bottom panel, corresponding to each cancer. And you can see that breast cancers in the far-right lower corner have higher expression of TROP2 than normal breast tissue on the upper right corner.

Sacituzumab govitecan is a first-in-class TROP2-directed antibody-drug conjugate. It's the very first ADC to be FDA approved for metastatic triple-negative breast cancer, and there are data now coming out about its activity in hormone receptor-positive HER2-negative breast cancer. This ADC is distinct from other ADCs, because it's highly specific for TROP2. It has a high drug-to-antibody ratio of 7 or 8, and its internalization and enzymatic cleavage by the tumor cell is not required for the liberation of the cytotoxic payload, which is SN-38. SN-38 is like irinotecan, the parent compound, but it is much more potent. It's a topoisomerase I inhibitor. Interestingly, the linker is also hydrolyzed, releasing the cytotoxic payload extracellularly in the tumor micro-environment, which provides a bystander effect which kills neighboring tumor cells that may have lower levels of TROP2 expression. This bystander effect is also responsible for a slightly higher risk of cytotoxicity to normal cells. And so toxicity can be experienced by patients treated with this, including diarrhea and neutropenia.

In the phase 3 ASCENT clinical trial, sacituzumab govitecan was compared to single-agent chemotherapy of physicians' choice in patients who have metastatic triple-negative breast cancer that was more heavily pretreated. In this study, patients treated with sacituzumab had not only a significantly improved progression-free survival, shown on the left side, but also an improved overall survival.

Biomarker analyses from this study also indicate that the benefits of sacituzumab govitecan appear to be regardless of the level of tumor

expression of TROP2. This is true for both progression-free survival, objective response rate, and overall survival.

Another antibody-drug conjugate that's in development, that targets TROP2 in breast cancer, is called datopotamab deruxtecan, or Dato-DXd. This is an ADC that also has an anti-TROP2 antibody, and a topoisomerase I inhibitor payload, which is an exatecan derivative. The linker is also cleavable. It's a tetrapeptide-based cleavable linker, and it's a high-potency payload with an optimized drug-to-antibody ratio of 4.

At San Antonio Breast Cancer Symposium in 2021, results from an early-phase clinical trial were presented from the breast cancer cohorts which included patients who had hormone receptor-positive and triple-negative breast cancer. The triple-negative breast cancer patients was the cohort presented at San Antonio, and patients were seen in this study to have a relatively good objective response rate of over 30% with this antibody-drug conjugate. So, very promising data early on. Those patients who had never received a prior topoisomerase I inhibitor-based antibody-drug conjugate had an objective response rate of greater than 50%, shown on the right side. And the duration of response was not yet reached. So again, all eyes are on further data relating to this agent, as it goes into larger later-phase clinical trials.

So in summary, targeting TROP2 in breast cancer makes sense, because of expression of TROP2 is very high in most breast cancers, and higher than is seen in normal tissue. Sacituzumab govitecan, a TROP2-targeted ADC, is the first ADC therapy approved for metastatic triple-negative breast cancer. It was shown to improve progression-free survival and overall survival, regardless of TROP2 expression level. And there are newer therapies on the horizon that also target TROP2. Thank you so much for your attention.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.
To receive your free CME credit, or to download this activity, go to ReachMD.com/CME. Thank you for listening.