Molecular subtype not immune response drives outcomes in endometrial carcinoma

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Translational relevance: We have entered a new era in endometrial carcinoma (EC) research and clinical care where pragmatic molecular classification tools enable consistent categorization/stratification of ECs and provide prognostic information to inform management. However, the ability of molecular classification to predict response to immunotherapy has not been defined, nor has the the impact of immune environment on outcomes within this new framework of molecular subtypes. Herein, we characterize the tumor-infiltrating lymphocytes and immunosuppressive factors across the four major molecular subtypes of EC demonstrating diversity even among characteristically ‘high’ and ‘low’ mutation load tumours. Molecular subtype is demonstrated to be the parameter most strongly associated with clinical outcomes (more than immune response) however, assessment of immune response (rather than molecular subtype) may better predict response to immunotherapy.
ABSTRACT

Purpose: Tumors with high mutation load are thought to engender stronger immune responses which in turn promote prolonged patient survival. To investigate this, we assessed tumor-infiltrating lymphocytes (TIL) and immunosuppressive factors across the four molecular subtypes of endometrial cancer (EC), which have characteristic mutation rates ranging from low to ultra-high.

Experimental design: 460 ECs were stratified by ProMisE (Proactive Molecular Risk Classifier in Endometrial cancer) into four molecular subtypes: mismatch repair-deficient (MMRd), POLE mutant (POLE), p53 abnormal (p53abn), and p53 wildtype (p53wt). Immune markers (CD3, CD8, CD79a, CD138, PD-1, PD-L1, FoxP3, IDO-1) were quantified by multiplex immunohistochemistry and tested for associations with ProMisE subtype, survival, and other clinicopathological parameters.

Results: Two major TIL patterns were observed. TIL\textsuperscript{high} tumors harbored dense T- and B-lineage infiltrates and multiple immunosuppressive features and were common in molecular subtypes associated with high mutation load (MMRd and POLE); however, equally strong responses were seen in significant numbers of p53abn and p53wt tumors, which have characteristically low mutation loads. TIL\textsuperscript{low} tumors were generally devoid of immunological features and more prevalent in p53abn and p53wt ECs, yet were also seen in MMRd and POLE subtypes. In multivariable models involving ProMisE subtype, T-cell markers, TIL clusters, only ProMisE showed independent prognostic significance.

Conclusions: Immune response correlates with EC molecular subtype but does not carry independent prognostic significance. Profound variation in immune response is seen across and within EC molecular subtypes, suggesting that assessment of immune response rather than molecular subtype may better predict response to immunotherapy.
Introduction

The recent success of immunotherapy has prompted a need to better understand the features of cancers that impart susceptibility to immune recognition and control. Among the best evidence for immunological control is the phenomenon of tumor-infiltrating lymphocytes (TIL), which are strongly associated with patient survival in almost all human cancers (1-4). Moreover, the presence of TIL is associated, albeit imperfectly, with clinical response to immunotherapies targeting the CTLA-4 and PD-1 pathways, referred to as “checkpoint blockade” (5-7). TIL responses generally show a positive association with mutation load, presumably due to an increased number of mutated antigens (neoantigens) available for T cell recognition (8,9). In addition, DNA damage can promote TIL responses by activating mechanisms such as the cGAS/STING pathway(10), leading to an immunologically permissive tumor microenvironment. Conversely, TIL responses can be inhibited by oncogenic signaling pathways, including the Wnt/beta-catenin and PI3 kinase signaling pathways (11-14). For a given patient, the magnitude of the TIL response likely reflects a balance of these factors, which in turn strongly influences the patient’s likelihood of survival and response to checkpoint blockade. A better understanding of the interplay between these factors is required for the development of cancer immunotherapies that benefit a broader spectrum of patients.

Endometrial cancer (EC) provides a unique opportunity to study the influence of the tumor genome on anti-tumor immunity while also presenting an urgent need for improved therapies. EC is the most common gynaecological malignancy in North America, and the fourth most common cancer in women overall, with 150,000 new cases in Europe and North America each year and an increasing trend in incidence and mortality (15,16). A woman diagnosed with EC first undergoes surgical staging, after which histomorphological classification and risk group stratification directs further adjuvant therapies or observation only. While the majority of women with EC have early stage disease and excellent outcomes, those with metastases or aggressive subtypes typically experience a modest and/or short-lived response to conventional therapies and frequently succumb to their disease (16).

EC pathological classification and risk stratification has advanced with the recent development of novel molecular classification tools that are objective, biologically based, and clinically
relevant, with implications for prognosis, treatment prediction and genetic heritability. The Cancer Genome Atlas (TCGA) characterized the transcriptional, proteomic, and genomic landscape of over 370 serous and endometrioid ECs and identified four genomic subgroups with distinct prognostic outcomes (17). From this, pared down, pragmatic classifiers have emerged that can use standard formalin-fixed paraffin embedded (FFPE) tissues obtained from hysterectomy(18-22) or diagnostic biopsies(22,23). ProMisE (Proactive Molecular Risk Classifier in Endometrial cancer) has been developed(18), confirmed(19) and validated(22) according to the Institute of Medicine Guidelines for the development of new biomarker tests. ProMisE stratifies EC into four groups: (a) a mismatch repair deficient subtype (MMRd, analogous to TCGA and TransPORTEC ‘MSI’); (b) a subtype with mutations in the exonuclease domain of polymerase epsilon, which is responsible for DNA proofreading repair and characterized by excellent outcomes (POLE, analogous to TCGA ‘ultramutated’ and ‘POLE-mutant’ TransPORTEC subgroups(20-22,24)); (c) a poor-prognosis subtype characterized by p53 abnormalities (p53abn, analogous to TCGA ‘copy-number high’ and TransPORTEC ‘p53-mutant’ subgroups (17,20,21)); and (d) an intermediate prognosis subtype with wildtype p53 and no specific mutational profile (p53wt, analogous to TCGA ‘copy-number low’, TransPORTEC ‘NSMP’ or no specific molecular profile)(18-22).

The molecular features of these subtypes influence the immune landscape of EC. Owing to intrinsic DNA repair deficiencies, the POLE and MMRd subtypes give rise to ultramutated (mean = 232×10^{-6} mutations/Mb) and hypermutated (18×10^{-6} mutations/Mb) tumors, respectively (17). Accordingly, these subtypes have been associated with high neoantigen loads and robust TIL responses (9,25-28). Given the general association between TIL and favorable prognosis across cancers, it has been suggested that the good to excellent prognosis associated with MMRd and POLE tumors is attributable to the anti-tumor immune response (29,30). However, prior studies of TIL in EC have not had sufficient sample size to test this hypothesis. Moreover, relatively less is known about the immune response within the p53wt and p53abn molecular subtypes, which encompass the majority of EC cases (12,30). Notably, p53wt cases have a similar prognosis as MMRd cases (18), despite an almost ten-fold lower mutation rate (2.9 versus 18×10^{-6} mutations/Mb) (17). Indeed, with mutation rates spanning two orders of magnitude, EC provides a powerful setting to investigate the paradigm that high mutation load drives favorable prognosis via the anti-tumor immune response.
As with other cancers, there is intense interest in the use of checkpoint blockade to treat recurrent EC (6,31-34). Although relapse is exceedingly rare among POLE cases, there are anecdotal reports of objective responses to anti-PD-1 antibody (35-37), which fits the paradigm that high mutation load predicts response to such agents. Anti-PD-1 antibody is an FDA-approved treatment option for MMRd cases(38), again based on the predictive value of high mutation load. However, it remains unclear whether the p53wt and p53abn subtypes of EC might also benefit from checkpoint blockade, as we have a relatively poor understanding of how the immune system responds to these characteristically low mutation load tumors.

To define the relationship between molecular subtype, TIL response, and prognosis in EC, we profiled the major TIL subsets (including CD4 and CD8 T cells and B-lineage cells) across a 460-case, molecularly subtyped EC cohort with full clinical data. To inform future immunotherapy strategies, we also evaluated immunosuppressive factors, including regulatory T cells (Tregs), IDO-1, and the PD-1/PD-L1 pathway. We report that TIL responses and immunosuppressive features vary in frequency but not magnitude across the molecular subtypes of EC. Moreover, the prognostic effect of molecular subtype outweighs TIL response, challenging the paradigm that high mutation load drives prognosis by promoting anti-tumor immunity. Our findings further suggest that molecular subtype alone may be inadequate to stratify EC patients for immunotherapy.

Materials and Methods

Patient cohort and ProMisE classification

Our cohort consisted of 460 EC cases from two previously published series that were used to develop and confirm the ProMisE molecular classifier (18,19). Clinical, pathological, molecular and outcome parameters have previously been described (18,19) and are detailed in the Supplementary Methods. The study was approved by the Research Ethics Board of BC Cancer and the University of British Columbia.

Tissue microarray and immunohistochemistry
Representative samples of pathology-reviewed EC from our Vancouver center were cored (0.6mm) in duplicate and arrayed as previously described (18,19). TMAs were cut at 4μm thickness onto Superfrost+ glass slides for IHC analysis. Single and multiplex IHC was used to profile immune cells and associated factors in both the epithelial and stromal compartments of tumors. Four antibody panels were used: (a) CD3/CD8/CD79a, (b) CD138/CD79a, (c) PD-L1/CD8/PD-L1, and (d) FoxP3/PD-1/CD3. IDO-1 was stained separately (Supplementary Methods). Slides were scanned in brightfield using the Vectra Multispectral Imaging System (PerkinElmer, Waltham, MA, USA). InForm 2.1 software (PerkinElmer, Waltham, MA, USA) was used to quantify signals. PD-L1 and IDO-1 positivity was scored visually as a binary variable (whereby >5% staining of immune cells and/or tumor cells was considered positive) or by image analysis as a continuous variable. Additional information is provided in Supplementary Methods.

**Statistical analyses**

For each tumor core, raw cell counts and marker values were normalized to epithelial and stromal area to yield a density value. For several markers, a substantial proportion of samples had scores of zero (i.e. zero-inflated/ right-skewed data). When log (base 2) transformed, the data followed a delta log normal distribution (Supplementary **Figure S1**) and were analyzed using a two-step approach (39,40). In the first step, the proportion of cases having no marker expression was modeled separately using a chi-square test. Conditional on a non-zero value, the second step followed a lognormal distribution and was assessed using a one-way analysis of variance.

Immune markers were further investigated using heatmaps, overlaying the previously validated ProMisE subtypes. Immune signatures were inferred using an unsupervised ensemble clustering approach implemented in the R package diceR (41). Briefly, several algorithms (Supplementary Methods) were used to cluster 100 random subsets of the data, each of which included 80% of samples. The results were combined to form a final consensus clustering using the k-modes method (42). Several numbers of clusters were tested, and the proportion of ambiguously clustered cases (PAC) (43) within the ensemble was used to determine the optimal number of clusters. Univariable associations between immune clusters, ProMisE subtypes, and other clinicopathological parameters were evaluated. Associations between immune clusters and clinical outcomes (overall, disease-specific and progression-free
survival) were assessed individually in univariable analyses using log rank tests and Kaplan-Meier analyses and collectively by adjusting for known risk factors in multivariable Cox proportional hazard models. Survival was also evaluated within each ProMisE subtype. Multivariate analysis was performed, correcting for the immune clusters, ProMisE subtype, age, BMI, grade, histotype, stage, Lymph Vascular Space Invasion (LVSI), myometrial invasion, nodal status or treatment. All statistical tests were two-sided, and statistical significance was set at 0.05 with no adjustment for multiple comparisons.

Results

Cohort and IHC analysis

ProMisE subtype distribution within the 460 EC cases included 105 MMRd, 42 POLE, 202 p53wt, and 111 p53abn cases. Clinicopathological parameters across ProMisE subgroups are shown in Supplementary Table S1. Patients were diagnosed between 1983 to 2013 and received treatment according to standard of care at our center over this time period (18,19). Adjuvant treatment, when given, consisted primarily of standard radiotherapy (RT; most commonly pelvic external beam RT or vaginal brachytherapy) with or without platinum/taxane chemotherapy. No patients were known to have received immune checkpoint inhibitors or other immunotherapies.

The densities of various TIL subsets and associated factors were assessed by multiplex IHC and automated image analysis with visual confirmation. Representative images are shown in Figure 1. The number of missing values (due to missing or uninterpretable cores) ranged from 10 to 28 for individual markers and were not significantly associated with subtype (Supplementary Table S2).

POLE and MMRd subtypes show increased infiltration by both T cells and B-lineage cells

The epithelial and stromal densities of immune markers are shown in Figure 2 and Supplementary Table S3. Consistent with prior reports(2,30), the density of epithelial and stromal CD3+CD8+ TIL (putative cytotoxic T cells) was highest in POLE tumors, followed closely by MMRd tumors, with p53abn and p53wt tumors showing the lowest levels (p<0.01; Supplementary Table S2). A similar, statistically significant pattern was seen for CD3+CD8-
TIL (putative CD4+ TIL), although the differences between molecular subtypes were less pronounced (p < 0.01). Similar patterns were seen in the stromal compartment (p < 0.01), although the densities of CD3+CD8+ and CD3+CD8- T cells were generally higher compared to epithelium.

In contrast to T cells, neither B cells (CD138-CD79a+) nor plasma cells (CD138+CD79a+) were prevalent in tumor epithelium, and neither subset showed a significant difference across ProMisE subtypes (p= 0.74 and p=0.22, respectively). However, in tumor stroma, higher densities of B cells and plasma cells were seen and varied by ProMisE subtype (p < 0.01 for both), with POLE tumors showing the highest density. Generally, elevated densities of epithelial and stromal T cells in POLE and MMRd tumors were accompanied by higher levels of B cells and plasma cells in the stromal compartment, with the next highest expression levels seen in MMRd (B cells) or p53abn (plasma cells) tumors (Figure 2 and Supplementary Table S2).

**Immunosuppressive factors across the ProMisE subtypes**

We also evaluated PD-1+ cells, PD-L1+ cells, and Tregs (defined as FoxP3+PD-1+CD3+ cells) (Figure 2, Supplementary Table S2). Consistent with overall TIL densities, POLE tumors expressed the highest densities of epithelial PD-1+CD8- (putative CD4+) and PD-1+CD8+ TIL, followed by MMRd tumors; significantly lower levels of these cells were seen in p53abn and p53wt tumors (p = 0.01 and p < 0.01, respectively). The stromal compartment showed a similar ranking, except that the p53abn subtype ranked second for PD-1+CD8- TIL (p< 0.01). The proportion of PD-1+CD8+ cells of all PD-1+ cells was similar in POLE, MMRd and p53abn tumors (78.4%, 74.7% and 77.9%, respectively (Supplementary Figure S2); however, this value dropped to 33.1% in p53wt tumors. A similar though less-pronounced pattern was seen in stroma. This suggests that CD8+ TIL have a lower level of activation and/or exhaustion in p53wt tumors compared to the other three subtypes.

To compare the extent of PD-L1 expression across subtypes, we measured the total area of PD-L1 positivity in tumor cores (i.e., irrespective of tumor versus lymphocyte expression, or stromal versus epithelial location). Using a binary scoring method (cores with >5% of cells
expressing PD-L1 were considered positive), the proportion of PD-L1+ cases was highest for POLE tumors (70%), followed by MMRd (56%), p53abn (32%), and p53wt tumors (16%) (p<0.01). Likewise, when evaluated as a continuous variable, PD-L1 expression differed significantly across ProMisE subtype (p<0.01) and followed a similar ranking as seen with binarized data.

Similar to other immune markers, Tregs were highest in the stromal compartment in POLE and MMRd tumors, followed in order by p53abn and p53wt tumors (p < 0.01). When the four subtypes were considered together, the ratio of CD3+CD8+ T cells to Tregs was approximately 4:1 in epithelium and 2:1 in stroma (Supplementary Table S4). Within subtypes, these ratios (in epithelium/stroma respectively) were 5.25/2.72 for POLE, 4.46/2.49 for MMRd, 3.80/1.72 for p53abn, and 3.46/2.28 for p53wt. Thus, POLE cases had the highest ratio of CD3+CD8+ T cells to Tregs.

**Lymphocyte infiltration and immunosuppressive factors within the MMRd subtype**

Within the MMRd group, we explored differences between patients with loss of MLH1/PMS2 versus MSH2/MSH6. MLH1 loss is usually somatic or epigenetic and generally occurs in older women, raising the possibility it may be associated with a weaker immune response. Of the 105 MMRd cases in our cohort, 71 showed MLH1/PMS2 loss and 13 showed MSH2/MSH6 loss. Although we were insufficiently powered to make strong conclusions, within the stromal compartment there was a trend toward decreased density of plasma cells in MLH1/PMS2-loss versus MSH2/MSH6-loss tumors (p=0.07). Moreover, MLH1/PMS2-loss tumors showed significantly lower stromal density of Tregs (FOXP3+PD-1+CD3+ cells; p=0.05) compared to MSH2/MSH6-loss tumors Supplementary Figure S3).

**Ensemble clustering reveals two major TIL patterns**

An ensemble clustering approach was used to identify TIL patterns present in EC based on the log-transformed IHC results for all TIL subsets (i.e. CD8+ T cells, putative CD4+ T cells, Tregs, B cells and plasma cells) and the PD-1/PD-L1 pathway in both the epithelial and stromal compartments. We tested different cluster sizes and found that PAC was lowest in the two clusters solution(Supplementary Table S5); nonetheless, we also explored the three
cluster solution. The two cluster solution separated tumors into two major groups: $\text{TIL}^{\text{high}}$ versus $\text{TIL}^{\text{low}}$ (Figure 3). $\text{TIL}^{\text{high}}$ tumors showed significantly higher densities of all five TIL subsets, including CD8+ and CD4+ T cells, B cells, plasma cells, and Tregs. High levels of PD-1+ and PD-L1+ cells also characterized this group. In contrast, $\text{TIL}^{\text{low}}$ tumors showed low or negligible levels of all five TIL subsets, as well as PD-1+ and PD-L1+ cells. In the three cluster solution, the $\text{TIL}^{\text{high}}$ cluster remained largely the same, whereas the $\text{TIL}^{\text{low}}$ cluster split into two subgroups referred to as $\text{TIL}^{\text{medium}}$ and $\text{TIL}^{\text{negative}}$. Relative to $\text{TIL}^{\text{high}}$ tumors, $\text{TIL}^{\text{medium}}$ tumors exhibited lower levels of all five TIL subsets and notably lower levels of PD-1+ and PD-L1+ cells. The majority of $\text{TIL}^{\text{medium}}$ tumors (75%) belonged to the p53wt subtype. $\text{TIL}^{\text{negative}}$ tumors exhibited negligible levels of all five TIL subsets and PD-1+ and PD-L1+ cells.

None of the ProMisE subtypes exhibited a TIL pattern that was not seen in the other subtypes; rather, they differed with respect to the prevalence of $\text{TIL}^{\text{high}}$ tumors: POLE (89.5%), MMRd (78%), p53abn (60%) and p53wt (37%). Associations were noted between TIL patterns and certain clinicopathological parameters such as BMI, LVSI, nodal status, grade and treatment (Supplementary Table S6). Further investigation revealed that there were no statistical differences in clinical parameters between POLE and MMRd cases with $\text{TIL}^{\text{high}}$ and $\text{TIL}^{\text{low}}$ immune patterns.

**Patient outcomes are more strongly associated with ProMisE subtype than immune pattern**

We have previously reported on progression-free and overall survival in this cohort, finding highly favorable outcomes in POLE cases, intermediate outcomes in MMRd and p53wt cases, and poor outcomes in p53abn tumours (18,19). Cox regression survival analysis with log rank test was performed across all four molecular subtypes to assess the association of individual or combined immune markers with clinical outcomes (Supplementary Table S6). High densities of epithelial CD3+CD8- or CD3+CD8+ TIL were associated with increased patient survival (OS p=0.05, DSS p=0.02, PFS p=0.06 and OS p<0.01, DSS p<0.01, PFS p<0.01 respectively). Likewise, FOXP3-PD-1-CD3+ cells were prognostically favorable in stroma (OS p< 0.01, DSS p=0.01, PFS p=0.01) and epithelium (PFS p<0.01). Conversely, epithelial PD-1+ CD8+ TIL were correlated with decreased OS (p= 0.01), and epithelial PD-1+ CD8- TIL were
correlated with decreased PFS (p<0.01). Stromal CD138-CD79a+ and CD138+CD79a+ TIL lacked prognostic significance as did PD-L1+ cells and epithelial or stromal Tregs. Expression of IDO-1 correlated with increased PFS (PFS p<0.01, OS p=0.16, DSS p=0.29). TIL\textsuperscript{high} versus TIL\textsuperscript{low} immune clusters showed no association with OS, DSS or PFS (Figure 4 A-C), even in multivariable analysis after adjusting for ProMisE subtype and other clinicopathological parameters associated with survival, which have been assessed previously (18,19) and include age, stage, LVSI, and myometrial invasion Table 1. However, ProMisE molecular classifier maintained a statistically significant association with outcomes for OS, DSS and PFS (p=0.04, p=0.04 and p<0.01 respectively(Table 1)).

We assessed the prognostic effect of epithelial CD3+CD8+ TIL in a multivariable model that included ProMisE subtype and these other clinicopathological parameters (Table 2). Although both ProMisE subtype and epithelial CD8+ TIL showed a trend toward increased OS and DSS, only ProMisE subtype retained a a significant independent prognostic effect (PFS p=0.02).

**Prognostic effect of immune markers within ProMisE subtypes.**

Next, we evaluated the prognostic significance of individual immune markers within ProMisE subtypes. In general, most immune markers failed to show prognostic significance, with a few exceptions (Table 3). Within MMRd cases, CD8+CD3+ and CD3+CD8- TIL were positively associated with DSS (p=.04 and .02, respectively), and within p53wt cases, stromal B cells (CD138-CD79a+) were associated with increased DSS (p=0.04) (Table 3). However, even when statistical significance was reached, differences in outcomes were small.

Finally, we evaluated the prognostic significance of the TIL\textsuperscript{high} versus TIL\textsuperscript{low} clusters within each of the four ProMisE subtypes. This analysis was not meaningful in the POLE subtype, as only four cases were TIL\textsuperscript{low}. Similarly, we were challenged to see a difference within p53wt where events were rare. In the remaining ProMisE subtypes, there was a non-significant trend toward inferior outcomes in TIL\textsuperscript{low} tumors within MMRd tumors. Collectively, these findings indicate that patient survival is more strongly influenced by ProMisE subtype than TIL.
DISCUSSION

There is increasing appreciation of the importance of the tumor microenvironment in defining outcomes and therapeutic opportunities in cancer. In particular, TIL have been shown to be both prognostic and predictive in that their presence is generally associated with improved outcomes and favorable response to conventional chemotherapies and immune targeting agents (1-4,44-48). We investigated the relationships between immune response, molecular subtype and patient survival in EC. Multiplexed, IHC-based analysis of 460 tumors spanning the four molecular subtypes of EC (MMRd, POLE, p53wt, and p53abn) identified two major TIL patterns: TIL\textsuperscript{high} and TIL\textsuperscript{low}. As expected, POLE and MMRd subtypes were enriched for TIL\textsuperscript{high} tumors; however, 22% of MMRd tumors were TIL\textsuperscript{low}. Conversely, p53abn and p53wt cases were enriched for TIL\textsuperscript{low} tumors, yet also contained significant proportions of TIL\textsuperscript{high} tumors. Therefore, all four molecular subtypes of EC can engender both immunologically “hot” and “cold” tumors, suggesting it may be inadequate to use molecular subtype alone to stratify patients for immunotherapy. As observed across many cancers, CD8+ TIL were associated with improved survival, but in multivariate analysis, individual immune markers and immune clusters were not prognostic. Rather, ProMisE molecular subtype retained prognostic value, demonstrating an association with both DSS (p=0.04) and PFS (<0.01) and a trend towards association with OS (p=0.08). Thus, molecular subtype, not immune response, was the most significant prognostic factor in this series, suggesting that the molecular/genomic features of tumors influence outcome through mechanisms apart from the immune response.

Immune markers have been assessed in EC in both the pre- (2,49) and post-TCGA eras (12,29,30,45,50). The latter have primarily focused on the newly recognized POLE ultramutated and MSI/MMRd hypermutated subtypes. Particular attention has been paid to the notion that the exceptionally high mutation rates in these subtypes drive the generation of neoantigens, making tumors more immunogenic. Indeed, POLE and MMRd tumors have been shown to harbor the highest levels of not only CD8+ T cells but also CD4+ T cells, stromal CD20+ B cells, FOXP3+ cells, PD-1+ cells, and PD-L1+ cells (25,26,29). Model systems have further demonstrated that POLE ultramutated tumors are able to stimulate greater cytotoxic CD8+ T cell responses compared to POLE-wt tumors (26). These findings are consistent with a mechanistic link between mutation load and TIL. On the other hand, our
findings demonstrate that not all POLE and MMRd tumors engender a significant immune response. Conversely, significant numbers of p53abn and p53wt cases exhibited TIL patterns that, by the clustering analyses performed here, were indistinguishable from TIL\textsuperscript{high} POLE and MMRd cases. Although we did not directly assess mutation load in this study, the TCGA study demonstrated minimal overlap in the mutation load between the POLE/MSI groups compared to the copy number high (p53abn) and low (p53wt) groups. Thus, neoantigen load cannot be the only factor influencing the strength of TIL responses. Other factors that merit consideration include DNA damage-induced activation of the cGAS/STING, as well as inhibitory factors such as activation of the Wnt/beta-catenin and PTEN/PI3 kinase pathways\cite{51-53}. Notably, recurrent mutations in the \textit{PTEN}, \textit{PIK3CA}, \textit{PIK3R1}, and \textit{CTNNB1} genes are common in EC\cite{54} and hence could play an important role in sculpting the immune response.

This series represents the most extensive assessment to date of B cell and plasma cell responses in EC. Consistent with prior reports in high-grade serous ovarian cancer (HGSC) and other malignancies, B cells and plasma cells were positively associated with CD8 and CD4 TIL \cite{47,55}. Given our use of TMA cores, we were unable to assess the extent to which B cell and plasma cell infiltrates were associated with tertiary lymphoid structures \cite{56}; this could be evaluated in future by analyzing whole tumor sections. We found B-lineage cells in both high- and low-mutation load molecular subtypes, consistent with their lack of association with mutation load in HGSC\cite{47}. Given the extraordinarily favorable prognosis associated with POLE tumors, the presence of dense B cell and plasma cell infiltrates in this subset challenges the view advanced by some researchers that B cell/plasma cell responses are detrimental to antitumor immunity. Instead, our findings are in line with the majority of studies showing a positive prognostic effect of B-lineage cells across human cancers \cite{57}.

On the surface, the generally higher TIL levels in POLE and MMRd tumors would support these subtypes as the most appropriate candidates for checkpoint blockade. Indeed, objective responses to PD-1 blockade have been demonstrated in patients harboring POLE and MMRd tumors \cite{31,35,37}. However, recent preclinical data as well as meta-analysis of all published cohorts of \textit{POLE} ECs indicates that these tumors may not require any adjuvant therapy \cite{58,59}, let alone costly immunotherapies. Thus, the need for checkpoint blockade in \textit{POLE}
ECs would be restricted to rare recurrences. The use of checkpoint blockade for relapsed MMRd tumors is well founded and indeed has recently received FDA approval(31,38). The major outstanding question is whether checkpoint blockade has a place in the treatment of p53abn and p53wt cases. Our findings indicate that significant proportions of these cases exhibit TIL patterns that are equally robust to those seen in POLE and MMRd tumors. Indeed, in our clustering analyses, POLE and MMRd tumors did not demonstrate categorically distinct TIL patterns but rather were part of a continuum shared with the p53wt and p53abn subtypes. This provides justification for evaluating the efficacy of checkpoint blockade in the p53wt and p53abn subtypes.

A major distinguishing feature of TIL clusters was the presence of PD-1+ and PD-L1+ cells. In particular, our three-cluster model (Figure 2B) revealed that the TIL\textsuperscript{low} cluster contained a subgroup with intermediate levels of the major TIL subsets (i.e. T cells, B cells, plasma cells, Tregs) but negligible levels of PD-1+ T cells and PD-L1+ macrophages/tumor cells. This subgroup was dominated by p53wt tumors, which as corroborating evidence also demonstrated markedly lower percentages of PD-1+ T cells. Thus, with either two- or three-cluster statistical models, only the TIL\textsuperscript{high} subset had the PD-1+/PD-L1+ pattern that is associated (albeit imperfectly) with response to checkpoint blockade in other cancers. This TIL\textsuperscript{high} group contained the majority of POLE and MMRd tumors but also 28% of p53wt and 25% of p53abn tumors. Thus, there may be merit in comparing the TIL\textsuperscript{high} pattern versus molecular subtype as predictive biomarkers for checkpoint blockade in EC.

With the MMRd subtype, we investigated whether the underlying genetic defect had an influence on TIL pattern. Somatic or epigenetic loss of PMS2/MLH1 is more common and usually arises in older individuals, who could conceivably mount less robust antitumor immune responses. In contrast, loss of MSH6/MSH2 is often seen in germline/Lynch Syndrome-associated ECs, which arise in younger individuals. Although our study was underpowered to address this issue definitively, cases with PMS2 loss showed a trend towards lower levels of several immune cells or markers (Tregs, B cells, plasma cells, PD-1, PD-L1), particularly in tumor stroma (Supplementary Figure S2). Sloan et al. showed higher PD-L1 expression in Lynch syndrome-associated ECs as compared to ECs with MLH1 promoter methylation (60). However, as in our series, these observations were not accompanied by data
on actual response rates to immune blockade, thus the predictive value of these differences within molecular subtype await verification through clinical trials.

In addition to the PD-1/PD-L1 pathway, we assessed the expression of IDO-1, which represents another pharmacologically targetable mechanism of immune suppression in cancer(61-65). Similar to PD-L1, IDO-1 expression was significantly higher in TIL\textsuperscript{high} tumors and spanned the four molecular subtypes. Prior publications have suggested high prevalence of IDO-1 expression in MMRd tumors, particularly Lynch syndrome-associated ECs(66,67). Our series confirmed this and revealed even higher expression in the POLE subtype. Given that IDO-1 is frequently co-expressed with PD-L1 (not specifically evaluated in this series), dual immunotherapy could be considered(68,69).

Strengths of this study include evaluation of a large, well-annotated cohort of ECs and a wide panel of immune markers. Moreover, we used a molecular classification tool that has undergone rigorous validation according to the Institute of Medicine criteria (70). Limitations of this study include the use of tissue microarrays instead of whole sections; however, we assessed cores in duplicates and the number of uninterpretable cases was very low in this series. Moreover, prior literature supports the use of tissue microarrays for immune studies of this type (71,72). Nonetheless, if TIL patterns were to be used as clinical biomarkers, additional studies would be required to determine whether whole sections provide more robust data for clinical decision making. A second limitation is that we evaluated only a single tumor site from each patient and hence were unable to assess the extent of intratumoral heterogeneity of TIL patterns, as we reported recently in high-grade serous ovarian cancer(55). Importantly, however, this phenomenon does not negate the clinicopathological significance of TIL when measured across large patient cohorts. A third limitation is that mutation load and other molecular/genomic features of tumors were inferred by ProMisE subtype rather than direct measurement. Finally, given that this cohort was accrued prior to the widespread use of immune modulatory agents in EC, we were unable to assess whether any immune cells or markers were predictive of response to PD-1/PD-L1 or IDO-1 inhibitors.
In summary, we have profiled the immune response in EC through the modern lens of a pragmatic molecular classification tool. Immune markers, alone or in combination, failed to match the prognostic ability of ProMisE molecular classification. We demonstrate the diversity of immune marker expression across and within molecular subtypes. Candidates for immunotherapy extend beyond the POLE and MMRd subtypes, and assessment of immune response rather than molecular subtype may be more helpful in patient selection. Continued work is needed to identify the most accurate biomarkers for stratification of EC patients for immunotherapy, so as to minimize toxicity and cost for women who are unlikely to respond while ensuring that opportunities for treatment are not missed.

ACKNOWLEDGEMENTS

We thank Dr. Phineas Hamilton for advice.

REFERENCES


Table 1 Multivariable Survival. Multivariable survival analysis, including immune clusters (K=2), ProMisE subtype, and other known risk factors and using Cox proportional hazard to estimate hazard ratios on overall (OS), disease specific (DSS), and progression-free (PFS). P values were evaluated using likelihood ratio test (LRT). Firth (F) confidence intervals were computed using the profile likelihood and may not match the LRT p value.

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>DSS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of events / n</td>
<td>Hazard Ratio</td>
<td>LRT</td>
</tr>
<tr>
<td></td>
<td>94 / 363</td>
<td>(95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Immune Cluster</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(ref: None) Low immune</td>
<td>High immune</td>
<td>0.80 (0.51-1.26)F</td>
<td>0.346</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ProMisE molecular</td>
<td>MMRD</td>
<td>1.71 (0.90-3.26)F</td>
<td><strong>0.036</strong></td>
</tr>
<tr>
<td>subgroup (ref:</td>
<td>POLE</td>
<td>0.87 (0.22-2.59)F</td>
<td></td>
</tr>
<tr>
<td>p53wt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.53 (1.26-5.18)F</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>1.02 (1.00-1.04)F</td>
<td><strong>0.036</strong></td>
</tr>
<tr>
<td>BMI</td>
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<td>0.98 (0.96-1.01)F</td>
<td>0.198</td>
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<tr>
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<td>Grade 3</td>
<td>1.13 (0.62-2.10)F</td>
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<td></td>
</tr>
<tr>
<td>Stage (reference</td>
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<td>2.44 (1.42-4.24)F</td>
<td><strong>0.001</strong></td>
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<td>group: I)</td>
<td></td>
<td></td>
<td></td>
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<td>LVSJ (ref: None)</td>
<td>Yes</td>
<td>1.89 (1.11-3.29)F</td>
<td><strong>0.018</strong></td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td></td>
<td>0.81 (0.38-1.92)F</td>
<td>0.022</td>
</tr>
<tr>
<td>(ref: None) &lt;50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.63 (0.75-3.93)F</td>
<td>2.40 (0.87-8.08)F</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;50</td>
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<td></td>
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<tr>
<td>Nodal Status (ref:</td>
<td>Not tested</td>
<td>1.41 (0.81-2.41)F</td>
<td>0.163</td>
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<tr>
<td>Negative)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Positive</td>
<td>0.66 (0.35-1.21)F</td>
<td>0.80 (0.40-1.54)F</td>
</tr>
<tr>
<td>Treatment (ref:</td>
<td>Any</td>
<td>0.73 (0.43-1.26)F</td>
<td>0.261</td>
</tr>
<tr>
<td>None)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
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Table 2 Multivariable Survival. Multivariable survival analysis, including epithelial cytotoxic T cells, ProMisE subtype, and other known risk factors using Cox proportional hazard to estimate hazard ratios on overall (OS), disease specific (DSS), and progression-free survival (PFS). P values were evaluated using likelihood ratio test (LRT). Firth (F) confidence intervals were computed using the profile likelihood and may not match the LRT p value.

<table>
<thead>
<tr>
<th></th>
<th>OS</th>
<th>DSS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># of events / n</td>
<td>Hazard Ratio (95% CI)</td>
<td>LRT P value</td>
</tr>
<tr>
<td>Epith CD3+CD8+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Cytotoxic T cells)</td>
<td>94 / 363</td>
<td>0.99 (0.98-1.00)</td>
<td>0.067</td>
</tr>
<tr>
<td>ProMisE molecular</td>
<td></td>
<td></td>
<td></td>
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<td>subgroup (ref: p53wt)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMRd</td>
<td>1.80 (0.95-3.40)</td>
<td>0.062</td>
<td>1.35 (0.63-2.87)</td>
</tr>
<tr>
<td>POLE</td>
<td>1.04 (0.26-3.15)</td>
<td></td>
<td>0.42 (0.04-1.84)</td>
</tr>
<tr>
<td>p53abn</td>
<td>2.38 (1.18-4.89)</td>
<td></td>
<td>2.02 (0.92-4.62)</td>
</tr>
<tr>
<td>Age</td>
<td>1.02 (1.00-1.05)</td>
<td>0.029</td>
<td>1.00 (0.97-1.02)</td>
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<tr>
<td>BMI</td>
<td>0.98 (0.96-1.01)</td>
<td>0.169</td>
<td>0.99 (0.96-1.01)</td>
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<td>Grade (ref: Grade 1/2)</td>
<td>Grade 3</td>
<td>1.17 (0.64-2.18)</td>
<td>0.645</td>
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<tr>
<td>Histology (ref:</td>
<td>Non-Endometrioid</td>
<td>1.07 (0.56-2.03)</td>
<td>0.841</td>
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<td>Endometrioid)</td>
<td></td>
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<td></td>
</tr>
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<td>Stage (ref:</td>
<td>Stage: I)</td>
<td>2.32 (1.34-4.04)</td>
<td>0.002</td>
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<tr>
<td>LVSI (ref: No)</td>
<td>Yes</td>
<td>1.82 (1.06-3.16)</td>
<td>0.028</td>
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<tr>
<td>Myometrial invasion</td>
<td>&lt;50</td>
<td>0.81 (0.38-1.91)</td>
<td>0.018</td>
</tr>
<tr>
<td>(ref: None)</td>
<td>&gt;50</td>
<td>1.66 (0.76-3.97)</td>
<td>0.018</td>
</tr>
<tr>
<td>Nodal Status (ref:</td>
<td>Not tested</td>
<td>1.45 (0.83-2.46)</td>
<td>0.025</td>
</tr>
<tr>
<td>Negative)</td>
<td>Positive</td>
<td>0.70 (0.37-1.29)</td>
<td>0.018</td>
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<td>Treatment (ref:</td>
<td>Any Rx</td>
<td>0.73 (0.43-1.25)</td>
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<tr>
<td>None)</td>
<td></td>
<td></td>
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Table 3: Univariable Survival of Selected Immune Markers within ProMisE subtype. The within subtype association between select immune markers binarized at the median with clinical outcome were assessed by Cox proportion hazard to compute hazard ratios (HR) of overall (OS), disease-specific (DSS) and progression-free survival (PFS) using a Kaplan-Meier survival analysis.

<table>
<thead>
<tr>
<th>Marker</th>
<th>OS HR (95% CI)</th>
<th>P value</th>
<th>DSS HR (95% CI)</th>
<th>P value</th>
<th>PFS HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
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<tr>
<td><strong>MMRd</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3+CD8+ (putative cytotoxic T cells)</td>
<td>0.482 (0.222-1.046)</td>
<td>0.059</td>
<td>0.393 (0.145-0.954)</td>
<td>0.037</td>
<td>0.536 (0.203-1.329)</td>
<td>0.173</td>
</tr>
<tr>
<td></td>
<td>0.487 (0.225-1.055)</td>
<td>0.062</td>
<td>0.489 (0.190-1.167)</td>
<td>0.103</td>
<td>0.884 (0.351-2.227)</td>
<td>0.793</td>
</tr>
<tr>
<td><strong>CD3+CD8- (putative CD4+)</strong></td>
<td>0.531 (0.245-1.150)</td>
<td>0.103</td>
<td>0.338 (0.116-0.845)</td>
<td>0.019</td>
<td>0.500 (0.190-1.239)</td>
<td>0.130</td>
</tr>
<tr>
<td></td>
<td>0.762 (0.361-1.612)</td>
<td>0.476</td>
<td>0.713 (0.287-1.687)</td>
<td>0.430</td>
<td>0.724 (0.284-1.791)</td>
<td>0.479</td>
</tr>
<tr>
<td><strong>CD138-CD79a+ (Bcells)</strong></td>
<td>0.816 (0.388-1.716)</td>
<td>0.590</td>
<td>1.078 (0.456-2.612)</td>
<td>0.850</td>
<td>0.881 (0.349-2.220)</td>
<td>0.788</td>
</tr>
<tr>
<td></td>
<td>0.421 (0.185-0.892)</td>
<td>0.023</td>
<td>0.306 (0.105-0.766)</td>
<td>0.010</td>
<td>0.740 (0.296-1.847)</td>
<td>0.521</td>
</tr>
<tr>
<td><strong>POLE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3+CD8+ (putative cytotoxic T cells)</td>
<td>0.965 (0.149-6.249)</td>
<td>0.971</td>
<td>0.995 (0.081-12.263)</td>
<td>0.997</td>
<td>0.333 (0.002-6.248)</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>2.404 (0.396-24.806)</td>
<td>0.303</td>
<td>1.061 (0.086-13.065)</td>
<td>0.967</td>
<td>3.000 (0.160-437.761)</td>
<td>0.317</td>
</tr>
<tr>
<td>CD3+CD8- (putative CD4+)</td>
<td>1.003 (0.155-6.490)</td>
<td>0.998</td>
<td>0.212 (0.002-2.608)</td>
<td>0.170</td>
<td>3.000 (0.160-437.761)</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>0.104 (0.001-0.976)</td>
<td>0.039</td>
<td>0.188 (0.001-2.316)</td>
<td>0.145</td>
<td>0.296 (0.002-5.554)</td>
<td>0.289</td>
</tr>
<tr>
<td>CD138-CD79a+ (Bcells)</td>
<td>0.429 (0.042-2.611)</td>
<td>0.318</td>
<td>0.212 (0.002-2.608)</td>
<td>0.170</td>
<td>0.333 (0.002-6.248)</td>
<td>0.317</td>
</tr>
<tr>
<td></td>
<td>0.402 (0.039-2.445)</td>
<td>0.287</td>
<td>0.199 (0.001-2.444)</td>
<td>0.156</td>
<td>0.269 (0.002-5.554)</td>
<td>0.289</td>
</tr>
<tr>
<td>CD8+PD-1+</td>
<td>0.402 (0.039-2.445)</td>
<td>0.287</td>
<td>0.199 (0.001-2.444)</td>
<td>0.156</td>
<td>0.296 (0.002-5.554)</td>
<td>0.289</td>
</tr>
<tr>
<td></td>
<td>1.030 (0.159-6.666)</td>
<td>0.976</td>
<td>1.061 (0.086-13.065)</td>
<td>0.967</td>
<td>0.333 (0.002-6.248)</td>
<td>0.317</td>
</tr>
<tr>
<td><strong>P53wt</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3+CD8+ (putative cytotoxic T cells)</td>
<td>0.706 (0.353-1.374)</td>
<td>0.301</td>
<td>0.455 (0.180-1.043)</td>
<td>0.061</td>
<td>0.748 (0.329-1.644)</td>
<td>0.460</td>
</tr>
<tr>
<td></td>
<td>1.558 (0.800-3.113)</td>
<td>0.189</td>
<td>1.409 (0.630-3.236)</td>
<td>0.398</td>
<td>1.178 (0.532-2.607)</td>
<td>0.689</td>
</tr>
<tr>
<td>CD3+CD8- (putative CD4+)</td>
<td>1.098 (0.565-2.156)</td>
<td>0.777</td>
<td>0.783 (0.341-1.750)</td>
<td>0.543</td>
<td>0.793 (0.348-1.743)</td>
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<td>0.715 (0.361-1.391)</td>
<td>0.320</td>
<td>0.704 (0.306-1.574)</td>
<td>0.387</td>
<td>0.604 (0.259-1.334)</td>
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<tr>
<td>CD138-CD79a+ (Bcells)</td>
<td>0.574 (0.283-1.122)</td>
<td>0.102</td>
<td>0.421 (0.167-0.967)</td>
<td>0.040</td>
<td>0.605 (0.259-1.338)</td>
<td>0.209</td>
</tr>
<tr>
<td></td>
<td>0.827 (0.421-1.609)</td>
<td>0.573</td>
<td>0.628 (0.268-1.408)</td>
<td>0.253</td>
<td>0.764 (0.336-1.679)</td>
<td>0.492</td>
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<tr>
<td>CD8+PD-1+</td>
<td>1.585 (0.770-3.115)</td>
<td>0.214</td>
<td>1.276 (0.506-2.926)</td>
<td>0.650</td>
<td>1.307 (0.521-2.969)</td>
<td>0.611</td>
</tr>
<tr>
<td></td>
<td>0.708 (0.354-1.377)</td>
<td>0.304</td>
<td>0.643 (0.274-1.439)</td>
<td>0.276</td>
<td>0.671 (0.295-1.474)</td>
<td>0.315</td>
</tr>
<tr>
<td><strong>P53abn</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD3+CD8+ (putative cytotoxic T cells)</td>
<td>0.929 (0.533-1.619)</td>
<td>0.796</td>
<td>1.066 (0.577-1.971)</td>
<td>0.838</td>
<td>1.136 (0.627-2.057)</td>
<td>0.676</td>
</tr>
<tr>
<td></td>
<td>0.851 (0.488-1.483)</td>
<td>0.570</td>
<td>1.039 (0.562-1.921)</td>
<td>0.903</td>
<td>0.768 (0.424-1.391)</td>
<td>0.381</td>
</tr>
<tr>
<td>CD3+CD8- (putative CD4+)&amp;  E &amp; 1.126 (0.644-1.966) &amp; 0.677 &amp; 1.431 (0.763-2.686) &amp; 0.262 &amp; 1.165 (0.643-2.111) &amp; 0.615</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.065 (0.610-1.860)</td>
<td>0.824</td>
<td>1.198 (0.643-2.233)</td>
<td>0.568</td>
<td>0.770 (0.425-1.394)</td>
<td>0.385</td>
</tr>
</tbody>
</table>
Figure 1. Representative images of multiplex IHC for TIL subsets (A-D). Specific marker combinations and colour legends are as shown, with left column H and E images magnified at 20X.

Figure 2. The epithelial (A) and stromal (B) densities of immune markers. The density of epithelial and stromal CD3+CD8+ TIL (putative cytotoxic T cells) and CD3+CD8- TIL (putative CD4+ TIL) was highest in POLE tumors, followed closely by MMRd tumors. For B cells (CD138-CD79a+) and plasma cells (CD138+CD79a+) markedly higher densities were seen in tumor stroma (not epithelium) and varied by ProMisE subtype (p < 0.01)(see also Supplementary Table S2).

Figure 3. Cluster analysis of TIL patterns in EC based on log-transformed IHC results for all TIL subsets and the PD-A/PD-L1 pathway in both A. epithelial and B. stromal compartments. TIL high tumors showed significantly higher densities of all five TIL subsets; CD8+ and CD4+ T cells, B cells, plasma cells, and Tregs and high levels of PD-1+ and PD-L1+ cells also characterized this group.

Figure 4. Survival analyses. TIL high versus TIL low immune clusters showed no association with A. OS, B. DSS or C. PFS across the full cohort. Within ProMisE subsets there was a trend toward inferior outcomes in TIL low MMRd ECs (p=ns, data not shown).
A.

B. 

Figure 2.
Figure 3B.
Figure 4A.

Overall Two Immune Clusters (OS)

Total follow-up (years)

Overall survival

HR 0.903 (95% CI: 0.626–1.305) ~ TIL\{high\} vs. low immune

Log Rank p = 0.588

TIL\{low\}  187  176  157  133  111  86

TIL\{high\} 240  218  188  146  126  92

Numbers at risk
Figure 4B.

Overall Two Immune Clusters (DSS)

Disease specific survival

0.00 0.25 0.50 0.75 1.00

Total follow-up (years)

HR(F) 0.866 (95% CI: 0.562–1.321) ~ TIL(high) vs. low immune
Log Rank p = 0.498

TIL(low) 181 171 156 132 110 86
TIL(high) 234 213 185 144 124 91

Numbers at risk
Molecular subtype not immune response drives outcomes in endometrial carcinoma

Aline Talhouk, Heather Derocher, Pascal Schmidt, et al.

Clin Cancer Res  Published OnlineFirst December 6, 2018.

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