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Commentary

A working group report from the 2024 National Cancer Institute / Gynecologic Cancer Steering Committee endometrial cancer clinical trials planning meeting: refining the approach to endometrial cancer in the immunotherapy era

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Abstract

Endometrial cancer is now the leading cause of gynecologic cancer death in the United States. Recognizing the urgent need to improve outcomes for patients diagnosed with endometrial cancer, the National Cancer Institute Gynecologic Cancer Steering Committee convened a clinical trials planning meeting, Refining the Approach to Endometrial Cancer in the Immunotherapy Era, on January 8 and 9, 2024. Multidisciplinary experts were charged with addressing critical challenges to optimize treatment of endometrial cancer in the new immunotherapy landscape. As part of the clinical trials planning meeting, working groups were assembled to address several important aspects of clinical trial design. Working group 1 focused on translational science and was tasked with reviewing the scientific literature for data on validated discriminants of response to immunotherapy to inform trial concept development by the therapy-focused groups. The working group established that molecular subtyping of endometrial cancer is now the standard approach for classifying endometrial tumors. Molecular subtyping for prognostic and predictive applications should be considered when assessing biomarkers as well as therapeutic targets. Additionally, strategies to improve immune response like incorporation of radiation as well as therapy sequencing considerations should continue to be explored. A major key observation from working group 1 was lack of validated discriminants for immunotherapy response beyond mismatch repair status, and tumor mutational burden and exploration of additional discriminants of response and resistance will be critical with the increasing use of immunotherapy in endometrial cancer.

Background

Endometrial cancer has overtaken ovarian cancer to become the gynecologic cancer with the most deaths in the United States in 2025.[1] This disease has seen an alarming increase in incidence and mortality, as well as a widening racial disparity gap, resulting in a critical need for improved risk stratification and therapeutic strategies.[1,2] Furthermore, endometrial cancer is the only cancer to have decreased survival over the past 4 decades in the United States.[3] Despite these trends, endometrial cancer ranked 24th in National Cancer Institute research funding.[4] It is imperative that we increase awareness and funding of this disease to help develop novel therapeutic strategies and a better

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understanding of mechanisms of treatment resistance in endometrial cancer to improve outcomes. There is specific need for predictive biomarkers to select patients and therapies to optimize outcomes and minimize unnecessary toxicities particularly with the recent practice changing data from the NRG-GY018[5] and RUBY[6] clinical trials leading to the approval of immune checkpoint inhibitors for the treatment of advanced or recurrent endometrial cancer. Additionally, regimens for patients with primary or acquired resistance to immunotherapy will need to be identified.

Clinical trial planning meeting in endometrial cancer

Recognizing the urgent need to improve outcomes for patients diagnosed with endometrial cancer, the National Cancer Institute Gynecologic Cancer Steering Committee convened a clinical trials planning meeting, Refining the Approach to Endometrial Cancer in the Immunotherapy Era, on January 8 and 9, 2024.[7] Multidisciplinary experts were charged with addressing critical challenges to optimize treatment of endometrial cancer in the new immunotherapy landscape (Figure 1).

The full clinical trials planning meeting report will be presented separately; here we present a report from working group 1. Working group 1 focused on translational science and was tasked with reviewing the scientific literature for data on validated discriminants of response to immunotherapy to inform trial concept development by the therapy-focused groups (working groups 2-4). Accumulating evidence indicates that immune conditions in the tumor microenvironment has clinical impact on treatment efficacy and disease outcomes in endometrial cancer. To date, established biomarkers to select patients with endometrial cancer for immunotherapy include mismatch repair status and tumor mutational burden. The value of programmed cell death 1 ligand 1 (PD-L1) expression as a predictive biomarker in endometrial cancer is limited, and recent recommendations from the Society for Immunotherapy of Cancer advise against using PD-L1 expression to guide treatment for endometrial cancer.[8] Heterogenous responses and the emergence of resistance to immunotherapy among patients who have mismatch repair deficiency and/or microsatellite instability or tumor mutational burden high tumors demonstrate the need for continued work to identify other biomarkers to guide treatment. Here we present a summary of key observations and priorities identified by working group 1 to advance clinical research and improve outcomes for patients with endometrial cancer (Figure 2).

Molecular classification

Molecular classification and immunotherapy

Molecular classification of endometrial cancer has substantially impacted clinical practice and treatment recommendations and has now been incorporated into clinical trial designs. Analyses of The Cancer Genome Atlas (TCGA) data identified 4 molecular classes: POLE (ultramutated), MSI (hypermutated), copy-number low (endometrioid like), and copy-number high (serous like).[9] Recognizing that the methods and bioinformatics used in TCGA are not clinically accessible, working group 1 felt that the Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) model currently provides the most clinically accessible testing application to date.[10] The ProMisE model overcomes the technical and bioinformatic challenges of the original TCGA classification by capitalizing on key observations from the TCGA. For the ProMisE model, the classification POLE status can be achieved either by a next-generation sequencing panel or directed *POLE* gene sequencing followed by mismatch repair immunohistochemistry or microsatellite instability testing. A key observation from TCGA was an enrichment in *TP53* mutations in the copy-number high group, and thus, abnormal p53 immunohistochemistry or identification of a *TP53* mutation is used as the final hierarchical step in ProMisE to assign tumors to either the copy-number high (mutated p53 staining or *TP53* mutation) or copy-number low (*TP53*/p53 wild-type) groups. Those tumors without a pathogenic *POLE* mutation that are mismatch repair proficient and with normal p53/*TP53* wild-type are termed "no specific molecular profile," which are analogous to the copy-number low group. Importantly, *TP53* status is considered the last step in hierarchical molecular classification for both prognostic and predictive counseling behind POLE and mismatch repair status[11] because *TP53* mutations can be seen in these molecular groups, particularly in the context of ultramutated and hypermutated tumors (multiple classifier tumors). Notably, beyond prognostic implications, these molecular classifications have been recognized as predictive for therapeutic decision making with immunotherapy in microsatellite instability tumors or those with mismatch repair deficiency. Importantly, despite the molecular classes in TCGA and ProMisE overlapping, there are distinctions, and attempts at consistent and correct nomenclature based on methods should be used. For instance, the commonly used ProMisE nomenclature (*POLE*mut, mismatch repair deficiency, p53abn, and no specific molecular profile) should be used when referring to endometrial cancers classified with ProMisE instead of TCGA nomenclature particularly regarding copy-number high and copy-number low because copy-number status is not assessed as part of the ProMisE classification.

Further subdivision of endometrial cancers and exploration by additional therapeutic targets (eg, HER2 expression[12-14]) or within molecular subtypes based on prognostic and/or predictive markers (eg, estrogen receptor expression[15] or *MLH1* methylation status[16-18]) should continue to be considered as well. For example, HER2,[12,13] as an important therapeutic target that has also demonstrated prognostic application[13] as well in endometrial cancer, was demonstrated in the DESTINY-PanTumor-02 (NCT04482309) trial,[14] which assessed the activity of a HER2-targeting antibody-drug conjugate trastuzumab deruxtecan and demonstrated an impressive 57.5% response rate in recurrent endometrial cancer with HER2 2+ or 3+ immunohistochemistry. Overall, the 4 main molecular classes as well as other therapeutic targets like HER2 present an opportunity to refine cohort selection in clinical trial design, as illustrated by recent studies (HER2 [NRG-GY026, NCT05256225]) and mismatch repair status (NRG-GY020, NCT04214067, and NRG-GY025, NCT05112601) and is expected to increasingly inform treatment recommendations.

Considerations by molecular subtype

Mismatch repair deficient and microsatellite instability

The molecular class that has had the most clinical implications from a treatment perspective to date is the mismatch repair deficiency or microsatellite instability group. Assessment of mismatch repair status was initially implemented for Lynch syndrome screening in endometrial cancer. Immunohistochemistry to assess mismatch repair expression as well as DNA-based microsatellite testing methods have been established for Lynch syndrome screening as well as biomarker status for immunotherapy although discordance between methods can occur.[19] The mismatch repair deficiency and/or microsatellite instability and *POLE*-mutated tumors have high tumor

- Identifying characteristics that are associated with magnitude of benefit from immunotherapy through analysis of preclinical and translational literature
- Developing treatment strategies for patient subgroups based on molecular and clinical characteristics
- Examining immunotherapy sequencing and timing across the EC life cycle
- Exploring combinations with which to optimize initial exposure and/or with which to reengage the immune system for second benefit from immunotherapy
- Promoting clinical trial designs to enhance access to the broadest population of EC patients

Figure 1. National Cancer Institute 2024 Clinical Trials Planning Meeting in endometrial cancer objectives. Abbreviation: EC = endometrial cancer.

Molecular subgrouping should be considered in clinical trial design.
- Appropriate nomenclature and definitions for molecular groups should continue to be prioritized.
  - The ProMisE model has the greatest clinical applicability to date.
- Within the four molecular subtypes further subclassification should be considered.
  - E.g., HER2, Estrogen Receptor, *MLH1* methylation
- EC specific definitions of biomarkers are necessary.
  - E.g., Estrogen Receptor Expression positivity threshold and homologous recombination deficiency

There are limited predictive biomarkers identified in EC response to immune checkpoint blockade.
- MMR status and TMB remain the established predictive biomarkers.
- There is an urgent need for additional predictive biomarkers.
- There remains need to understand microenvironmental features like immune infiltrate differences in EC.

There remains a critical need for EC specific data regarding resistance mechanisms to immune checkpoint blockade.

Additional strategies to enhance tumor immunity warrant continued evaluation.
- Exploration of multi-agent approaches, multi-modality therapies, impact of radiation as well as therapeutic sequencing considerations should continue to be addressed.

Figure 2. Highest priority observations and recommendations from working group 1. Abbreviations: EC = endometrial cancer; MMR = mismatch repair; ProMisE = Proactive Molecular Risk Classifier for Endometrial Cancer; TMB = tumor mutational burden.

mutational burdens and derive the most benefit to immunotherapy. Recent positive data from 2 pivotal trials,[5,6] RUBY (NCT03981796) and NRG-GY018 (NCT03914612), which incorporated anti-PD-1 agents with chemotherapy in metastatic and recurrent endometrial cancer and led to US Food and Drug Administration approval and increased immune checkpoint blockade use. However, there remains a need for novel strategies for patients whose tumors demonstrate primary or acquired resistance while on immunotherapy, including 40% of mismatch repair deficiency and 70% of mismatch repair proficient patient's tumors observed in these trials. Potential causes for immunotherapy resistance in the mismatch repair deficiency group are proposed to include low neo-antigen presentation, multiple immune checkpoints at play, and/or immune cell-driven immunosuppression.[20] Strategies to augment immune response to overcome resistance will become increasingly important as the use of immunotherapy increases as will improved upfront biomarkers to identify those individuals who may or may not benefit to immunotherapy.

Conversely, there also may be an opportunity to modify treatment for the mismatch repair deficiency group. In the highly publicized study of 12 patients from Cercek and colleagues,[21] all 12 patients who received single agent neoadjuvant dostarlimab for their locally advanced rectal cancer had a complete clinical response. This led to elimination of definitive surgical intervention for some; long-term safety and efficacy for those patients are pending. The use of immunotherapy-alone approaches may mitigate some of the toxicity of traditional oncologic therapies although at the cost of immune-associated toxicities for some. This strategy of an immunotherapy alone approach may expand opportunities for fertility preservation or for treatment in non-surgical candidates in endometrial cancer. Neoadjuvant approaches may also have the potential to prime the immune system with intact tumors and lymphatics as a strategy to enhance antitumor immunity as recently reported by Eerkens and team.[22] In this phase 1 study, 10 women with mismatch repair deficiency endometrial cancer were safely treated with 2 cycles of pembrolizumab and had 50% pathologic and 37.5% radiographic response.

Notably, early data suggest that molecular mechanisms associated with response to anti-PD-1 therapy may differ in epigenetic vs mutational mismatch repair deficiency.[23] Epigenetic silencing of *MLH1* is the most common mechanism for mismatch repair deficiency function in endometrial cancer, making up 75%-80% of mismatch repair deficiency cases.[16-21,24] The remainder come from somatic and germline mismatch repair gene mutations.[25] Multiple cohorts[17,24] have shown that there is a statistically significant prognostic difference with reduced progression-free survival associated with *MLH1* methylated mismatch repair deficiency. Emerging data also suggest that differential immune milieus in tumors with an epigenetic cause of mismatch repair deficiency, characterized by natural killer (NK) cell drivers, with T-cell–driven immunity seemingly more common in mutationally driven mismatch repair deficiency.[23] The

mechanisms behind the worse prognosis of *MLH1* methylation, and somewhat reduced responses to immunotherapy, have not been uncovered, and further discriminants of response will require continued exploration across mismatch repair deficiency tumors. Data from the Garnet study,[26] as well as GY018,[27] suggest that regardless of MLH1 status, major benefit is observed. Although not statistically different, it is notable that in GY018, progression-free survival at 12 months was 85% vs 75% in *MLH1* nonmethylated vs methylated cases.[27] This should remain an area of continued investigation.

JAK1, downstream of IL-6 and other immunomodulators, has been shown to be associated with immunoresistance in melanoma, lung cancer and mismatch repair deficient colon cancer.[28,29] *JAK1* frameshift mutations are prevalent in 14% of endometrial cancers, with higher rates noted in mismatch repair deficiency tumors (35%).[23,30] More frequent *JAK1* mutations have been observed in recurrent vs newly diagnosed tumors, with some suggesting that *JAK1* mutations may allow immune escape promoting endometrial cancer outgrowth via abrogation of interferon-gamma signaling.[23,30,31] However, available data from small studies on whether *JAK1* mutations confer resistance to immune checkpoint blockade are conflicting[23,31] and may not be tumor agnostic. Interestingly, Chow et al.[23] reported that pretreatment *JAK1* mutations did not seem to confer primary resistance; rather, acquired mutations in *JAK1* following pembrolizumab administration seemed to lead to resistance.

TP53 mutated and/or copy-number high

TP53 mutational status, determined by sequencing or inferred by altered immunohistochemical staining, defines a clinically accessible method to identify the TCGA copy-number high group, which has traditionally been considered less immunogenic than other molecular groups.[9,10] Tumors in the *TP53*-mutated (copy-number high) molecular class typically are mismatch repair proficient (95%) and may include HER2 amplification, PPP2R1A (25%), PIK3CA (35%), CDKN2A, LRP1B, FBXW7, SPOP, CHD4, TAF1 and focal amplifications of MYC, ERRB2, and CCNE1.9.[32] *CCNE1* amplification particularly has been associated with chemotherapy resistance and worse overall survival in uterine serous carcinomas and other tumor types;[33,34] however, the role of *CCNE1* as a therapeutic target has yet to be established.[35,36]

Homologous recombination deficiency and poly(ADP-ribose) polymerase (PARP) inhibitors

A homologous recombination deficiency phenotype has been neither reliably defined nor validated in endometrial cancer; it has been recognized that assays vary, and results are disease-site specific.[37] Some suggest an association with *TP53*-mutated tumors as a result of the frequent copy-number alterations. Lin and colleagues[38] reported that, using ovarian cancer homologous recombination deficiency scoring in endometrial cancer from Foundation Medicine, 22% of 2159 serous endometrial cancer patient tumors analyzed could be classified as loss of heterozygosity high. Loss of heterozygosity has been used alone or with other genomic findings such as large-scale state transitions and telomeric allelic imbalance in assigning genomic instability scores. Homologous recombination deficiency gene mutations (*BRCA1*, *BRCA2*) were enriched in the homologous recombination deficiency group; however, these were present in only 23% of the homologous recombination deficiency cases, suggesting that other mechanisms may be involved. This remains an area requiring careful continued investigation. Data on the use of PARP inhibitors in endometrial cancer continue to evolve, absent a validated selection biomarker.[39-41]

Targeting TP53 and p53 and/or MDM2

The majority of *TP53* mutations in this *TP53*-mutated copy-number high tumor class are missense mutations and fall within the DNA-binding domain.[9,32] It is possible that loss of function and gain of function mutations are different in endometrial cancer, and further refinement based on type of mutation is needed and should remain an area of active investigation in endometrial cancer. It is appealing to consider agents with novel mechanisms for this high-risk group, such as reactivation of wild-type p53 function or MDM-2 inhibition.[42-47]

HER2

HER2 amplification or overexpression is most common in the *TP53*-mutated molecular class of endometrial cancer, occurring in up to 35% of serous and 12%-15% of carcinosarcoma endometrial cancer patients's tumors.[12,13] HER2 has become increasingly important for therapeutic and prognostic management of endometrial cancer. Preliminary data from a small, randomized phase 2 trial[12] showed progression-free survival and overall survival benefit of the use of trastuzumab, and recent data show benefit of trastuzumab deruxtecan in a single-arm phase 2 study.[14] Further studies are ongoing, including testing the benefit of trastuzumab alone in a definitive phase 3 study vs the benefit of the fixed dose trastuzumab and pertuzumab combination (NRG-GY026; NCT05256225). Future directions to leverage the antibody-dependent cellular cytotoxicity effect of the backbone of trastuzumab could test a HER2 monoclonal antibody with anti-PD1 and with and without chemotherapy or HER2 antibody drug conjugates with immunotherapy. The value of extending this targeted therapy to patients with lower HER2 expression (1-2+) needs to be examined, as there may be a negative prognostic influence of any amount of HER2.[48] The STATICE trial reported clinical responses to trastuzumab deruxtecan in HER2 low and high uterine carcinosarcomas of 54.5% and 70%, respectively.[49] Furthermore, median progression-free survival was 3.2 vs 6.7 months in HER2-high and HER2-low tumors, respectively.

No specific molecular profile

The no specific molecular profile group is the largest of the 4 molecular subtypes, comprising approximately half of endometrial cancer diagnoses, and is mostly endometrioid histology but also includes rarer histologic subtypes such as clear cell.[10,15,50] The outcomes for no specific molecular profile tumors are intermediate, and in most studies of immunotherapy, no specific molecular profile–specific outcomes have not been reported. Exploratory analyses from RUBY however indicated that no specific molecular profile tumors appeared to have the smallest benefit to dostarlimab usage in combination with chemotherapy.[51] Notably, there is clinically significant heterogeneity within the no specific molecular profile group, and subclassification based on common mutations may identify unique immune phenotypes.

Estrogen receptor status

Estrogen receptor status has been identified as an opportunity for prognostic refinement within the no specific molecular profile molecular group.[15,52] Jamieson et al.[15] reported their assessment of 1110 no specific molecular profile endometrial cancers and found that low-grade tumors and estrogen receptor–positive tumors showed a 5-year disease-specific death rate of 1.6%

across all stages. In their work, a threshold of more than 1% was considered estrogen receptor positive. Their work identified that most deaths in this large group of no specific molecular profile tumors were high grade (grade 3 or nonendometrioid) and/or estrogen receptor negative. Similarly, Vermij and colleagues[52] reported estrogen receptor positivity as a favorable prognostic factor among high-risk no specific molecular profile tumors with a reduced risk of recurrence (hazard ratio [HR] = 0.33, 95% confidence interval [CI] = 0.15 to 0.75). In the Vermij and colleagues study, a cutoff of 10% was used for estrogen receptor positivity. The threshold for prognostication still requires validation.

Other molecular considerations

Beyond estrogen receptor status and tumor grade, there has been limited discriminators for this large heterogenous molecular group. Several commonly mutated genes were discussed in the context of the molecular group including PTEN, CTNNB1, and ARID1A. The working group felt that although these genes and others warranted discussions, their immediate impact in endometrial cancer remains uncertain.

PTEN loss

PTEN loss is one of the most frequent abnormalities (>50%) in endometrial cancer and is especially enriched in the no specific molecular profile group[9,53] making it an appealing potential target for trials particularly with some data suggesting inferior outcomes with PD-1 inhibitors in preclinical melanoma models.[54,55] PTEN loss in endometrial cancer is not associated with PD-L1 expression or lymphocyte and macrophage infiltration (CD3+ lymphocytes, CD8+ lymphocytes, or CD68+ macrophages).[56] Strategies to enhance lymphocyte infiltration have been tested using combinatorial immunotherapy reporting results by PTEN status in the no specific molecular profile group.[57,58]

CTNNB1 mutations

There is evidence that tumor *CTNNB1* mutation is associated with immune exclusion across tumor types.[59-61] The impact of WNT/beta-catenin signaling on immune response warrants evaluation in endometrial cancer. In one study, there was no difference in PD-L1 expression between *CTNNB1*-mutated vs wild-type tumors reported.[62] There is evidence that tyrosine kinase inhibitors like lenvatinib and axitinib can downregulate Wnt-beta-catenin signaling in several preclinical models.[63,64] Interestingly, *CTNNB1*-mutated tumors were particularly vulnerable to bevacizumab in GOG86P,[65] which presents opportunities to correlate changes in signaling with immune infiltrates in clinical samples.

ARID1A mutations

ARID1A is most frequently mutated component of the SWItch/sucrose nonfermentable chromatin remodeling complex. Chromatin remodeling via the SWItch/sucrose nonfermentable complex has been implicated in oncogenesis and has emerged as a potential therapeutic target.[66] SWItch/sucrose nonfermentable deficiency has been reported in aggressive histologies like undifferentiated endometrial cancer, although are most common in endometrioid no specific molecular profile tumors.[67] *ARID1A* mutations have been associated with a higher risk of recurrence in no specific molecular profile tumors.[68,69]

Mismatch repair status and ARID1A have been correlated[9,70-73] with mixed results reported regarding an association between *ARID1A* mutations and response to immune checkpoint inhibitors.[74,75] ATR inhibition has been combined with immunotherapy in *ARID1A*-mutated melanoma and lung tumors with evidence of clinical benefit.[76,77] In endometrial cancer,[78] tumors bearing *ARID1A* mutations were associated with higher PD1, LAG3, and TIGIT immune checkpoint expression, higher CD8+ T-cell infiltration, and a higher incidence of microsatellite instability; the clinical relevance of these changes is unknown. In addition, tumors with *ARID1A* mutations were not associated with differential response to immune checkpoint inhibitors in a trial of avelumab and talazoparib.[79] Further study is needed to determine whether ARID1A status can be used as a predictive biomarker of response to immunotherapy, along with assessing strategies for SWItch/sucrose nonfermentable alterations.

Immune biomarkers

Treatment predictive biomarkers

To date, mismatch repair status and tumor mutational burden have been correlated as predictive biomarkers of response to immunotherapy in endometrial cancer.[80] Tumor mutational burden of no less than 10 mut/Mb has been defined as tumor mutational burden high across numerous cancers, and tumor mutational burden–high tumors currently have a tumor type agnostic indication for pembrolizumab, based on FoundationOne Cdx from a prespecified statistical analysis plan from KEYNOTE 158.[81-84] In KEYNOTE 158, tumor mutational burden analyses showed that 10 of the 15 endometrial cancer tumors with high tumor mutational burden were also microsatellite instability. Additionally, a planned exploratory analysis from the Garnet trial showed that the dostarlimab response rate among mismatch repair proficient tumors was 12.1% in the tumor mutational burden–low group and 45.5% in the tumor mutational burden–high group.[85]

One opportunity that is being evaluated as a predictor of durable response is T-cell expansion, clonality, and dynamics, which can be tested through blood sampling; data are sparse in endometrial cancer to date[86-88] but warrants further evaluation. There remains a critical need to identify additional immune biomarkers beyond mismatch repair status and tumor mutational burden in endometrial cancer to inform treatment recommendations and advance our understanding of tumor biology.

Tumor-infiltrating lymphocytes and microenvironmental features

To date, there is limited evidence supporting the prognostic utility of specific immune biomarkers to guide endometrial cancer treatment.

CD8 T-cell infiltration is associated with mismatch repair deficiency status in endometrial cancer but has not been validated as a selection biomarker. An established biomarker for immunotherapy efficacy, such as validated correlated associations between T-cell infiltration and immunotherapy response in other diseases, could broaden applications for immunotherapy. Retrospective analysis of tumor biopsy samples from patients participating in a recent small phase II trial indicated that gamma-delta T cells were associated with response to combined immune checkpoint blockade and anti-angiogenic therapy in patients previously treated with immunotherapy.[89] Validation of a treatment-predictive role for gamma delta T cells would be valuable, particularly in selecting patients for combinatorial regimens following progression on immunotherapy. CD16+ NK cells have also been associated with immune checkpoint inhibitor responsiveness in epigenetic mismatch repair deficiency tumors but also requires further validation.[20] Analyses should be continued to distinguish CD16+ NK cells from CD16+ γδ T cells. Other considerations regarding the tumor microenvironment that were

felt of potential importance were tertiary lymphoid structures, CD20+ B cells, IDO1 in tumor islets, CD14+ macrophages, and CD15 neutrophils within the tumor bed among others.

Additional strategies to enhance tumor immunity

Multimodal therapy with radiation

Radiation therapy has been proposed as a strategy to enhance tumor immunity through the induction of immunogenic cell death, as well as modulation of conditions in the tumor microenvironment. Considerations in the design of trials combining radiation with immune checkpoint inhibitors include sequencing, treatment volumes, inclusion of tumor-draining lymph nodes, and management of oligometastatic disease. Data in other tumor types[90] indicate that inclusion of regional lymph nodes in the irradiation field mitigated local and systemic immunity and may be an important consideration in trial design in endometrial cancer. Draining lymph nodes may be important for initial immune response to stereotactic body radiation therapy + immune checkpoint blockade but are not required for maintenance of immunity, suggesting that lymph node irradiation or dissection after establishment of immune memory could be an optimal treatment approach. Results from studies in lung cancer and head and neck cancers provide a rationale for neoadjuvant approaches and suggest that administering radiation while the primary tumor is in situ may promote the expansion of immune cells that recognize tumor antigens. The use of other still-to-be validated surrogate markers, including immune infiltration or T-cell expansion, may provide opportunities to assess the potential impact of these approaches in endometrial cancer.

In another example to augment multimodal therapy with radiation, the PRIMMO trial[91] evaluated induction with an immunomodulatory 5-drug cocktail consisting of low-dose cyclophosphamide, aspirin, lansoprazole, vitamin D, and curcumin in combination with stereotactic body radiation therapy (8 Gy x3) and pembrolizumab for cervical cancer as well as endometrial cancer. There was a 12% objective response rate per immune-related response criteria in endometrial cancer where responses were noted to be durable.

Treatment sequencing considerations

The use of neoadjuvant immunotherapy has been successful in other disease sites;[18] however, data in endometrial cancer are limited. For instance, work from Eerkens and colleagues[22] studied this approach using pembrolizumab in mismatch repair deficiency tumors where they noted radiographic response in 3 of 8 patients and no progression events in this pilot study. An important observation was that treatment response was associated with monoclonal T-cell expansion, suggesting that this may be a candidate biomarker of response. The group also identified T-cell clones localizing to tumor-draining lymph nodes once again reenforcing the concepts of intact lymphatics during initial immune response both in this neoadjuvant approach and supporting the discussion regarding radiation.

Acknowledging the limitations of disease site comparisons, the use of neoadjuvant immunotherapy could provide an opportunity for enhanced activity in endometrial cancer as has been demonstrated in melanoma,[92] lung cancer,[93] and triple-negative breast cancer.[94] Importantly, neoadjuvant treatment did not delay surgery and was not associated with any clinically significant dose-limiting toxicity.

Opportunities to enhance immunotherapy response like radiation or neoadjuvant approaches are of increasing need, given the recent negative KEYNOTE B21 trial (NCT04634877).[95] This randomized phase III trial testing pembrolizumab in combination with chemotherapy did not show benefit in a population of high-risk endometrial cancer after surgery with curative intent. It is notable that the mismatch repair deficiency group did have substantial benefit in B21 (HR = 0.31, 95% CI = 0.14 to 0.69), despite the negative overall trial.[96] A key difference between the negative B21 study and the positive GY018 and RUBY trials was the presence of measurable disease, and this could suggest that it may be necessary to have tumor present for immune education particularly in the mismatch repair proficient group. Although the cornerstone for treatment of endometrial cancer over the past several decades has been hysterectomy followed by adjuvant therapy, changes in this treatment paradigm may be essential to improve therapeutic efficacy.

Conclusion

The incidence and death rate of endometrial cancer has increased at an alarming pace. Although there have been substantial therapeutic advancements, there is an urgent need to identify novel clinical trial designs. Emphasis on molecular classification and tailored approaches will be essential, and there is a need for increasing correlative and translational science in clinical trial populations. After extensive review of published studies, the clinical trials planning meeting working group 1 identified no discriminants of immunotherapy response in endometrial cancer beyond mismatch repair status or tumor mutational burden that have been validated for prospective treatment allocation and noted that the quality and quantity of data specific to endometrial cancer are limited and should be evaluated with caution. Consequently, the working group concluded that there is an immediate and urgent need for endometrial cancer–specific translational research to be undertaken and prioritized. The identification and development of preclinical models representing the spectrum of molecular features in endometrial cancer and immunocompetent hosts are also critical for hypothesis generation and early-stage treatment testing.

It is important to emphasize that several factors that impact conditions in the endometrial cancer tumor immune microenvironment should also be considered in the design and interpretation of clinical trials, including obesity, estrogen status, microbiome, and medical comorbidities, all of which may impact the antitumor immune response. Once again, the increasing disparities and impact of race and ethnicity could not be emphasized enough. Finally, molecular classification is recommended when able in endometrial cancer clinical trial design with further evaluation of biomarkers for prognostic and predictive refinement.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The data presented in this review are available in the references, and the CTPM executive statement can be found online at https://www.cancer.gov/about-nci/organization/ccct/steering-committees/nctn/gynecologic/gcsc-2024-ctpm-executive-summary.pdf.

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Commentary