Combined T- and NK-cell immune activity is associated with improved survival after immune checkpoint inhibition (ICI) in advanced/recurrent pMMR endometrial cancer (EC)

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Background

- *ICI, in combination with chemotherapy, has demonstrated significant clinical activity in newly diagnosed, advanced EC.*
- *Although the greatest benefit has been observed in tumors with mismatch repair deficiency (dMMR), a subset of patients with **mismatch repair proficient (pMMR) disease also experience meaningful clinical responses** (Table 1).*
- *The antitumor activity of ICIs is largely attributed to reinvigoration of exhausted cytotoxic T cells within an immunosuppressive tumor microenvironment (TME), characterized by inhibitory checkpoint signaling through PD-1/PD-L1, CTLA-4, LAG-3, TIM-3, and TIGIT, as well as suppressive cytokines including TGF-β, IL-10, and IL-6.*
- *In dMMR EC, ICI efficacy is thought to be enhanced by high tumor mutational burden, increased PD-1/PD-L1 expression, and an immune-inflamed phenotype.*
- *In contrast, the mechanisms underlying ICI responsiveness in pMMR EC remain poorly understood.*
- *Natural killer (NK) cells represent another major cytotoxic immune population within the EC TME and, like CD8+ T cells, exhibit functional impairment driven by immunosuppressive signaling pathways.*

Table 1. Summary of Hazard ratios (HR) for prospective randomized controlled trials involving chemotherapy with ICI in EC

Trial	Experimental Arm	PFS HR – dMMR (95% CI)	PFS HR – pMMR (95% CI)	OS HR – dMMR (95% CI)	OS HR – pMMR (95% CI)
NRG GY018	Pembro + C/T → Pembro maint	**0.30** (0.19–0.48)	**0.54** (0.41–0.71)	0.55 (0.25–1.19)‡	0.79 (0.53–1.17)‡
RUBY Part 1	Dostar + C/T → Dostar maint	**0.28** (0.16–0.50)	**0.76** (0.59–0.98)	**0.32** (0.17–0.63)	0.79 (0.60–1.04)
RUBY Part 2	Dostar + Niraparib as maint	NR	**0.63** (0.44–0.91)	NR	NR
DUO-E (D arm)	Durva + C/T→ Durva maint	**0.42** (0.22–0.80)	**0.77** (0.60–0.97)	0.77 (0.56–1.07)	NR
DUO-E (D+O arm)	Durva + C/T→ Durva/Olap maint	**0.41** (0.21–0.75)	**0.57** (0.44–0.73)	**0.59** (0.42–0.83)	NR
AtTEnd	Atezo + C/T→ Atezo maint	**0.36** (0.23–0.57)	0.92 (0.73-1.16)	**0.41** (0.22–0.76)	1.00 (0.74-1.35)

‡NRG GY018 OS data remain immature at the most recent analysis. C/T = carboplatin/paclitaxel, pembro = pembrolizumab,maint = maintenance, dostar = dostarlimab, durva = durvalumab, olap = olaparib, atezo = atezolizumab, NS = not statistically significant; NR = not separately reported.

- *However, the contribution of NK-cell reactivation to ICI efficacy, particularly in pMMR EC, has not been well defined. To address this gap, we evaluated established biomarkers of a T cell–inflamed TME alongside alternative immune pathways, with a specific focus on NK-cell activity, to identify determinants of overall survival (OS) benefit in EC patients treated with ICI.*

Methods

- *5,258 patients with pMMR/MSS EC treated with pembrolizumab or dostarlimab were identified from the Caris database. Whole exome and transcriptome sequencing were used to characterize molecular features and immune-related gene expression. pMMR/MSS were defined by sequencing or IHC.*
- *OS was defined from ICI initiation to death or last contact.*
- *Associations between individual T- and NK-cell activity–related genes, combined T/NK immune signatures, and OS were evaluated with Kaplan-Meier and Cox proportional hazards analyses.*

Results and Future Directions

Figure 1.The T- and NK-cell–related genes most associated with OS on multivariable analysis in patients with pMMR/MSS EC treated with ICI (all p < 0.01).

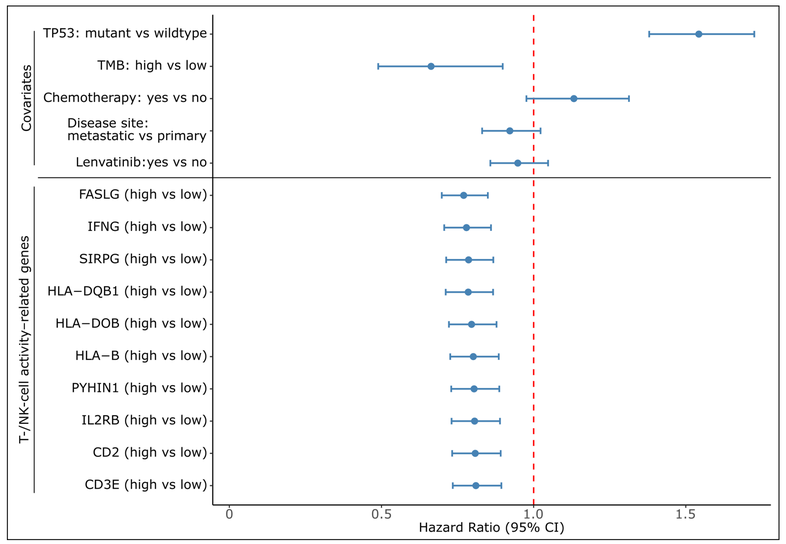
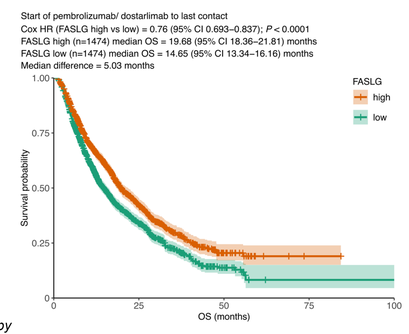


Table 2. T-cell, NK-cell and combined T/NK immune signatures are independently associated with improved OS in pMMR/MSS EC.

Label	HR (95% CI)	P value
Gene set		
NK (high vs low)	0.82 (0.74–0.90)	<0.0001*
T+NK (high vs low)	0.84 (0.77–0.93)	0.0008*
T (high vs low)	0.84 (0.77–0.93)	0.0009*
Covariate		
p53: mutant vs wildtype	1.54 (1.38–1.73)	<0.0001*
TMB: high vs low	0.66 (0.49–0.90)	0.008*
Chemotherapy: yes vs no	1.13 (0.98–1.31)	0.101
Biopsy site: metastasis vs primary	0.92 (0.83–1.02)	0.124
Lenvatinib: yes vs no	0.95 (0.86–1.05)	0.293

*Multivariable Cox models adjusted for p53 status, TMB, site, chemotherapy and lenvatinib. *Two-sided p-value < 0.05 considered significant.*

Figure 2. K-M curve of FASLG, the gene most significantly associated with OS in pMMR/MSS cohort after ICI.



Improved OS after ICI in pMMR/MSS endometrial cancer is associated with both NK cell and T cell activation, suggesting that NK cells may play a critical role in ICI efficacy in endometrial cancer.

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