Editorial Commentary

Antibody-drug conjugates (ADCs) targeting trophoblast cell surface antigen 2 (Trop-2) and precision treatment of breast cancer

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With the development of new molecular technologies, the landscape of cancer therapy is changing from unspecific, systemic "one strategy fits all" therapy towards a more personalized strategy. Antibody-drug conjugates (ADC) are precision cancer treatments that combines the potential of more or less tumor specific antigen targeted therapy with drugs that are already on label for treatment for cancer (e.g., irinotecan/SN-38), or drugs that are too toxic for normal anticancer use (as e.g., emtansine). By conjugating these drugs to antigen targeting antibodies, it is possible to reduce the plasma concentration of the anticancer drug and at the same time deliver a higher dose of the drug to the antigen expressing cancer cells (1-3). A successful example is the publication in April 2021 in the *New England Journal of Medicine* on the results from therapy with sacituzumab govitecan (Trodelvy) in relapsed or refractory metastatic Triple-Negative Breast Cancer (TNBC) patients (4).

Sacituzumab govitecan is an ADC composed of a monoclonal antibody targeting the human trophoblast cell-surface antigen 2 (Trop-2), which is expressed in more than 90% of breast cancer cells but only scarcely in normal cells, coupled to SN-38 [a topoisomerase I (Top I) inhibitor] through a proprietary hydrolyzable linker (4).

From 2013 to 2021 about 12 ADC's including sacituzumab govitecan, have been approved in the treatment of hematological cancers, breast cancer, urothelial tumors and cervical cancer. In the beginning of 2022, more than 15 ADC's are in clinical phase II or III trials with indications such as hematological diseases, non-small and small cell lung cancer, prostate cancer, glioblastoma, mesothelioma, ovarian cancer and renal cell carcinoma and other (3).

The caveats of ADC therapy are related to the mode of action. The duality in the mode of action is also one of the limitations of the potential treatment indication. The tumor cells must have some degree of expression of the targeted antigen (as e.g., the more than 90% expression of Trop-2 in breast cancer (4), and the cytotoxic conjugates must be active against the tumor type in question. One of the major quests is to find an antigen with increased expression on the tumor cells and minimal expression on normal healthy cells and targeting this with an antibody combined with a cytotoxic drug (or radioactive isotope, or another drug attracting for instance the immune cells) that will then mainly be released in the specific tumor cells.

If the ADC targets and release its cytotoxic conjugate on vulnerable and essential normal cells (e.g., in the gut) the toxicity may be limiting the clinical use of the ADC. If the linking of the toxic drug conjugate to the antibody is weak

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and results in release of the drug into the blood before the ADC has targeted the tumor cells, the systemic toxicity may be dose limiting and hamper efficacy. On the other hand, this may potentially also have a positive effect on the efficacy if the antigen distribution is scarce. In that case a weak linker may facilitate the deconjugation of the cytotoxic drug in the vicinity of the antigen-positive tumor cells and facilitate a bystander cell kill.

The ADC sacituzumab govitecan was evaluated in a randomized phase III trial (ASCENT) treating late line patients with TNBC who had received two or more previous standard chemotherapy including a taxane (4). Therapy with sacituzumab govitecan was compared with standard chemo-monotherapy by physicians' choice (eribulin, vinorelbine, capecitabine, or gemcitabine). The primary end point was progression-free survival among patients without brain metastases.

A total of 468 patients was enrolled in the study and 235 patients received sacituzumab govitecan and 233 patients received chemotherapy. The benefit with sacituzumab govitecan was observed in all clinical and prespecified subgroups. All major efficacy parameters were improved: median progression free survival (PFS) was prolonged from 1.7 to 5.6 months [HR 0.41 (0.32–0.52), P<0.001], median overall survival (OS) was prolonged from 6.7 to 12.1 months [HR 0.48 (0.38–0.59) P<0.001], and objective response rate (ORR) was increased from 5% to 35%.

Although the key to tumor efficacy was targeting of the Top1 enzyme in the tumor cells, severe adverse events likely due to off target activity were more frequent in patients receiving sacituzumab govitecan with neutropenia (51% *vs.* 33%), diarrhea (10% *vs.* <1%), and febrile neutropenia (6% *vs.* 2%). Although there were 3 deaths owing to adverse events in each group, no deaths were considered to be related to sacituzumab govitecan treatment. Importantly, sacituzumab govitecan also improved quality of life (QoL) (5).

Recently the final data from the phase III ASCENT study was released with the final databased locked at Feb 25, 2021 (6). The final data is in full alignment with the previously published observations. The results were that sacituzumab govitecan significantly improved median PFS (5.6 *vs.* 1.7 months; HR: 0.39; P<0.0001) and significantly improved median OS (12.1 *vs.* 6.7 months; HR: 0.48; P<0.0001). Even though treatment-related grade ≥3 adverse events with Sacituzumab govitecan were more frequent than in the chemotherapy comparator group [diarrhea (11% *vs.* 0.4%), neutropenia (52% *vs.* 33%), anemia (8% *vs.* 5%), and febrile neutropenia (6% *vs.* 2%)] a significant improvement was observed in the scores for all primary focus health-related QoL domains.

In an Editorial Commentary in this journal, Santi *et al.* raised the question whether sacituzumab govitecan is a classic ADC or rather has a function as a prodrug that releases SN-38 either in the vicinity of the tumor or systemically (7). The ADC drug targets the Trop-2 antigen, but the drug is efficient regardless of Trop-2 expression (7,8) indicating that the ADC may function as a slow-release delivery system of the Top1 inhibitor SN-38.

The authors point out that "*A knowledge of the mechanism of action of sacituzumab govitecan in Trop-2 low or absent tumors would facilitate further development of SN-38-based drugs or ADCs targeting Trop-2*". The hypothesis is that the internalization of sacituzumab govitecan may not be very efficient. It has been suggested that the hydrolytically labile linker allows time-dependent extracellular release of free drug in the tumor microenvironment and that sacituzumab govitecan releases a large amount of the SN-38 cargo systemically (9), and thus is a drug with a targeted mechanism, however with limited target capacity.

Thus, the question should be asked as to whether the antitumor effects of sacituzumab govitecan are due to a conventional ADC mechanism, a bystander effect, systemically released SN-38 or a combination thereof.

Pharmacokinetic properties

The serum pharmacokinetics of sacituzumab govitecan and SN-38 were evaluated in the ASCENT study in a population of metastatic TNBC patients who received i.v. sacituzumab govitecan as a single agent at a dose of 10 mg/kg (4). The data showed marked differences in the PK of SN-38 in treatment with Sacituzumab govitecan compared to standard irinotecan 350 mg/m^2 and trastuzumab deruxtecan (an ADC which targets HER2, and the Top1 targeting deruxtecan, is released intracellular and contains a strong linker) (*Table 1*).

In contrast to sacituzumab govitecan, trastuzumab deruxtecan undergoes intracellular cleavage by lysosomal enzymes to release deruxtecan and this points to a clear targeting on the HER2 antigen. Despite this deruxtecan cause appreciable rate of neutropenia and interstitial lung disease, and this may relate to the dispersity of the targeting with a tighter linker, compared to sacituzumab govitecan. At ASCO 2022 the DESTINY-Breast4 trial where trastuzumab deruxtecan targets HER2 antigen in patients with HER2 low levels revealed an impressive increase of the median

Table 1 Cmax, AUC and T1/2 for Irinotecan, sacituzumab Govitecan and trastuzumab deruxtecan

Drug	Cmax (ng/mL)	AUC (ng*h/mL)	T½ (hours)
Irinotecan 350 mg i.v. (10)	56	451	13.8
Sacituzumab Govitecan (11)	90	2,730	19.7
Trastuzumab deruxtecan (12-14)	1	NA	168

AUC, area under the curve; NA, not available.

survival of 6.4 months in patients with metastatic breast cancer. Among these patients, 14% developed grade 3 or 4 neutropenia. This indicates that even intracellular cleavage, even at low levels of target antigen, releases substantial systemic levels of chemotherapy (15).

Indication landscape of ADC's

Irinotecan as monotherapy for breast cancer have previously shown relatively low response rates between 10% and 30% (16). Newer formulations of irinotecan with prolonged exposure are in the pipeline, but until now without convincing efficacy (17,18).

The approvals of ADCs with Top1 inhibitors that target HER2 in HER2 positive breast cancer and the Trop-2 antigen in TNBC is of great interest.

At the San Antonio Breast Cancer Symposium in 2021, DatoDXd, sacituzumab govitecan, trastuzumab deruxtecan (T-Dxd), ladiratuzumab vedotin and patritumab DXd were presented with targeting antigens as Trop-2, LIV1, HER2, HER3 PTK7 in breast cancer (3). Many of the new ADC's exploit a Top1 inhibitor, often SN-38.

Establishing more effective PK profiles in SN-38 therapy

Top1 inhibitor-based treatments have become the reference therapy for both metastatic colorectal cancer (mCRC) and pancreatic cancer (19). Other indications are currently being investigated (20).

Weakly bound Top1 ADCs have a broader indication based on a systemically increased concentration of SN-38 in the plasma, and a longer exposure of the tumor cells to the active cytotoxic drug SN-38.

New conceptual approaches to the treatment of cancer with SN-38 has been developed in the past years with new treatment modalities showing acceptable toxicity and improved efficacy, e.g., Onivyde.

Perspective

Cancer chemotherapy has developed from a systemic treatment that targets all cells, through targeted therapy in the form of ADC's that target specific antigens on the cancer cells and are internalized in the cells where the payload is released, over new types of ADC's with weaker linkers where the payload is released in the vicinity of the targeted cells and thus demonstrating bystander effect and having an impact on the PK of the payload (SN-38). Other mechanisms of changing the PK profile are found in liposome encased chemotherapy. It will be interesting to follow the effect on the PK and the relation to the clinical effect of the active drug in upcoming treatments with targeted and PK modulating mode of actions.

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