

REVIEW

Antibody-Drug Conjugates in the Treatment of Metastatic Breast Cancer: The Emerging Questions of Sequence and Resistance

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Keywords: breast cancer, antibody-drug conjugates, treatment sequence, resistance to therapy

<https://doi.org/10.36000/HBT.OH.2024.21.155>

healthbook TIMES Oncology Hematology

Vol. 21, Issue 3, 2024

Metastatic breast cancer continues to present significant therapeutic challenges, necessitating ongoing exploration of innovative treatments. The use of antibody-drug conjugates (ADCs) represents an effective treatment strategy that combines the targeting capabilities of monoclonal antibodies with the cytotoxic effects of chemotherapeutic agents to deliver therapy directly to cancer cells. This article reviews recent advancements and the efficacy of ADCs in clinical trials and explores the mechanisms of resistance and the implications of ADC sequencing in treatment protocols.

PEER REVIEWED ARTICLE

Peer reviewers:

Dr Bérénice Deletang, Clinique des Grangettes, Geneva, Switzerland

One anonymous peer reviewer

Received on May 16, 2024; accepted after peer review on September 12, 2024; published online on October 05, 2024.

Recent advancements in ADCs in metastatic breast cancer

Metastatic breast cancer (MBC) remains a complex and challenging disease, necessitating continuous exploration of innovative therapeutic approaches. One recent important advance in the treatment of MBC is the development of antibody-drug conjugates (ADCs), which combine the specificity of monoclonal antibodies with the potent cytotoxicity of chemotherapeutic agents to deliver targeted therapy directly to cancer cells.¹⁻³ ADCs generally consist of three key components: a monoclonal antibody, a linker and a cytotoxic payload. Their use has shown promising results, particularly in a specific subgroup of breast cancer. Since the publication of the practice-

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changing trials EMILIA in 2012^{4,5} and KATHERINE in 2019,⁶ the use of ado-trastuzumab emtansine (T-DM1), a microtubule inhibitor, for human epidermal growth factor receptor 2 (HER2)-positive (HER2+) metastatic and early breast cancer has been endorsed in international guidelines. This success has paved the way for further exploration of ADCs, leading to the availability of two new molecules in our clinical practice.

Trastuzumab deruxtecan (T-DXd) is an ADC designed for HER2+ breast cancer. It comprises a monoclonal antibody targeting the well-known HER2 receptor, a cleavable linker and a potent topoisomerase I inhibitor payload, deruxtecan, which induces DNA damage and subsequent apoptosis in cancer cells after internalization.⁷ It has a higher drug-to-antibody ratio than T-DM1 (approximately 8 vs 3–4). The tetrapeptide-based linker is selectively cleaved by cathepsins, which are up-regulated in cancer cells.⁸ The payload easily crosses the cell membrane and exerts a cytotoxic effect on neighboring tumor cells regardless of target expression (bystander effect).⁹

The DESTINY-Breast01 trial was a landmark phase II study that enrolled 184 patients with HER2+ MBC who had previously received multiple lines of HER2-targeted therapies.¹⁰ In that trial, this new ADC demonstrated an impressive overall response rate (ORR) of 60.9%, with a median duration of response (DoR) exceeding 14 months. The median progression-free survival (PFS) reached 16.4 months. The safety profile was manageable, with adverse events primarily comprising nausea, neutropenia and decreased appetite. The drug was associated with interstitial lung disease (ILD) in 13.6% of patients (grade 1–2, 10.9%; grade 3–4, 0.5%; and grade 5, 2.2%).¹⁰ The phase III DESTINY-Breast02 trial confirmed these results in a population of 608 patients with HER2+ MBC who had previously received T-DM1.¹¹ The median PFS was 17.8 months in the T-DXd group versus 6.9 months in the treatment of physician's choice (TPC) group (HR: 0.36 [95% CI: 0.28–0.45]; $p < 0.0001$). The median overall survival (OS) was 39.2 months (95% CI: 32.7–not evaluable [NE]) for patients treated with T-DXd, compared to 26.5 months (95% CI: 21.0–NE) for those receiving TPC (HR: 0.66 [95% CI: 0.50–0.86]; $p = 0.0021$). Concerning safety, drug-related ILD occurred in 10% of patients who received the ADC versus <1% in the TPC group. Finally, the phase III trial DESTINY-Breast03 demonstrated better efficacy of T-DXd than T-DM1 in 524 patients with HER2+ MBC previously treated with trastuzumab and a taxane.^{12,13} The median PFS by blinded independent central review was 28.8 months (95% CI: 22.4–37.9) with T-DXd and 6.8 months (95% CI: 5.6–8.2) with T-DM1 (HR: 0.33 [95% CI: 0.26–0.43]; $p < 0.0001$). The median OS was not reached in either group, with 72 events (28%) in the T-DXd group and 97 events (37%) in the T-DM1 group (HR: 0.64 [95% CI: 0.47–0.87]; $p = 0.0037$). Drug-related ILD occurred in 15% of the patients in the T-DXd group and in 3% of those in the T-DM1 group. These data changed our practice and promoted T-DXd as a new second-line treatment in HER2+ MBC.¹⁴

In contrast to all available HER2-directed therapies, this new ADC is effective even in hormone receptor-positive (HR+) breast cancers expressing low levels of HER2. Low expression of HER2 is defined as a score of 1+ or 2+ on immunohistochemical analysis and negative results on *in situ* hybridization.¹⁵ The phase III DESTINY-Breast04 trial enrolled 557 patients with HER2-low MBC, with 88.7% having HR+ disease, who had received one or two previous lines of chemotherapy.¹⁶ The median PFS in the HR+ cohort (primary endpoint) was 9.6 months (95% CI: 8.4–10.0) in the T-DXd group and 4.2 months (95% CI: 3.4–4.9) in the TPC group (HR: 0.37 [95% CI: 0.30–0.46]), and OS was 23.9 months (95% CI: 21.7–25.2) and 17.6 months (95% CI: 15.1–20.2), respectively (HR: 0.69 [95% CI: 0.55–0.87]).¹⁷ Regarding the patients with HR-negative disease, this subgroup constituted only 10.5% of total participants, warranting caution when interpreting the results, which are exploratory. In this patient subgroup, T-DXd treatment was associated with a median PFS of 6.3 months (95% CI: 4.2–8.5) versus 2.9 months (95% CI: 1.4–4.2) in the TPC group. The median OS with T-DXd was 17.1 months (95% CI: 16.3–23.0) versus 8.3 months (95% CI: 5.6–20.4) in the TPC group.

More recently, the DESTINY-Breast06 trial evaluated the efficacy of T-DXd in patients with HER2-low and HER2-ultralow, HR+ MBC who had previously undergone disease progression on endocrine therapy and had not received prior chemotherapy for metastatic disease. In the study, 866 patients were randomized 1:1 to receive either T-DXd or TPC, which included capecitabine, nab-paclitaxel or paclitaxel. T-DXd significantly improved PFS in HER2-low patients compared to TPC (HR: 0.62 [95% CI: 0.51–0.74]; $p < 0.0001$; median PFS of 13.2 vs 8.1 months for T-DXd and TPC). The ORR was 56.5% with T-DXd versus 32.2% with TPC. The OS data was immature, with a trend favoring T-DXd treatment (HR: 0.83 [95% CI: 0.66–1.05]; $p = 0.12$). Consistent results were reported in the intention-to-treat and HER2-ultralow populations.¹⁸

Sacituzumab govitecan (SG) is an ADC that specifically targets the trophoblast cell surface antigen 2 (Trop2), a cell surface protein usually highly expressed in breast cancer cells.¹⁹ The antibody is linked to the small molecule drug SN-38, another potent topoisomerase I inhibitor. After internalization, this inhibition causes DNA damage leading to apoptosis. Similar to T-DXd, the drug can also target neighboring cancer cells.²⁰

The pivotal phase III ASCENT trial demonstrated significant clinical benefits of SG in metastatic triple-negative breast cancer (TNBC).²¹ The trial included 468 patients who had received at least two prior lines of therapy for metastatic disease or one prior line in the metastatic setting if progression occurred within 12 months of completing (neo)adjuvant therapy. Patients treated with SG achieved a median PFS of 4.8 months (95% CI: 4.1–5.8) compared to 1.7 months (95% CI: 1.5–2.5) in the standard chemotherapy

group (HR: 0.41 [95% CI: 0.33–0.52]). The median OS was significantly extended to 11.8 months (95% CI: 10.5–13.8) with SG, as opposed to 6.9 months (95% CI: 5.9–7.7) with standard therapy (HR: 0.51 [95% CI: 0.42–0.63]). ORR was observed in 31% of patients treated with SG and only 5% of patients treated with chemotherapy, with a median DoR of 6.3 months. Adverse events commonly associated with this ADC included neutropenia, diarrhea and nausea, which were generally manageable.²² For this reason, SG is today the standard second-line therapy for metastatic TNBC according to the European Society for Medical Oncology (ESMO) guidelines.¹⁴

The TROPICS-02 phase III study evaluated the efficacy of SG in patients with metastatic HR+/HER2-negative (HER2-) breast cancer.²³ It enrolled 543 women whose disease had progressed after two to four lines of systemic therapy in a metastatic setting (at least one endocrine therapy, one cyclin-dependent kinase 4 and 6 [CDK4/6] inhibitor and one taxane). The median PFS was 5.5 months with SG compared to 4.0 months with physician-selected single-agent chemotherapy (HR: 0.66 [95% CI: 0.53–0.83]; $p=0.0003$). The median OS was 14.4 months versus 11.2 months (HR: 0.79 [95% CI: 0.65–0.96]; $p=0.02$). The ORR was 21% with SG compared to 14% in the chemotherapy arm (odds ratio: 1.63 [95% CI: 1.03–2.56]; $p=0.035$).²⁴ The safety profile was consistent with the data from previous studies. Given its significant advantage over single-agent chemotherapy in the treatment of heavily pretreated patients with HR+/HER2- MBC, SG is now used in this setting.

Mechanisms of resistance to antibody-drug conjugates

As previously mentioned, the antitumor action of ADCs depends on the targeted delivery of a cytotoxic payload to tumor cells. This process relies on the recognition of a tumor-specific antigen by the monoclonal antibody moiety, allowing for the internalization of the ADC in the tumor cell by receptor-mediated endocytosis. The linker is then cleaved in the lysosome, with subsequent release of the payload, which can then exert its cytotoxic effect on tumor cells. Possible mechanisms of resistance have been identified at multiple steps of this pathway.

Low antigen expression levels on tumor cells may impair their targeting by ADCs, accounting for the potential primary resistance to these agents. Treatments targeting HER2 may result in reduced levels of HER2 expression in the tumor, possibly due to the on-treatment selection of low-antigen-expressing clones. The reduced expression of the target antigen resulting from this selective pressure has been identified as a possible mechanism of secondary resistance to anti-HER2 therapy.^{25,26} Heterogeneity in HER2 expression in the tumor is also relevant, having been shown to correlate with drug resistance and poorer treatment outcomes in both preclinical and clinical studies.²⁷ ADCs with cleavable linkers and cell-permeable payloads

may maintain efficacy when faced with lower and/or heterogeneous antigen expression through the bystander effect, accounting for possible ways to overcome these pathways of resistance.^{28,29} The demonstrated benefit of T-DXd in tumors with very low HER2 expression is encouraging in this regard, as is its observed potency of T-DXd in patients having progressed following T-DM1 treatment.^{16,30} The development of ADCs recognizing more than one tumor antigen (bispecific ADCs) represents another means to address the importance of antigen expression heterogeneity in ADCs' efficacy.

The recognition of antigens by ADCs may also be impaired by other mechanisms such as mutations impacting the molecular structure or dimerization of the antigen with another cell surface receptor. The presence of the NRG-1beta ligand, known to promote HER2/HER3 heterodimerization, is associated with reduced T-DM1 cytotoxic action in HER2-overexpressing breast cancer cells. Pertuzumab blocks HER2/HER3 dimerization, allowing this drug combination to overcome this resistance mechanism in preclinical models.³¹

Resistance to ADCs may also occur during later intracellular uptake and processing phases inside their target cell. Mechanisms impairing endosomal transit of ADCs were shown to interfere with T-DM1 cytotoxic potential in preclinical models.^{32,33} Alterations in lysosomal function may also influence ADC potency by interfering with the enzymatic or chemical cleavage necessary for payload release.³⁴ Interestingly, ADCs with cleavable linkers maintained their cytotoxic effect despite impaired lysosomal function in some preclinical models,²⁵ further supporting the importance of ADC biochemical structure in addressing specific resistance pathways.

Following successful payload release into the tumor cell, its cytotoxicity may be impacted by further resistance mechanisms, including drug-efflux pumps. These mediators of chemotherapy resistance have many ADC payloads as their substrates, and increased expression of ATP-binding cassettes were observed in several cell lines developing resistance to ADCs.³⁵ Resistance to payload may also arise from other mechanisms known to mediate chemotherapy resistance, such as activating signaling pathways involved in cell growth and activation (e.g., PI3K/AKT/mTOR pathway).³⁶ Such mechanisms resulting in payload resistance suggest a potential benefit in changing the nature of the payload when sequencing ADC treatments. A switch from an auristatin payload to an anthracycline payload resulted in further responses to ADC treatment in non-Hodgkin's lymphoma tumor models, supporting this approach.³⁷

Sequencing ADCs in the treatment of metastatic breast cancer

Except in HER2+ disease, where T-DXd was studied after T-DM1 in the DESTINY-Breast02 trial, no phase III trial assessed prospectively the optimal sequences of ADCs. As such, the only available data stem from real-world data studies that aimed to describe the safety and efficacy of sequencing ADCs.

Three studies have been presented at the San Antonio Breast Cancer Symposium 2023, describing the survival outcomes of patients receiving ADCs in sequence. The first study was a retrospective study conducted across 19 French comprehensive cancer centers.³⁸ It included all patients diagnosed with either HR+ or HR- and HER2-low MBC treated with SG followed by T-DXd or vice versa. The study's primary objective was to evaluate PFS with the second ADC (ADC2) in the entire cohort. OS was still immature when the analysis was performed. Of the 179 included patients, the majority (115 patients, 64.2%) received SG as the first ADC (ADC1), while 64 (35.8%) received T-DXd as ADC1.³⁸ A total of 104 patients (58.1%) were treated with ADC1 followed immediately by ADC2, whereas 75 patients (41.9%) received ADC2 after intermediary chemotherapy lines. After a median follow-up of 6 months, 122 (68.2%) patients discontinued ADC2, 112 (93.3%) due to disease progression and five (4.2%) due to toxicity from T-DXd. Notably, at the time of the analysis, 31.8% of patients (n=57) were still receiving ADC2. In the whole population, the median PFS with ADC2 was 2.7 months (95% CI: 2.4–3.3). In HR+/HER2-low patients who received SG after T-DXd, PFS with ADC2 was 2.2 months (95% CI: 1.9–2.7). Similar results were observed in HR-/HER2-low patients receiving T-DXd after SG (PFS with ADC2: 3.1 months [95% CI: 2.6–3.6]).

The second study included patients from three US academic medical centers who received multiple ADCs.³⁹ The concept of “cross-resistance” to the subsequent ADC was defined as either progressive disease upon the first radiological assessment or progression within 60 days of treatment initiation. Of the 68 included patients, 30 (44.1%) had HR+/HER2- disease and 38 (55.9%) had TNBC; 50 patients (73.5%) were identified as having HER2-low disease. The median age at the time of the second ADC treatment was 59.6 years (range, 29.9–88.6). These patients had undergone a median of four lines of treatment in the metastatic setting before initiating the second ADC. The median PFS with ADC1 and ADC2 was 5.3 months (95% CI: 4.3–7.4) and 2.5 months (95% CI: 1.7–3.7), respectively. In patients with TNBC receiving T-DXd after SG, PFS with ADC2 was 2.7 months (95% CI: 1.5–4.2). In patients with HR+/HER2- tumors receiving SG after T-DXd, PFS with ADC2 was 1.6 months (95% CI: 1.4–2.4).

The third study was also performed in the United States using data from five academic centers.⁴⁰ It included 84 patients with MBC who were sequentially treated with T-DXd and SG, comprising 56 patients (66.6%) with HR+/HER2-low MBC and 28 patients (33.3%) with HR-/HER2-low MBC. Patients with HR+/HER2-low MBC had a median time from metastatic disease diagnosis to the first ADC of 44 months and had a median of four prior lines of therapy in the metastatic setting (two endocrine and two chemotherapy). Of the HR+ patients, 32 (57.1%) received T-DXd as the first ADC, whereas 24 (42.9%) received SG. Consistent with the previously mentioned studies, patients receiving SG after T-DXd had a median PFS of 2.6 months, with an ORR of 18.5%, while a median PFS of 3.7 months and an ORR of 34.8% were observed in patients receiving the inverse sequence (T-DXd after SG).

Patients with HR-/HER2-low MBC had a median time from metastatic disease diagnosis to the first ADC treatment of 10.2 months.⁴⁰ They had received two median lines of prior therapy in the metastatic setting, and 64.3% (n=18) had received immunotherapy. The majority first received SG (n=25, 89.3%). Only three patients (10.7%) were treated with SG after T-DXd, precluding a correct median PFS and ORR estimation. In those treated with T-DXd after SG, the median PFS was 2.8 months and the ORR was 35.0%.

Key safety findings revealed that a considerable proportion of patients discontinued treatment due to toxicity (n=7 [8.3%] for SG and n=9 [10.7%] for T-DXd).⁴⁰ Also, dose reductions were frequent during treatment with T-DXd (13/84; 15.5%) and SG (39/84; 46.4%). Finally, the incidence of ILD/pneumonitis during T-DXd treatment (any grade, n=14 [16.7%]; grade 3–4, n=4 [4.8%]; and grade 5, n=3 [3.6%]) and treatment delays due to SG treatment-related neutropenia (n=15 [17.9%]) were also described.

Novel ADCs for the treatment of breast cancer

The targets of ADCs under development include Trop2, B7-H4, B7-H3, Nectin-4, HER3, ROR, EFNA4, LIV-1 and gNMB. Several ADCs have shown possible efficacy, for example, in advanced TNBC, such as datopotamab deruxtecan (Dato-DXd) (ORR: 32%),⁴¹ SKB264 (ORR: 40%),⁴² ladiratzumab vedotin (ORR: 32%)⁴³ and PF-06647263 (ORR: approximately 10%).⁴⁴

Moreover, ADCs in breast cancer are also currently being studied in earlier settings, including as (neo)adjuvant agents. For example, neoadjuvant Dato-DXd plus durvalumab followed by adjuvant durvalumab with or without chemotherapy is being evaluated versus neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab with or without chemotherapy (TROPION-Breast04, [NCT06112379](https://clinicaltrials.gov/ct2/show/study/NCT06112379)).⁴⁵ ADCs are also being tested as escalated adjuvant treatments in cases of incomplete

pathological response after neoadjuvant treatment. For example, Dato-DXd is being assessed with or without durvalumab compared to TPC in participants with stage I–III TNBC (TROPION-Breast03, [NCT05629585](#))⁴⁶ Other examples include SG versus TPC in patients with HER2- breast cancer (SASCIA, [NCT04595565](#))⁴⁷ and SG and atezolizumab for residual disease and positive circulating tumor DNA (ASPIRA trial, [NCT04434040](#)).⁴⁸

The efficacy of numerous novel ADCs is being tested in MBC, such as SHR-A1811 ([NCT05749588](#)),⁴⁹ NBE-002 ([NCT04441099](#), trial completed in August 2023 with pending results),⁵⁰ ARX788 ([NCT06224673](#))⁵¹ and CAB-ROR2-ADC ([NCT03504488](#)),⁵² with additional ADCs being expected to be available in the coming years. Of note, there is currently no trial addressing the sequencing of ADCs, particularly those that share the same payload.

Discussion and take-home messages

The development of ADCs is currently transforming the treatment of breast cancer and could soon be an option for the first-line treatment in HER2+ MBC and a potential first-line of chemotherapy in estrogen receptor-positive/HER2- MBC. As ADCs are used earlier in the treatment strategies of most patients with MBC, the question of sequence and resistance will be routinely posed in clinical practice. Current data, which are entirely based on real-world and non-interventional studies, clearly suggest the minimal efficacy of sequencing ADCs with payloads with the same mechanism of action. Until new ADCs with payloads other than a TOPO1 inhibitor become available, the parsimonious use of ADCs in sequence is advised. As there are no randomized studies of an ADC sequence compared to one ADC followed only by standard chemotherapy, it is unclear if ADC sequencing results in improved patient survival and/or quality of life. Furthermore, the costs associated with using several ADCs are much higher than those associated with using only one ADC. In the absence of robust efficacy data and available data suggesting a very short PFS, ADC sequencing (with the currently available TOPO1 ADCs) is probably not cost-effective and may be associated with higher financial toxicity when compared to conventional chemotherapy.

Conflict of interest

Mathieu Chevallier received consulting fees from AstraZeneca and MSD and travel grants from Eli Lilly to attend conferences as an auditor. José Luis Sandoval received consulting fees from Eli Lilly and travel grants for attending conferences from Eli Lilly and Pfizer. The funding entities and sponsors of the authors did not play a role in the development of the manuscript and

did not influence its content in any way. Other authors have declared that the manuscript was written in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

The authors have declared that no financial support has been received from any organization for the submitted work.

Author contributions

All authors contributed to and approved the final manuscript.

Submitted: May 16, 2024 CEST. Accepted: September 12, 2024 CEST. Published: October 05, 2024 CEST.



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