Treatment of endocrine resistant metastatic breast cancer in the era of antibody drug conjugates

Natalie K. Heater[1], Stephanie Franco[1], Ami Shah[2]^

[1]Department of Hematology and Oncology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [2]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, USA

Correspondence to: Ami Shah. Robert H. Lurie Comprehensive Cancer Center of Northwestern University, 676 N St., Clair, Suite 850, Chicago, IL 60611, USA. Email: ami.shah@nm.org.

Comment on: Rugo HS, Bardia A, Marmé F, *et al.* Sacituzumab Govitecan in Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Metastatic Breast Cancer. J Clin Oncol 2022;40:3365-76.

Keywords: Breast cancer; hormone-receptor positive (HR$^+$); antibody drug conjugates; sacituzumab govitecan (SG); trastuzumab deruxtecan (T-DXd)

Submitted Jan 18, 2023. Accepted for publication Feb 24, 2023. Published online Feb 27, 2023.
doi: 10.21037/atm-23-314
View this article at: https://dx.doi.org/10.21037/atm-23-314

Introduction

The central goal for anti-cancer therapy in advanced disease is to help patients live longer and better. Unfortunately, once cancer has progressed on initial therapies, subsequent treatments are inadequate, often causing significant side effects with only a modest impact on survival. Antibody-drug conjugates (ADCs) present a novel approach for overcoming challenges of resistance and toxicity by preferentially targeting chemotherapy to malignant cells, resulting in greater efficacy often with more manageable side effects. Data from two important randomized phase III trials of the ADCs sacituzumab govitecan (SG) and trastuzumab deruxtecan (T-DXd) presented in 2022 represent a significant step forward in improving outcomes for patients with hormone-receptor positive (HR$^+$) human epidermal growth factor receptor-2 negative (HER2$^-$) metastatic breast cancer (MBC) (1,2).

MBC remains the second most common cause of cancer related death among American women and globally, accounting for an estimated 685,000 deaths globally (3,4). Breast cancer is classified and treated based on HR and HER2 status, with HR$^+$ HER2$^-$ breast cancer accounting for the majority of cases (4).

Endocrine therapies, including aromatase inhibitors (AIs), gonadotropin-releasing hormone (GnRH) agonists, selective estrogen receptor modulators (SERMs), and the selective estrogen receptor down-regulator (SERD), are initial treatments of HR$^+$ HER2$^-$ MBC (5).These are typically coupled with a targeted agent, such as CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib), mTOR inhibitors (everolimus), PI3K inhibitors (alpelisib) and in cases of a BRCA 1 or 2 mutation with a PARP-inhibitor (olaparib or talazoparib). Once endocrine resistance has developed, sequential single agent chemotherapy is utilized with a large array of options to consider. Unfortunately, in the endocrine-resistant setting overall response rates (ORR), progression-free survival (PFS), and overall survival (OS) is poor. ORR for second or third line chemotherapy is often under 20%, with a PFS of 3–5 months, and OS under 18 months (1,2).

ADCs

ADCs utilize monoclonal antibodies (mAbs) in order to deliver cytotoxic agents (referred to as the "payload") at higher concentrations into antigen-expressing tumor cells. The cytotoxic drug and humanized mAb are bound

^ ORCID: 0000-0003-1347-3782.

by a molecular linker in a drug-to-antibody ratio of up to 8:1 (6). Once the fragment antigen-binding (Fab) component recognizes and binds to its target antigen, the ADC-antigen complex is internalized via endocytosis, resulting in endosome formation (6,7). The molecular linker is either (I) cleavable, meaning it is cleaved in endosomes via hydrolysis, reduction or proteolytic cleavage, or (II) non-cleavable, meaning it is cleaved in lysosomes via complex proteolytic cleavage. After cleavage, the payload is released within the tumor cell, causing cell death.

Some ADCs also exhibit the bystander effect, in which cells adjacent to the antigen-expressing tumor cell are also killed by the cytotoxic payload. The effect occurs either through diffusion within the tumor microenvironment or from expulsion of the payload after internalization and cleavage within the target cell. The bystander effect is mediated by features such as membrane permeability of the ADC, presence of a cleavable linker, and degree of internalization (8).

Ado-trastuzumab emtansine (T-DM1) was the first ADC to receive FDA approval in breast cancer based on its superior PFS and OS compared to previous standard therapies for HER2-positive MBC (6,9). Subsequently it demonstrated improved outcomes for HER2-positive breast cancer with residual disease after neoadjuvant chemotherapy (10).

ADC advances in treatment of endocrine resistant MBC

T-DXd

T-DXd is a next-generation humanized anti-HER2 IgG1 antibody coupled to a topoisomerase I inhibitor via a cleavable tetrapeptide linker in an 8:1 drug-to-antibody ratio (6). Unlike T-DM1, T-DXd exhibits a bystander effect, diffusing into neighboring tumor cells with heterogenous HER2 expression (11).

A phase 1 study of T-DXd demonstrated responses in over a third of patients with MBC that had some HER2 expression, but did not meet the traditional criteria for HER2-positivity (12). This redefined HER2 status in MBC from a binary classification (positive or negative) to include an additional category, HER2-low [immunohistochemistry (IHC) 1+ or 2+, in-situ-hybridization (ISH) negative], which encompasses over 40% of breast cancers.

Subsequent results from the landmark DESTINY-03 trial (phase III, randomized trial) in HER2+ MBC showed a dramatic improvement in PFS to 28.8 months from 6.8 months [hazard ratio (HR) 0.33, 95% confidence interval (CI): 0.26–0.43] with T-DXd compared to T-DM1 as a second-line therapy after treatment with trastuzumab and a taxane (13). A remarkable 21.1% of patients treated with T-DXd had a complete response *vs.* 9.5% in the T-DM1 group and OS was higher in the T-DXd arm (HR 0.64, P=0.0037) (13,14). Patient-reported outcomes revealed those treated with T-DXd had no significant change from baseline quality of life metrics, including emotional functioning and pain (15). In 2019, T-DXd was approved for unresectable or metastatic HER2+ breast cancer after 2 or more previous HER2-based treatments (11,16).

In the DESTINY-04 trial (phase III, randomized trial) T-DXd 5.4 mg/kg every 21 days was compared to chemotherapy treatment of physician's choice (TPC, eribulin, capecitabine, nab-paclitaxel, paclitaxel, gemcitabine) in patients with HER2 low (1+ IHC or 2+ with negative ISH) MBC who had received at least one prior chemotherapy. In the HR+ subgroup, patients had received endocrine therapy and at least one line of chemotherapy in the metastatic setting or had recurrence within 6 months after adjuvant chemotherapy. PFS in patients receiving T-DXd was 10.1 *vs.* 5.4 months in patients treated with TPC (HR 0.51, P<0.001), with OS 23.9 *vs.* 17.5 months, respectively (HR 0.64, P=0.003). Additionally, 12 patients treated with T-DXd showed a complete response, *vs.* 1 patient who received TPC (2).

Overall, T-DXd is well tolerated, with most common adverse effects of any grade being nausea (73–77%), fatigue (31–48%), alopecia (38–40%) and interstitial lung disease or pneumonitis (12–15%). Grade 3 or higher adverse events were neutropenia (14–16%), anemia (8–9.0%), fatigue (6–8%) (2,14,15). Notably, interstitial lung disease secondary to T-DXd occurred in 12% of patients in DESTINY-04, of which 37 patients (10%) experienced grade 1 or 2, 5 patients (1.3%) experienced grade 3, and 3 patients (0.8%) experienced grade 5. It is advised to hold treatment if patients develop any evidence of pneumonitis, and to permanently discontinue T-DXd if the patient exhibits grade 2+ interstitial lung disease (ILD)/pneumonitis (17,18).

Current NCCN guidelines recommend T-DXd as the Category 1 preferred systemic therapy option for unresectable or MBC in HER2-low, HR+ disease refractory to endocrine therapy (19).

Anticipated future studies of T-DXd in HR+ breast cancer include DESTINY-Breast06 (phase III, randomized trial), which will evaluate T-DXd *vs.* capecitabine or

paclitaxel in patients with HR$^+$, HER2-low MBC without prior chemotherapy, with primary results expected in 2023 (NCT04494425). DESTINY-Breast08 (phase 1b modular study) will combine T-DXd with capecitabine, durvalumab, pertuzumab + paclitaxel, capivasertib, anastrazole, or fulvestrant in the first-or-second line setting for patients with advanced HR$^+$/HER2-low disease, with results expected in 2024 (NCT04556773).

SG

SG is composed of a trophoblast cell-surface antigen 2 (Trop-2)-targeted antibody coupled to SN-38, a topoisomerase I inhibitor and the active metabolite of irinotecan. SG's structure is linked by a cleavable CL2A linker in a drug-to-antibody ratio of 7.6:1 (6,20). Trop-2 is a calcium signal transducer found to play a role in signaling pathways critical for tumor cell survival and proliferation. It is widely overexpressed on many malignant epithelial cells (>90% of breast cancers) making it an ideal therapeutic target for the treatment of breast cancer (1,20,21).

The IMMU-132-01 study (phase 1–2, single arm, basket trial) evaluated SG in a variety of metastatic epithelial cancers. The triple negative cohort included 108 patients who received at least 2 prior lines of chemotherapy (median 3, range 2–10) and were treated with SG 10 mg/kg days 1 and 8 of a 21-day cycle. The ORR was 33.3%, median PFS was 5.5 months, and OS was 13 months. The demonstrated efficacy and safety prolife led to its accelerated approval for treatment of metastatic triple negative breast cancer (mTNBC) in April 2020 (20,22).

The subsequent ASCENT trial (a phase 3, randomized trial) compared SG to TPC (eribulin, vinorelbine, capecitabine, gemcitabine) in patients with relapsed or refractory mTNBC. Both PFS and OS were significantly greater in those receiving SG compared to single-agent chemotherapy (hazard ratios of 0.41 and 0.48, respectively) with a 5.4-month absolute improvement in OS. Those treated with SG also displayed a significantly higher objective response to treatment (35% *vs.* 5%) (20).

The TROPiCS-02 trial (phase 3, randomized trial) investigating SG *vs.* TPC in patients with endocrine-resistant HR$^+$ HER2$^-$ MBC. Patients must have received 2–4 lines of systemic chemotherapy for metastatic disease and have received prior therapy with endocrine therapy, taxane, and CDK4/6 inhibitor (1). Patients were randomized 1:1 to receive SG *vs.* one of four pre-specified TPC agents (capecitabine, eribulin, vinorelbine, or gemcitabine). Randomization was stratified based on the presence or absence of visceral metastatic lesions, the duration of endocrine treatment in the setting of metastatic disease, and the number of previously failed lines of chemotherapy. Primary endpoints were PFS and ORR, while secondary endpoints included OS, duration of response (DOR), and clinical benefit rate (CBR). A total of 543 patients were randomized, with 272 receiving SG and 271 receiving TPC.

In the intention to treat population, the median PFS was significantly improved in SG compared to TPC (median 5.5 *vs.* 4.0 months; HR 0.66, 95% CI: 0.53–0.83, P<0.001), with a 1-year PFS of 21.3% *vs.* 7.1% (1). ORR was greater in those receiving SG compared to TPC (21% *vs.* 14%, P=0.035) as was the CBR (34% *vs.* 22%). At the second interim analysis, those receiving SG also demonstrated improved OS when compared to TPC (median 14.4 *vs.* 11.2 months; HR 0.79, CI: 0.65–0.96, P=0.02) (23). These results demonstrated the utility of SG as a novel therapeutic option for individuals with endocrine therapy-resistant HR$^+$ HER2$^-$ MBC. Current NCCN guidelines list SG as a preferred therapy in HR$^+$ HER2$^-$ MBC after prior endocrine therapy, CDK4/6 inhibitor, and taxane and after at least 2 lines of chemotherapy for MBC (19).

Given its near ubiquitous expression in breast cancer, trials have not utilized a predictive biomarker assay for Trop-2 in selecting candidates for therapy. A post-hoc analysis of TROPiCS-02 data showed SG was effective across all levels of Trop-2 expression, thus Trop-2 testing is not indicated prior to treatment with SG.

The most common toxicities related to SG include neutropenia and diarrhea, followed by nausea, alopecia, fatigue, dyspnea, and anemia. One post-hoc analysis of TROPiCS-02 data found a higher incidence of treatment-related diarrhea and neutropenia in those receiving SG *vs.* TPC, however, exposure-adjusted incidence rates of adverse events were similar between the two groups (SABCS Poster ID: P3-07-08). Another post-hoc analysis looking at patient reported outcomes from the TROPiCS-02 study found that, with the exception of quantity of hair loss and frequency of diarrhea, SG delayed worsening quality of life, functionality, and symptoms including fatigue and dyspnea when compared to TPC (SABCS Poster ID: P4-07-65). Additional subgroup analyses have confirmed the advantage of SG even in older patients and patients with

Table 1 Phase III ADC trials in HR+ BC

Study characteristics	Trastuzumab-deruxtecan DESTINY-04 (HR+ cohort)	Sacituzumab-govitecan TROPiCS-02
Patient characteristics	494 patients HR+, 2:1 randomization, 1–2 prior lines of chemotherapy for MBC, prior ET	543 patients, 1:1 randomization, 2–4 prior lines of chemotherapy for MBC, prior ET, taxane, and CDK4/6i
Drug	Trastuzumab deruxtecan	Sacituzumab govitecan
Antibody	Humanized anti-HER2 IgG1	Trop-2
Payload	Deruxtecan, topoisomerase I inhibitor	SN-38, topoisomerase I inhibitor
Drug: antibody ratio	8:1	7.6:1
Control arm	Eribulin, capecitabine, nab-paclitaxel, paclitaxel, gemcitabine	Eribulin, capecitabine, gemcitabine, or vinorelbine
ORR	53% *vs.* 16%	21% *vs.* 14%
PFS	10.1 *vs.* 5.4 months, HR 0.51, P<0.001	5.5 *vs.* 4.0 months, HR 0.66, P=0.0003
OS	23.9 *vs.* 17.5 months, HR 0.64, P=0.003	14.4 *vs.* 11.2 months, HR 0.79, P=0.020
Duration of response	10.7 *vs.* 6.8 months	8.1 *vs.* 5.6 months
Common/noteworthy toxicities	Nausea (73%), fatigue (47.7%), alopecia (37.7%) ILD/ pneumonitis (12.1%)	Neutropenia 70%, diarrhea 57%, nausea 55%, alopecia 46%, fatigue 37%, anemia 34%
ILD	12.1% (any grade); 0.8% grade 5	N/A

ADC, antibody-drug conjugate; HR+, hormone-receptor positive; BC, breast cancer; MBC, metastatic breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor-2; Trop-2, trophoblast cell-surface antigen 2; ORR, overall response rates; PFS, progression-free survival; HR, hazard ratio; OS, overall survival; ILD, interstitial lung disease; N/A, not applicable.

brain metastases.

Findings from these studies are summarized in *Table 1*.

Discussion and future directions

Despite advances in initial lines of therapy for HR+ HER2− MBC, later lines of treatment are limited by increasing toxicity and diminishing efficacy. The efficacy of ADC in endocrine-resistant HR+ HER2− MBC represents a significant advance in therapeutic options for the majority of patients with MBC. However, many questions remain.

Optimizing patient selection with predictors of efficacy and toxicity should be a goal of ongoing research for ADCs. For T-DXd, it is clear we do not understand the optimal biomarker to predict benefit given heterogeneity across biopsy sites and time in HER2 expression, HER2 IHC inter-reader variability, and its activity in some cases of IHC 0. Furthermore, we are in need of better strategies for ILD risk-stratification, monitoring, and management.

Additionally, the optimal setting and sequencing for these drugs remains to be determined. Studies are planned to evaluate these drugs as earlier lines of therapy for MBC, for early stage disease after incomplete response to neoadjuvant therapy, in brain metastases, and in combination with immunotherapy.

Resistance mechanisms to ADCs require significant further study, but may include a number of mechanisms related including antibody-mediated resistance (i.e., change in antigen expression), resistance to the payload, inadequate delivery to target tissue (i.e., poor central nervous system penetration), and disrupted lysosomal function. We do not have data to guide decision making about appropriate sequencing of these drugs, but resistance mechanisms may be relevant to this decision making.

Ongoing trials and real-world data from patients who have received these drugs will begin to answer some questions, but inevitably raise new ones. As we learn to better utilize these ADCs and novel ADCs in the pipeline, we can continue our incremental improvements in outcomes for patients with HR+ HER2− MBC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned

by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-23-314/coif). AS reports participation in an advisory board from AstraZeneca and Gilead and payment for this service. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Heater NK, Franco S, Shah A. Treatment of endocrine resistant metastatic breast cancer in the era of antibody drug conjugates. Ann Transl Med 2023;11(11):399. doi: 10.21037/atm-23-314