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The molecular landscape of pembrolizumab and lenvatinib treatment in endometrial cancer

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Background:

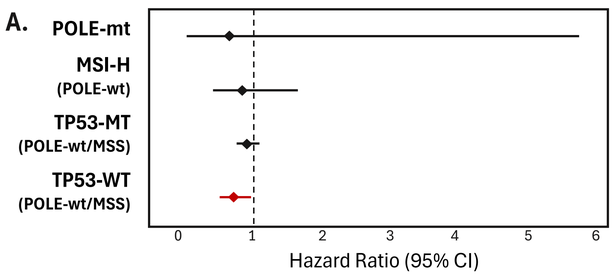
- Pembrolizumab and lenvatinib in combination (pembro-lenv) has resulted in improved outcomes compared to standard chemotherapy for second-line treatment of endometrial cancer (EC)
- Lenvatinib currently is only indicated for microsatellite stable (MSS) tumors as it is associated with significant toxicities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

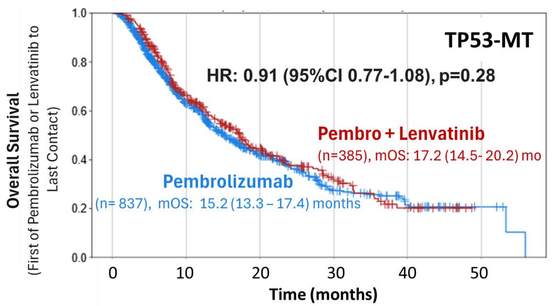
Objective: To identify molecular characteristics of patients who may benefit most from the addition of lenvatinib to pembrolizumab beyond MSI/MMR status

Methods:

- EC patients who received pembro or pembro-lenv were analyzed using NGS (NextSeq, 592 genes or NovaSeq, WES) and RNA (NovaSeq, WTS) (Caris Life Sciences, Phoenix, AZ)
  - **Pembro/Lenv**
    - *POLE-mt, n=6*
    - *MSI-H (POLE-wt), n=36*
    - *TP53-mt (POLE-wt/MSS), n=195*
    - *TP53-wt (POLE-wt/MSS), n=385*
  - **Pembro only**
    - *POLE-mt, n=31*
    - *MSI-H (POLE-wt), n=692*
    - *TP53-mt (POLE-wt/MSS), n=359*
    - *TP53-wt (POLE-wt/MSS), n=838*
- 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:





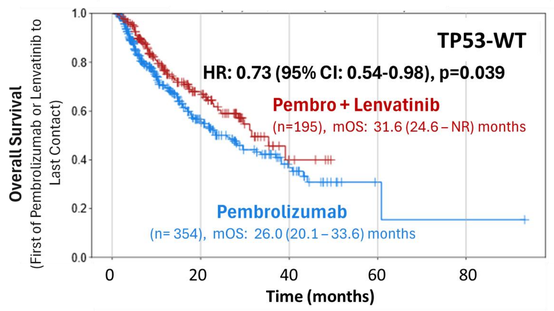


Figure 1. Comparing post-pembrolizumab and post-pembrolizumab/lenvatinib real-world overall survival (rwOS) by molecular subtype. rwOS was calculated from date of first treatment of pembrolizumab or lenvatinib to last contact categorized by treatment of either pembrolizumab or pembro/lenv and molecular subtypes (POLE-mt, MSI-H [POLE-wt], TP53-mt [POLE-wt/MSS] as a surrogate for copy number-high and TP53-wt [POLE-wt/MSS] as a surrogate for copy number-low). **A.** Forest plot of rwOS shown by molecular subtype comparing pembrolizumab only vs pembro/lenv with only the TP53-wt cohort showing a statistically significant difference in treatment arms. When comparing pembro-lenv vs pembro in the POLE-mt and MSI-H cohorts, there was no significant difference in OS (p = 0.70, p = 0.60, p=0.28, respectively). **B.** There was also no significant difference in the TP53-mt cohort (17.2 vs 15.2 mo; HR 0.91 (95%CI 0.77-1.08), p=0.28). **C.** In the TP53-wt cohort, the addition of lenvatinib was associated with longer median OS (31.6 vs 26 mo; HR: 0.73 (0.54-0.99), p = 0.039).

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*.

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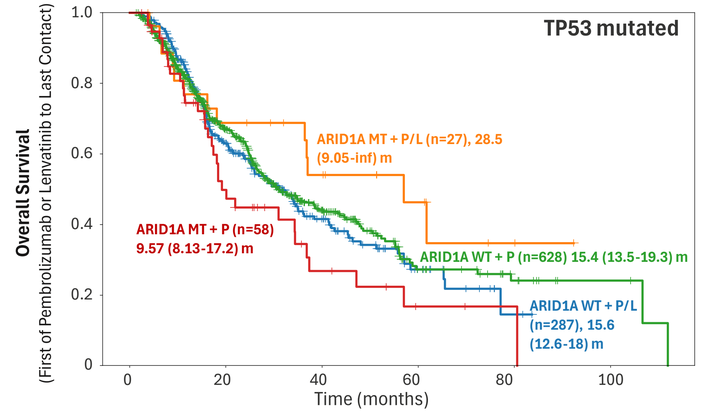
Figure 2. Association of ARID1A and post-treatment survival in patients treated with pembrolizumab alone vs pembrolizumab and lenvatinib. A. rwOS showing the association of ARID1A-mt vs wt tumors treated with pembrolizumab (P) vs pembrolizumab + lenvatinib (P/L) in TP53-mt tumors. In TP53-mt patients, ARID1A-mt patients had improved post-pembro/lenv survival compared to pembro alone (HR: 0.50, 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 > and < 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 P/L compared to P was not seen in the TP53-wt cohort as it was in the Tp53-mt group.

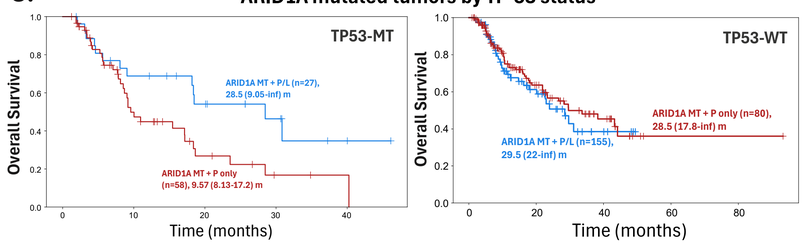
A.



B.

Fig 2A.	Pembrolizumab + Lenvatinib				Pembrolizumab only			
	>median survival	<median survival	Δ%	p-value	>median survival	<median survival	Δ%	p-value
ARID1A-mt frequency	17.28%	5.97%	11.31%	0.008	2.16%	2.48%	-0.32%	0.4636

C.



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 pembro-lenv survival but not pembro alone
- Our findings suggest a need to further investigate use of lenvatinib in TP53-mt (POLE-wt/MSS) patients' and further explore genomic alterations that may promote treatment response to optimize use of this agent in endometrial cancer