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 tested for:

- 1) somatic mutations (incl. MMR gene mutations), tumor mutational burden (TMB) and neoantigen load derived from targeted 298-gene sequencing data.
- 2) *MLH1* promoter methylation
- 3) Genome-wide DNA methylation changes using the Illumina HMEPIC array

Results:

Table 1/Figure 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%)

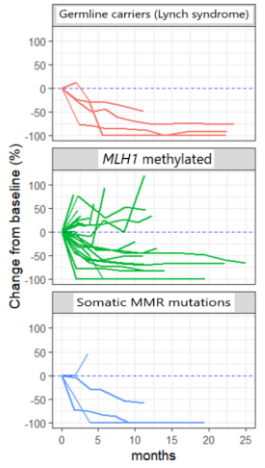


Figure 2: Somatic mutation landscape of AECs by response

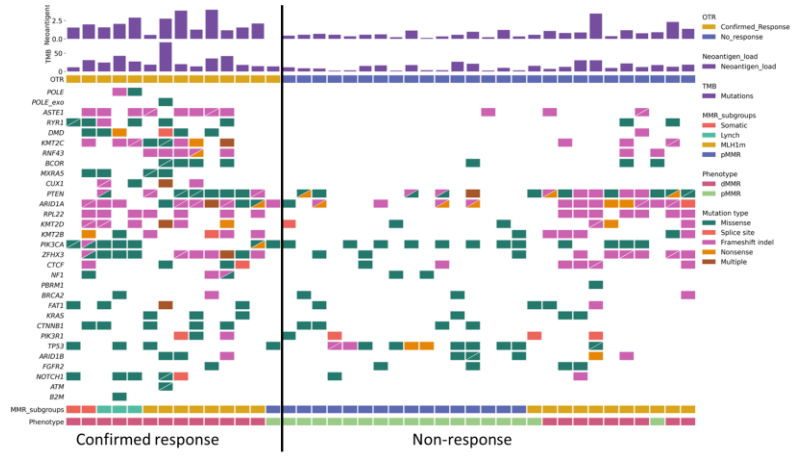


Figure 3: TMB and neoantigen load for *MLH1* methylated AECs by durvalumab response

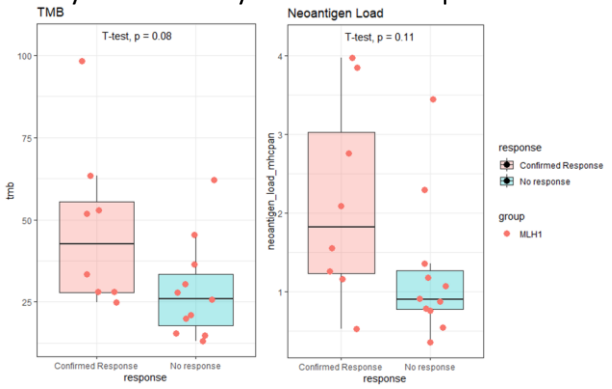
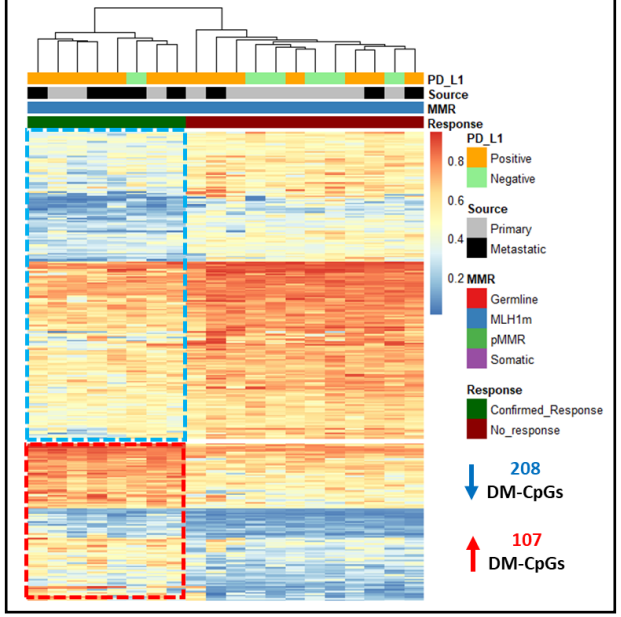


Figure 4: Significantly differentially methylated CpG sites in *MLH1* methylated AECs by response



Conclusions:

Differences in TMB and neoantigen load as well as differentially methylated CpGs may underlie the heterogeneity in durvalumab response in dMMR-*MLH1* methylated AECs.

➢ 1. Antill *et al. J Immunother Cancer*. 2021 Vol.9 Issue 6. PMID: 34103352