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CASE REPORT

New treatment options for advanced endometrial carcinoma Special Issue

Long sustained response during second-line pembrolizumab plus lenvatinib in a patient with recurrent endometrial carcinoma: a case report

Laura Fabbri[1‡], Linda Galvani[1‡], Claudio Zamagni[2]

[1]Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy; [2] IRCCS Azienda Ospedaliero-Universitaria di Bologna, Italy
‡These authors contributed equally.

Abstract

The combination of the immune-checkpoint inhibitor pembrolizumab plus lenvatinib, an angiogenesis inhibitor targeting VEGFR/FGFR, has been approved as standard second-line treatment for patients with recurrent or metastatic endometrial cancer progressed to first-line platinum-based chemotherapy regardless of mismatch repair status and based on the results of the KEYNOTE-775 trial. This article reports on the case of a middle-aged woman with advanced microsatellite stable, p53-mutant endometrial cancer who achieved a meaningful and sustained partial response, with good tolerability, to second-line treatment with pembrolizumab plus lenvatinib. This favourable outcome was compared with efficacy and toxicity data available in the current literature. Pembrolizumab plus lenvatinib can significantly prolong progression-free survival, especially in patients with a negative prognostic molecular profile, who at most can benefit from combining different therapeutic strategies. The heterogeneous treatment-related adverse events landscape should not discourage therapy prescription because most adverse events are easily manageable following simple precautions.

This article is part of the *New treatment options for advanced endometrial carcinoma* Special Issue: https://www.drugsincontext.com/special_issues/new-treatment-options-for-advanced-endometrial-carcinoma

Keywords: adverse events, antiangiogenic therapy, endometrial cancer, immunotherapy, progression-free survival.

Citation

Fabbri L, Galvani L, Zamagni C. Long sustained response during second-line pembrolizumab plus lenvatinib in a patient with recurrent endometrial carcinoma: a case report. *Drugs Context*. 2025;14:2025-4-3. https://doi.org/10.7573/dic.2025-4-3

Introduction

Endometrial cancer (EC) is emerging as a critical public health concern, with projections indicating that it could become the fourth leading cause of female mortality by 2040.[1–4] Traditionally, the cornerstone of treatment for recurrent or metastatic EC has been polychemotherapy with the carboplatin–paclitaxel combination established as the gold standard based on the pivotal GOG0209 trial.[5]

Recent advancements in the diagnostic and therapeutic landscape of EC have been driven by the integration of The Cancer Genome Atlas molecular classification, which stratifies EC into four prognostic subgroups: POLE/ultra-mutated (excellent prognosis), copy-number-high/TP53-mutant (poor prognosis) microsatellite-instable /hypermutated (MSI) and copy-number-low/TP53-wild-type (intermediate prognosis). The implementation of the PROMISE algorithm has standardized the molecular analysis process facilitating accurate disease characterization.[6] This classification has been incorporated into the FIGO 2023 staging system.

Approximately 30% of ECs are MSI-H or mismatch repair deficient (dMMR), prompting extensive investigation into immune-checkpoint inhibitors as monotherapy and in combination with targeted therapies such as VEGFR

inhibitors. The initial evidence of clinical benefit from anti-PD-1/PD-L1 agents emerged from several phase I and II trials, demonstrating statistically significant outcome improvements primarily in MSI-H/dMMR tumours.[7–11]

To extend efficacy to mismatch repair proficient (pMMR) disease, combinations of immune checkpoint inhibitors and antiangiogenic agents have been explored. The phase II KEYNOTE-146 and phase III KEYNOTE-775 trials led to the approval of pembrolizumab plus lenvatinib (P+L) as standard second-line treatment for both pMMR and dMMR populations after progression on platinum-based chemotherapy.[9,12] However, the phase III ENGOT-En9/LEAP-001 trial, comparing pembrolizumab plus lenvatinib with paclitaxel–carboplatin as first-line therapy in advanced EC, did not demonstrate statistical non-inferiority for overall survival in the pMMR population.[13] Meanwhile, the paradigm for first-line treatment has evolved with the emergence of chemo-immunotherapy combinations, as evidenced by the RUBY, DUO-E, MITO-END-3 and NRG-GY018 trials.[14–17] In this rapidly evolving landscape, the positioning of pembrolizumab plus lenvatinib in the treatment algorithm for advanced EC is likely to undergo further refinement.

We present a clinical case with a favourable outcome aiming to compare the patient's response and tolerability with efficacy and toxicity data reported in clinical studies.

Case report

Consent for publication: The patient signed informed consent for the publication of data and any related images.

In June 2022, a 69-year-old woman presented to the gynaecological department of Sant' Orsola – Malpighi Hospital of Bologna complaining about many episodes of vaginal bleeding, the first observed some months before. Hypertension was her only comorbidity and was being treated with ramipril (1.25 mg/daily). She underwent gynaecological examination and transvaginal ultrasound with evidence of a vascularized neoformation measuring approximately 59×29×58 cm. Subsequent diagnostic hysteroscopy confirmed the presence of a pseudopolypoid neoplasm. The result of the histological report pointed towards the diagnosis of high-grade serous endometrial adenocarcinoma according to 2020 WHO classification.[18] The disease framework was completed by conducting a complete instrumental staging with thoraco-abdominal CT that confirmed the local extension of the disease.

The clinical case was discussed in a multidisciplinary team in the presence of gynaecological surgeons, oncologists and pathologists and the decision of upfront surgical approach was unanimously taken. On July 2022, the patient underwent radical surgery with robot-assisted laparoscopy and mini-laparotomic approach that consisted of total hysterectomy, bilateral oophorosalpingectomy, removal of bilateral pelvic sentinel lymph nodes, Douglas cavity peritonectomy and peritoneal washing. The definitive pathological report confirmed the diagnosis of high-grade (G3) EC of serous histology with clear cell aspects and myometrial invasion of more than 50% (M2). Right obturator sentinel lymph node tested positive for tumoural cells, defining a pathological stage of IIIC1. The disease showed microsatellite stability and next-generation sequencing highlighted the presence of a pathogenetic p53 mutation.

Post-operative CT documented metastasis to para-aortic and inter-aortic-caval lymph nodes. These findings were confirmed with fluorodeoxyglucose-PET-CT, along with the presence of hypercaptation in the right femur. At this time, the patient underwent the first oncological examination by our team and was administered systemic first-line therapy with carboplatin and paclitaxel. From October 2022 to December 2022, she underwent four cycles of chemotherapy with fair compliance and tolerance, burdened by the onset of G2 peripheral sensory neuropathy. The first restaging CT indicated progressive thoraco-abdominal lymph nodal disease and confirmed the right femur lesion. The patient was assessed by the orthopaedic team, who ruled out the need for mobility aids and recommended a radiotherapy evaluation for the skeletal lesion, along with bisphosphonate therapy, provided there were no dental contraindications. After excluding the possibility of enrolment in a clinical trial, we proposed a standard second-line treatment consisting of pembrolizumab at a fixed dose of 200 mg every 3 weeks in combination with lenvatinib 20 mg daily. The patient initiated this regimen in February 2023.

One week later, she presented to our unit with grade 2 hypertension. In response, we increased the dose of ramipril to 2.5 mg daily, without discontinuing lenvatinib. We strongly advised regular home blood pressure monitoring, at least twice weekly, and instructed her to withhold treatment if systolic blood pressure reached 160 mmHg or higher or diastolic pressure reached 100 mmHg or higher. Following the optimization of her antihypertensive therapy, a gradual and satisfactory improvement in blood pressure control was observed.

In March 2023, patient underwent stereotactic radiation therapy on the femur lesion (30 Gy in 4 fractions). Shortly thereafter, she developed grade 1 hypothyroidism, for which levothyroxine was initiated at a dose of 50 µg daily, following endocrinology consultation.

The first radiological assessment since the initiation of second-line treatment was performed in June 2023, demonstrating a partial response. During the continuation of pembrolizumab plus lenvatinib, the patient subsequently developed grade 1 stomatitis, grade 1 diarrhoea, grade 1 decreased appetite, grade 2 fatigue, grade 1 weight loss, and grade 1 hypertransaminasaemia. In June 2023, it was also necessary to increase the levothyroxine dose to 75 µg 3 days per week and 100 µg on the remaining 4 days, which led to normalization of thyroid-stimulating hormone levels at subsequent evaluations. Additionally, a progressive increase in blood pressure was observed, requiring an escalation of ramipril dosage to a total of 5 mg/daily.

In October 2023, the lenvatinib dose was reduced to 14 mg daily due to weight loss, grade 2 fatigue and persistent grade 2 hypertension. The hypertension was managed by adding the calcium antagonist amlodipine (5 mg daily), leading to a rapid normalization of home blood pressure without any pressure surges. No proteinuria was observed.

Subsequent radiological restaging with CT scans, performed every 3–4 months, demonstrated a sustained response. The patient is currently continuing the same therapeutic regimen, with 14 mg of lenvatinib daily and pembrolizumab 200 mg every 3 weeks.

In July 2024, bisphosphonate therapy was initiated after the patient completed necessary dental procedures.

Discussion

The phase Ib/II KEYNOTE-146 study showed promising efficacy and tolerable safety of pembrolizumab (200 mg every 3 weeks) and lenvatinib (20 mg daily) in patients with advanced EC, with an objective response rate (ORR) of 39.8%, a median duration of response (mDOR) of 22.9 months, and median progression-free survival (PFS) and median overall survival of 7.4 and 17.7 months, respectively.[9] In non-MSI-H/pMMR tumours, the ORR was 38.3%, with an mDOR of 23.0 months. The phase III KEYNOTE-775 trial confirmed a significant clinical benefit in the pMMR population, with a median overall survival of 18.0 months and median PFS of 6.7 months for pembrolizumab plus lenvatinib *versus* 12.2 months and 3.8 months for chemotherapy, respectively. ORR was 32.4% with pembrolizumab plus lenvatinib *versus* 15.1% with chemotherapy, and the mDOR was 9.3 months *versus* 5.7 months.[12] Similar results were observed in a Japanese single-centre experience, with an ORR of 40.0%, median treatment duration of 118 days and PFS of 258 days.[19] A Korean multi-centre study showed slightly worse efficacy outcomes but similar discontinuation rates.[20]. These encouraging results led to the FDA approval of pembrolizumab plus lenvatinib as second-line treatment for advanced EC in 2019, followed by EMA and AIFA (Italian Medicines Agency) approvals.[21] Relevant studies are summarized in Table 1.

When prescribing pembrolizumab plus lenvatinib, clinicians must consider the suboptimal tolerability and safety profile, which can affect patient compliance. In practice, for persistent or recurrent grade 2–3 adverse events (AEs) after their second occurrence, lenvatinib dose should be reduced through three levels (14 mg, 10 mg and 8 mg), whereas grade 4 AEs require treatment discontinuation. In the phase Ib/II KEYNOTE-146 study, 99% of patients experienced at least one AE, with fatigue, diarrhoea and hypertension being the most common. Grade 3 or higher AEs occurred in 57% of patients, with hypertension being the most prevalent. AEs led to death in three cases, and therapy discontinuation, temporary interruption and dose reduction occurred in 19%, 76% and 65% of cases, respectively.[9] In the phase III KEYNOTE-775 trial, nearly all patients in both arms (pembrolizumab plus lenvatinib and chemotherapy) experienced AEs. Grade 3 or higher AEs occurred in 90.1% of patients receiving pembrolizumab plus lenvatinib, and grade 5 AEs occurred in 6.4% of cases. The most common AE was hypertension, affecting 65% of patients administered pembrolizumab plus lenvatinib. Dose reductions, interruptions and discontinuations were seen in 67.2%, 71.9% and 39.2% of patients, respectively.[12,13] Real-world data from the University of Texas MD Anderson Cancer Center and Kim et al. highlighted high rates of hospitalization and dose adjustments due to treatment-related toxicities, including fatigue and hypertension.[20,22] Detailed toxicity profiles are presented in Table 2.

Compared to the outcomes reported in the aforementioned trials, the efficacy observed in our patient was significantly improved, with a PFS of 17 months and a DOR of 13 months. These results may be attributed to the optimal integration of systemic treatment, locoregional approaches and effective management of AEs. Indeed, in our opinion, this case report exemplifies a successful balance between therapy tolerability and the preservation of efficacy. The patient experienced grade 1 stomatitis, grade 2 hypertension, grade 1 hypothyroidism, grade 1 diarrhoea, grade 1 decreased appetite, grade 1 weight loss, grade 1 hypertransaminasaemia and grade 2 fatigue. These AEs align closely with the safety profile observed in the primary clinical trials. Notably, the majority of AEs were of low grade and were effectively managed either through conservative treatment or dose reduction. Additionally, the timing of onset of these symptoms is consistent with the findings of Makker et al., with hypertension being the first to manifest.[23] Hypothyroidism

Table 1. Efficacy outcomes of the combination of pembrolizumab plus lenvatinib in literature.[9,12,19,20,22,31]

	KEYNOTE-775						KEYNOTE-146			Tochigi et al.[19]	Kim et al.[20]	How et al.[22]	Taylor et al.[31]
Patients	**All**		**pMMR**		**dMMR**		**All**	**pMMR**	**dMMR**	**All**	**All**	**All**	**All**
Outcome	P+L	CHT	P+L	CHT	P+L	CHT	P+L			P+L	P+L	P+L	P+L
ORR(%)	**33.8**	**14.7**	**32.4**	**15.1**	**41.5**	**12.3**	**39.8**	**38.3**	**63.6**	**40**	**23.8**	**36.1**	**52**
CR(%)	7.5	2.6	5.8	2.6	16.9	3.1	8.3	8.5	9.1	/	0	3.3	9
PR (%)	26.3	12	26.6	12.5	24.6	9.2	31.5	29.8	54.5	/	23.8	32.8	44
SD (%)	45	40.1	46.5	39.6	36.9	43.1	42.6	43.6	27.3	/	52.4	32.8	44
mDOR (months)	12.9	5.7	9.3	5.7	NR	4.1	22.9	23.0	21.2	3.9 m	4.9	2.1	NR
mPFS (months)	**7.3**	**3.8**	**6.7**	**3.8**	**10.7**	**3.7**	**7.4**	**7.4**	**26.4**	**8.6 m**	**5.3**	**4.6**	**9.7**
mOS (months)	**18.7**	**11.9**	**18**	**12.2**	**31.9**	**8.6**	**17.7**	**17.2**	**NR**	**/**	**NR**	**8.6**	**/**

The most relevant results summarized in the table are shown in bold.

CHT, chemotherapy; CR, complete response; dMMR, mismatch repair deficient; mDOR, median duration of response; mPFS, median progression-free survival; mOS, median overall survival; NR, not reached; ORR, overall response rate; P+L, pembrolizumab plus lenvatinib; pMMR, mismatch repair proficient; PR, partial response; SD, stable disease.

Table 2. Toxicity profile of pembrolizumab + lenvatinib combination.[9,12,19,20,22,31]

	Keynote-775											Keynote-146							
	AEs any G (%)	AEs G>3 (%)	Discontinuation rate (%)				Dose red. (%)	Interruption rate (%)				AEs any G (%)	AEs G>3 (%)	Discontinuation rate (%)			Dose red. (%)	Treatment interruption (%)		
	P+L	P+L	P/L	P+L	L	P	L	P/L	P+L	L	P	P+L	P+L	P+L	L	P	L	P+L	L	P
Any AE	99.8	90.1	39.2				67.2	71.9				96.3	71.3	21.3			67.6	74.1		
Hypertension	65	39.2	2.2	0.2	2.2	0.2	17.2	13.3	1.7	12.3	3.2	60.2	33.3	8.3	17.6	15.7		31.5	71.3	43.5
Hypothyroidism	58.9	1.5						/	/	/	/	46.3	0.9							
Diarrhoea	55.7	8.1	2.2	0.5	1.5	1.2	11.8	14	4.7	10.8	8.6	53.7	7.4							
Nausea	51.7	3.4						5.2	0.7	4.4	1.5	43.5	2.8							
Decreased appetite	46.6	7.6	2.0	0.7	2.0	0.7	6.2	6.2	0.5	4.7	2.0	50.0	0.9							
Vomiting	37.7	3.0	1.0	0	0.7	0.2		5.7	1.0	5.7	1.2	30.6	0							
Weight decrease	35.5	10.8	2.0	0.2	2.0	0.2	5.4	/	/	/	/	29.6	1.9							
Fatigue	34.0	5.4	2.0	0.2	2.0	0.2	6.2	5.7	1.0	4.4	2.5	53.7	8.3							
Arthralgia	32.3	1.7						/	/	/	/	31.5	1.9							
Proteinuria	30.5	5.2	1.2	0.2	1.2	0.2	8.4	8.1	0.5	6.7	2.0	26.9	3.7							

(*Continued*)

Table 2. (Continued)

	Tochigi et al.[19]					Kim et al.[20]					How et al.[22]					Taylor				
	AEs any G	**AEs G>3**	**Disc. Rate**	**Dose Red**	**Inter. Rate**	**AEs any G**	**AEs G>3**	**Disc. Rate**	**Dose Red.**	**Inter. Rate**	**AEs any G**	**AEs G>3**	**Disc. Rate**	**Dose Red.**	**Inter. Rate**	**AEs any G**	**AEs G>3**	**Disc. Rate**	**Dose Red**	**Inter. Rate**
	P+L	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**	**P+L**
Any AE	100					70.8					/	/				100	87			
Hypertension	80	40				16.7	/				5.7	/				47	20			
Hypo-thiroidism	93.3	0				14.6	/				/	/				42	1			
Diarrhoea	26.6	0				12.5	/				18.6	/				52	9			
Nausea	/	/				12.5	/				18.6	/				32	0			
Decreased appetite	40	26.6	40	86	100	/	/	16.7	56.2	16.7	10	/	38.6	42.9	82.9	39	2	13	701	87
Vomiting						12.5					18.6	/				19	0			
Weight decrease	/	/				/	/				/	/				21	2			
Fatigue	53.2	26.6				18.8					20	/				58	12			
Arthralgia	/	/				4.2	/				2.9	/				28	2			
Proteinuria	33.3	26.6				/	/				/	/				36	8			

AEs, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; dose red., dose reduction; G, grade; HFS, hand-foot syndrome; L, lenvatinib; P, pembrolizumab; P+L, pembrolizumab plus lenvatinib; P/L, pembrolizumab or lenvatinib.

was effectively managed through a gradual increase in substitution therapy and ongoing monitoring. Similarly, hypertension was controlled by optimizing cardiological therapy. The weight loss, coupled with worsening fatigue, prompted the first dose reduction to 14 mg. Recurrent and poorly controlled diarrhoea necessitated a further dose reduction to 10 mg, which the patient is currently tolerating without experiencing additional AEs.

Conclusions

Our patient represents a case of optimal response and satisfactory tolerability to second-line combination treatment with pembrolizumab plus lenvatinib, despite an unfavourable molecular disease profile. *p53* mutations are known to be a negative prognostic factor, and tumours with *p53* mutations typically have the worst outcomes amongst the four molecular subgroups.[6,24–28] As such, these patients benefit most from therapy intensification, which may involve combining different treatment modalities such as radiotherapy and chemotherapy for locally advanced disease, and chemotherapy plus immunotherapy or other targeted agents like antiangiogenic therapies or PARP inhibitors in the metastatic setting.[29,30] Several ongoing trials are exploring these strategies with promising results emerging progressively.

Contributions: LF and LG contributed to the conceptualization, resources, data curation, and drafting, as well as reviewing and editing the manuscript. CZ reviewed the final manuscript. All authors have read and approved the submitted version of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Disclosure and potential conflicts of interest: CZ received grants, consulting fees, honoraria and support for attending meetings from Roche, AstraZeneca, Daiichi-Sankyo, Gilead, MSD, GSK, Eisai, Pfizer, Lilly, Novartis, ExactSciences and Menarini Stemline. LG and LF declare no conflicts of interests. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors is available for download at: https://www.drugsincontext.com/wp-content/uploads/2025/06/dic.2025-4-3-COI.pdf

Acknowledgements: None.

Funding declaration: There was no funding associated with the preparation of this article.

Article URL: https://www.drugsincontext.com/long-sustained-response-during-second-line-pembrolizumab-plus-lenvatinib-in-a-patient-with-recurrent-endometrial-carcinoma-a-case-report

Correspondence: Laura Fabbri, Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna, 40126 Bologna, Italy. Email: laura.fabbri21@studio.unibo.it

Provenance: Submitted; externally peer reviewed.

Submitted: 11 April 2025; **Accepted:** 27 May 2025; **Published:** 24 June 2025.

Drugs in Context is published by BioExcel Publishing Ltd. Registered office: 6 Green Lane Business Park, 238 Green Lane, New Eltham, London, SE9 3TL, UK.

BioExcel Publishing Limited is registered in England Number 10038393. VAT GB 252 7720 07.

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