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Original Article

# Evaluation of Treatment Effects in Patients With Endometrial Cancer and *POLE* Mutations: An Individual Patient Data Meta-Analysis

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**BACKGROUND:** Endometrial cancers (ECs) with somatic mutations in DNA polymerase epsilon (*POLE*) are characterized by unfavorable pathological features, which prompt adjuvant treatment. Paradoxically, women with *POLE*-mutated EC have outstanding clinical outcomes, and this raises concerns of overtreatment. The authors investigated whether favorable outcomes were independent of treatment. **METHODS:** A PubMed search for *POLE* and *endometrial* was restricted to articles published between March 1, 2012, and March 1, 2018, that provided individual patient data (IPD), adjuvant treatment, and survival. Following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting guidelines for IPD, the authors used univariate and multivariate one-stage meta-analyses with mixed effects Cox models (random effects for study cohorts) to infer the associations of treatment, traditional prognostic factors, and outcome, which was defined as the time from first diagnosis to any adverse event (progression/recurrence or death from EC). **RESULTS:** Three hundred fifty-nine women with *POLE*-mutated EC were identified; 294 (82%) had pathogenic mutations. Worse outcomes were demonstrated in patients with nonpathogenic *POLE* mutations (hazard ratio, 3.42; 95% confidence interval, 1.47-7.58; log-rank $P < .01$). Except for stage ($P < .01$), traditional prognosticators were not associated with progression/recurrence or death from disease. Adverse events were rare (11 progressions/recurrences and 3 disease-specific deaths). Salvage rates in patients who experienced recurrence were high and sustained, with 8 of 11 alive without evidence of disease (range, 5.5-14.2 years). Adjuvant treatment was not associated with outcome. **CONCLUSIONS:** Clinical outcomes for ECs with pathogenic *POLE* mutations are not associated with most traditional risk parameters, and patients do not appear to benefit from adjuvant therapy. The observed low rates of recurrence/progression and the high and sustained salvage rates raise the possibility of safely de-escalating treatment for these patients. ***Cancer* 2021;127:2409-2422**. © *2021 American Cancer Society*.

**LAY SUMMARY:**

- Ten percent of all endometrial cancers have mutations in the DNA repair gene DNA polymerase epsilon (*POLE*).
- Women who have endometrial cancers with true *POLE* mutations experience almost no recurrences or deaths from their cancer even when their tumors appear to have very unfavorable characteristics.
- Additional therapy (radiation and chemotherapy) does not appear to improve outcomes for women with *POLE*-mutated endometrial cancer, and this supports the move to less therapy and less associated toxicity.
- Diligent classification of endometrial cancers by molecular features provides valuable information to inform prognosis and to direct treatment/no treatment.

**KEYWORDS:** adjuvant therapy, de-escalation, DNA polymerase epsilon (*POLE*), endometrial cancer, individual patient data (IPD) meta-analysis, molecular classification, overtreatment.

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## INTRODUCTION

Endometrial cancer (EC) is the most common gynecological malignancy in the developed world and the second most common gynecological cancer worldwide.[1] Many women with EC may be cured by surgery alone, but some are at risk of disease recurrence and in need of adjuvant treatment to reduce that risk. Identifying women who will benefit from adjuvant treatment remains a challenge. For decades, risk stratification of EC for postsurgical treatment decision-making has been based on clinicopathological parameters, principally stage, histology, and grade. Both histotype and grade assignment have been demonstrated to be poorly reproducible,[2-5] and molecular features, reflecting tumor biology and prognosis, increasingly are being integrated into clinical care decision-making.[6-8]

The Cancer Genome Atlas (TCGA)[9] identified a novel subgroup of ECs with mutations in DNA polymerase epsilon (*POLE*) that are responsible for DNA replication and lead to exceedingly high somatic mutation frequencies ("ultramutated": >100 mutations per megabase).[9] It is now recognized that approximately 5% to 10% of all ECs harbor *POLE* mutations.[10-16] Pragmatic molecular classification systems have moved to identify this subgroup simply by testing for pathogenic mutations within the exonuclease domain (EDM) of *POLE,* termed *POLE*mut.[11,13,17-19] Composed mostly, but not exclusively, of the endometrioid histotype, *POLE*mut ECs commonly have unfavorable histomorphological features, including high grade, deep myometrial invasion, and/or lymphovascular invasion (LVI). Even with these worrisome features, patients with *POLE*mut ECs have exceptionally good survival outcomes (>96% 5-year survival).[9,10,12,15,20-23]

Current risk stratification systems used in EC management[24,25] identify the aggressive/unfavorable clinicopathological features in *POLE*mut cancers and direct many of these women to receive adjuvant therapy. Because of the significant short- and long-term side effects associated with both systemic chemotherapy and radiation and the resulting substantial cost to health systems from administering these therapies, it is of great importance to determine whether patients with *POLE*mut EC actually need these regimens and whether traditional risk factors and stratification systems are appropriate to apply within this molecular subtype.

Clinical trials currently underway are anticipated to produce high-quality evidence for determining whether patients with *POLE*mut EC can safely forgo adjuvant therapy.[26,27] However, data from these trials may take several years to mature. Moreover, it remains uncertain whether a definitive answer can be reached: 1) *POLE*mut ECs are rare and represent <10% of all ECs, and 2) this patient group enjoys excellent outcomes, and this results in a very small number of adverse events (recurrences and deaths), which drive power in most statistical analyses. For the same reasons, individual retrospective studies are not sufficiently powered to address this research question.

In this study, we systematically reviewed and pooled individual patient data (IPD) from all available and/or published studies involving women with *POLE*mut ECs to estimate the association, if any, of adjuvant treatment and clinical outcomes in an IPD meta-analysis. Although IPD meta-analyses of randomized trials are considered the gold standard for systematic reviews, the absence of randomized treatment means that the causal effects of treatment and outcome can only be interpreted as associations, particularly in the presence of possible unmeasured confounders.

## MATERIALS AND METHODS

We adopted the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines[28] for IPD (PRISMA-IPD) in the conduct and reporting of findings (see the checklist in Appendix A in the supporting information). A study protocol was developed and shared with investigators when individual participant data were requested (see Appendix B in the supporting information), but it was not registered. All published studies had ethics approval from their respective institutions. The BC Cancer research ethics board approved the secondary analysis of previously published data (REB# H18-02000).

### *Study Selection*

We conducted a PubMed search for the words *POLE* and *endometrial* in articles published between March 1, 2012, and March 1, 2018. We selected studies where *POLE* mutation data were available and where adjuvant treatments and survival outcomes could be obtained. For publications reporting on the same patients, we included the most comprehensive or most recent report. We excluded case reports, studies with fewer than 5 patients with *POLE* mutations, reviews, editorials, and studies that reported on *POLE* in other cancers. We also excluded highly selected series of rare cancers to avoid introducing bias to the results. Two reviewers (A.T. and P.S.) searched and reviewed eligibility criteria, and 2 reviewers (P.S. and S.L.) read through the full publications and extracted study characteristics (see Appendix C in the supporting information).

### Data Acquisition, IPD Integrity, and Case Selection

We requested anonymized IPD from investigators of studies that met our study inclusion criteria. We also solicited from our network any unpublished data that met the same criteria. We received individual records of participants with any *POLE* mutations, including those who had other molecular features such as microsatellite instability (MSI)/mismatch repair deficiency (MMRd) or an abnormal p53 status. We excluded patients who may have received neoadjuvant chemotherapy and those with less than 2 years of potential follow-up. We verified data integrity by comparing available data with what may have been previously reported in publications. When data were missing or when discrepancies were found, we contacted the study authors and requested further clarifications (see Appendix C in the supporting information). We excluded cases in which adjuvant treatments or clinical outcomes could not be definitively determined. Data from EC patients with MMRd (but without a *POLE* mutation) from Vancouver and Germany were used to boost the propensity score analysis, which attempted to correct confounding by indication (described in the Statistical Analysis section) by modeling the probability of receiving treatment based on clinical characteristics.

The primary outcome was the time from first diagnosis to any adverse event attributed to EC; this included either progression/recurrence or death from EC. *POLE* mutations were categorized according to recently published criteria,[29] which distinguished those with pathogenic mutations and an ultramutated phenotype versus nonpathogenic mutations. We also considered the MSI/mismatch repair (MMR) and p53/TP53 status when available as well as other known prognostic clinical and pathological parameters in EC: age of the patient at diagnosis, body mass index, histological subtype, stage, grade, myometrial invasion, LVI, adjuvant treatment, and European Society for Medical Oncology (ESMO) clinical risk group.[25] Exact definitions of outcomes and prognostic factors can be found in the supporting information.

### Risk of Bias

The risk of bias was assessed with the Quality in Prognosis Study (QUIPS) tool.[30] The QUIPS tool categorizes the risk of bias as high, moderate, or low according to the following criteria: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis/reporting. We also explored variations between participant-level characteristics across studies with summary statistics and graphical plots.

### Statistical Analysis

We characterized clinicopathological and survival differences between patients with pathogenic *POLE* mutations and those with nonpathogenic mutations in the *POLE* EDM. We explored whether traditional risk factors, known to be prognostic in EC, were also individually or jointly prognostic within the *POLE*mut subtype. We used a one-stage meta-analysis because it was the most appropriate approach for addressing the challenges of small study size and rare events.[31]

Our study included data from observational studies as well as clinical trials; as such, treatment was not always randomized and was likely associated with both clinicopathological variables and outcomes, which may result in confounding. We addressed this with a propensity score analysis. We adjusted for confounders based on the disjunctive cause criterion[32] (Supporting Fig. 1) and computed the probability of assigning any adjuvant treatment, given the measured covariates, with a mixed effects logistic regression model, with random effects assigned to each cohort. Because the mutation status was not known at the time of treatment assignment, we augmented our data set with data from additional cases from Vancouver and Germany without a *POLE* mutation to compute the propensity scores. We evaluated different approaches to adjust for propensity scores.[33] Because of the small number of events, and to preserve statistical power, we adjusted for confounding by including the propensity score as a continuous predictor in all survival models. We imputed missing values for age, histotype, and LVI by using the Moritz and Feng framework[34] and the least absolute shrinkage and selection operator regularization algorithm.

To fit survival models, we used mixed effects Cox regression (the coxme R package)[35,36] with random effects for each cohort. We investigated, in turn, the univariable associations of age, stage, histotype, grade, myometrial invasion, LVI, and ESMO risk groups with outcome. In multivariable models, we estimated the association of treatment with outcome after simultaneously adjusting for multiple prognostic factors: age, LVI, ESMO risk groups, and propensity of receiving treatment. Because traditional clinicopathological parameters and risk stratification systems may not apply to *POLE*mut ECs, we stratified patients similarly to 2 currently active clinical trials (PORTEC-4a[26] and TAPER[27]) in which de-escalated therapy (observation only/no adjuvant therapy) is recommended for intermediate- and high-risk, early-stage (stage I and II [microscopic]) ECs harboring *POLE* mutations. These trial-eligible patients, in addition to patients with

low-risk, early-stage ECs, for whom routinely no therapy would be recommended (eg, stage IA and grade 1/2), were grouped together as "trial-based low-risk" in comparison with trial-ineligible patients and/or patients with higher stage *POLE*mut ECs for whom clinicians may be uncomfortable omitting adjuvant therapy (Supporting Table 1).

We also attempted to evaluate heterogeneity in associations between treatment and outcome across different risk groups within the *POLE*mut group. We did this by modeling an interaction between treatment and risk groups (defined by both ESMO and trial-based criteria). We tested the constant hazard assumption with Schoenfeld residual plots, by comparing the fit with the apparent area under the curve.[37] We used omnibus likelihood ratio tests to compute *P* values in multivariable models. All statistical tests were 2-sided, and the level of significance was set at .05.

## RESULTS

### Cohort Description

The electronic PubMed search returned 105 publications, and collaborators provided 3 additional cohorts unpublished at the time of the search. Among the 108 studies, 60 were not relevant to EC or did not have available data. A full-text review of the remaining 48 studies resulted in the exclusion of 11 studies that reported on fewer than 5 cases and 2 studies with highly selected rare types of EC (Fig. 1). The final 35 publications that met our inclusion criteria were grouped into 15 unique data cohorts. Principal investigators and data stewards associated with those cohorts were contacted, and 13 of 15 provided individual participant records. This included data from Vancouver,[12] the PORTEC-1&2 series,[11] the University of Tübingen,[19] the University of Washington (UWash),[16] the TCGA[9] and Pan-Cancer[38] cohorts, Yale University,[39,40] TransPORTEC,[18] Singapore Health,[41] Calgary,[21] Toronto,[42] Leuven,[10] and Ohio State University (OSU).[22] We received data from a total of 359 patients with *POLE*-mutated ECs; this is the largest collection of women with *POLE*mut ECs to be studied simultaneously.

### Risk of Bias Assessment

The QUIPS criteria revealed a variable risk of bias among the included studies. The retrospective design of most studies meant a large degree of participation and access to complete follow-up data, but it also resulted in a selection bias. Most studies provided detailed descriptions of the measurement and validation of prognostic factors and thus were low for the risk of prognostic factor measurement bias. Clear definitions of outcomes, provided by most included studies, resulted in low outcome measurement bias. Several studies exhibited a high risk of bias in study confounding because of a lack of multivariable analysis; however, this did not affect the analysis in this project because we requested IPD data on known confounders. Treatment was not randomized in the majority of studies that we evaluated, and this likely resulted in confounders associated with both treatment assignment and unfavorable clinicopathological features. The full QUIPS analysis and rankings are in Supporting Table 2.

### Characterization of ECs With POLE Mutations: Stratification by Pathogenic and Nonpathogenic Mutations

Following Leon-Castillo et al,[29] we reviewed our list of candidate *POLE* mutations and stratified cases as pathogenic versus unknown or nonpathogenic. In all, 359 cases were identified: 294 (82%) were pathogenic, and 65 (18%) were nonpathogenic (for details by cohort, see Supporting Table 3). P286R (149 of 294 or 51%) and V411 (91 of 294 or 31%) were the most common pathogenic mutations observed, with the full distribution of mutations shown in Supporting Table 4. Among the nonpathogenic *POLE* mutations (n = 65), the MMR or MSI status was unknown in 14 cases; however, when it was known, 28 of 51 (55%) were associated with MMRd/MSI-high and mutations in *POLE*. This raises the possibility that the *POLE* mutation arose as a secondary event in a hypermutated EC. In contrast, among pathogenic *POLE* mutated ECs for which MMR/MSI data were available, the majority of cases (89%) were MMR proficient. Table 1 shows the clinicopathological characteristics and treatment data for *POLE* pathogenic and nonpathogenic/variant of uncertain significance ECs. Outcomes were also different in the 2 groups, with more than 3-fold increase in hazard ratio for disease-related adverse events in the nonpathogenic *POLE* mutation cohort versus the pathogenic *POLE* mutation cohort (hazard ratio, 3.4; 95% confidence interval, 1.5-7.6; log-rank $P < .01$; Supporting Fig. 2).

All subsequent analyses were restricted to the pathogenic *POLE* mutation cohort (n = 294), which is called *POLE*mut hereafter. Table 1 demonstrates the unfavorable pathological features observed within *POLE*mut ECs: 51% were at grade 3, 32% had LVI, over 36% had deep myometrial invasion, 5% were identified as having lymph node metastases, and 10% were assigned nonendometrioid histologies. This was also reflected in the high

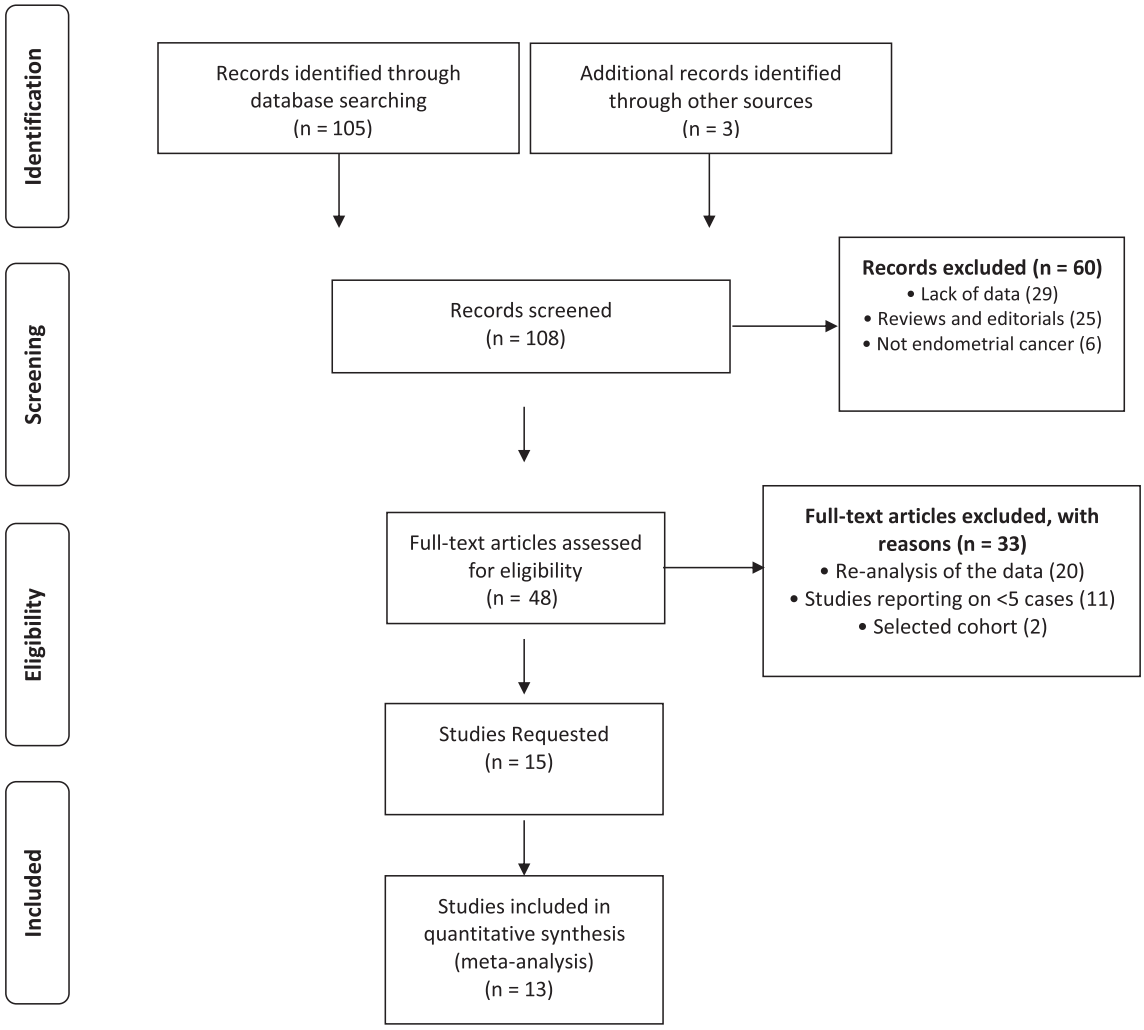


**Figure 1.** Preferred Reporting Items for Systematic Review and Meta-Analysis flowchart.

proportions of ESMO intermediate-risk designations (29%) and high-risk designations (38%) and the observation that 60% of these women received some form of treatment. Women with *POLE*mut ECs were younger and thinner than historical averages observed for other EC molecular subtypes.[12,13,19] Treatment data were not available for 23 patients with *POLE*mut ECs, which left a total of 271 fully evaluable cases for the analysis (Supporting Fig. 3).

### *Variability Across Cohorts*

Most of the data were from retrospective cohort studies that included participants with varied characteristics by design or because of differing population distributions. Clinicopathological variables, including histotype, stage, grade, and treatment, varied significantly across each cohort (Supporting Table 5). In most cohorts, the most prevalent histotype was endometrioid; however, PORTEC-1&2, UWash, TCGA, SingHealth, and Calgary included only patients with an endometrioid histotype by design. The Yale and Leuven cohorts had relatively even representations of endometrioid and nonendometrioid/mixed histotypes. Most patients across all cohorts were at stage IA/B. In particular, PORTEC-1&2, Calgary, and OSU did not include any stage II+ patients in their cohorts. There was variation in grade within each cohort, which reflected the type of center or the setting from which data were gathered (population-based, referral, or clinical trial) and the subjectivity of grade assignment. Vancouver, which presented data from a tertiary cancer center, had a majority of grade 3 cases, whereas PORTEC-1&2 had a majority

**TABLE 1.** Clinicopathological Characteristics, Treatments, and Outcomes for *POLE* Pathogenic and Nonpathogenic/Variant of Uncertain Significance Endometrial Cancers

| Variable | Total (n = 359) | Pathogenic (n = 294) | Nonpathogenic (n = 65) | *P* |
|---|---|---|---|---|
| Age, y[a] | | | | .002 |
| Median (range) | 58.0 (31.0-92.6) | 57.0 (31.0-92.6) | 64.0 (35.0-82.3) | |
| BMI, kg/m$^2$ | | | | .359 |
| Median (range) | 27.3 (17.4-213.5) | 27.1 (18.0-54.2) | 28.3 (17.4-213.5) | |
| Missing | 104 | 95 | 9 | |
| Stage, No. (%)[a] | | | | .095 |
| IA | 193 (53.8) | 165 (56.1) | 28 (43.1) | |
| IB | 101 (28.1) | 81 (27.6) | 20 (30.8) | |
| II | 22 (6.1) | 19 (6.5) | 3 (4.6) | |
| IIIA | 16 (4.5) | 10 (3.4) | 6 (9.2) | |
| IIIB | 5 (1.4) | 3 (1.0) | 2 (3.1) | |
| IIIC | 15 (4.2) | 12 (4.1) | 3 (4.6) | |
| IV | 7 (1.9) | 4 (1.4) | 3 (4.6) | |
| Myometrial invasion, No. (%) | | | | .449 |
| None | 39 (11.4) | 35 (12.4) | 4 (6.8) | |
| 1%-50% | 175 (51.3) | 144 (51.1) | 31 (52.5) | |
| >50% | 127 (37.2) | 103 (36.5) | 24 (40.7) | |
| Missing | 18 | 12 | 6 | |
| Tumor grade, No. (%)[a] | | | | .572 |
| 1 | 107 (29.8) | 91 (31.0) | 16 (24.6) | |
| 2 | 66 (18.4) | 54 (18.4) | 12 (18.5) | |
| 3 | 186 (51.8) | 149 (50.7) | 37 (56.9) | |
| Histological subtype, No. (%)[a] | | | | .024 |
| Endometrioid | 316 (88.3) | 263 (89.5) | 53 (82.8) | |
| Serous | 14 (3.9) | 7 (2.4) | 7 (10.9) | |
| Clear cell | 2 (0.6) | 2 (0.7) | 0 (0.0) | |
| Mixed | 23 (6.4) | 19 (6.5) | 4 (6.2) | |
| Undifferentiated | 3 (0.8) | 3 (1.0) | 0 (0.0) | |
| Lymphovascular invasion, No. (%) | | | | .057 |
| Negative | 229 (66.2) | 195 (68.4) | 34 (55.7) | |
| Positive | 117 (33.8) | 90 (31.6) | 27 (44.3) | |
| Missing | 13 | 9 | 4 | |
| Nodal status, No. (%)[a] | | | | .577 |
| Not tested | 36 (10.2) | 31 (10.7) | 5 (8.1) | |
| Negative | 297 (84.1) | 245 (84.2) | 52 (83.9) | |
| Positive | 20 (5.7) | 15 (5.2) | 5 (8.1) | |
| Postsurgical treatment, No. (%) | | | | .184[b] |
| None | 124 (38.0) | 109 (40.2) | 15 (27.3) | |
| Any | 202 (62.0) | 162 (59.8) | 40 (72.7) | |
| Vaginal brachytherapy only | 32 (9.8) | 28 (10.3) | 4 (7.3) | |
| EBRT without chemotherapy | 108 (33.1) | 86 (31.7) | 22 (40.0) | |
| Any chemotherapy | 62 (19.0) | 48 (17.7) | 14 (25.5) | |
| Missing | 33 | 23 | 10 | |
| ESMO (2013) risk group, No. (%)[a] | | | | .119 |
| Low | 111 (31.0) | 98 (33.3) | 13 (20.3) | |
| Intermediate | 106 (29.6) | 85 (28.9) | 21 (32.8) | |
| High | 141 (39.4) | 111 (37.8) | 30 (46.9) | |
| *TP53*/p53 status, No. (%) | | | | .775 |
| Normal | 121 (77.1) | 87 (77.7) | 34 (75.6) | |
| Abnormal | 36 (22.9) | 25 (22.3) | 11 (24.4) | |
| Missing | 202 | 182 | 20 | |
| MMR/MSI status, No. (%) | | | | <.001 |
| Proficient or MSS or MSI-low | 219 (76.6) | 196 (87.5) | 23 (37.1) | |
| Deficient or MSI-high | 67 (23.4) | 28 (12.5) | 39 (62.9) | |
| Missing | 73 | 70 | 3 | |

Abbreviations: BMI, body mass index; EBRT, external-beam radiotherapy; ESMO, European Society for Medical Oncology; POLE, DNA polymerase epsilon; MMR, mismatch repair; MSS, microsatellite stability; MSI, microsatellite instability.
[a]The variable had fewer than 5 missing cases in each *POLE* group.
[b]The *P* value pertains to the comparison of all treatment groups with *POLE*.

of grade 1 cases (trial inclusion criteria). Calgary and Canadian High Risk Endometrial Cancer–Toronto (CHREC-Toronto) were the only cohorts with only grade 3 participants. The proportion of women who received treatment for their *POLE*mut ECs also varied across cohorts; treatment was defined by clinical trial protocol in some cases, and by institutional practice in others. The follow-up time also varied across studies,

with the TCGA, Pan-Cancer, and OSU cohorts having a high proportion of cases with follow-up missing after 3 years (Supporting Fig. 4).

There were also similarities across cohorts. The median age for most cohorts was less than 60 years except for CHREC-Toronto and PORTEC-1&2, whose median age was 62.3 and 62.0 years, respectively. Additionally, the median body mass index was below the moderate-risk obesity range (35-40 kg/m$^2$) in most cohorts. Body mass index data were not reported for PORTEC-1&2, TransPORTEC, or CHREC-Toronto. In all cohorts, the majority of patients (85.6%) had a negative nodal status, with nodes not tested in 11%. Positive nodes were found only in the Vancouver (n = 2), TCGA (n = 3), and Yale (n = 1) cohorts.

Methodologies for *POLE* testing varied across the collected cohorts. Cases from PORTEC-1&2, UWash, Yale, TransPORTEC, Calgary, Leuven, and OSU underwent Sanger sequencing. The Vancouver, Germany, SingHealth, and Calgary cohorts assessed exons 9 to 14, whereas PORTEC-1&2, TransPORTEC, and Leuven were restricted to exons 9 to 13 of the EDM of *POLE*. The other cohorts did not specify which exons were encompassed. Three cohorts—Vancouver, Germany, and SingHealth—validated their detected *POLE* mutations by resequencing with other techniques, including high-depth MiSeq and/or Sanger sequencing, with the others using the same polymerase chain reaction primers (Supporting Table 6).

### Characterization by Treatment

Treatment data, when available, were broadly grouped as none (40%) or any (60%), which in turn was categorized as vaginal brachytherapy only (10%), any radiation given without chemotherapy (eg, external-beam pelvic radiotherapy with or without vaginal brachytherapy with or without a para-aortic boost; 32%), and any chemotherapy given with or without radiation (18%). *POLE*mut ECs receiving any treatment were primarily at stage IA (41%) or stage IB (38%), 9% were at stage II, and 12% were at stage III/IV. Although reasons for giving/not giving treatment could not be ascertained from these retrospective series, it appeared that younger age was associated with receiving adjuvant therapy ($P < .001$), specifically chemotherapy (median age, 51 years for women receiving chemotherapy vs 58 years for women receiving no therapy or vaginal brachytherapy and 59 years for women receiving any radiation without chemotherapy). Moreover, treatment was often associated with unfavorable histopathological features; patients with a nonendometrioid histology, a higher stage, a higher grade, and LVI were more likely to be treated (Supporting Table 7).

We had a limited number of untreated patients within this cohort for considering the natural history of *POLE*mut ECs. Although 40% of the assessed patients (109 of 271) had no recorded treatment, the majority of these (n = 67; 61%) were low-risk by ESMO criteria[25] and would likely not have been recommended to undergo any additional therapy or have been expected to have adverse outcomes. There were 28 patients with intermediate-risk EC (26% of the cohort) and 14 patients with high-risk EC (13%) who did not receive adjuvant therapy, including 3 high-risk patients who had an adverse event (stage 1B, grade 3, endometrioid ECs with LVI; Table 2), but we were unable to determine why they had not been treated.

### Adverse Events

Patient follow-up was similar among the different treatment groups (5 years by reverse Kaplan-Meier). A total of 12 adverse events were recorded; they encompassed 11 progression-free survival (PFS) events, 2 of which occurred in patients with advanced-stage disease (IIIC/IV) within 3 to 4 months of surgery (Table 2) and were followed by a disease-specific death within a year. One patient had a disease-specific death with unknown timing of her progression (no PFS recorded). Among the 9 women with recorded progression of disease (a PFS event), 1 died for reasons unrelated to her cancer 3 years from her diagnosis, and the remainder were alive with no evidence of disease at the time of censoring 5.5 to 14.2 years from the diagnosis; this demonstrated highly favorable and sustained salvage rates (Table 2). This no-evidence-of-disease-after-PFS group included a woman with stage IIIB EC and 6 at high risk (ESMO). We have limited treatment data on these patients after their recurrence (eg, specifics on dose and duration), but both chemotherapy (carboplatin and paclitaxel) and radiation were recorded. Because of the era of data collection in these cases, it is not suspected that any of these women received immune blockade/PD1 inhibitor therapy either at the primary diagnosis or at recurrence.

Adverse events in relationship to adjuvant treatment are detailed in Table 3, with no apparent differences in outcome according to the treatment received. Although 29 (almost 10%) of the *POLE*mut EC cohort were at stage III/IV (including 5% node-positive cases), only 3 adverse events occurred in women with advanced-stage disease, and all of these had received treatment (radiotherapy with or without chemotherapy). Figure 2 shows adverse events in relationship to ESMO risk groups, and

**TABLE 2.** Characteristics of patients with any Disease-Related Adverse Events (n = 12) Progression Events (n = 11) and Disease-Specific Deaths (n = 3)

| Cohort[a] | *POLE* Mutation | Age, y | BMI, kg/m$^2$ | Stage | Grade | Nodes | LVI | Histotype | Myo, % | ESMO (2013) | Trial Risk[b] | Treatment | PFS | Site of Recurrence | DSS | OS | PFS, y | DSS, y | OS, y |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PORTEC-1&2 | P286R | 56.0 | NA | IA | 1 | Negative | Negative | EM | 1-50 | Low | Low | RT only | Yes | Distant | No | No | 1.26 | 12.15 | 12.15 |
| PORTEC-1&2 | P286R | 70.9 | NA | IB | 1 | Negative | Negative | EM | >50 | Intermediate | Low | Brachy only | Yes | Distant | No | No | 0.83 | 7.20 | 7.20 |
| TransPORTEC | P286R | 74.0 | NA | IB | 3 | Negative | Negative | EM | >50 | High | Low | RT only | Yes | Pelvic | No | No | 1.69 | 5.29 | 5.29 |
| Calgary | P286R | 60.0 | 24.9 | IB | 3 | Negative | Positive | EM | >50 | High | High | None | Yes | Unknown | No | No | 1.67 | 5.50 | 5.50 |
| UWash | A456P | 55.2 | NA | IB | 3 | Negative | Positive | EM | >50 | High | High | None | Yes | Unknown | No | No | 1.96 | 14.22 | 14.22 |
| Yale | P286R | 49.0 | 50.5 | IIIB | 3 | Negative | Negative | EM/CC | >50 | High | High | Chemotherapy + RT | Yes | Unknown | No | No | 4.62 | 10.60 | 10.60 |
| Germany | V411L | 66.3 | NA | IV | 3 | Negative | Positive | EM | >50 | High | High | RT only | Yes | Unknown | Yes | Yes | 0.31 | 1.14 | 1.14 |
| Vancouver | P286R | 75.3 | 21.0 | IB | 2 | Not tested | Negative | EM | >50 | Intermediate | Low | RT only | Unknown | Unknown | Yes | Yes | NA | 2.94 | 2.94 |
| Vancouver | P286R | 73.6 | NA | IIIC | 3 | Positive | Positive | EM/SC | >50 | High | High | Chemotherapy + RT | Yes | Distant | Yes | Yes | 0.24 | 0.91 | 0.91 |
| Vancouver | P286R | 51.7 | 20.2 | IB | 3 | Negative | Positive | EM | >50 | High | High | RT only | Yes | Vaginal | No | Yes | 0.71 | 3.05 | 3.05 |
| Vancouver | P286R | 61.3 | 27.6 | IA | 3 | Negative | Negative | EM | 1-50 | Intermediate | Low | Chemotherapy only | Yes | Distant | No | No | 2.65 | 12.09 | 12.09 |
| Vancouver | V411L | 44.2 | 23.2 | IB | 3 | Negative | Positive | EM | >50 | High | High | None | Yes | Pelvic | No | No | 3.07 | 11.80 | 11.80 |

Abbreviations: BMI, body mass index; brachy, vaginal brachytherapy; CC, clear cell; DSS, Disease specific survival event; ESMO, European Society for Medical Oncology; EM, endometrioid; LVI, lymphovascular invasion; Myo, myometrial invasion; NA, not available; OS, overall survival event; PFS, progression-free survival event; POLE, DNA polymerase epsilon; RT, radiation therapy; SC, serous; UWash, University of Washington.

[a]Adverse events were noted across a mix of clinical trials and single-institution series.

[b]*Low* encompasses patients who would be eligible for the PORTEC-4a or TAPER trial or at lower risk than the eligibility criteria; *high* encompasses advanced-stage/noneligible high-risk patients (see Supporting Table 1).

**TABLE 3.** Any Disease-Related Adverse Survival Events and Adjuvant Treatments Received With No Differences Noted

| | Adverse Events (PFS and/or DSS) and Adjuvant Treatment Received | | | | |
|---|---|---|---|---|---|
| Variable | Level | Censored | Event | Total | *P* |
| Treatment, No. (%) | None | 106 (97) | 3 (3) | 109 (100) | .673 |
| | Vaginal brachytherapy only | 27 (96) | 1 (4) | 28 (100) | |
| | EBRT without chemotherapy | 81 (94) | 5 (6) | 86 (100) | |
| | Any chemotherapy | 45 (94) | 3 (6) | 48 (100) | |
| Total, No. (%)[a] | | 259 (96) | 12 (4) | 271 (100) | |

| | Adverse Events (PFS and/or DSS) and Adjuvant Treatment Received (None vs Any) | | | | |
|---|---|---|---|---|---|
| Variable | Level | Censored | Event | Total | *P* |
| Treatment, No. (%) | None | 106 (97) | 3 (3) | 109 (100) | .424 |
| | Any[b] | 153 (94) | 9 (6) | 162 (100) | |
| Total, No. (%)[a] | | 259 (96) | 12 (4) | 271 (100) | |

Abbreviations: DSS, disease-specific survival; EBRT, external-beam radiotherapy; PFS, progression-free survival.
[a]Row-wise percentages were computed.
[b]*Any* encompasses any form of adjuvant radiation (EBRT and/or vaginal brachytherapy) or chemotherapy.

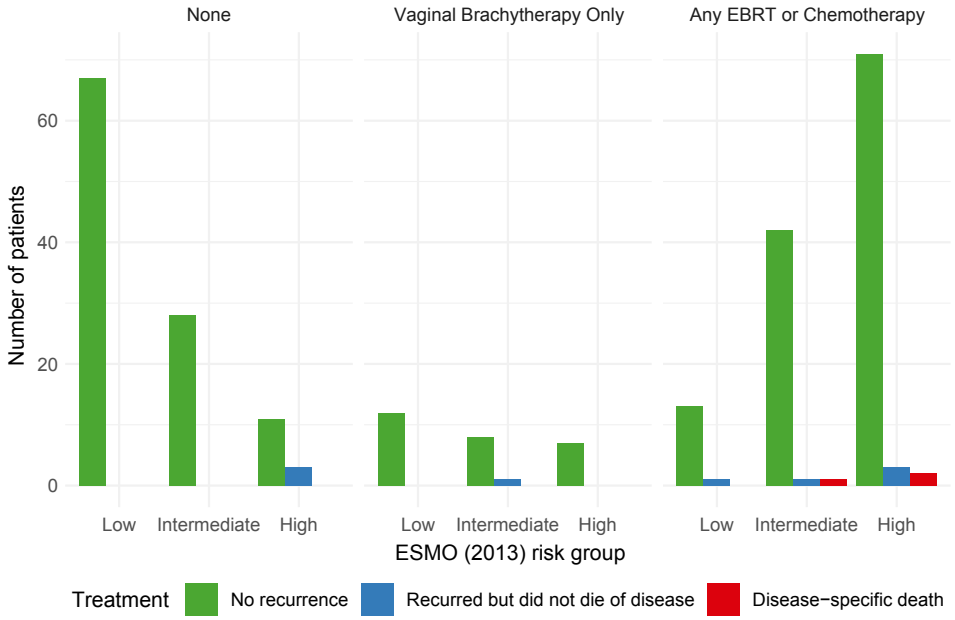


**Figure 2.** Patient distribution of *POLE*mut endometrial cancers showing the ESMO (2013) risk group, treatment received, and adverse events. EBRT indicates external-beam radiotherapy; ESMO, European Society for Medical Oncology.

there is no clear pattern to suggest that ESMO risk stratification can predict outcomes for *POLE*mut ECs.

### *Survival Analysis*

#### Univariable survival

Adopting a one-stage meta-analysis using mixed effects Cox models with a random intercept by cohort and correcting for propensity of treatment (Supporting Table 8 and Supporting Fig. 5), we evaluated in turn the prognostic association of each clinical or pathological variable traditionally prognostic in EC within the *POLE*mut subtype. This analysis revealed that prognosticators such as age, histotype, grade, and LVI did not seem to carry the same relevance within the *POLE*mut subtype. Only stage (reflecting myometrial invasion and nodal status) appeared to be significantly associated with a recurrence or death from disease ($P < .01$; Table 4).

**TABLE 4.** Mixed Effects Survival Models

| | Univariable Model[a] | | Multivariable Model (ESMO)[b] | | Multivariable Model (Trial-Based Risk)[b] | |
|---|---|---|---|---|---|---|
| | HR (95% CI) | LRT *P* | HR (95% CI) | LRT *P* | HR (95% CI) | LRT *P* |
| Age | | | | | | |
| Age | 1.04 (0.99-1.1) | .167 | 1.02 (0.97-1.08) | .459 | 1.04 (0.99-1.09) | .156 |
| Grade (reference: 1) | | | | | | |
| 2 | 0.76 (0.07-8.54) | .364 | | | | |
| 3 | 2.33 (0.44-12.36) | | | | | |
| Stage (reference: IA) | | | | | | |
| IB | 14.94 (1.99-112.28) | .009 | | | | |
| II | 0 (0-infinity) | | | | | |
| III/IV | 38.77 (2.56-587.85) | | | | | |
| Histotype (reference: endometrioid) | | | | | | |
| Nonendometrioid or mixed | 1.1 (0.22-5.6) | .907 | | | | |
| LVI (reference: negative) | | | | | | |
| Positive | 1.84 (0.56-5.96) | .315 | 1.35 (0.4-4.54) | .632 | 0.51 (0.1-2.54) | .415 |
| ESMO (2013) (reference: low) | | | | | | |
| Intermediate | 4.21 (0.4-43.91) | .091 | 3.2 (0.28-36.89) | .266 | | |
| High | 13.56 (1.02-180.35) | | 8.35 (0.51-136.48) | | | |
| Trial-based risk (reference: low) | | | | | | |
| High | 5.92 (1.37-25.56) | .013 | | | 9.53 (1.46-62.2) | .015 |
| Treatment (reference: none) | | | | | | |
| Any | 1.21 (0.24-6.07) | .811 | 1 (0.2-5.09) | .996 | 1.53 (0.27-8.5) | .626 |

Abbreviations: CI, confidence interval; ESMO, European Society for Medical Oncology; HR, hazard ratio; LRT, likelihood ratio test; LVI, lymphovascular invasion.
[a]The univariable models included each of the covariates separately and were adjusted for propensity score.
[b]The multivariable models were adjusted for age, LVI, either ESMO (2013) or trial-based risk groups, treatment, and propensity score. Grade, stage, and histotype were not considered for the multivariable models, but these variables were used to adjust for confounding by indication in the propensity score.
[Correction added on 30 June 2021 after first online publication: footnote b was revised with minor edits]

### Multivariable models

In the multivariable analysis, we compared traditional ESMO and clinical trial–based risk groups by correcting for age, LVI, any treatment, and propensity score. In both models, with other predictors held constant and with adjustments made for propensity of treatment, the hazard ratio associated with treatment did not appear to be statistically significant from 1. Time-dependent receiver operating characteristic curves and area under the curve calculations showed that the model using risk groups mirroring current clinical risk assessments was superior in fit to the model that used traditional ESMO risk groups (Supporting Fig. 6A,B). This suggests that these newly defined trial-based groups are perhaps more reflective of the risk of recurrence in *POLE*mut patients than traditional ESMO groups. We had only 59 cases of trial-based high-risk ECs in this collection of *POLEmut* cases (n = 271); however, we saw a large and statistically significant association between trial-based high-risk ECs and an increased hazard of adverse events (hazard ratio, 9.53; 95% confidence interval, 1.46-62.2; $P = .01$ [likelihood ratio test]). The small number of events observed in this cohort, especially because no events were observed among low-risk patients who had not received treatment according to both ESMO and trial-based criteria (Table 2), made it difficult to evaluate interactions between risk groups and treatment.

## DISCUSSION

This year's publication of the fifth edition of the World Health Organization's *Female Genital Tumours*[6] has outlined a clear path to integration of molecular classification into standard pathological reporting. The ability of molecular classification to provide consistent categorization of tumors in EC is now well recognized. The prognostic value of molecular classification, including the identification of a subgroup of ECs with highly favorable outcomes (*POLE*mut), has been demonstrated in multiple series. Most recently, with the publication of PORTEC-3 data evaluating the response of high-risk ECs to adjuvant radiation with or without chemotherapy by molecular subtype,[20] the powerful predictive potential of molecular subgroups is apparent and dictates application into clinical care. Although drawn from retrospective series, there is evidence of improved outcomes for EC patients with abnormal p53 (p53abn) with the administration of chemotherapy[20] and targeted agents[43-46]; there is a suggestion of an improved response to radiation[47] and immune

blockade[48-50] with no apparent benefit of conventional chemotherapy in MMRd ECs[20] , as well as the possibility of de-escalated therapy or no additional therapy for *POLE*mut ECs.[20,51,52] With the 5-year recurrence-free survival and overall survival rates both at 98% for patients with *POLE*mut ECs in PORTEC3 (high-risk ECs by ESMO risk stratification; data unavailable at the time of assembly of this cohort), was any adjuvant therapy needed for these women? Or were their excellent outcomes the result of increased sensitivity of *POLE*mut ECs to treatment? Preclinical data suggest that *POLE*mut ECs did not show high response rates to the conventional chemotherapy agents most commonly used in EC (carboplatin and paclitaxel) or to radiation.[52] If *POLE*mut ECs are effectively cured by surgery alone and do not require adjuvant therapy, the implications for both personal quality of life (decreased toxicity) and the health system (decreased costs associated with treatment) would be profound. On the other hand, extreme caution must be taken to ensure that we are not jeopardizing these excellent outcomes for women with *POLE*mut ECs by recommending that they forgo adjuvant treatment.

In this IPD meta-analysis, we systematically assembled and analyzed the collective global (retrospective) experience with *POLE*mut ECs. We were interested to see whether these data would support or call into question the current move to de-escalate therapy in *POLE*mut ECs. Specifically, we wished to ask whether the favorable outcomes observed in women with *POLE*mut ECs were independent of the receipt of adjuvant therapy.

This has been a challenging research question to answer. First, *POLE*mut ECs compose a relatively small proportion (<10%) of all ECs.[9-12,19] Second, the total number of collected events (recurrences or disease-specific deaths) was exceptionally low, even after the largest known cohort of *POLE*mut ECs had been assembled. Finally, the majority of these collected patients with *POLE*mut ECs (approximately 60%) received some form of adjuvant therapy, and this was consistent with the aggressive pathological features common in *POLE*mut ECs. Thus, we were limited in our ability to observe the natural history of untreated *POLE*mut ECs (eg, no large historical cohort exists that has undergone molecular classification and in which no treatment has been given to women who would normally have been prescribed treatment that would allow the study of the natural disease course). We were unable to determine reasons for receiving or forgoing treatment in series that were outside the confines of a clinical trial. Patient factors (preferences and comorbidities), physician preference, and/or institutional guidelines all may have affected the delivery of therapy and are known challenges in observational cohorts. Standard meta-analyses based on published literature would not permit the estimation of the association of treatment after adjustments for tumor features; therefore, IPD were needed. IPD approaches similar to standard meta-analyses may be limited by the selection and inclusion of eligible studies and suffer from publication bias, with only positive studies published; we tried to mitigate the impact of this in our study by inquiring with researchers in our network, but our effort was not exhaustive. We have attempted to encompass all published cases of *POLE* mutations in EC for which treatment details and clinical outcomes were known. However, some published studies that were contacted opted to not contribute their IPD data.

Our analyses suggest that the favorable outcomes observed in women with *POLE*mut ECs, at least stage I/II *POLE*mut ECs that would be eligible for clinical trial participation, appear to not be associated with treatment. The association of treatment within advanced-stage *POLE*mut ECs is less clear. Of the approximately 9% of patients with pathogenic *POLE*mut ECs found to be at an advanced stage (stage III/IV; n = 29), only 3 had recurrence events, but almost all had received some form of treatment. These data, in addition to the previously outlined preclinical data suggesting that *POLE*mut ECs are not particularly chemoresponsive or radiosensitive, should prompt us to question how women with *POLE*mut ECs are managed. Can we withhold adjuvant treatment of any kind (radiation, chemotherapy, or targeted) from women with *POLE*-mutated ECs, regardless of clinicopathological features and traditional risk group assignment? Because of the dramatically high salvage rates observed in the small proportion of *POLE*mut ECs with recurrence events (followed 5-14 years without further evidence of a disease/death event) both in our series and in others,[14] reserving treatment (conventional and/or targeted) for these rare recurrence events may be the most reasonable approach.

We have long suspected that many women with EC may be cured by surgery alone. Identifying inherently indolent tumors[53] or using molecular subtyping to help to stratify risk and identify individuals who can safely forgo treatment is not new, nor is it limited to this disease site.[54-58] The morbidity and toxicity of treatments must be weighed against the benefit to clinical outcomes. Our results, although challenged by the low prevalence of *POLE*mut ECs, several potentially unmeasured confounders, and low statistical power due to the small number of events, suggest that women with earlier stage *POLE*mut ECs who receive treatment actually appear to have worse outcomes

than if they had not received treatment. Conservatively, no evidence of improved outcomes in this subset is noted, and it becomes difficult to justify treatment for this large population of women (up to 10% of all patients with EC, representing more than 380,000 new EC cases diagnosed every year globally, the majority of which are early-stage/trial-based low-risk). Moreover, the observed high salvage rate for rare recurrent *POLE*mut ECs provides added justification for de-escalation and close observation only.

Transitioning to action on clinical management on the basis of molecular subtype requires prospective trials to document safety and education/knowledge translation for pathologists, clinicians, and patients to understand the prognostic and predictive value of molecular classification for driving EC management. Two clinical trials are in progress,[26,27] with a third trial in development.[59] Knowledge translation initiatives for clinicians have demonstrated early success,[60] and this communicates that *POLE*mut ECs represent a unique subgroup in which the usual pathological prognostic factors and risk stratification systems appear not to be as relevant. We are now working with patient partners to develop material that we hope will further improve dissemination and uptake.

For changing clinical care, it is critical to ensure that only pathogenic *POLE* mutations are acted on. Leon-Castillo et al[29] performed encompassing molecular characterization to conservatively define what *POLE* mutations should be considered pathogenic. This list differs from other publications on EC[61,62] in which subsets of the *POLE* EDM or even mutations outside the EDM were considered *POLE* mutant. Reviewing our collected cohort for this analysis, which encompassed published clinical trials and institutional series of *POLE*mut ECs, we found that a high proportion of these cases were actually ECs with nonpathogenic *POLE* mutations (n = 65; 18% of this assembled cohort) with clear differences in clinical outcomes (hazard ratio, 3.4; 95% confidence interval, 1.5-7.6; log-rank $P < .01$). We anticipate in the future that the list of *POLE* mutations considered pathogenic may expand as new cases with adequate clinical and molecular data are further characterized. For now, this list of 11 mutations is what we would recommend as the gold standard for the clinical setting (eg, for trial enrollment and/or for considering de-escalation of therapy).

Notably, approximately 3% of all ECs harbor more than 1 molecular feature used in classification.[63] The scenario of MMR/MSI-high ECs with *POLE* mutations may arise as a secondary event in a hypermutated phenotype. The characterization of these multiple-classifier cases[29,63] has demonstrated that the behavior of nonpathogenic *POLE* mutations seen with MMRd tumors mirrors MMRd. In contrast, pathogenic *POLE* mutations, with MMRd, p53 abnormalities, or both, follow a favorable clinical course consistent with *POLE*mut ECs. Therefore, the recommended algorithm for segregating cases begins with first pulling out ECs with pathogenic *POLE* mutations (*POLE*mut), then segregating by MMR status to identify MMRd, and finally interpreting p53 by immunohistochemistry, in the context of *POLE* and MMR (for wild-type p53 (p53wt) and p53abn subtypes). In short, pathogenic *POLE* (*POLE*mut) is the defining feature, regardless of what other mutations or IHC changes accompany it.

In summary, global data on *POLE*mut ECs fail to demonstrate a clear benefit of adjuvant therapy, at least in early-stage disease or for patients who would be eligible to participate in clinical trials for de-escalation of adjuvant therapy. There are insufficient data to determine the impact of treatment in advanced-stage *POLE*mut ECs. Recurrence rates and disease-specific death rates across all *POLE*mut ECs (early and advanced stage) are extremely low, with salvage rates following recurrence events extremely high and seemingly long-lasting/durable. While we await maturation of prospective clinical trials assessing the safety of withholding treatment from women with early-stage *POLE*mut ECs, the data presented herein support a move to implementation of molecular classification for all women with ECs. In addition to providing the benefit of identifying women who may be able to forgo additional therapy (*POLE*mut ECs), molecular classification serves as an opportunity to direct management in other molecular subtypes: women who may benefit from chemotherapy (p53abn) and women who should be directed to a hereditary cancer program for germline testing and are candidates for immune blockade therapy (MMRd). Furthermore, novel initiatives stratifying ECs for clinical trials according to molecular subtype are underway (a TransPORTEC initiative: Refining Adjuvant Treatment in Endometrial Cancer Based on Molecular Profile [RAINBO]), and they are providing a step toward precision medicine in ECs.

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**Jessica N. McAlpine:** Conceptualization, validation, investigation, resources, data curation, writing–original draft, writing–review and editing, visualization, project administration, and funding acquisition. **Derek S. Chiu:** Methodology, software, validation, formal analysis, investigation, data curation, writing–original draft, writing–review and editing, and visualization. **Remi A. Nout:** Investigation, resources, data curation, and writing–review and editing. **David N. Church:** Investigation, resources, data curation, writing–review and editing, and funding acquisition. **Pascal Schmidt:** Software, validation, formal analysis, and visualization. **Stephanie Lam:** Validation, formal analysis, investigation, writing–original draft, and visualization. **Samuel Leung:** Software, validation, formal analysis, data curation, and visualization. **Stefania Bellone:** Investigation, resources, data curation, and funding acquisition. **Adele Wong:** Investigation, resources, data curation, writing–review and editing, and funding acquisition. **Sara Y. Brucker:** Investigation, resources, and data curation. **Cheng Han Lee:** Investigation, resources, data curation, writing–review and editing, and funding acquisition. **Blaise A. Clarke:** Investigation, resources, data curation, and funding acquisition. **David G. Huntsman:** Conceptualization, writing–review and editing, and funding acquisition. **Marcus Q. Bernardini:** Investigation, resources, data curation, and funding acquisition. **Joanne Ngeow:** Investigation, resources, data curation, writing–review and editing, and funding acquisition. **Alessandro D. Santin:** Investigation, resources, data curation, and funding acquisition. **Paul Goodfellow:** Conceptualization, investigation, resources, data curation, and funding acquisition. **Douglas A. Levine:** Conceptualization, investigation, resources, data curation, and funding acquisition. **Martin Köbel:** Investigation, resources, data curation, writing–review and editing, and funding acquisition. **Stefan Kommoss:** Investigation, resources, and data curation. **Tjalling Bosse:** Investigation, resources, data curation, and writing–review and editing. **C. Blake Gilks:** Conceptualization, writing–review and editing, and funding acquisition. **Aline Talhouk:** Conceptualization, methodology, software, validation, formal analysis, investigation, resources, data curation, writing–original draft, visualization, supervision, project administration, and funding acquisition.

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