Abstract #5604: The impact of cause of mismatch repair deficiency and other molecular markers on clinical outcomes with the use of durvalumab in advanced endometrial cancer in phase 2 PHAEDRA trial (ANZGOG1601)

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Background:

- The PHAEDRA trial is a single arm, phase 2 trial of durvalumab (1500mg IV Q4W) in women with advanced endometrial cancer (AEC)[1].
- The objective tumor response (OTR) rate (confirmed CR or PR according to iRECIST) was 47% in mismatch repair deficient (dMMR) compared with 3% in MMR proficient (pMMR) AEC[1].
- This substudy investigated the cause of dMMR and other genomic tumor features and their correlation with treatment outcomes.

Methods:

- DNA from formalin-fixed paraffin-embedded tumor tissue for 41/71 (25 dMMR, 16 pMMR) trial participants was sequenced using a custom capture-based 298-gene targeted panel (2.005Mb) and tested for *MLH1* gene promoter methylation.
- Derived genomic features included tumor mutational burden (TMB), COSMIC v.3.2 mutational signatures and insertion/deletion (Indel) somatic mutations.

Results:

Table 1: Objective tumor response (OTR= confirmed CR or PR) according to molecular subtype

Molecular subtype	No response, N = 53	OTR, N = 18	OTR rate (95% CI)
dMMR subtype, n (%)			
Germline PV	0 (0)	4 (100)	100% (40-100%)
Somatic MMR	1 (25)	3 (75)	75% (22-99%)
MLH1 methylation	15 (60)	10 (40)	40% (22-61%)
pMMR	33 (97)	1 (2.9)	2.9% (0.15-17%)
No treatment	2 (100)	0 (0)	0 (0.0-80%)
Unknown	2 (100)	0 (0)	0 (0.0-80%)

Figure 1: Somatic mutated genes in non-responders and responders. Median TMB (assessed in 41/71) was higher in those with a confirmed radiological response (37, IQR:26-50) vs non-responders (16, IQR:9-25; p<0.001)

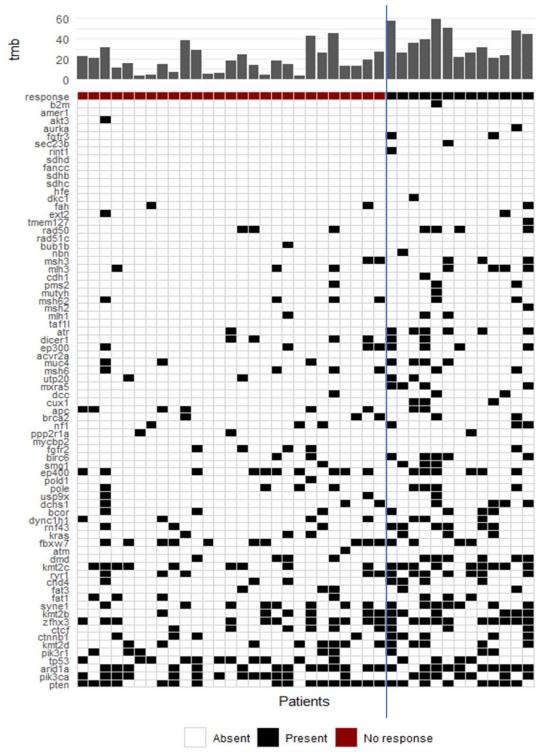
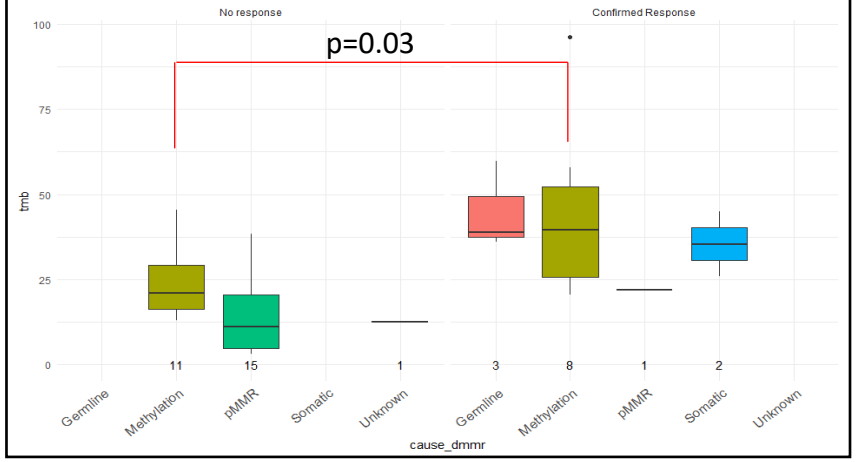


Figure 2: MMR subtypes by TMB stratified by response



Conclusions:

- dMMR-*MLH1* methylated AEC demonstrated greater heterogeneity in OTR to single agent durvalumab than the dMMR-Lynch and dMMR-somatic MMR mutation subtypes.
- Higher TMB was seen in responders, and specifically within dMMR-*MLH1* methylated responders, compared to non-responders.

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1. Antill *et al*. Clinical Activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer: a nonrandomized phase 2 clinical trial. *J Immunother Cancer*. 2021 Vol.9 Issue 6. PMID: 34103352