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**CASE REPORT**

# Sequential Antibody-Drug Conjugate Therapy in Advanced HR+/HER2- Metastatic Breast Cancer After Endocrine and Chemotherapy Resistance: A Case Report

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## ABSTRACT

Antibody-drug conjugates (ADCs) are an emerging therapeutic option for patients with hormone receptor positive/ human epidermal growth factor receptor-2 negative (HR+/HER2-) metastatic breast cancer (MBC), providing new options when conventional treatments are no longer effective. This case report presents the therapeutic journey of a HR+/HER2- MBC patient, who developed resistance to standard endocrine and chemotherapeutic regimens. Two ADCs, TQB2103 (targeting CLDN18.2) and sacituzumab govitecan (targeting TROP2) with similar payload, were used sequentially. Despite low efficacy with TQB2103, sacituzumab govitecan achieved a progression-free survival (PFS) of 7 months, surpassing expectations based on previous studies. This report underscores the promise and complexities of ADCs in advanced breast cancer, particularly concerning cross-resistance when similar payloads are used consecutively. It highlights the necessity for strategic ADC selection and sequencing in treatment-resistant HR+/HER2- MBC to optimize outcomes and avoid potential resistance mechanisms.

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**KEYWORDS**

Metastatic breast cancer; Antibody-Drug Conjugate; Sequential; Resistance; Sacituzumab govitecan

## INTRODUCTION

HR+/HER2- metastatic breast cancer (MBC) is the most prevalent subtype of breast cancer, characterized by hormone receptor (HR) positivity and human epidermal growth factor receptor 2 (HER2) negativity [1]. The standard first-line treatment for HR+/HER2- MBC is endocrine therapy (ET) combined with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i), which has demonstrated efficacy in delaying disease progression [2]. However, as resistance to ET is inevitable, subsequent treatment option often shifts to sequential lines of chemotherapy. Unfortunately, chemotherapy is associated with lower response rates, shorter progression-free survival (PFS), and increased toxicity, thereby challenging long-term disease management [3-5].

Antibody-drug conjugates (ADCs) are an emerging therapeutic option for HR+/HER2- MBC, particularly for patients who have exhausted ET and chemotherapy options. ADCs such as sacituzumab govitecan [6,7] and trastuzumab deruxtecan [8], along with newer agents targeting proteins like CLDN18.2 [9] and HER3 [10], provide potential benefits for treatment-resistant cases. However, recent studies suggest that ADCs may face limitations due to cross-resistance, especially with the sequential use of ADCs that share similar payloads [11,12]. To address these challenges, a personalized approach that incorporates novel agents and carefully considers therapy sequencing is essential for improving outcomes in patient with HR+/HER2- MBC.

Here, we present the case of a female with HR+/HER2- MBC who experienced disease progression despite multiple lines of endocrine and chemotherapy regimens, yet achieved an impressive clinical response to a second ADC following progression on a first ADC with a similar payload. This case underscores the complexities of managing HR+/HER2- MBC, highlighting the considerations required for sequential ADC use in the context of therapeutic resistance.

## CASE PRESENTATION

A 59-year-old female patient was diagnosed with breast cancer and underwent a lumpectomy of the right breast, along with sentinel-node biopsy of the right axilla in October 2019. Pathological examination confirmed the diagnosis of invasive ductal carcinoma. The size of tumor was 2.0 cm, with estrogen receptor (ER) positive at 40%, low progesterone receptor (PR) expression at 15%, and HER2 1+, negatively. These findings were consistent with a diagnosis of Luminal B-type breast cancer. One sentinel lymph node and 5 axillary lymph nodes were negative for carcinoma. Genetic testing revealed no pathogenic variants in BRCA1 and BRCA2. Postoperatively, the patient completed six cycles of adjuvant chemotherapy with epirubicin and cyclophosphamide. Although adjuvant ET was recommended, she declined the treatment for personal reason. During the subsequent 10 months, surveillance imaging showed no evidence of disease recurrence.

In August 2020, computed tomography (CT) revealed multiple metastases lesions in both lungs. Given the Luminal B breast cancer subtype, the patient was initiated ET with anastrozole and palbociclib, which continued for 11 months. However, by July 2021, follow-up CT imaging revealed disease progression, with an increase in both the number and volume of pulmonary metastases and new metastatic sites in the liver and bones. Due to

progressive disease, several treatment regimens were attempted, including chemotherapy with vinorelbine and cisplatin, monotherapy with fulvestrant, and a combination of fulvestrant and palbociclib, however, these treatments failed to achieve clinical benefit. Subsequently, the patient received nab-paclitaxel and capecitabine for 5 cycles, followed by Capecitabine monotherapy for 8 months. In March 2023, magnetic resonance imaging (MRI) indicated significant progression of liver metastases, while lung and bone metastases remained stable. Then gemcitabine plus carboplatin were taken for three cycles, however, this regimen also failed to control disease progression.

Due to insufficient efficacy of prior chemotherapy and ET, a new biopsy of the liver metastases was conducted in July 2023. Pathological examination confirmed the diagnosis of metastatic breast cancer with immunohistochemistry results indicating Luminal B-type characteristics (ER 10%, PR -, HER-2 1+). Compared to previous assessments, the levels of ER and PR expression had decreased. For financial reasons, the patient declined treatment with trastuzumab deruxtecan and sacituzumab govitecan, opting instead to enroll in clinical trials. In July 2023, she began participation in a phase 1 clinical trial of TQB2103 (NCT05867563), a CLDN18.2-targeted ADC conjugated with the DDDXD payload [13].

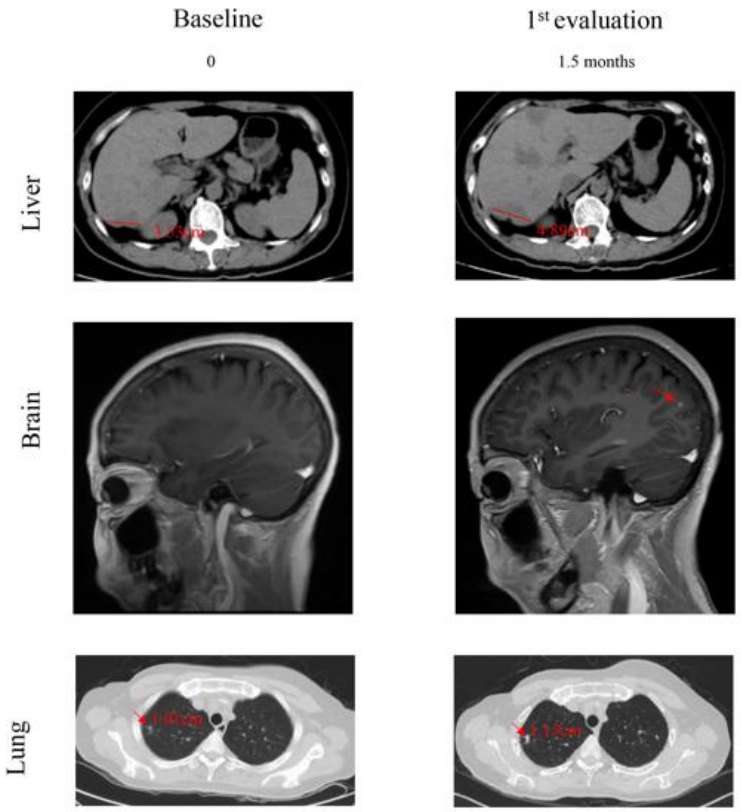


**Figure 1:** Tumor size before and after TQB2103 treatment. MRI scans and CT scans were performed 1month before starting TQB2103 (column 1), at progression of new metastatic site in brain and increased site in liver (MRI scans and CT scans 1.5 months after starting TQB2103, column 2).

While CLDN18.2 expression is typically low in breast cancer, it may be upregulated in metastatic or treatment-resistant contexts. After two cycles of TQB2103, however, the patient was withdrawn from the trial due to disease progression, including the emergence of a new brain metastasis in the right occipital lobe and progression of liver

(Figure 1). Subsequently, she enrolled in another clinical trial investigating LF0397, an ATR inhib-itor, but did not achieve clinical benefit after two cycles. On November 29, 2023, she commenced treatment with sacituzumab govitecan, a TROP2-targeted ADC conjugated with the SN-38 payload, 540 mg on days 1 and 8 of each 21-day cycle. The liver, lung, bone and brain metastases showed stable disease according to MRI or CT evaluation and the patient tolerated the treatment well with no observed 3-4 grade adverse events over the course of 8 treatment cycles. By June 2024, MRI indicated new metastatic sites in the liver and increased volume of brain metastases, while the lung and bone metastases remain stable (Figure 2). The PFS with Sacituzumab Govitecan was 7 months. Changes in tumor-associated antigens including Cancer antigen 15-3 (CA15-3) and Carcinoem-bryonic antigen (CEA) before-and-after Sacituzumab Govitecan were exhibited in Figure 3. Treatment course outlined in Figure 4.

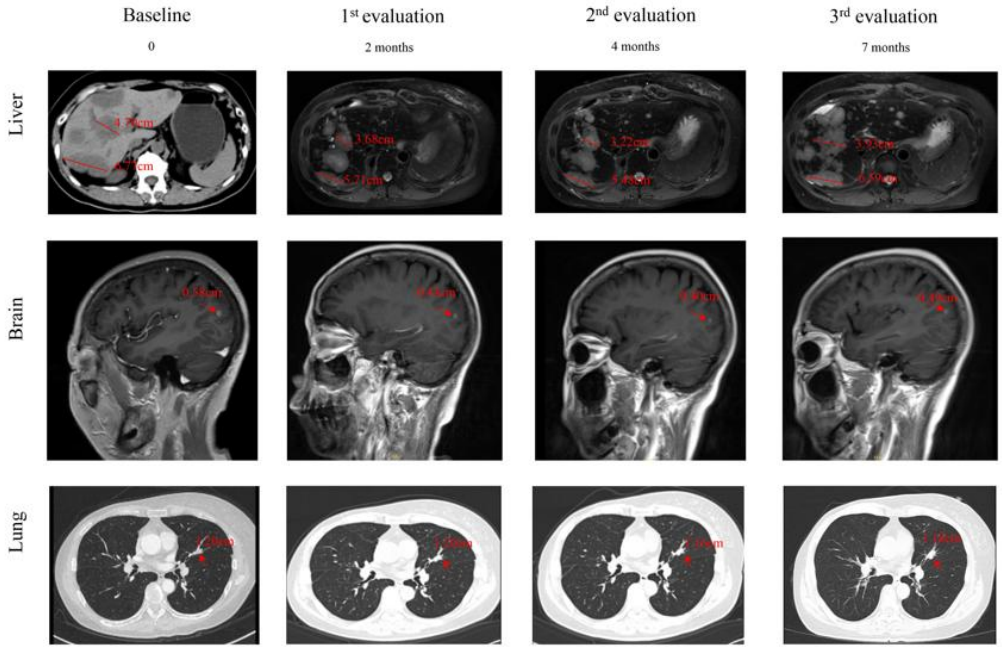


**Figure 2:** Tumor size before and during the course sacituzumab govitecan treatment. MRI scans and CT scans were performed 1.5 months before starting sacituzumab govitecan (column 1), at first evaluation (MRI scans and CT scans 2months after starting sacituzumab govitecan, column 2), at best response (MRI scans CT scans 4 months after starting sacituzumab govitecan, column 3), and at progression (MRI scans and CT scans 7 months after starting sacituzumab govitecan, column 4).

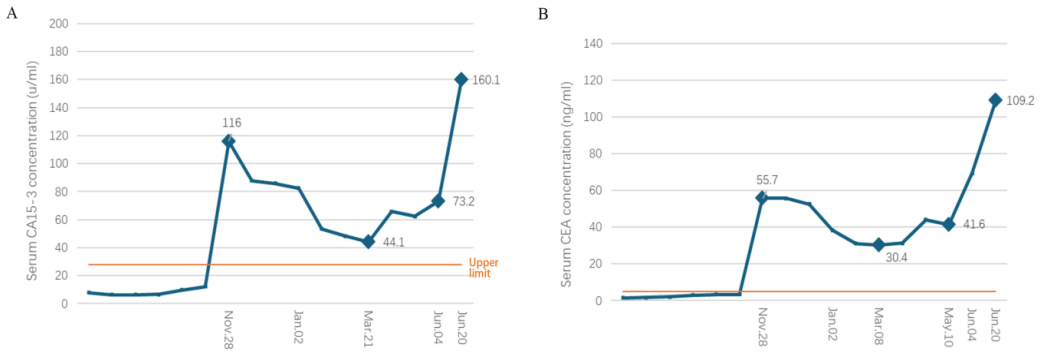


**Figure 3:** Changes in tumor-associated antigens before and during the course sacituzumab govitecan treatment. CA15-3, cancer antigen 15-3; CEA, carcinoembryonic antigen. A: The change in CA15-3, B: The change in CEA.

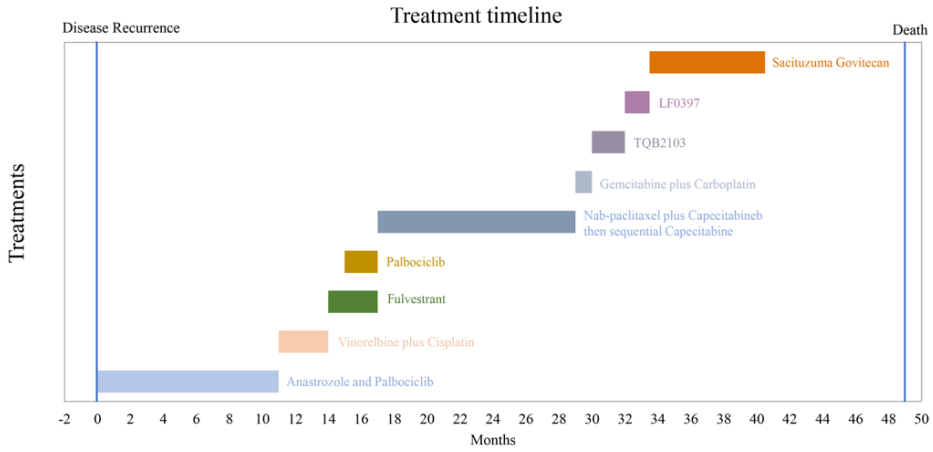


**Figure 4:** Treatment timeline.

## DISCUSSION

This case underscores both the therapeutic challenges and the potential of sequential ADCs in managing HR+/HER2- MBC after standard endocrine and chemotherapy options have been exhausted. Initially diagnosed with luminal B-type breast cancer, the patient progressed through multiple lines of ET and chemotherapy, demonstrating the limited durability of response in HR+/HER2- MBC. This progression highlights the critical challenge of resistance in HR+/HER2- MBC and underscores the need for novel therapeutic approaches.

HR+/HER2- MBC is particularly challenging due to the frequent development of resistance. ET [14], the backbone of HR+ MBC treatment, targets hormonal pathways essential for tumor growth, including aromatase inhibitors (e.g., anastrozole), selective estrogen receptor modulators (SERMs) like tamoxifen, and selective estrogen receptor degraders (SERDs) like fulvestrant. Despite their initial effectiveness, resistance to ET often develops, necessitating alternative treatments to maintain disease control [15]. CDK4/6 inhibitors [16], such as palbociclib, ribociclib, and abemaciclib, have become essential in managing endocrine-resistant HR+ MBC by inhibiting cell cycle progression. Clinical trials like PALOMA [17], MONALEESA [18], and MONARCH [19] have shown that combining CDK4/6 inhibitors with ET can nearly double PFS compared to ET alone. Specifically, in the MONARCH 2 study [20], abemaciclib combined with fulvestrant achieved a PFS of 16.4 months compared to 9.3 months with fulvestrant alone in patients with endocrine-resistant disease. In this case, anastrozole and palbociclib provided a PFS of 11 months. But the patient showed no clinical benefit from subsequent fulvestrant and palbociclib, which potentially due to HR and PR downregulation-a common feature of acquired resistance [21]. Additional mechanisms, such as activation of the PI3K/AKT/mTOR pathway [22] or altered cell cycle regulation [23], may also contribute to resistance by bypassing CDK4/6 inhibition.

When progression occurs following ET and CDK4/6 inhibitors, chemotherapy becomes the standard option. However, chemotherapy is associated with significant side effects and often provides limited efficacy, especially in heavily pretreated patients. In this case, various chemotherapeutic agents including vinorelbine, cisplatin, nab-paclitaxel, capecitabine, gemcitabine and carboplatin were applied but achieved minimal benefit. The accumulation of resistance to both ET and chemotherapy underscores the limited options available for patients in advanced stages and emphasizes the need for alternative therapies that can deliver effective cytotoxic agents while

minimizing toxicity. ADCs, with their targeted approach, offer a promising option for such heavily pretreated patients by selectively delivering cytotoxic payloads to tumor cells and sparing normal tissues.

ADCs consist of three key components: a monoclonal antibody specific to a tumor-associated antigen, a cytotoxic payload, and a linker that releases the payload in a targeted manner [24]. This design provides particular advantages for HR+/HER2- MBC patients who have developed resistance to ET and chemotherapy, as ADCs can bypass mechanisms of resistance through hormone receptor downregulation or activation of alternative pathways [25]. Additionally, the targeted delivery of cytotoxic agents reduces systemic toxicity, making ADCs a safer alternative compared to conventional chemotherapy. Current guideline [26] recommends Sacituzumab Govitecan and Trastuzumab Deruxtecan for HR+/HER2- MBC in posterior-line treatment. Sacituzumab govitecan has been shown in clinical trials to significantly improve PFS and overall survival (OS) in patients who have progressed on multiple lines of ET and chemotherapy [6]. The phase 3 DESTINY-Breast 04 trial [27] demonstrated that trastuzumab deruxtecan enhanced PFS and OS in HER2-low MBC, which included many HR+ cases. Beyond HER2 and TROP2, emerging ADC targets like HER3, CLDN18.2, and LIV-1 et.al are under investigation for their potential to further improve treatment outcomes in MBC.

Despite their therapeutic promise, ADCs present challenges, particularly with respect to cross-resistance when sequential therapies utilize similar payloads or mechanisms [11]. For example, in cases where an MBC patient is first treated with trastuzumab deruxtecan (targeting HER2 with a topoisomerase I inhibitor payload) followed by sacituzumab govitecan (targeting TROP2 but also utilizing a topoisomerase I inhibitor payload), the cancer cells may develop resistance mechanisms against the shared payload type [12]. This can compromise the efficacy of the subsequent ADC therapy. In this case, two ADCs-TQB2103, which targets CLDN18.2, and sacituzumab govitecan, which targets TROP2-were administered sequentially, demonstrating the complexities associated with potential cross-resistance in HR+/HER2- MBC. TQB2103 was selected initially for the possibility that CLDN18.2 expression may be upregulated in metastatic or treatment-resistant conditions [9], despite typically low expression in breast cancer. However, TQB2103 displayed limited efficacy. Given that both TQB2103 and sacituzumab govitecan employ topoisomerase I inhibitors as their cytotoxic payloads, there was a risk of cross-resistance. Nonetheless, sacituzumab govitecan achieved a PFS of 7 months in this case, exceeding the median PFS of 5.5 months observed in the TROPiCS-02 study [6].

In retrospect, starting with sacituzumab govitecan or trastuzumab deruxtecan and reserving TQB2103 for later might have provided a better therapeutic outcome. However, financial considerations influenced the choice of TQB2103 as the initial ADC in this case. This experience highlights the importance of strategic ADC sequencing and target selection based on tumor biology, expression patterns, and resistance mechanisms. As ADCs become more integral to the treatment landscape for HR+/HER2- MBC, especially for patients with advanced, treatment-resistant disease, selecting the optimal ADC sequence for each patient will be essential for maximizing therapeutic efficacy.

## CONCLUSION

This case demonstrates the potential of ADCs as a viable treatment strategy for HR+/HER2- MBC in patients who have exhausted standard therapies, as exemplified by the clinical response to sacituzumab govitecan. The findings

also highlight the limitations of sequential ADC use, particularly when cross-resistance may arise due to similar payloads or mechanisms of action. Future research should focus on identifying biomarkers that predict ADC efficacy and exploring novel ADC targets to optimize treatment outcomes in HR+/HER2- MBC. A personalized treatment approach, guided by tumor biology and resistance profiles, is crucial to maximizing the benefits of ADCs in this challenging patient population.

## CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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