Editorial Commentary



# The role of sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer

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Antibody-drug conjugates (ADCs) represent a major new subclass of antibody related therapeutics in oncology. ADCs combine the cancer-targeting abilities of monoclonal antibodies with the delivery of highly cytotoxic drugs into tumor as a targeted chemotherapy (1). There are currently 3 ADCs approved for the treatment of breast cancer (BC); 2 of them: trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) for human epidermal growth factor receptor 2 (HER2) positive BC; and most recently sacituzumab govitecan (SG) for triple negative breast cancer (TNBC) (2,3).

SG is a new ADC directed against the trophoblast cell-surface antigen 2 (Trop-2) (4). Trop-2 is a transmembrane calcium signal transducer highly expressed in solid tumors, especially hormone receptor (HR)$^+$/HER2$^-$ and TNBC. Upon ligation, the ADC is internalized via endocytosis which allows for the targeted delivery of its payload SN-38 into the tumor cells. This process allows SG to kill tumor cells expressing Trop-2 and also the adjacent tumor cells (5,6). Zhu *et al.* suggested that the expression level of Trop-2 differs among cell lines, independent of their subtype, and is highly variable on treatment with kinase inhibitors, tamoxifen, radiation and chemotherapy agents including irinotecan. BC with acquired resistance to tamoxifen exhibit higher levels of Trop-2, possibly via transcription factor EB (TFEB) (7).

Based on this mechanism, it would be expected that the targeted antigen needs to be overexpressed to permit antitumor activity, nonetheless, further observations challenged this paradigm, suggesting a more complex picture for ADC predictive biomarkers (8). In fact, in the case of T-Dxd, HER2 mutations could be more reliable than HER2 expression itself, possibly because of increased binding and internalization of ADCs conferred by HER2 mutations (9).

In 2020, SG received accelerated approval in TNBC after promising results were presented by Bardia *et al.* (10). More recently, Rugo *et al.* reported the results of the TROPiCS-02 phase III study assessing SG as compared to single-agent chemotherapy (eribulin, vinorelbine, capecitabine, or gemcitabine) in patients with endocrine-resistant, HR$^+$/HER2$^-$ locally recurrent inoperable or metastatic BC, and previously treated with 2–4 systemic chemotherapy regimens.

A total of 543 patients were enrolled and randomly assigned to the SG group (272 patients) or chemotherapy group (271 patients); 26 patients were randomized but not treated. The primary end point of progression free

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survival (PFS) was met with a 34% reduction in risk of progression or death in favor of the SG group [hazard ratio (HR) =0.66; 95% CI: 0.53–0.83; P=0.003]. PFS was 5.5 months for the SG group and 4.0 months for the single-agent chemotherapy. However, the difference in overall survival (OS) was not significant; 13.9 months for SG and 12.3 months for chemotherapy (HR for death, 0.84; 95% CI: 0.67–1.06; P=0.14); so due to the hierarchical statistical design, objective response and quality of life end points were not formally tested. The incidence of key grade ≥3 treatment-related adverse events (SG *vs.* chemotherapy) were neutropenia (51% *vs.* 38%), diarrhea (9% *vs.* 1%), anemia (6% *vs.* 3%) and fatigue (6% *vs.* 2%) (11). More recently, Rugo *et al.* presented the planned second interim analysis of OS from the TROPiCS-02 study in The European Society for Medical Oncology (ESMO) 2022. The results showed that SG significantly improved OS (14.4 *vs.* 11.2; P=0.020) when compared to chemotherapy (12). We await the reporting on the types of treatments administered post progression.

These data demonstrated that SG is an acceptable treatment option for patients with heavily pretreated, endocrine-resistant HR+/HER2− advanced BC. Because of this, the Food and Drug Administration granted a priority review to SG for this type of BC in October 2022 (13).

Strengths of TROPiCS-02 include the relevance of the research question, addressing an area of unmet need in the management of metastatic HR+/HER2− BC. Another important strength is that the trial included a contemporary cohort of patients who nearly all had prior therapy with CDK 4/6 inhibitors, making the interpretation of the results very applicable to the management of our current patients. Although OS was not statistically significant between the groups, this represented the first planned interim analysis, and further follow-up was required.

The results of TROPiCS-02 need to be considered along with the results from the recently reported DESTINY-Breast 04, a clinical trial that evaluated T-DXd in pre-treated HER2-low metastatic BC, given that TROPiCS-02 population overlaps with the one in DESTINY-Breast 04. However, DESTINY-Breast 04 included less heavily pre-treated patients with a median number of 1 line of prior chemotherapy in the metastatic setting, as compared with 3 in TROPiCS-02. Nonetheless both trials provide strong evidence supporting that ADCs significantly improve outcomes in patients with metastatic HR+ BC in populations that overlap but are not identical, namely DESTINY-Breast 04 included only patients with HER2 low disease. However, a large number of patients we see in clinic will fit criteria for both trials. A key question for patients that fit criteria for both ADCs is which agent to use first and how to sequence them. Although the target for both antibodies is different (Trop-2 for SG and HER2 for T-DXd), both payloads are topoisomerase I inhibitors. Additional research is necessary to understand the best sequence for using these ADCs, hopefully from a randomized clinical trial that compares them head to head. In understanding this sequence, it will be critical to collect data on the efficacy of these ADCs after progression to a prior ADC.

Additional questions from TROPiCS-02 include whether and by how much the efficacy of SG may depend on the bystander effect. It is possible that SG can exert this given that SN-38 is a membrane-permeable free molecule that gets released in the tumor microenvironment, however additional data supporting this hypothesis is required. Given the efficacy of SG independent from the TROP2 expression, further studies on the mechanism of action (and resistance) to this drug are needed and would be helpful to inform patient selection. Currently, there are different clinical trials evaluating the use of SG in HR+ BC. One of them (NCT04639986) will study the efficacy of SG in HR+/HER2− metastatic BC in the Asian population. Two other ongoing trials, SASCIA (NCT04595565) and COGNITION-GUIDE (NCT05332561), will evaluate SG after neoadjuvant therapy, in non-metastatic BC (14-16). These studies will provide further insights on the efficacy and biomarkers of response to SG in this type of BC.

This could also represent a promising path for the future development of ADCs focusing on the creation of combinations to exploit the tumor microenvironment (3). Nowadays, different assays on the characterization of other types of anti-trop monoclonal antibodies are also under development for the detection of TROP2 in a wide variety of BC types (17,18) and may help refine the predictive value for drugs like SG.

Other points to consider about the TROPiCS-02 trial include that in the chemotherapy group, the distribution was not homogeneous among the different treatment options, as 48% received eribulin, 23% vinorelbine, 21% gemcitabine, and only 8% capecitabine. Given the known superiority of eribulin when compared with other agents in third line and beyond (19), the heterogeneity of the control group in TROPiCS-02 prevents us from being able to draw conclusions about the comparative efficacy between SG and eribulin, which remains an important question. In addition, at the data cutoff date, only 7% of patients from the SG

and 1.5% from the chemotherapy group remained on the study, as most of the patients discontinued study treatment because of disease progression (77% and 73% respectively). Despite the efficacy seen with SG, unfortunately the chances of progression are still very similar and high in both groups.

TROPiCS-02 provides key data on the efficacy of SG in $HR^+$ BC, and adds to the known efficacy profile of SG in TNBC. It is encouraging to see the efficacy of a new class of anti-cancer agents—the ADCs, and in particular with SG in TROPiCS-02, within different subgroups of BC.

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