predictive biomarkers. The Cancer Genome Atlas made significant progress at identifying these subsets through the comprehensive molecular analysis of 373 endometrial cancers involving whole exome sequencing, gene expression, and copy number analysis.[5] Four distinct subsets of endometrial cancer that spanned histologic subtypes were identified with differing prognoses: *POLE* ultramutated, microsatellite instability hypermutated, copy number low, and copy number high.[5] The copy number high tumors had high rates of *TP53* mutations and had the worst prognosis. Patients with mismatch repair (MMR) deficient cancers and copy number low tumors had intermediate prognoses. *POLE* ultramutated tumors had the best prognosis, with very few relapses reported in these patients.

A workflow for defining these subsets without the need for expensive next generation sequencing techniques was developed by different groups.[9,69] Immunohistochemistry can be performed to identify p53 abnormal cancers. *TP53* is commonly stabilized after mutation so it can be detected with immunohistochemistry within the cell nuclease when mutant. MMR-deficient cancers can be identified by noting the absence of the MMR proteins MLH1, MSH2, MSH6, and PMS2 or by detecting the consequence of the absence of functional MMR proteins, the accumulation of repeats of a short sequence of DNA, called *microsatellite repeats*. This is referred to as *microsatellite instability*, and it can be detected with a polymerase chain reaction–based assay using DNA from tumors. Detection of *POLE* mutations requires sequencing of this single *POLE* gene, which, when mutated, causes accumulation of many mutations throughout the genome.

With these molecular classifications of endometrial cancer readily defined, the question of their effect on adjuvant therapy is being addressed. Some of the most informative data collections come from secondary molecular analyses of the PORTEC studies.[9,69] In PORTEC-3, the primary aim of this study was to determine whether the addition of chemotherapy to EBRT for women with high-risk and advanced endometrial cancer improved RFS and OS.[53] The 5-year RFS and OS were significantly improved with the addition of chemotherapy, and this was most significant among the stage III and serous carcinoma subgroups.[16] A molecular analysis of these patients was performed to determine which of these molecular subsets derived the benefit from chemotherapy.[69] Interestingly, the only molecular subgroup found to benefit from chemotherapy was among patients whose tumors were p53 abnormal. The 5-year RFS was significantly improved from 36% to 59% with the addition of chemotherapy for patients with p53 abnormal tumors.[69] As a result, combined modality treatment for patients with p53 abnormal or *TP53* mutated myoinvasive FIGO stage IA to IIIC2 endometrial cancer is conditionally recommended.

Among patients with MMR deficiency, there was no difference in survival for patients who did or did not receive chemotherapy. Five-year rates of RFS were 68% for patients who received chemotherapy versus 76% for those who did not.[69] These findings suggest that it is reasonable to consider EBRT alone for patients with MMR deficiency. Given the response to immunotherapy for patients with metastatic disease with MMR deficiency, adjuvant immunotherapy may improve outcomes in the adjuvant setting. The NRG-GY020 *(NCT04214067)* study is testing this hypothesis by randomizing patients with early-stage endometrial cancer to treatment with and without pembrolizumab.

Patients with the *POLE* ultramutated phenotype, even with high-grade and/or advanced stage tumors, have excellent outcomes whether treated with EBRT with concurrent chemotherapy followed by sequential chemotherapy or EBRT alone. In the PORTEC-3 molecular classification series, there were 51 patients in the *POLE* subset, and only 1 patient (treated with EBRT alone) had disease recurrence.[69] Given these findings, simplifying adjuvant therapy to a single modality approach is reasonable, and thus RT alone is an option for patients with *POLE* ultramutated tumors who are eligible for adjuvant therapy based on clinical and pathologic factors. Further study is needed to understand the improved survival in this population to determine whether it is attributable to the biologic consequences of the high mutational burden and potential effect of sensitivity to adjuvant therapies. In the combined analysis of PORTEC-1 and PORTEC-2, the 49 patients with the *POLE* ultramutated phenotype had a favorable prognosis with no locoregional recurrences, only 2 distant recurrences, and a 5-year disease-specific survival rate of 100%.[70] An important remaining question is whether these low recurrence rates also will be seen in locally advanced patients who are observed after surgery. Observation after surgery is an arm of the ongoing PORTEC-4a *(NCT03469674)* and the Tailored Adjuvant Therapy in POLE-mutated and p53-wildtype Early-Stage Endometrial Cancer (TAPER) studies *(NCT04705649)*. Until data demonstrating these same excellent outcomes after observation are available, omitting adjuvant therapy is not recommended for patients with uterine risk factors or node-positive disease.

Additionally, among those "multiple classifier" patients with both MMR deficiency and p53 abnormal tumors, prognosis clusters closely with the MMR deficiency group. Similarly, for patients with both *POLE* ultramutated and p53 abnormal tumors, prognosis clusters closely with the *POLE* ultramutated group.[115]

Among high-risk histologies, p53 abnormal most commonly is associated with serous carcinomas, thus carrying an unfavorable prognosis. Human epidermal growth factor receptor 2 (HER2) is overexpressed in about 30% of uterine serous carcinomas, and HER2 is a target for the humanized monoclonal antibody trastuzumab. A phase II clinical trial of patients with stage III to IV or recurrent serous carcinoma with HER2 overexpression randomized patients to chemotherapy with or without trastuzumab. The study demonstrated significantly improved PFS and OS without differences in toxicity.[116] HER2 expression is an emerging marker of interest for guiding systemic therapy.