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A Case of Nivolumab in Recurrence of Endometrial Cancer

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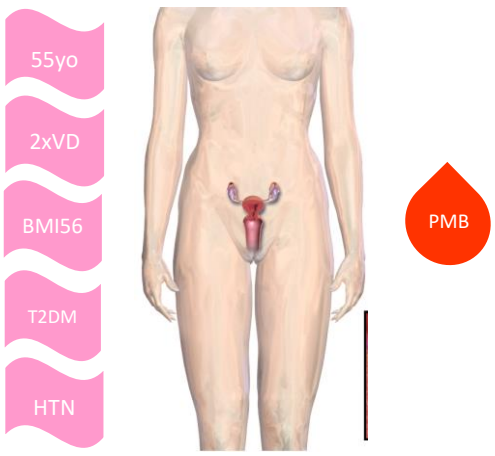
Introduction:

In Ireland, approximately 300 women are diagnosed with endometrial cancer each year. In Australia, 3,343 women were diagnosed with endometrial cancer in 2022. This is consistent with a doubling in the number of endometrial cancer diagnoses in Australia over the last 20 years. Globally, another rise in cases of over 50% is expected by 2040.

In addition to a rise in incidence there has been an increase in the number of women dying each year from this disease. Mortality data published by the Australian Bureau of Statistics reported that between the years 2001 and 2018 endometrial cancer was the only gynecological cancer that exhibited increasing mortality rates. 5YS is approximately 81% in early-stage disease, however remains poor at 15% in advanced disease. Novel therapies, beyond chemotherapeutics, aim to improve prognosis.

The Case:



Initial Investigations:

Hysteroscopy with dilatation and curettage was performed. Endometrial curetting's showed endometrial adenocarcinoma grade 1. There was no radiological evidence of metastatic disease.

Initial Management:

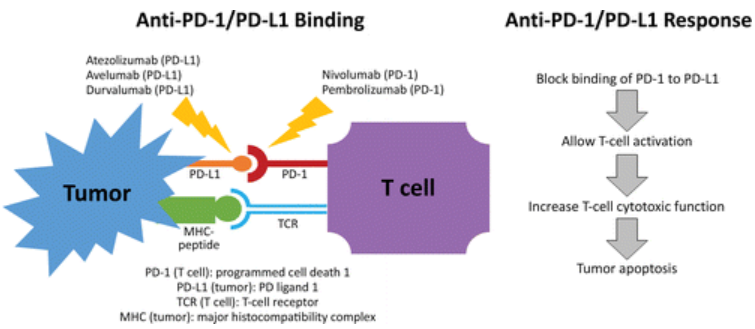
Initial management included Mirena insertion and sleeve gastrectomy, with a weight loss of 38kg (21% of TBW). Total laparoscopic hysterectomy and bilateral salpingo-oophorectomy were performed six months post gastrectomy.

Final Histology and Immunohistochemistry:

Histology showed EAC grade 2. Immunohistochemistry showed MMR-deficient, MSI-Hi, PD-L1 positive tumour. Overall staging was pT1bNX FIGO Stage1B.

Adjuvant Therapy:

The patient received adjuvant vaginal vault brachytherapy.

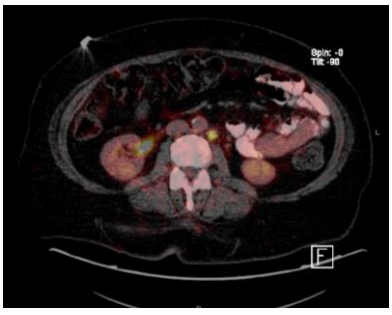


PD-L1 is a checkpoint protein which in normal cells prevents over response from the immune system. This is exploited by tumors. PD-L1 produced by tumor cells binds to PD-1 on T cells, inhibiting cytotoxic T cells thereby evading apoptosis. Nivolumab is a PD-L1 inhibitor that prevents the binding of PD-L1 and PD-1, allowing the immune system to mount an immune attack.

1 Year Later:

The patient re-presented with vaginal discharge and left groin pain one year post treatment completion. PET revealed FDG avid left retroperitoneal node consistent with metastasis.

The patient was an excellent candidate for immunotherapy as previous histology showed PD-L1 expression. The patient has received 9 cycles of nivolumab to date achieving interval reduction in volume of metastatic nodes consistent with treatment response.



	Patient Population	Agent	Results
Single-Agent Immunotherapy			
Le et al (2018)[40]	Mismatch repair deficient (MMRd) tumors (2 EC patients included)	Pembrolizumab	ORR, 71%
Ott et al (2017), KEYNOTE 028[41]	24 PD-L1+ patients	Pembrolizumab	ORR, 13%
KEYNOTE 158, 028, 016[48]	Multicohort microsatellite instability high (MSI-H; 17 EC patients included)	Pembrolizumab	ORR, 37.7%
Fader et al (2016)[42]	MMRd tumors, recurrent EC	Pembrolizumab	ORR, 56%; DCR, 88.9%
Santin et al (2016)[47]	2 patients (POLE and MSI-H)	Nivolumab	Prolonged response (> 7 months) in 2 patients
Hasegawa et al (2018)[45]	23 metastatic EC patients	Nivolumab	ORR, 23%; PFS, 3.6 months
Fleming et al (2017)[46]	15 metastatic EC patients	Atezolizumab	ORR, 13% (1 MSI-H); PFS, 1.7 months
Oaknin et al (2019), GARNET[49]	MSI-H recurrent/advanced EC	TSR-042	ORR, 52%
Antiangiogenesis + Immunotherapy			
Makker et al (2018), KEYNOTE 775[50]	Metastatic EC	Lenvatinib + pembrolizumab	ORR, 48%; DCR, 96%
NCT03526432	Recurrent EC	Bevacizumab + atezolizumab	Ongoing
NCT03367741	Recurrent EC	Nivolumab ± cabozantinib	Ongoing
Chemo + Immunotherapy			
NCT02549209	Advanced recurrent EC	Chemotherapy + pembrolizumab	Ongoing
NCT03276013	Recurrent EC	Doxorubicin + pembrolizumab	Ongoing
NCT03603184 (AtEND)	Advanced recurrent EC	Chemotherapy ± atezolizumab	Ongoing
NCT03503786 (MITO-END3)	Advanced recurrent EC	Chemotherapy ± avelumab	Ongoing

Discussion:

This case supports use of PDL-1 inhibitors in advanced endometrial cancer with PDL-1 expression. Endometrial cancer has some of the highest PD-1 and PD-L1 expression levels among gynaecological cancer; 40%–80% in endometrioid, 10%–68% in serous, and 23%–69% in clear cell subtypes.

Checkpoint inhibitors such as nivolumab targeting pro-oncogenic immunosuppressive pathways may be highly effective in these tumours.

Key to future success of these treatments is understanding tumour biology, molecular and immunological characteristics to identify suitable targets.

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