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Trastuzumab deruxtecan in recurrent uterine serous carcinoma resistant to trastuzmab based-chemotherapy

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ABSTRACT

Background: Treatment of uterine serous carcinoma (USC) is challenging; effective treatment options for metastatic and recurrent disease are needed.
Case: A 68-year-old woman with recurrent, metastatic, USC overexpressing HER2/neu experienced durable response to the antibody drug conjugate (ADC) trastuzumab-deruxtecan (T-DXd), after failing multiple standard and experimental treatments targeting HER2/neu. She experienced a significant reduction in disease burden, disappearance of metastatic back bone pain as well as normalization of CA-125 quickly after starting treatment. Her disease continued to show response to treatment over 5 months and 7 cycles of T-DXd therapy. She did not experience any dose-limiting side effects and tolerated treatment with 5.4 mg/kg T-DXd without issue.
Conclusion: T-DXd may present a new treatment option for chemotherapy-resistant uterine serous carcinoma.

1. Introduction

Uterine serous carcinoma (USC) is an aggressive histologic subtype of endometrial cancer. It accounts for only 5% of all endometrial carcinomas, yet causes 40% of endometrial cancer deaths (Siegel et al., 2023; Lee et al., 2021). USC is characterized by a high-grade histology, advanced stage at diagnosis, and a poor prognosis.

The current standard of care for USC is primary cytoreductive surgery followed by adjuvant chemotherapy. However, even with aggressive treatment, a large number of patients with USC will experience recurrence and progression of their disease (McGunigal et al., 2017). Importantly, about one-third of USC may overexpress HER2/neu at 3+ level by immunohistochemistry (IHC) and/or harbor gene amplification of c-erBb2 (i.e., the gene encoding for HER2/neu) by Fluorescent In Situ Hybridization (FISH) (Buza et al., 2013). These findings have opened new treatment opportunities for the treatment of a subset of USC patients using a variety of HER2/neu targeted agents.

There is a clear unmet need for effective therapies for patients with USC who have failed standard treatments. Trastuzumab deruxtecan (T-DXd) is a novel HER2-directed antibody-drug conjugate (ADC) with a topoisomerase I inhibitor payload, recently approved by the Food and Drug Administration (FDA) for multiple tumor indications (Narayan et al., 2021; C. for D.E. and Research, 2022). There is promising preclinical and early clinical evidence supporting its effectivity among gynecologic malignancies that overexpress HER2, such as carcinosarcoma (Mauricio et al., 2023; Nishikawa et al., 2023).

We present a patient with recurrent USC with HER2 overexpression who previously failed multiple lines of standard and experimental therapies including trastuzumab as well as additional HER2/neu targeted treatments. Treatment with T-DXd, approved on a compassionate basis, elicited an impressive and durable disease response.

2. Case

The patient is a 68-year-old woman who was originally diagnosed with stage IVB USC (with omental involvement) in May 2018 after laparotomy with complete staging. The final pathology revealed USC with 90% depth of invasion, extensive LVSI with involvement of the cervical stroma, omentum, right pericolic gutters, diaphragm, ovaries, and fallopian tubes. Her tumor was sequenced which demonstrated a copy number gain in HER2, microsatellite stable (MSS), with a tumor mutational burden (TMB) of 1.7. The tumor was found to have mutations in TP53 and PIK3R1. She then received 6 cycles of adjuvant carboplatin/paclitaxel. Trastuzumab was added beginning with cycle #3 of chemotherapy due to the overexpression of HER2 in her tumor (by IHC, HER2 score was 3+). Her CA-125 values normalized after her adjuvant

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therapy, and she had no evidence of disease on imaging. In December 2018, she started maintenance trastuzumab, which she continued for 14 additional cycles.

Per report, in October 2019, her CA-125 began to rise. This prompted imaging, and in November 2019, a CT scan was performed, which did not show any evidence of recurrence. However, a PET CT scan performed in February 2020 demonstrated a pelvic peritoneal and nodal recurrence. She was then treated with 4 cycles of single-agent carboplatin (4/2020–7/2020). She notably developed a hypersensitivity reaction to carboplatin at her last infusion. A CT scan in late July 2020 demonstrated increased pulmonary nodules, as well as increased supraclavicular and paraesophageal lymph nodes and a rectal serosal implant. By 9/16/2020, another CT scan demonstrated significant increases in the size of all aforementioned lesions, with "innumerable" solid pulmonary nodules.

Given this progression, she was suggested to enroll in a Phase II clinical trial evaluating Vic-trastuzumab duocarmazine (SYD985) in patients with recurrent endometrial cancer with HER2 overexpression. She began treatment with Cycle #1 Vic-trastuzumab duocarmazine (SYD985) on 10/1/2020. She experienced a 53.5% reduction in tumor volume per RECIST criteria, while on study for five months. However, by June 2021, she did not experience further decrease in tumor volume on CT scan. In September 2021, while her disease remained stable after 15 cycles, she required treatment delays for pneumonia as well as grade 2 corneal toxicity and received a reduced dose of 0.9 mg/kg SYD985 for cycle 16 on 10/21/22. Unfortunately, her CT scan dated 11/29/2021 demonstrated a new metastatic lesion in the adrenal gland, which was biopsied and proven to be recurrent USC, while the rest of her disease remained stable from June 2021. Due to this progression, she was taken off trial.

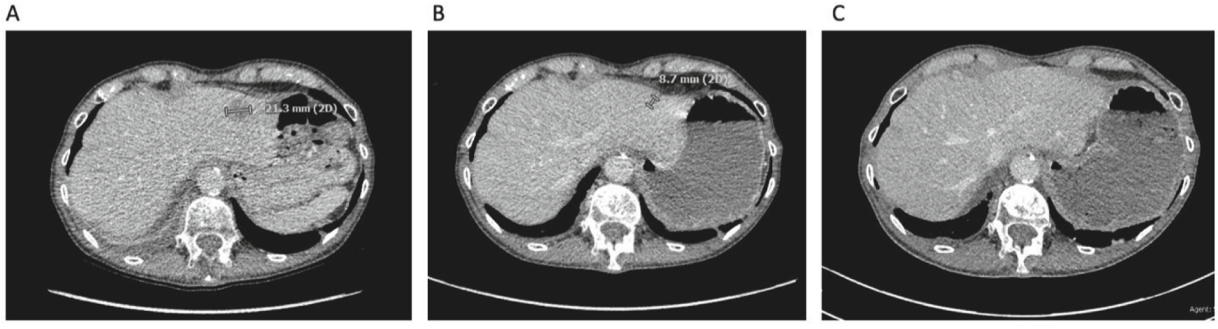
She was then enrolled in a subsequent clinical trial of Sacituzumab Govitecan (SG), a Trop-2 targeting ADC. She received 12 cycles at a dose of 10 mg/kg from 12/23/21–8/30/22. While several scans during this period demonstrated stable disease, the patient developed worsening back pain, and an MRI of the spine dated 9/12/2022 demonstrated worsening bony metastases. From 10/7–10/13/2022 she received 2,400 cGy over 2 fractions to each metastases, T3 and T10-T-11. Her SG was held for several weeks before/after her palliative radiation treatment; a CT scan from 10/17/22 demonstrated progression of disease, with new pulmonary and hepatic lesions.

She was next enrolled in a trial of afatinib. While she tolerated the oral treatment well, her next two scans showed progression of disease, with her hepatic lesion increased in size to 2.1 cm, from 1.3 cm (MRI 12/12/22). With this progression, afatinib was stopped, and as her tumor was known to overexpress HER2, she was started on trastuzumab-deruxtecan off-label. She began treatment 12/23/22, at a dose of 5.4 mg/kg. Rapidly after initiating treatment, her CA-125 serum values dropped from 466 U/mL (12/12/22) to 56 on 1/24/23. By 2/24/23, her CA-125 was back in the normal range (27.8 U/mL). While on T-DXd, the patient had resolution of her back pain from her bony metastases. CT scans (2/20/23 and 5/1/23) showed regression of all metastatic sites, and ultimate resolution of her 2.1 cm liver lesion (Fig. 1). She has received 7 cycles of T-DXd without dose reduction or interruption. The patient's disease course with treatments is illustrated in Fig. 2 and Fig. 3.

3. Discussion

Uterine serous carcinoma is an aggressive and difficult-to-treat gynecologic malignancy; we present a case of a patient with HER2-overexpressing USC who has had a significant and lasting response to T-DXd, a novel ADC targeting HER2.

HER2 overexpression is detected in approximately 35% of USC and is a known poor prognostic indicator (Buza et al., 2013; Santin et al., 2005). Consistent with this patient's tumor's genetic profile, previous publications have reported that copy number variations in multiple oncogenes, such as c-erbB2 encoding for HER2, play a major role in the pathogenesis of USC (Zhao et al., 2013). While historically HER2 overexpression conferred poor prognosis, it is emerging as an attractive target for novel antibody-based therapies such as trastuzumab and T-DXd. Per NCCN guidelines, Trastuzumab in combination with carboplatin and paclitaxel chemotherapy is now the recommended treatment for advanced/recurrent HER2-overexpressing USC (Fader et al., 2018),



A. CT scan 12/12/2022: Interval growth in hepatobiliary segment 2 hypodensity- measuring 2.1cm from 1.3cm prior.

B. Scan 2/20/23: Regression of index lesion after two months of T-DXd treatment. Hepatic metastasis decreased from 2.1cm to 0.9cm.

C. Scan 5/1/23: Complete regression of 0.9cm index lesion after five months of T-DXd treatment. Decrease, but not complete resolution, of pulmonary nodules and lymphadenopathy.

Fig. 1. CT scans demonstrating activity of T-DXd in uterine serous carcinoma. Representative hepatic lesion. A. CT scan 12/12/2022: Interval growth in hepatobiliary segment 2 hypodensity- measuring 2.1 cm from 1.3 cm prior. B. Scan 2/20/23: Regression of index lesion after two months of T-DXd treatment. Hepatic metastasis decreased from 2.1 cm to 0.9 cm. C. Scan 5/1/23: Complete regression of 0.9 cm index lesion after five months of T-DXd treatment. Decrease, but not complete resolution, of pulmonary nodules and lymphadenopathy.

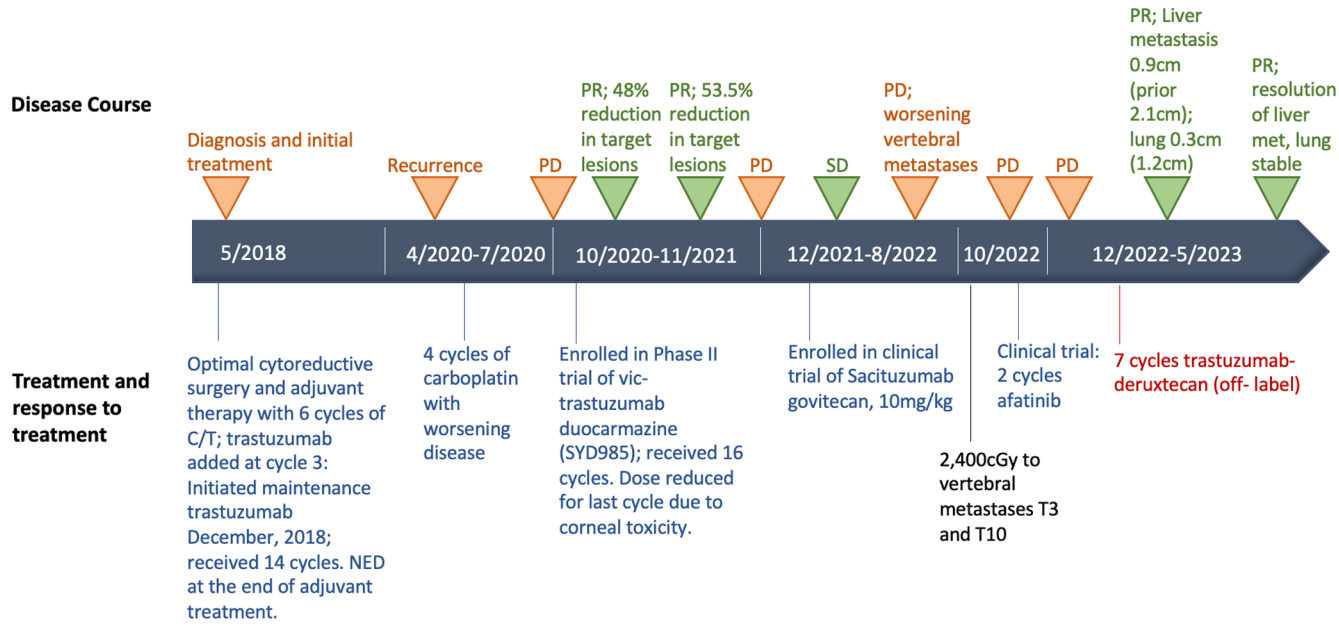


Fig. 2. Timeline of patient's disease course with treatment: (C/T, carboplatin/paclitaxel: PD, progression of disease; SD, stable disease; PR, partial response; NED, no evidence of disease.

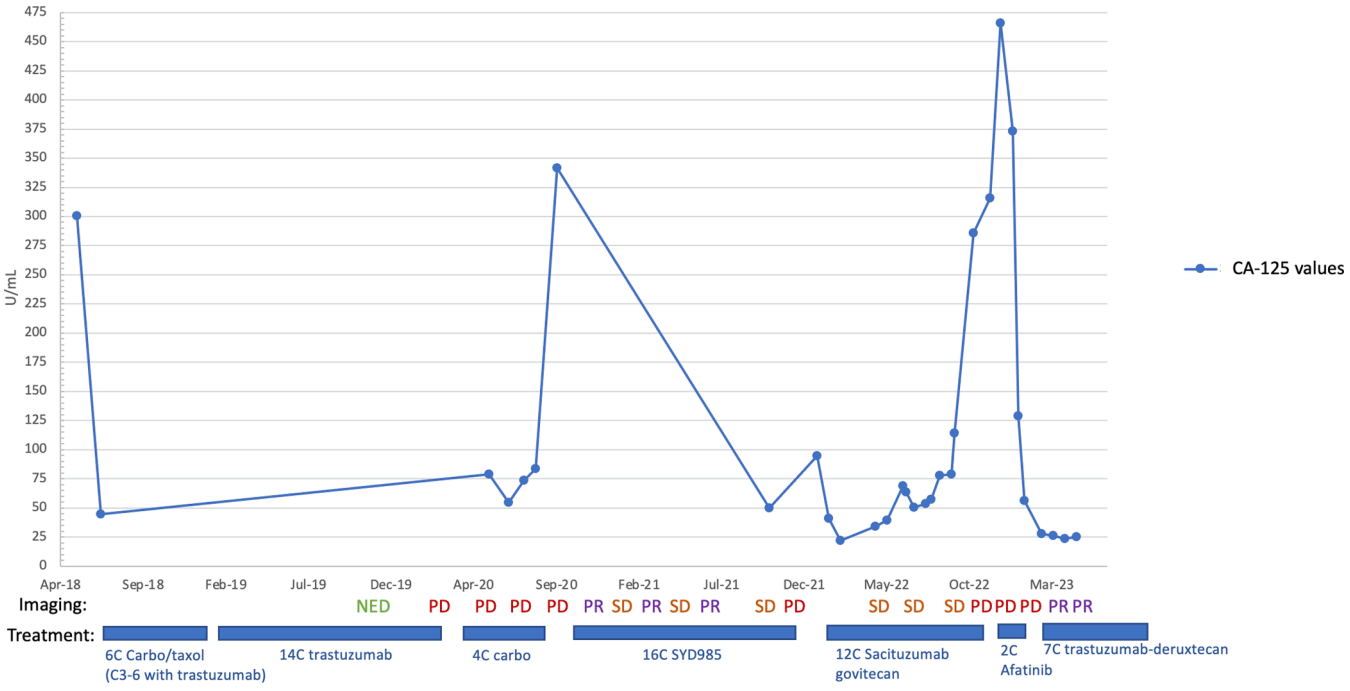


Fig. 3. Graphical representation of patient's CA-125 values alongside disease and treatment course.

and several HER2-directed ADCs and other novel therapies have shown promising preclinical activity in trastuzumab resistant USC (Tymon-Rosario et al., 2021; English et al., 2014). Importantly, a large NRG/GOG Phase 2/3 clinical trial (i.e., NRG-GY026) is currently evaluating the activity of the pertuzumab/trastuzumab combination in chemotherapy-naïve USC and carcinosarcoma patients overexpressing HER2 (NCT05256225).

It is notable that our patient developed tumoral resistance to trastuzumab as well as Vic-trastuzumab duocarmazine and afatinib, all of which are HER2-directed therapies. Resistance to trastuzumab and afatinib has been ascribed to several different mechanisms, including shedding of the HER2 receptor into circulation, PI3K-activating mutations causing downstream resistance to induction of apoptosis, and heterogenous intra-tumoral expression of HER2 surface proteins within USC tumors (Todeschini et al., 2011). ADCs such as T-DXd have several characteristics that may enable them to overcome these resistance mechanisms. T-DXd has a high drug-to-antibody ratio, with a membrane-permeable toxic payload. This enables it to deliver its cytotoxic payload to HER2 non-expressing cells that neighbor HER2 3+ cells, and thus has a potent bystander effect (Mauricio et al., 2023). While the patient presented here has only been on T-DXd for five months, her tumor's initial response to T-DXd was much more pronounced than her response to Vic-trastuzumab duocarmazine. She experienced more rapid resolution of CA-125 as well as consistent decrease in tumor volume on

imaging with T-DXd therapy, whereas while on trastuzumab duocarmazine, her CA-125 values never normalized, and CT scans showed stable disease as best response.

T-DXd is now approved by the FDA for metastatic gastric, breast, and NSCLC. Currently there are over 40 ongoing trials of T-DXd registered on ClinicalTrials.gov, including one trial evaluating T-DXd combined with olaparib in patients with USC (NCT04585958). The safety of T-DXd has been proven in several Phase II and III studies. The most common adverse events in a randomized phase 3 trial of T-DXd for patient with HER2-positive metastatic breast cancer (DESTINY-Breast02) were vomiting, fatigue, alopecia, and fatigue (André et al., 2023).

The use of T-DXd may represent a novel and effective treatment option for patients with recurrent, treatment-resistant, trastuzumab-resistant USC. We await results from upcoming clinical trials and support further investigation of the safety and efficacy of this compound in patients with USC.

Consent

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contributions

Blair McNamara, Cem Demirkiran, and Alessandro D. Santin participated in drafting and revising this manuscript. Stefania Bellone provided materials for the figures. All authors read and approved this manuscript to be submitted.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [A.D.S. reports grants from PUMA, grants from IMMUNOMEDICS, grants from GILEAD, grants from SYNTHON, grants and personal fees from MERCK, grants from BOEHINGER-INGELHEIM, grants from GENENTECH, grants and personal fees from TESARO and grants and personal fees from EISAI. The other authors declare no conflict of interest.]

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