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THE POWER OF SHARED PURPOSE: Transforming Gynecologic Cancer Care

Frequency and outcomes of co-mutations according to ProMisE classifiers in Endometrial Cancer

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Background

- ProMisE criteria classifies four molecular subtypes of endometrial tumors (ET): DNA polymerase epsilon (*POLE*) mutated, mismatch repair deficient (MMRd), p53 wild type and mutant. There is limited understanding about prognosis when tumors have alterations in multiple classifiers.
- We report the frequency and outcomes of multi-classifier tumors in addition to high-grade biomarkers (loss of heterozygosity [LOH] and cyclin E1 amplification [*CCNE1*-amp]).

Methods

- 5,158 ET underwent whole exome sequencing.
- MMRd was defined as complete loss of ≥1 IHC stains (MLH1, MSH2/6, or PMS2).
- MSI-High (determined from 7000 targeted microsatellite loci) was used as a surrogate for MMRd.
- TP53 mutant (MT) was defined as any pathogenic or likely pathogenic (PLP) SNV, or indel. *POLE*-MT was defined as PLP mutations in the exonuclease domain.
- Autosomal chromosomes were split into 552 segments and the LOH within each segment was calculated (LOH High [H] ≥ 16%).
- *CCNE1*-amp was defined as ≥ 6 gene copies.
- Real-world overall survival was obtained from insurance claims and calculated from tissue collection to last contact (OS) for molecularly defined patients using the Cox proportional hazards model. P values were calculated using the log-rank test.

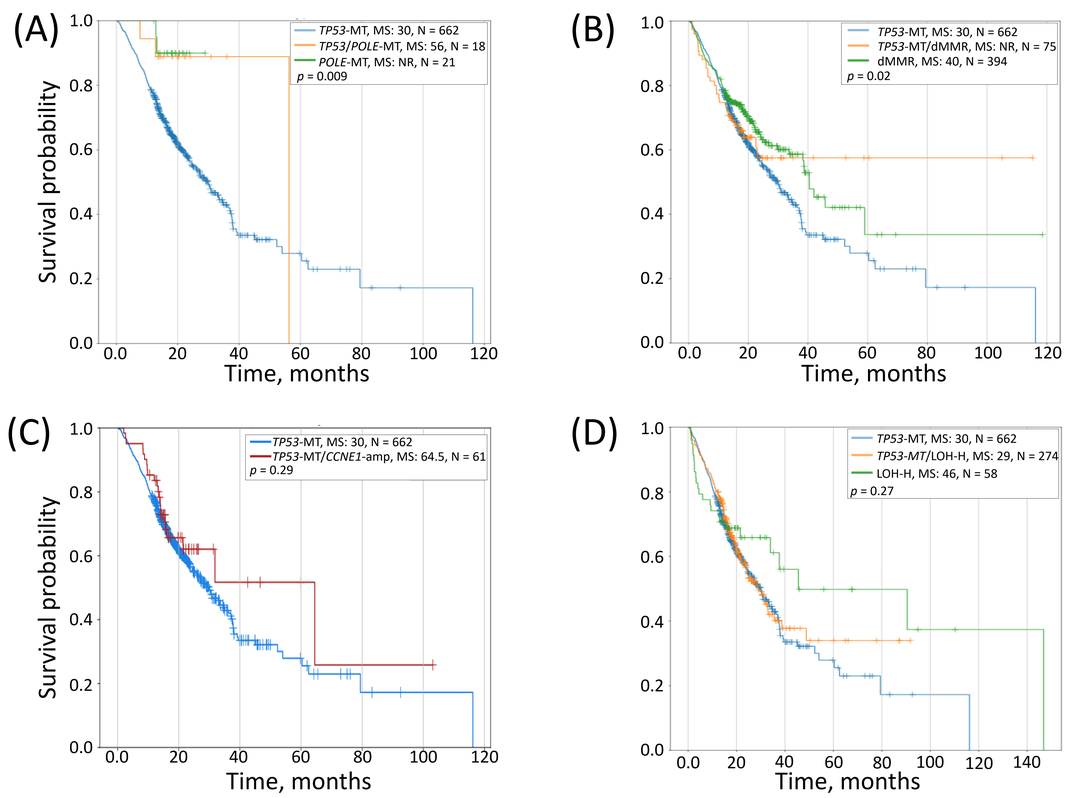
Results

Molecular Classification	Frequency	Median OS (months)
CCNE1-amp + MMRd	N = 0 (0.0%)	ND
CCNE1-amp + *TP53*-MT	N = 147 (2.8%)	64.5
CCNE1-amp + *POLE*-MT	N = 0 (0.0%)	ND
CCNE1-amp + LOH-H	N = 3 (0.1%)	MNR
MMRd + *TP53*-MT	N = 172 (3.3%)	MNR
MMRd + *POLE*-MT	N = 8 (0.2%)	MNR
MMRd + LOH-H	N = 13 (0.3%)	MNR
TP53-MT + *POLE*-MT	N = 29 (0.6%)	56.3
TP53-MT + LOH-H	N = 591 (11.5%)	29.1
POLE + LOH-H	N = 0 (0.0%)	ND
TP53-MT	N = 1493 (28.9%)	30
POLE-MT	N = 60 (1.2%)	MNR
MMRd	N = 921 (17.9%)	40.5
CCNE1-amp	N = 2 (0.0%)	MNR
LOH-H	N = 81 (1.6%)	45.5
Out of 5158, MNR: median not reached, ND: No data		

Table 1: Overlap between ET subtype and biomarkers and their median survival.

Overlapping subtypes with MMRd, TP53-MT and POLE-MT were observed in 4.1% of cases (MMRd and TP53-MT, n=172 [3.3%]; MMRd and POLE-MT, n=8 [0.2%]; TP53-MT and POLE-MT, n=29 [0.6%])

Figure 1: Kaplan Meier curves for OS of *TP53*-MT tumors and their overlapping subtypes: **(A)** *POLE*-MT, **(B)** dMMR, **(C)** *CCNE1*-amp, **(D)** LOH-H.



Study Highlights

- We report on the co-occurrence of MMR, LOH, *TP53*, *POLE* and *CCNE1* alterations in a large cohort of ET.
- We note that co-occurring *POLE*-MT/*TP53*-MT behaves like *POLE*-MT and follows the ProMisE algorithm, whereas co-occurrence of dMMR/*TP53*-MT tumors are not significantly different than either alone.

Conclusions

- Future work should investigate treatment options for these distinct subtypes.

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