



## Case report

## Response to lenvatinib and pembrolizumab combination therapy in pembrolizumab-pretreated relapsed endometrial cancer

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## ABSTRACT

Uterine endometrial cancer is one of the most common gynecological malignancies worldwide. With relatively few options for late-line therapies for advanced or relapsed endometrial cancer, the use of pretreated therapies may broaden the choice of treatments. Here, we report a case of recurrent microsatellite instability-high endometrial cancer that acquired resistance to pembrolizumab but favorably responded to the lenvatinib and pembrolizumab combination therapy. Lenvatinib combined with pembrolizumab may be effective against endometrial cancer resistant to pembrolizumab monotherapy, encouraging its use regardless of prior administration of immune checkpoint inhibitors. Further investigation on the lenvatinib and pembrolizumab combination therapy and the mechanism underlying its anticancer effect may provide new insights into cancer immunotherapy and tumor microenvironments.

### 1. Introduction

Uterine cancer is the second most common gynecological malignancy worldwide, with high incidence rates in developed countries (Sung et al., 2021). Endometrial cancer accounts for over 90 % of uterine cancer cases. For advanced endometrial cancer, chemotherapy with carboplatin and paclitaxel or doxorubicin and cisplatin is considered the standard course of treatment (Lu and Broaddus, 2020; Miller et al., 2020). For patients with platinum-resistant tumors, pembrolizumab, an immune checkpoint inhibitor (ICI), can be used to treat advanced microsatellite instability (MSI)-high cancers. When platinum-based chemotherapy and ICIs fail, late-line treatments include either hormone therapy or chemotherapy with paclitaxel or doxorubicin; however, currently, there is no globally accepted standard for treatment (Lu and Broaddus, 2020).

Lenvatinib is an oral multiple receptor tyrosine kinase inhibitor that mainly targets the vascular endothelial growth factor (VEGF) and fibroblast growth factor receptors. Recent studies have reported promising results of combination therapy using lenvatinib with ICIs for

various cancers (Hao and Wang, 2020). The recent KEYNOTE-775 trial demonstrated significantly longer progression-free survival and overall survival using lenvatinib and pembrolizumab combination therapy among patients with advanced endometrial cancer (Makker et al., 2022). Although this study established the benefits of lenvatinib and pembrolizumab combination therapy in patients with endometrial cancer pretreated with platinum-based chemotherapy, its efficacy in pembrolizumab-pretreated patients remains unknown, as the eligible patients had no history of exposure to treatment regimens targeting the programmed death-1 (PD-1) pathway. Similarly, a recent study demonstrated the efficacy of lenvatinib and pembrolizumab combination therapy in patients with metastatic renal cancer pretreated with ICI therapy (Lee et al., 2021), but whether this practice can be successfully applied to endometrial cancer remains elusive.

Here, we report a case of recurrent endometrial cancer pretreated with pembrolizumab that showed a favorable response to combination therapy with lenvatinib and pembrolizumab.

*Abbreviations:* ICI, immune checkpoint inhibitor; MSI, microsatellite instability; PD-1, programmed death-1; CT, computed tomography; MMR, mismatch repair; VEGF, vascular endothelial growth factor; IFN, interferon.

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## 2. Case presentation

A 64-year-old female patient presented with postmenopausal bleeding. Transvaginal ultrasonography and computed tomography (CT) revealed a space-occupying lesion in the cervix and corpus of the uterus, along with the presence of a metastatic pelvic lymph node and multiple lung metastases. Diagnosed with cervical cancer, the patient was treated with neoadjuvant therapy using paclitaxel and cisplatin every 3 weeks for six cycles and achieved a partial response for both the primary tumor and lung metastatic lesions. Subsequently, total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy were performed. The post-surgical diagnosis changed to endometrial cancer in the corpus uteri. The pathological evaluation suggested endometrial adenocarcinoma (G2), ypT3bpN1M1.

Chemotherapy with carboplatin and paclitaxel was administered but was discontinued after one cycle because of severe complications, including febrile neutropenia and pelvic lymphocyst infection requiring antibiotic treatment. Doxorubicin was selected as the second-line treatment and was administered every 3 weeks, with the patient showing progressive disease after four cycles of administration. The tumor showed high microsatellite instability; therefore, the patient was further administered 200 mg pembrolizumab every 3 weeks. After three cycles of treatment, a partial response was observed. During treatment, hyperthyroidism was detected, which seemed to be an immune-related adverse event, but improved without requiring specific intervention. After eight cycles of pembrolizumab treatment, CT revealed vaginal stump recurrence and several lymph node metastases. Positron emission tomography/CT confirmed abnormal uptake in the vaginal stump (Fig. 1A), lymph nodes in the right clavicular fossa, right hilar region, right common iliac region, and left external iliac region (Fig. 1B). The pelvic regions, vaginal stump, and paraaortic lymph nodes were treated with radiation therapy, with a total dose of 45 Gy administered in 25 fractions. Subsequently, a boost treatment of 9 Gy in five fractions was administered to the vaginal stump and pelvic regions. After 17 cycles, pembrolizumab treatment was discontinued after a follow-up CT, which demonstrated an increase in the tumor size of both vaginal stump and pelvic lymph nodes and a new infiltration in the posterior wall of the bladder, indicating that the relapsed tumor had acquired resistance to pembrolizumab.

The next course of treatment included paclitaxel, resulting in a partial response after four cycles and progression of local recurrence after seven cycles (Fig. 2A). Due to a scarcity of available therapies, a combination of lenvatinib (20 mg/day) and pembrolizumab (200 mg/3 weeks) was administered despite the lack of evidence on the efficacy of this combination against pembrolizumab-resistant tumors. The treatment was well-tolerated without significant hypertension, hypothyroidism, nausea, or fatigue, but the patient experienced grade 2

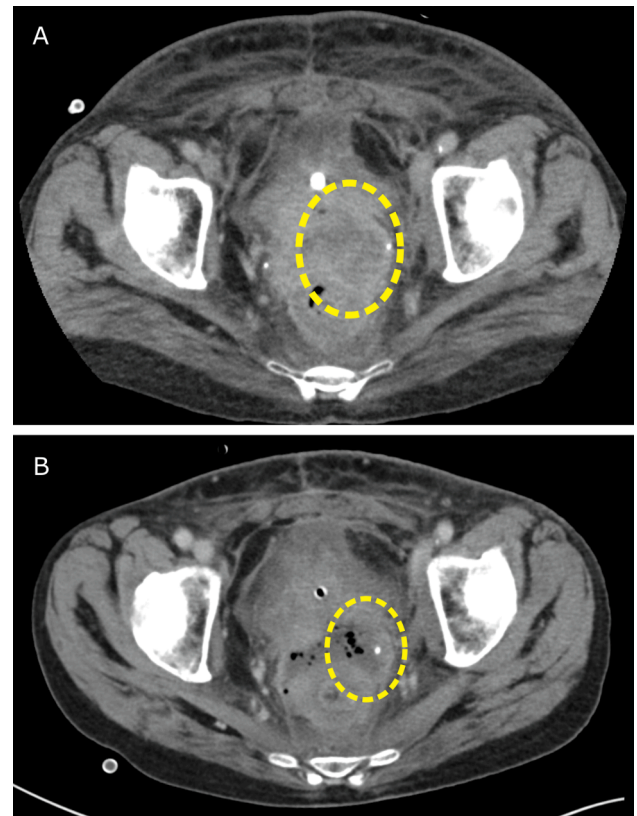


Fig. 2. Vaginal stump recurrence (A) before and (B) after the administration of lenvatinib and pembrolizumab.

diarrhea. A follow-up CT performed 22 days after 1 cycle of pembrolizumab followed by daily oral lenvatinib showed a reduction in tumor mass (Fig. 2B). A vesicovaginal fistula, which developed due to tumor infiltration into the bladder and was revealed by CT 5 months before the administration of lenvatinib, worsened because of tumor regression. A grade 3 urinary tract infection occurred, which was assumed to be a consequence of the worsening of the vesicovaginal fistula; accordingly, a urinary diversion surgery was planned. Lenvatinib should be interrupted before surgery and was consequently administered for 24 days. A CT scan performed before surgery revealed enlargement of the paraaortic lymph nodes, which resulted in 43 days of absence of progression.

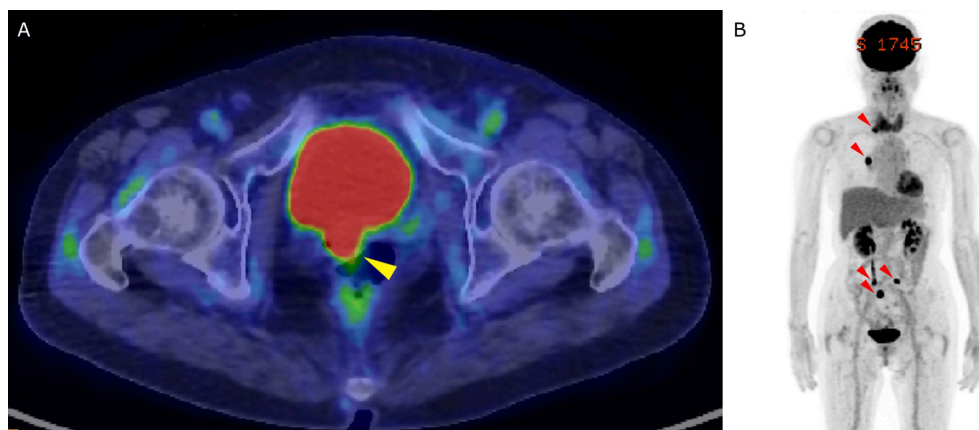


Fig. 1. Positron emission tomography scan confirming the abnormal uptake in the (A) vaginal stump and (B) lymph nodes.

### 3. Discussion

The relatively few options of effective therapies for advanced or relapsed endometrial cancer encourage the reuse of previous therapies. In the current case, the patient initially responded to pembrolizumab but acquired resistance after several cycles of treatment. The response to the combination of lenvatinib and pembrolizumab observed in this case may help in developing new treatment options for tumors that have acquired resistance to ICIs.

ICIs are characterized by their durable responses. For instance, a clinical trial of ipilimumab reported that the survival curve plateaued for more than 10 years in 21 % of the patients (Schadendorf et al., 2015). However, some patients still develop resistance to ICIs despite the presence of an initial response (Sharma et al., 2017). There are several hypotheses regarding the acquired resistance to ICI therapy—a tumor-cell-intrinsic mechanism, such as alterations in tumor antigen expression or presentation; mutations in interferon (IFN) signaling; or a tumor-cell-extrinsic mechanism, such as downregulation of immune reaction within the tumor microenvironment (Sharma et al., 2017).

In addition to its anti-angiogenic effects, several studies in mouse tumor models have demonstrated the immunomodulatory effects of lenvatinib when combined with ICIs. The immunomodulatory effects of lenvatinib may be attributed to the reduction in tumor-associated macrophages or modulation of the IFN signaling pathway (Kato et al., 2019). It could also be associated with the enhancement of the tumor-infiltration capacity of natural killer cells (Zhang, 2019). Moreover, inhibition of the VEGF receptor 2 axis not only inhibits angiogenesis but may also enhance the antitumor efficacy of cancer immunotherapy by modulating the immune cells in the tumor microenvironment (Shigeta et al., 2020; Galon and Bruni, 2019). Further analysis of the mutation profiles and tumor microenvironments of ICI-resistant tumors responsive to lenvatinib and ICI combination therapy may aid in elucidating the mechanisms underlying ICI resistance and immunomodulatory effects of lenvatinib.

MSI, usually arising from mutations in the mismatch repair (MMR) machinery, enhances the effects of PD-1 inhibitors by increasing mutations, thereby leading to increased emergence of neoepitopes and intensifying lymphocytic infiltration and immune responses in cancer (Dudley et al., 2016). Contrastingly, the KEYNOTE-775 trial demonstrated the efficacy of the lenvatinib and pembrolizumab combination therapy in MMR-proficient populations (Makker et al., 2022), while pembrolizumab monotherapy was shown to be less effective in patients with MMR-proficient disease than in those with MSI-High or MMR-deficient disease (Marabelle et al., 2020). Additionally, lenvatinib monotherapy has shown to exert antitumor effects in patients with recurrent endometrial cancer (Vergote et al., 2020). These findings suggest that the antitumor activity of the lenvatinib and pembrolizumab combination may not be due to the MSI status of the tumor. Moreover, the activity of lenvatinib as a single agent remains to be considered.

To the best of our knowledge, this is the first report to demonstrate the efficacy of lenvatinib and pembrolizumab combination therapy in pembrolizumab-pretreated endometrial cancer, encouraging the use of this combination therapy regardless of prior administration of ICIs. However, the underlying mechanism of action remains elusive, and further investigation in this field may provide new insights into cancer immunotherapy and tumor microenvironments.

#### CRedit authorship contribution statement

**Kaito Mimura:** Investigation, Data curation, Writing – original draft, Visualization. **Akihiko Shimomura:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Project administration. **Tomoko Gota:** Writing – review & editing. **Kenju Ando:** Writing – review & editing. **Yukino Kawamura:** Writing – review & editing. **Tomoko Taniyama:** Writing – review & editing. **Hajime Oishi:** Writing – review & editing, Supervision. **Chikako Shimizu:** Writing –

review & editing, Supervision.

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#### Consent for Publication

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. This study is exempted from ethical approval by the National Center for Global Health and Medicine Institutional Review Board.

#### Disclosures

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#### Declaration of Competing 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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