

## 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)<sup>1</sup>.
- 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<sup>1</sup>.
- This substudy investigated the cause of dMMR and other genomic tumor features and their correlation with treatment outcomes.

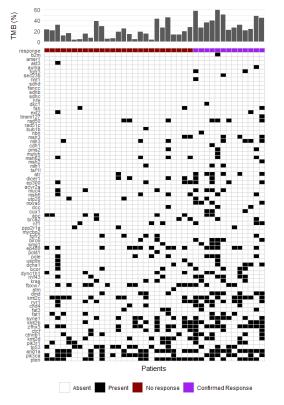
## Methods:

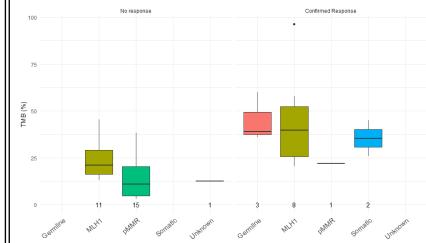
- DNA from formalin-fixed paraffin-embedded tumor tissue for 41/71 (25 dMMR, 16 pMMR) trial participants was sequenced using a custom capture-based 298gene targeted panel (2.005Mb) and tested for MLH1 gene promoter methylation.
- Derived genomic features included tumor mutational burden (TMB), COSMIC
   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,	OTR,	OTR rate (95% CI)
	N = 53	N = 18	
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%)
Notreatment	2 (100)	0 (0)	0 (0.0-80%)
Unknown	2 (100)	0 (0)	0 (0.0-80%)

Figure 1: Somatic mutated genes in nonresponders 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)





## **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.

Author contact: A/Prof. Yoland Antill (Yoland.Antill@monash.edu) Funding Acknowledgements: Astra Zeneca Investigator Grant, ANZGOG Fund for New Research, DDB- NHMRC GNT1194896 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