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### Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Uterine Neoplasms
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Uterine Neoplasms

## Disclosure of Relevant Financial Relationships

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**Nadeem R. Abu-Rustum, MD**, Panel Chair, has disclosed receiving grant/research support from GRAIL, Inc.

**Susana M. Campos, MD, MPH, MS**, Panel Vice Chair, has disclosed receiving consulting fees from AstraZeneca Pharmaceuticals LP, Eisai Inc., GSK plc, and Merck & Co., Inc.

**Brooke E. Howitt, MD**, Panel Member, has disclosed receiving royalty income from Elsevier.

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# Uterine Neoplasms, Version 3.2025

## Featured Updates to the NCCN Guidelines®

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### Abstract

The NCCN Guidelines for Uterine Neoplasms provide recommendations for diagnostic workup, clinical staging, and treatment options for patients with endometrial cancer and uterine sarcoma. The NCCN Cervical Uterine Panel meets at least annually to review comments from reviewers within their institutions; examine relevant new data from publications, abstracts, and recent FDA approvals; and reevaluate and update recommendations. These NCCN Guidelines Insights summarize the panel's deliberations on the new FIGO 2023 staging system and updates on the new systemic therapy recommendations for the management of endometrial cancer.

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### Overview

Endometrial cancer—also referred to more broadly as uterine cancer or carcinoma of the uterine corpus—is the most common malignancy of the female genital tract in the United States and has the fastest increasing mortality rate among gynecologic cancers. It is estimated that 69,120 new uterine cancer cases will occur in 2025, with 13,860 deaths resulting from the disease.<sup>1</sup> The incidence of uterine cancer has also continued to increase by approximately 1% per year since the mid-2000s.<sup>2</sup> It is also the only cancer with reduced survival over the past 4 decades. Stromal or mesenchymal sarcomas are uncommon subtypes, accounting for approximately 3% of all uterine cancers.<sup>3,4</sup> The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Uterine Neoplasms describe malignant epithelial tumors and uterine sarcomas; each of these major categories contains specific histologic groups that require different management. Risk factors for uterine neoplasms include increased levels of estrogen (caused by obesity, diabetes, and high-fat diet), early age at menarche, nulliparity, late age at menopause, Lynch syndrome, age between 55 and 64 years, and tamoxifen use.<sup>5–8</sup>

At the 2024 NCCN Uterine Neoplasms Panel meeting, the newly proposed 2023 International Federation of Gynecology and Obstetrics (FIGO) staging system was critically discussed, highlighting both its advantages and challenges. After thorough deliberation, the panel concluded that the 2009 FIGO staging system would remain in use until further refinements are made. Meanwhile, recent updates to clinical guidelines have added 3 immune checkpoint inhibitors (ICIs) in combination with chemotherapy as primary or adjuvant therapy for advanced endometrial carcinoma. These NCCN Guidelines Insights explore the panel's rationale for maintaining the 2009 FIGO staging system and discuss the latest advancements in the treatment of advanced endometrial carcinoma.

### New FIGO 2023 Staging System Major Changes in the New Staging System

In June 2023, the FIGO Women's Cancer Committee introduced an updated staging system for endometrial carcinoma.<sup>9</sup> This revision marks a paradigm shift in the concept of staging from being anatomic to a more integrated model that incorporates key pathologic and molecular features. The new system includes

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The full and most current version of these NCCN Guidelines is available at [NCCN.org](https://www.nccn.org).

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**Category 1:** Based upon high-level evidence ( $\geq 1$  randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ( $\geq 85\%$  support of the Panel) that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus ( $\geq 85\%$  support of the Panel) that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus ( $\geq 50\%$ , but  $< 85\%$  support of the Panel) that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

**PLEASE NOTE**

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment.

The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

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parameters such as histologic type, tumor grade, lymphovascular space invasion (LVI), and molecular classification, aiming to provide a more personalized and clinically relevant framework for patient management.

Although it is an attempt to make staging more relevant by incorporating several prognostic and molecular factors, concerns were raised at the panel meeting regarding the complexity of the revised staging, which may hinder its widespread adoption, practical implementation, and global applicability. The most significant changes discussed at the meeting involved the introduction of nonanatomic parameters in stage I and II cancers, specifically histologic type and grade, LVI, and molecular classification; some of which are further detailed in the following section.

**Caveats of the New Staging System****Dichotomization of Histology for Staging**

Histology has become a central feature of the 2023 FIGO staging. Although nonaggressive histologic types are composed of low-grade (grade 1 and 2) endometrioid carcinomas (EECs), aggressive types include high-grade EECs (grade 3), serous, clear cell, mixed, undifferentiated, mesonephric-like, and gastrointestinal type mucinous carcinomas and carcinosarcomas.<sup>9</sup> However, grade 3 EECs and several of the other “aggressive histology” tumors are a prognostically, clinically, and molecularly heterogeneous group of diseases with a mixture of different molecular subtypes and oncologic outcomes and should not be grouped into one category. The panel agrees that universal molecular classification benefits grade 3 EECs as well as many tumors in the “aggressive histology” category by enabling more appropriate allocation to risk groups; however, universal comprehensive molecular profiling and classification are still lacking in most institutions and practices, both nationally and internationally.

Concerns over grouping diverse histologies under “aggressive histology,” which changes staging, were discussed at the panel meeting. The molecular classification of endometrial cancer highlights that the 4 subtypes—*POLE* mutated, mismatch repair-deficient (dMMR), no specific molecular profile (NSMP), and p53 aberrant—are found across various histologic subtypes, including those considered aggressive.<sup>10</sup> In a 2018 study, grade 3 EECs were

**NCCN CATEGORIES OF PREFERENCE**

**Preferred intervention:** Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.

**Other recommended intervention:** Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.

**Useful in certain circumstances:** Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

investigated to determine whether the heterogeneity of molecular subtypes could be used to refine prognosis.<sup>11</sup> Among 381 patients with grade 3 EECs, compared with patients with NSMP (n=115), those with *POLE*-mutant tumors (n=49) had significantly better recurrence-free survival (hazard ratio [HR], 0.17 [95% CI, 0.05–0.54];  $P=.003$ ), whereas those with p53-aberrant tumors (n=79) had significantly worse recurrence-free survival (HR, 1.73 [95% CI, 1.09–2.74];  $P=.021$ ). These results highlight the prognostic diversity of grade 3 EECs and the need for molecular markers to guide risk stratification. Of note, the NCCN Guidelines for Cervical/Uterine Cancers emphasize the importance of molecular testing in endometrial tumors to identify prognostic subgroups (available at NCCN.org).

When a large series of endometrial carcinomas (n=1,834) with clinical tumor-normal MSK-IMPACT next-generation sequencing (NGS) results were retrospectively classified by integrating molecular data,<sup>12</sup> 40% were found to be copy number-high (CN-H), 32% copy number-low (CN-L), 23% microsatellite instability (MSI)-high, and 5% *POLE*. The molecular subtypes were significantly associated with progression-free survival (PFS) in stage I/II EECs, with *POLE* and CN-L endometrial carcinomas having the best outcomes (PFS, 96% [95% CI, 86%–99%] and 98% [95% CI, 95%–99%], respectively), MSI-H having intermediate outcomes (PFS, 88% [95% CI, 80%–93%]), and CN-H endometrial carcinomas having the worst outcomes (PFS, 72% [95% CI, 43%–88%];  $P<.001$ ).

Other studies have also revealed that molecular heterogeneity exists within other histologic types. For instance, dMMR uterine carcinosarcomas (UCSs) display distinct clinical, morphologic, and molecular features compared with traditional UCSs.<sup>13</sup> dMMR clear cell carcinomas seem to have a favorable prognosis,<sup>14</sup> and the differences in prognostic value of The Cancer Genome Atlas (TCGA) groups were similar in EECs.<sup>15</sup> Another recent study<sup>16</sup> further reinforced that high-grade aggressive histologies in endometrial cancer are diverse entities with distinct oncologic outcomes, and therefore should not be treated as a single entity in staging or prognostic tools.

**LVI Quantification to Assign Staging**

The 2023 FIGO staging uses the presence of substantial LVI to upstage grade 1 and 2 endometrioid adenocarcinomas that are limited to the uterus and/or cervix.<sup>17</sup> Substantial LVI used in

the new FIGO staging is defined by the WHO<sup>18</sup> as multifocal or diffuse arrangement of LVSIs or tumor cells in ≥5 lymphovascular spaces. However, the terms “multifocal” or “diffuse” remain poorly defined, and the cutoff number of lymphovascular spaces used to define “substantial” remains debated.<sup>17</sup> Although the adverse prognostic value of LVSIs has been highlighted in several studies,<sup>19,20</sup> inconsistent definitions of substantial LVSIs across these studies complicate its integration into the staging criterion.

Peters et al<sup>21</sup> attempted to standardize the definition of substantial LVSIs using data from the PORTEC-1 and PORTEC-2 trials and the Danish Gynecologic Cancer Database (DGCD). They evaluated various lymphovascular space cutoffs with the risk of pelvic lymph node recurrence (PLNR) at 5 years and found minimal difference in 5-year risk of PLNR rate across cutoffs of 2 (20%), 3 (21%), 5 (26%), 6 (30%), or even more spaces. Based on these findings, they proposed that ≥4 spaces is the clinically meaningful cutoff for substantial LVSIs. A major concern in prior publications is the lack of uniform comprehensive surgical staging, and many of the original studies on extensive LVSIs included patients who were not surgically staged and had minimal or no lymph node assessment.

Incorporating LVSIs into staging is further complicated by interobserver variability among pathologists. The intraclass correlation coefficient (ICC) for interpathologist reproducibility in assessing just the presence or absence of LVSIs—evaluated by a panel of 6 European gynecologic pathologists—was only 0.6, and declined to 0.54 for substantial LVSIs, defined as diffuse or multifocal LVSIs surrounding a tumor.<sup>22</sup>

A study by Dagher et al<sup>23</sup> involving 1,555 surgically staged patients found that focal and no LVSIs had different prognostic

outcomes and should not be combined into one category. Interestingly, when compared with focal LVSIs, substantial LVSIs were not linked to an increased risk of local recurrence (adjusted HR, 0.59 [95% CI, 0.36–0.96]). The 5-year cumulative incidence failure rates for any recurrence were 6.0% for no LVSIs, 19.5% for focal LVSIs, and 19.0% for substantial invasion.<sup>24</sup> These findings suggest that grouping “no LVSIs” and “focal LVSIs” into a single risk category may be inappropriate, because the risk of recurrence increases sharply even with involvement of ≤4 vessels.

Moreover, the number of microscopic sections examined can influence the detection and quantification of LVSIs, and no standardized protocol exists for section sampling.<sup>25</sup> This lack of standardization further complicates reliable LVSIs assessment in clinical practice.

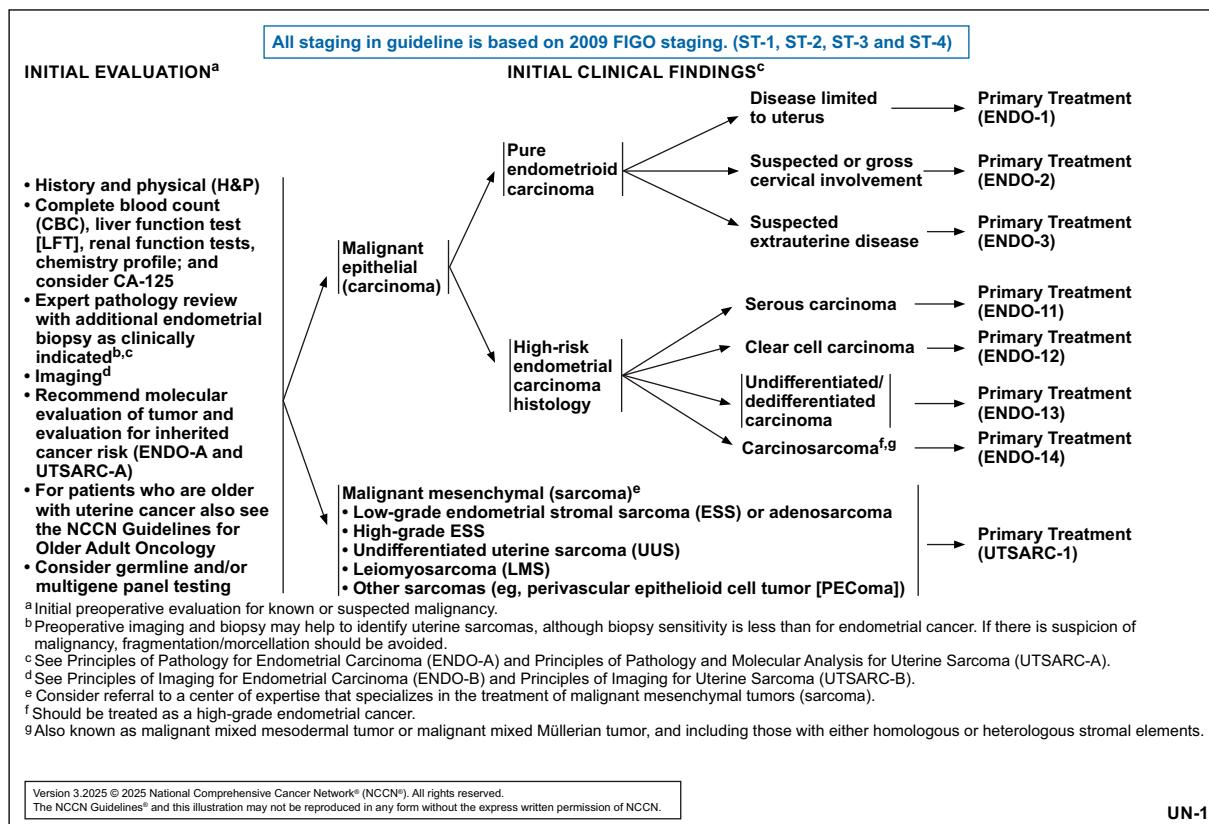
### Panel Consensus on Non-Migration to the FIGO 2023 Staging System

The advantages and pitfalls of the new FIGO 2023 staging system were extensively discussed at the panel meeting. Ultimately, the panel decided to retain the FIGO 2009 anatomic staging system, given its broader global applicability and ease of integration, until further refinements are made (Figure 1).

### Advances in Systemic Therapy

#### Inclusion of ICIs in Chemotherapy Regimens as Primary/Adjuvant Therapy for Endometrial Carcinoma

After GOG-0209 established the combination of carboplatin and paclitaxel as a standard first-line treatment for advanced or



**Figure 1.** UN-1. NCCN Clinical Practice Guidelines in Oncology for Uterine Neoplasms, Version 3.2025.

recurrent endometrial cancer,<sup>26</sup> the addition of ICIs to chemotherapy has led to a paradigm shift in treatment strategies, addressing the diverse needs of patients. Recently, several FDA-approved, practice-changing recommendations have redefined the treatment landscape. Following a comprehensive data review at the annual meeting, the panel incorporated these advancements into the guidelines, as summarized in Table 1.

#### **RUBY Trial: Evaluating Dostarlimab in Advanced Endometrial Cancer**

The RUBY trial is the first clinical trial to show a statistically significant and clinically meaningful improvement in overall survival (OS) with an immuno-oncology therapy in combination with chemotherapy in patients with primary advanced or recurrent endometrial cancer. This phase III trial aims to identify which patients with primary advanced or recurrent endometrial cancer could potentially benefit from treatment with dostarlimab-gly plus chemotherapy.

Part 1 of the RUBY trial evaluated dostarlimab plus carboplatin/paclitaxel (treatment arm) compared with placebo plus carboplatin/paclitaxel (control arm) in patients with primary advanced or recurrent endometrial cancer.<sup>27</sup> In the dMMR/MSI-H population (n=118), estimated PFS at 24 months was 61.4% (95% CI, 46.3–73.4) in the treatment arm versus 15.7% (95% CI, 7.2–27.0) in the control arm (HR, 0.28 [95% CI, 0.16–0.50];  $P<.001$ ). In the overall population (n=494), PFS at 24 months was 36.1% (95% CI, 29.3–42.9) in the treatment arm versus 18.1% (95% CI, 13.0–23.9) in the control arm (HR, 0.64 [95% CI, 0.51–0.80];  $P<.001$ ), and OS at 24 months was 71.3% (95% CI, 64.5–77.1) versus 56.0% (95% CI, 48.9–62.5), respectively (HR, 0.64 [95% CI, 0.4–0.87];  $P=.0021$ ). Although OS improvement was observed in the first interim analysis, it did not meet the predefined statistical threshold for stopping ( $P=.00177$ ). The second interim analysis confirmed a statistically significant and clinically meaningful OS benefit in the dostarlimab treatment arm, meeting the dual primary endpoint of the study (HR, 0.69 [95% CI, 0.54–0.89];  $P=.0020$ ).<sup>28</sup> The most common adverse events that occurred or worsened during treatment were nausea (53.9% of patients in the treatment arm and

45.9% in the control arm), alopecia (53.5% and 50.0%), and fatigue (51.9% and 54.5%). Severe and serious adverse events were more frequent in the dostarlimab treatment arm than in the control arm.

Based on the RUBY trial data, the panel added the carboplatin/paclitaxel/dostarlimab regimen as a category 1, preferred primary or adjuvant therapy option for stage III–IV endometrial carcinoma. Additionally, footnotes were added to note that dostarlimab maintenance therapy is recommended and to incorporate the inclusion criteria from the RUBY trial (Figure 2). On July 31, 2023, the FDA approved dostarlimab-gly with carboplatin and paclitaxel, followed by single-agent dostarlimab-gly, initially for dMMR primary advanced or recurrent endometrial carcinoma,<sup>29</sup> and the indications were further expanded to include the treatment of primary advanced or recurrent endometrial cancer, regardless of MMR/MSS status, on August 1, 2024.<sup>30</sup>

#### **DUO-E Trial: Evaluating Durvalumab in Advanced Endometrial Cancer**

The DUO-E/GOG-3041/ENGOT-EN10 trial<sup>31</sup> investigated whether adding the anti-PD-L1 antibody durvalumab to carboplatin plus paclitaxel improved outcomes in advanced or recurrent endometrial cancer. This phase III, global, double-blind, placebo-controlled trial randomly assigned eligible patients with newly diagnosed advanced or recurrent endometrial carcinoma in a 1:1:1 ratio to carboplatin/paclitaxel plus durvalumab placebo followed by placebo maintenance (control arm); carboplatin/paclitaxel plus durvalumab followed by maintenance durvalumab plus olaparib placebo (durvalumab arm); and carboplatin/paclitaxel plus durvalumab followed by maintenance durvalumab plus olaparib (durvalumab + olaparib arm).

In the intention-to-treat (ITT) population (n=718), a statistically significant PFS benefit was observed in the durvalumab (HR, 0.71 [95% CI, 0.57–0.89];  $P=.003$ ) and durvalumab + olaparib arms (HR, 0.55 [95% CI, 0.43–0.69];  $P<.0001$ ) versus the control arm. Interestingly, in prespecified, exploratory subgroup analyses of PFS in the dMMR group, similar clinically meaningful benefit was observed in both experimental arms versus the control arm

**Table 1.** Summary of 4 Clinical Trials From the Systemic Therapy Section

Summary	NRG-GY018 <sup>36</sup>	KEYNOTE-B21 <sup>39</sup>	RUBY <sup>27</sup>	DUO-E <sup>31</sup>
Regimen	Pembrolizumab/Carboplatin/Paclitaxel	Pembrolizumab/Carboplatin/Paclitaxel	Dostarlimab/Carboplatin/Paclitaxel	Durvalumab/Carboplatin/Paclitaxel
Biomarker	dMMR/pMMR	dMMR only	dMMR/pMMR	dMMR only
Histology	Any histologic subtype (except carcinosarcoma)	Any histologic subtype	Any histologic subtype	Any histologic subtype
Stage/Measurable disease	<ul style="list-style-type: none"> <li>• Stage III with measurable disease postsurgery</li> <li>• Stage IVA with measurable disease postsurgery</li> <li>• Stage IVB with or without measurable disease</li> <li>• Recurrent disease with or without measurable disease</li> </ul>	<ul style="list-style-type: none"> <li>• Stage III–IV with no evidence of disease</li> </ul>	<ul style="list-style-type: none"> <li>• Stage IIIA, IIIB, IIIC1 with measurable disease postsurgery</li> <li>• Stage IIIC1 disease with carcinosarcoma, clear-cell, serous, or mixed histologic characteristics regardless of the presence of measurable disease</li> <li>• Stage IIIC2 or IV disease regardless of the presence of measurable disease</li> <li>• Recurrent disease with or without measurable disease</li> </ul>	<ul style="list-style-type: none"> <li>• Stage III with measurable disease</li> <li>• Stage IV with or without measurable disease</li> <li>• Recurrent disease with or without measurable disease</li> </ul>
Duration of immunotherapy maintenance <sup>a</sup>	2 years	Pembrolizumab 400 mg every 6 weeks for 6 cycles	3 years	Indefinite

Abbreviations: dMMR, mismatch repair-deficient; pMMR, mismatch repair-proficient.

<sup>a</sup>Refer to the NCCN Chemotherapy Order Templates, available at NCCN.org.

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA <sup>a</sup>	
Chemoradiation Therapy	Primary or Adjuvant Therapy (Stage I–IV)
<b>Preferred Regimen</b> • Cisplatin plus RT followed by carboplatin/paclitaxel <sup>1,2</sup>	<b>Preferred Regimens</b> • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1) <sup>b,c,d,7,8</sup> • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1) <sup>c,d,e,9</sup> • Carboplatin/paclitaxel/durvalumab (for stage III–IV dMMR tumors only) (category 1) <sup>c,f,10</sup> • Carboplatin/paclitaxel/trastuzumab (for stage III–IV HER2-positive uterine serous carcinoma or carcinosarcoma) <sup>d,g,11</sup> • Carboplatin/paclitaxel/bevacizumab (stage III–IV with measurable disease) <sup>d,12,13</sup> • Carboplatin/paclitaxel <sup>14</sup>
<b>Other Recommended Regimens (if cisplatin and carboplatin are unavailable)</b> • Capecitabine/mitomycin <sup>3</sup> (category 2B) • Gemcitabine <sup>4</sup> (category 2B) • Paclitaxel <sup>5,6</sup> (category 2B)	

<sup>a</sup> An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.  
<sup>b</sup> For stage III or IVa with measurable disease post surgery or stage IVb with or without measurable disease. For patients not meeting the eligibility criteria for NRG-GY018, carboplatin/paclitaxel + pembrolizumab should be considered for stage III–IV dMMR tumors (Van Gorp T, et al. Ann Oncol. Published online August 23, 2024).  
<sup>c</sup> NCCN Guidelines for Management of Immunotherapy-Related Toxicities.  
<sup>d</sup> Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.  
<sup>e</sup> For adult patients with primary advanced endometrial carcinoma: stage IIIC<sub>1</sub>, IIIC<sub>2</sub>, or IIIC<sub>3</sub> with measurable disease post surgery, stage IIIC<sub>1</sub> with carcinosarcoma, clear-cell, serous, or mixed histology regardless of the presence of measurable disease, and stage IIIC<sub>2</sub> or stage IV regardless of the presence of measurable disease.  
<sup>f</sup> For stage III with measurable disease post surgery and stage IV with or without measurable disease.  
<sup>g</sup> For patients who have not received prior trastuzumab therapy.

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ENDO-D  
1 OF 5**Figure 2.** ENDO-D 1 of 5. NCCN Clinical Practice Guidelines in Oncology for Uterine Neoplasms, Version 3.2025.

(HR for durvalumab vs control: 0.42 [95% CI, 0.22–0.80]; HR for durvalumab + olaparib vs control: 0.41 [95% CI, 0.21–0.75]). MMR-proficient (pMMR) subgroups also showed PFS benefit in both groups (HR for durvalumab vs control: 0.77 [95% CI, 0.60–0.97]; HR for durvalumab + olaparib vs control: 0.57 [95% CI, 0.44–0.73]).<sup>31</sup> The safety profiles of the experimental arms were generally consistent with individual agents.

The interim OS subgroup analysis presented at the Society of Gynecologic Oncology 2024 Annual Meeting<sup>32</sup> showed similar OS improvement for both of the experimental arms versus the control arm in the dMMR subgroup (HR for durvalumab vs control: 0.34 [95% CI, 0.13–0.79]; HR for durvalumab + olaparib vs control: 0.28 [95% CI, 0.10–0.68]) compared with the pMMR subgroup, which showed only a trend toward benefit. Based on these findings, the FDA approved durvalumab with carboplatin plus paclitaxel followed by single-agent durvalumab only for adult patients with primary advanced or recurrent endometrial cancer that is dMMR.<sup>33</sup>

Of note, the benefit of adding a PARP inhibitor as maintenance therapy remains uncertain, as current clinical data have shown conflicting results. The GINECO randomized phase IIb UTOLA trial<sup>34</sup> evaluated the efficacy of olaparib versus placebo as maintenance therapy after platinum-based chemotherapy in patients with advanced/metastatic endometrial cancer. This trial showed no significant clinical benefit between the olaparib and control arms, with a median PFS in the ITT population of 5.6 months (90% CI, 3.8–7.4) and 4.0 months (90% CI, 3.6–7.4), respectively (HR, 0.94;  $P=.29$ ). On the other hand, the recent findings from a phase II study (ClinicalTrials.gov identifier: NCT03617679)<sup>35</sup> showed clinical benefit with PARP inhibitor maintenance therapy in patients with metastatic and recurrent endometrial cancer who had received 1 to 2 prior lines of cytotoxic chemotherapy. In the ITT population, this study showed a 19.4-month improvement in PFS with the PARP inhibitor versus placebo (HR, 0.45 [95% CI, 0.26–0.80];  $P=.005$ ) and a median OS of 28.4 months (HR, 0.48 [95% CI, 0.23–1.03];  $P=.055$ ).<sup>35</sup> Due to

inconsistent data, the addition of olaparib for maintenance therapy was not endorsed by the panel at the 2024 meeting.

Based on the FDA approval, the panel added the carboplatin/paclitaxel/durvalumab regimen in Version 3.2024 of the NCCN Guidelines with a category 1 recommendation as a preferred regimen for primary or adjuvant therapy for stage III–IV dMMR tumors. In Version 1.2025, the panel added a footnote to include patient criteria (Figure 2).

#### NRG-GY018 Trial: Evaluating Pembrolizumab in Advanced Endometrial Cancer

NRG-GY018 is a double-blind, placebo-controlled, randomized phase III trial that evaluated the benefit of adding pembrolizumab to chemotherapy for patients with advanced or recurrent endometrial cancer (excluding carcinosarcoma).<sup>36</sup> A total of 816 patients were randomized in a 1:1 ratio to receive pembrolizumab or placebo along with paclitaxel plus carboplatin. The patients were stratified into dMMR and pMMR cohorts. In the 12-month analysis, Kaplan-Meier estimates of PFS in the dMMR cohort were 74% and 38% in the pembrolizumab and placebo groups, respectively (HR, 0.30 [95% CI, 0.19–0.48];  $P<.001$ ), representing a 70% difference in relative risk. In the pMMR cohort, median PFS was 13.1 months with pembrolizumab and 8.7 months with placebo (HR, 0.54 [95% CI, 0.41–0.71];  $P<.001$ ). OS data also favored pembrolizumab plus chemotherapy in both the pMMR and dMMR groups<sup>37</sup> (HR, 0.79 [95% CI, 0.53–1.17];  $P=.1157$ , and 0.55 [95% CI, 0.25–1.19];  $P=.0617$ , respectively). HRs for PFS per blinded independent central review favored pembrolizumab in these cohorts (HR, 0.64 [95% CI, 0.49–0.85];  $P=.0008$ , and 0.45 [95% CI, 0.27–0.73];  $P=.0005$ , respectively). Hence, the subgroup analyses of primary and secondary endpoints in both the dMMR and pMMR cohorts favored the pembrolizumab group regardless of MMR status. Based on these findings, carboplatin/paclitaxel/pembrolizumab was added as category 1, preferred regimen for stage III–IV tumors, except for

carcinosarcoma, in Version 2.2023 (see Figure 2). This regimen received full FDA approval on June 17, 2024.<sup>38</sup>

#### **KEYNOTE-B21 Trial: Evaluating Pembrolizumab in Advanced Endometrial Cancer**

The panel chairs also reviewed the recently published interim results of KEYNOTE-B21.<sup>39</sup> This study investigated the addition of pembrolizumab to adjuvant chemotherapy (with or without radiation therapy) among patients with newly diagnosed, high-risk endometrial cancer without any residual macroscopic disease following curative-intent surgery. Although adjuvant pembrolizumab plus chemotherapy did not improve disease-free survival (DFS) in all-comer patients with endometrial cancer, preplanned subgroup analyses suggest that pembrolizumab plus chemotherapy improved DFS in patients with dMMR tumors. A total of 1,095 patients were randomized to pembrolizumab (n=545) or placebo (n=550). At this interim analysis, 119 (22%) DFS events occurred in the pembrolizumab group and 121 (22%) in the placebo group (HR, 1.02 [95% CI, 0.79–1.32]; P=.570). Subgroup analysis of DFS

favored the dMMR population (n=281) over the pMMR population (n=814) (HR, 0.31 [95% CI, 0.14–0.69] vs 1.20 [95% CI, 0.91–1.57], respectively). In light of these emerging data, the guidelines were updated to recommend consideration of this regimen for the management of stage III–IV dMMR tumors (Figure 2).

#### **Conclusions**

The treatment landscape for uterine neoplasms is rapidly evolving with the advent of biomarker-driven targeted therapies and ICI combinations. The NCCN panel is committed to providing evidence-based, consensus-driven recommendations by systematically reviewing emerging data from peer-reviewed publications, scientific abstracts, and recent FDA approvals. The panel will reassess the FIGO 2023 staging system as additional data become available.



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