The molecular landscape of pembrolizumab and lenvatinib treatment in endometrial cancer

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Background:
- Pembrolizumab and lenvatinib in combination (pembro-lenv) has resulted in improved outcomes compared to standard chemotherapy for second-line treatment of endometrial cancer (EC)
- Lenvatinib currently is only indicated for microsatellite unstable (MSI) endometrial cancers as it is associated with significant toxicities and many microsatellite instability high ( MSI-H) tumors respond to pembrolizumab alone.

Methods:
- **EC patients who received pembro or lenvatinib alone were analyzed using NGS** (NextSeq, 592 genes or NovaSeq, WES) and RNA (NovaSeq, WTS) (Carts Life Sciences, Phoenix, AZ)
- **Pembrol/Lenv**
  - POLE mt, n=64
  - POLE wt (POLE-wt), n=126
  - TP53 mt (POLE-wt/MMS), n=120
  - TP53 wt (POLE-wt/MMS), n=205
  - Pembrol-only
    - POLE mt, n=132
    - POLE wt (POLE-wt), n=692
    - TP53 wt (POLE-wt/MMS), n=213
    - TP53 wt (POLE-wt/MMS), n=683
- **Overall survival (OS)** was obtained from insurance claims data and calculated from first treatment to last contact
- Hazard ratio (HR) was calculated by Cox proportional hazards, with p-value calculated by log-rank test
- Patients were separated into those with >median post-Tx survival and those with <median post-Tx survival and genetic alterations were assessed
- Statistical significance calculated by Mann-Whitney U test.

Results:

- Among MSS/POLE-wt patients, **TP53 wild type patients have longer OS after pembrolizumab with lenvatinib compared to pembrolizumab alone. In the TP53 mutated cohort, there was no difference.**

![Figure 1. Comparing post-pembrolizumab and post-pembrolizumab/lenvatinib real-world overall survival (rwOS) by molecular subtype. rwOS was calculated from date of first treatment of pembrolizumab or lenvatinib to last contact categorized by treatment of either pembrolizumab or pembrolizumab and molecular subtypes (POLE-mt, POLE-wt (POLE-wt), TP53-mt (POLE-wt/MMS) as a surrogate for copy number high and TP53-wt (POLE-wt/MMS) as a surrogate for copy number low.)](image1)

- **Figure 2. Association of ARID1A and post-treatment survival in patients treated with pembrolizumab alone vs pembrolizumab and lenvatinib.** A. nWOS showing the association of ARID1A-mt vs wt tumors treated with pembrolizumab (P) vs pembrolizumab + lenvatinib (PL) in TP53-mt patients. In TP53-mt patients, ARID1A-mt patients had improved post-pembrolizumab survival compared to pembrolizumab alone (HR: 0.60, 95% CI: 0.26-0.95, p=0.032) but there was no difference in ARID1A-wt (p=0.60). B. Table showing mutational prevalence of ARID1A between patients with > median survival by treatment regimen. C. Kaplan-Meier curve looking specifically at ARID1A-mt cohort by TP53 status. The association with ARID1A mutation and improved survival following PL compared to P was not seen in the TP53-wt as it was in the TP53-mt group.

Conclusions:
- Among MSS/POLE-wt patients, TP53-wt patients have longer OS after pembrolizumab with lenvatinib compared to pembrolizumab alone, but in the TP53 mt cohort, there was no difference.
- Among TP53-mt patients, ARID1A-mt is associated with improved pembrolizumab survival but not lenvatinib alone.
- Our findings suggest a need to further investigate use of lenvatinib in TP53-mt (POLE-wt/MMS) patients and further explore genomic alterations that may promote treatment response to optimize use of this agent in endometrial cancer.