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Durable partial response to pembrolizumab, lenvatinib, and letrozole in a case of recurrent uterine carcinosarcoma with *ESR1* gene amplification

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1. Introduction

Uterine carcinosarcoma (UCS) is a less common, aggressive histologic subtype of endometrial carcinoma that accounts for less than 5 % of uterine malignancies but up to 15 % of uterine cancer-specific mortality (Cantrell et al., 2015). UCS has a poor prognosis and a high risk of recurrence. Five-year disease-specific survival decreases with higher stages of disease: stage I/II 59 %, stage III 22 %, and stage IV 9 % (Gonzalez Bosquet et al., 2010). Recurrence is observed in 37 % to 80 % of patients based on stage following surgery and adjuvant therapy (Cantrell et al., 2015).

A limited number of prospective trials have evaluated systemic therapy for UCS. GOG 261 has established paclitaxel and carboplatin as the standard-of-care first-line chemotherapy for metastatic or recurrent UCS (Powell et al., 2022). Few treatment options are available for diseases that have progressed after platinum-based therapy. Single-agent chemotherapy, including ifosfamide/mesna and cisplatin, has demonstrated limited activity for UCS. More effective therapy is needed.

The combination of anti-PD-1 monoclonal antibody pembrolizumab with tyrosine kinase inhibitor lenvatinib has recently been adopted for recurrent or metastatic endometrial cancer. KEYNOTE-146 and KEYNOTE-775 demonstrated significant improvement in both progression-free survival and overall survival in the investigative immunotherapy arms, providing the rationale for the use of pembrolizumab plus lenvatinib for patients with advanced or recurrent endometrial cancer (Lee et al., 2021; Makker et al., 2022). In KEYNOTE-775, the combination of pembrolizumab and lenvatinib was associated with a higher objective response rate when compared to chemotherapy (31.9 % vs. 14.7 %) and an increase in median response duration of 8.7 months (Makker et al., 2022). While UCS was excluded from these studies, the impressive antitumor activity of this treatment combination has led to the adoption of this regimen for recurrent or metastatic UCS. How et al. recently published single institution data regarding the efficacy of pembrolizumab plus lenvatinib in recurrent endometrial cancer, demonstrating clinical benefit in UCS (How et al., 2021).

Hormonal therapy, including progestin therapy and aromatase inhibitors (AI), is a treatment option for endometrioid endometrial carcinoma, with data supporting their use for disease recurrence in phase II trials (Slomovitz et al., 2015). The use of hormone therapy has been primarily limited to endometrioid endometrial carcinoma, with only scattered reports supporting applicability for UCS. Martin-Romano et al. described a case of estrogen receptor alpha (ERα) positive UCS with a pathological complete response and long-term disease control with a multi-modal treatment approach, including five years of letrozole therapy (Martin-Romano et al., 2017). The use of megestrol acetate and letrozole was also recently reported in a case of ERα-positive, recurrent UCS (Liang et al., 2021).

Presented herein is the case of a patient with ERα-positive, recurrent UCS with estrogen receptor alpha gene (*ESR1* gene) amplification, with a durable partial response to letrozole, pembrolizumab and lenvatinib.

2. Case report

A 68-year-old woman with a history of hypertension presented in March 2019 with a seven-month history of intermittent postmenopausal bleeding. A transvaginal ultrasound performed during the evaluation showed a 40-mm endometrial echo complex with internal flow. Endometrial biopsy demonstrated high-grade endometrial adenocarcinoma. Subsequent chest x-ray showed no evidence of pulmonary disease. Her CT scan did not demonstrate evidence of metastatic disease.

In April 2019, the patient underwent total laparoscopic hysterectomy, bilateral salpingo-oophorectomy and sentinel lymph node biopsy,

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with intraoperative findings notable for metastatic implants along the left uterosacral ligament as well as a 3-cm mass in the posterior cul-de-sac. The final pathologic diagnosis was carcinosarcoma with more than 50 % myometrial invasion, lymphovascular invasion and involvement of the pelvic side wall consistent with FIGO stage IVB disease (Fig. 1A).

The patient received adjuvant therapy with a total of 6 cycles of intravenous paclitaxel and carboplatin chemotherapy and external beam radiation of 45 Gy to the whole pelvis with a boost of 14.4 Gy to the left pelvic sidewall, completing her therapy in November 2019. The patient remained without evidence of disease until December 2020, when she reported a one-month history of a painful lump in the left lower abdomen. CT scan demonstrated a 5-cm mass along the left vaginal cuff, multiple new peritoneal implants, and a 5-cm mass invading the anterior abdominal wall musculature. A CT-guided core needle biopsy of the abdominal mass confirmed recurrent UCS. Somatic tumor testing of the biopsy specimen demonstrated a microsatellite stable (MSS) tumor with a low tumor mutation burden (TMB) 6 muts/Mb. Genomic alterations with known or likely function included short variants in *PTEN* (K128T), *PIK3R1* (V589_T603del and L449S), and *TP53* (R175H), and amplification of *ESR1* (8/8 exons, estimated 11 copies) with equivocal amplifications of *RAF1* and *MYC*. A review of her initial pathologic report revealed that immunohistochemical staining of the primary tumor specimen for ER was diffusely positive (Fig. 1B).

The patient was initiated on intravenous pembrolizumab with oral lenvatinib for the management of recurrent disease in January 2021. Subsequent CT imaging after 6 cycles of immunotherapy demonstrated partial response with interval decrease in foci of abdominal carcinomatosis and vaginal cuff mass. Given the *ESR1* gene amplification detected by somatic tumor testing, letrozole was added to her treatment regimen in June 2021. Letrozole was briefly discontinued after a few weeks of therapy due to Grade 1 arthralgias and the patient's concern for additional side effects. However, it was restarted in August 2021 and has been tolerated well.

The patient most recently underwent CT imaging in December 2023, 36 months from diagnosis of disease recurrence, with evidence of sustained partial response following 39 cycles of pembrolizumab and lenvatinib with letrozole (Fig. 2). The pelvic lesion is barely visible, and the left-sided abdominal wall lesion has remained no greater than 2 cm. She has required intermittent dose adjustments with treatment pauses of pembrolizumab and lenvatinib due to grade 2 diarrhea; however, the patient has tolerated the therapy well. See Fig. 3 for an overview of the treatment course.

3. Discussion

We report the identification of *ESR1* gene amplification in a case of recurrent uterine carcinosarcoma and its durable response to the combined regimen of pembrolizumab, lenvatinib, and letrozole. At the time of this manuscript's preparation, the patient continued to have a partial response for three years with two lesions less than three centimeters each.

We are unable to determine the relative contributions of the immune checkpoint blockade (pembrolizumab), the antiangiogenic effect (lenvatinib) and the hormone therapy (letrozole). We observed an initial shrinkage of the tumor foci with the pembrolizumab/lenvatinib combination alone. However, this appeared to be enhanced by the addition of letrozole and the duration of this patient's response to the three-agent combination has greatly exceeded the median duration of response (DOR) seen in KEYNOTE-775 (36 months vs. 9.2 months) (Makker et al., 2022). It is interesting to note that anti-estrogen agents can enhance the efficacy of immune checkpoint blockade in a murine melanoma model (Chakraborty et al., 2021). Therefore, letrozole can be added to pembrolizumab and lenvatinib for potential synergistic therapeutic effects without adding additional toxicities.

ESR1 gene encodes for estrogen receptor alpha (ERα) protein, an essential transcriptional mediator of estrogen-driven biological responses, including proliferation of the endometrium. *ESR1* gene amplification has been reported in breast cancer; however, its clinicopathological and prognostic significance is not well understood (Rahman et al., 2013). *ESR1* gene amplification has also been reported in endometrial cancer, predominantly in endometrioid endometrial carcinoma (Rahman et al., 2013). Notably, *ESR1* gene amplification is also present in 7 % of cases in the TCGA UCS dataset (Cherniack et al., 2017). *ESR1* gene amplification has also been reported in ovarian cancer and has been detected in approximately 2 % of high-grade serous ovarian carcinoma (Issa et al., 2009). A recent report described a patient with metastatic ovarian cancer with ERα positivity and *ESR1* gene amplification treated with hormone therapy who had a five-month DOR (Wang et al., 2022). While it remains unclear whether *ESR1* amplification has prognostic and therapeutic relevance in UCS, the patient described in this report is consistent with the growing body of literature that it may contribute to the tumor biology and clinical behavior of UCS.

Most of the previous UCS literature has focused on ERα protein expression, often utilizing immunohistochemistry (IHC), with some reporting promising treatment response to hormone therapy. Liang et al. have described several UCS patients with ERα expression who had a durable response to hormonal therapies, including progestins and aromatase inhibitors (Liang et al., 2021). Studies have estimated the rate of

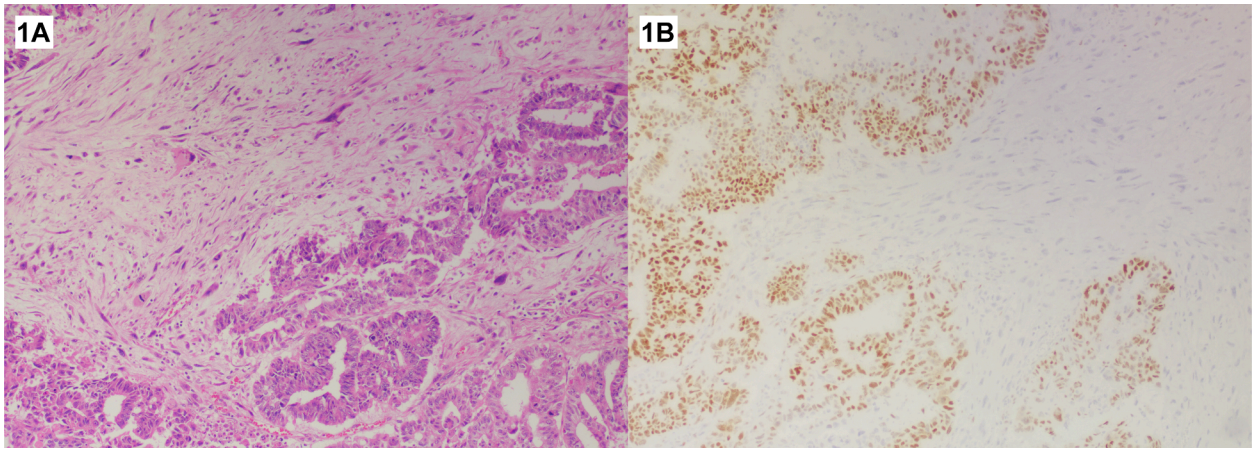

Fig. 1. Primary tumor showing both carcinomatous and sarcomatous components, with malignant cytologic features including nuclear pleomorphism and mitotic activity, consistent with uterine carcinosarcoma (H&E, 100X) (1A). Diffuse nuclear expression of estrogen receptor in the carcinomatous component (Estrogen Receptor, 100X) (1B).

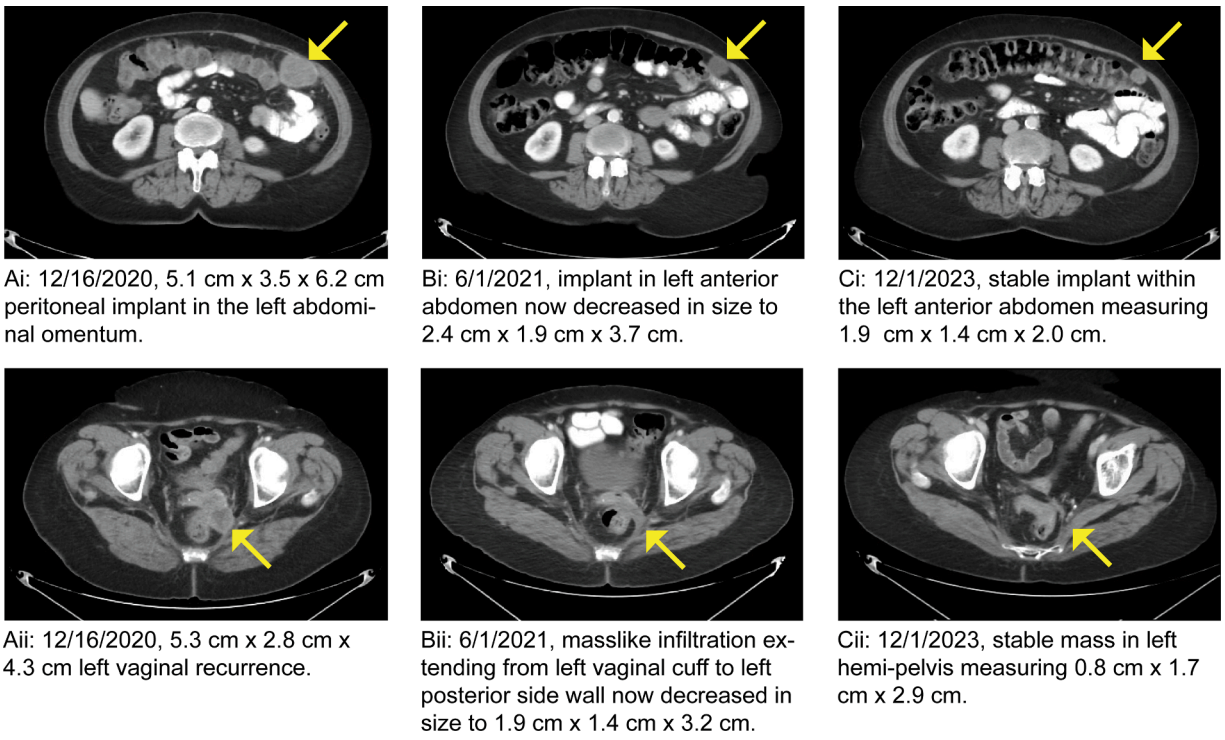

Fig. 2. CT images of the abdomen (i) and pelvis (ii) demonstrating presence of left abdominal wall recurrence (Ai) and left vaginal recurrence (Aii), partial response after 6 cycles of pembrolizumab and lenvatinib (Bi, Bii), and sustained partial response after further treatment with pembrolizumab, lenvatinib and letrozole (Ci, Cii).

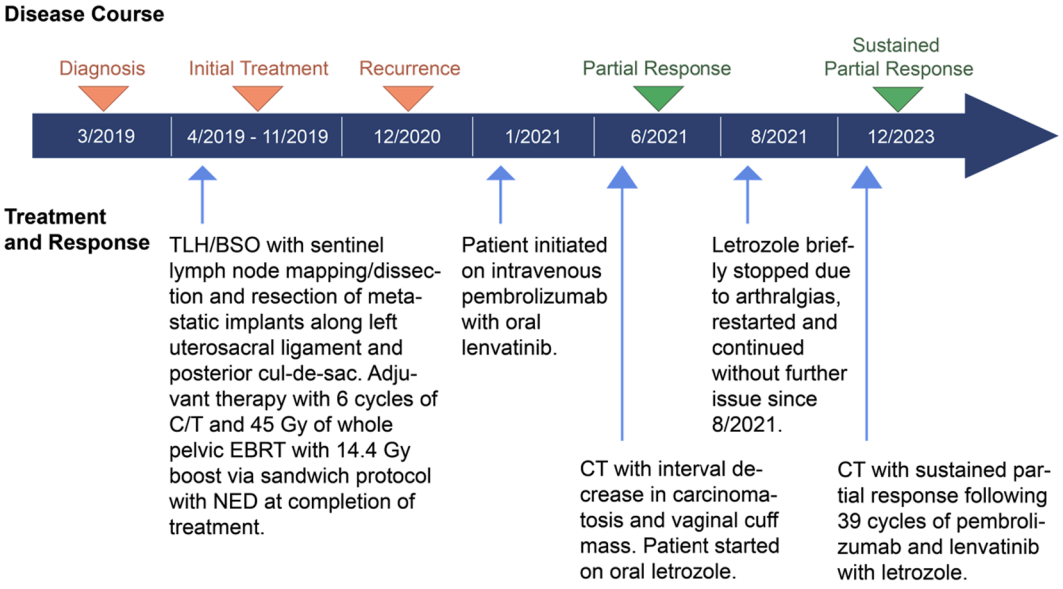

Fig. 3. Timeline of the patient's disease course and treatment. (TLH/BSO, total laparoscopic hysterectomy and bilateral salpingo-oophorectomy; C/T, carboplatin and paclitaxel; NED, no evidence of disease).

ERα positivity in UCS between 8 % and 23 %, with more frequent expression in the epithelial component than in the mesenchymal component (de Jong et al., 2011; Koivisto-Korander et al., 2011). ERα expression has been found to be associated with improved survival in UCS (Rahman et al., 2013). However, the rate of *ESR1* gene amplification in UCS has not been reported.

The *ESR1* gene amplification for the patient described herein was identified at disease recurrence. There may be a role for earlier testing for ERα expression. IHC can be used to detect ERα protein expression. However, ERα protein expression does not necessarily mean that there is *ESR1* gene amplification. For patients with positive ERα expression, subsequent testing to determine the presence of *ESR1* gene amplification may help guide the choice of adjuvant therapy or maintenance therapy. While amplifications of some clinically actionable oncogenes, such as *ERBB2*, *MYC*, and *MET*, can be evaluated using clinically validated fluorescent in situ hybridization (FISH) assays, one for *ESR1* is not currently commercially available. Therefore, at this time, a validated tumor profiling assay is required to detect *ESR1* gene amplification.

To our knowledge, this study is the first report to describe uterine carcinosarcoma with *ESR1* gene amplification. Future work could

validate our findings by determining the prevalence of *ESR1* gene amplification in a large patient cohort of UCS, and by detecting *ESR1* gene amplification using both genomic assays and FISH. Additional studies should investigate the utility of *ESR1* gene amplification as a prognostic or predictive biomarker in UCS.

4. Consent

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

CRediT authorship contribution statement

Jenny L. Soiffer: Writing – review & editing, Writing – original draft, Conceptualization. **Alexander J. Fife:** Writing – review & editing. **Shrikanth S. Gadad:** Writing – review & editing, Conceptualization. **Javier A. Laurini:** Writing – review & editing, Conceptualization. **Julia A. Elvin:** Writing – review & editing. **Sara S. Isani:** Writing – review & editing. **Ken Y. Lin:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Julia Elvin is an employee of Foundation Medicine, a subsidiary of Hoffmann LaRoche. The remaining authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

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