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Clinical Benefit of PIK3CA Inhibition in Therapy-Refractory Endometrial Cancer: A Single-Case Report

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1 Background and Objectives

PIK3CA mutations occur frequently across various solid tumors, including breast, colorectal, and endometrial cancers. These alterations are associated with mechanisms of therapeutic resistance, often leading to the failure of established treatment options and thus posing a significant challenge in daily clinical practice. Here, we present a clinical case of metastatic endometrial cancer harboring a PIK3CA mutation after multiple prior treatment lines, which demonstrated a remarkable and durable response to the combination of Fulvestrant and the PIK3CA inhibitor Capivasertib.

2 Methods (Case Presentation)

- 64-years old woman, endometrial cancer (pT1 pN0 M0 G2, ER 100%, PR 0%, p53 negativ, pMMR, FIGO IB), first diagnosis 07/2021, no comorbidities
- *Prior therapies:*
  - 07/2021 laparoscopic hysterectomy with bilateral salpingo-oophorectomy
  - 12/2022 systemic recurrence (inguinal lymph nodes, bone metastasis left pelvis)
  - 01 – 05/2023 1st line Carboplatin/Paclitaxel (PR)
  - 04/2023 palliative radiotherapy to the left pelvis (28 Gy)
  - 09/2023 – 07/2024 2nd line Pembrolizumab/Lenvatinib (PR)
  - 08/2024 – 12/2024 3rd line Letrozol/Palbociclib (SD)
  - 01/2025 – 03/2025 Rechallenge Carboplatin/Paclitaxel (SD)
  - Since 03/2025 4th line **Fulvestrant (500 mg, q4w)** in combination with **Capivasertib (2 × 400 mg, intermittent dosing schedule)**
- *Molecular diagnostics (liquid biopsy, after 3rdline treatment, 12/2024):*
  - **ESR1 p.(D538G), c.1612A>G VAF 21.41%**
  - KRAS p.(G12C), c.32G>T VAF 20.71%
  - **PIK3CA p.(N345K), c.1035T>A VAF 44.03%**
- *Orthopeadic interventions:*
  - 08/2025 Girdlestone resection arthroplasty indicated for multiple pathological fractures

3 Results

- **Tumor markers:** Rapid CA 125 decline indicated early response to Fulvestrant/Capivasertib.
- **Imaging:** CT follow-up according to RECIST criteria confirmed treatment effect
- **Histology (Girdlestone resection):** Fat necrosis with macrophage reaction, focal hemorrhagic residues, scant trilinear maturing bone marrow. No evidence of malignancy.
- **Clinical course:** Rapid clinical improvement with reduced analgesic use supported early treatment response.
- **Side effects:** Hyperglycemia (manageable)

Figure 1: Serum tumor marker (CA125) decline after treatment initiation with Fulvestrant and Capivasertib

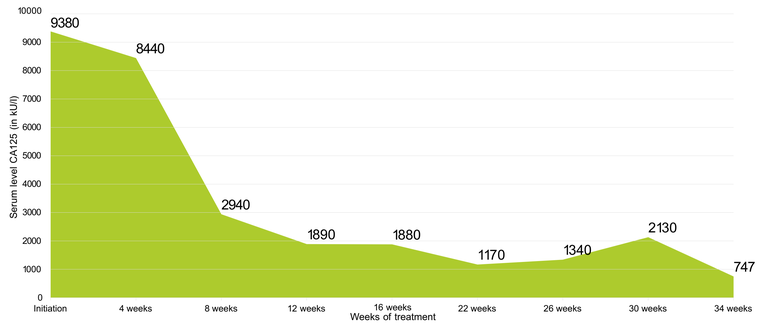
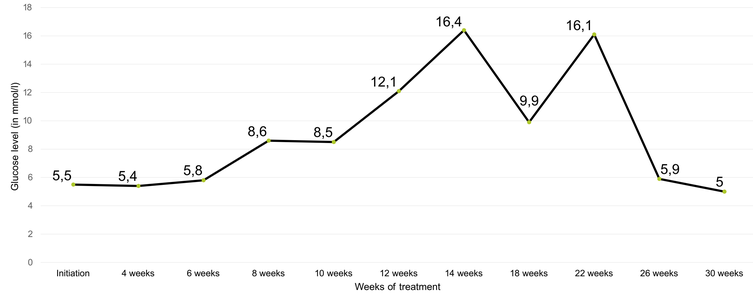


Figure 2: Treatment-associated elevation of blood glucose levels (manageable)



5 Conclusion

- Fulvestrant + PIK3CA inhibitor capivasertib shows **encouraging antitumor activity** in therapy-refractory PIK3CA-mutated endometrial cancer.
- Treatment associated side effect was **hyperglycemia**, but no new safety signals were observed.
- This single-case report supports **efficacy in PIK3CA-mutated endometrial cancer**, but findings are not generalisable.
- **Importance of personalised medicine:** Early molecular profiling (including *PIK3CA*) should be integrated into the treatment pathway to **identify further therapeutic options.**

6 References

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2. *Makker V, Aghajanian C, Cohn AL, et al. Lenvatinib + pembrolizumab in advanced endometrial carcinoma (Study 111/KEYNOTE-146). J Clin Oncol. 2023;41(5):974–9.*
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