

# Uterine Sarcoma, Version 1.2016

## Featured Updates to the NCCN Guidelines

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### Abstract

The NCCN Guidelines for Uterine Neoplasms provide interdisciplinary recommendations for treating endometrial carcinoma and uterine sarcomas. These NCCN Guidelines Insights summarize the NCCN Uterine Neoplasms Panel's 2016 discussions and major guideline updates for treating uterine sarcomas. During this most recent update, the panel updated the mesenchymal tumor classification to correspond with recent updates to the WHO tumor classification system. Additionally, the panel revised its systemic therapy recommendations to reflect new data and collective clinical experience. These NCCN Guidelines Insights elaborate on the rationale behind these recent changes. (J Natl Compr Canc Netw 2015;13:1321–1331)

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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 Sarcoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Uterine Sarcoma

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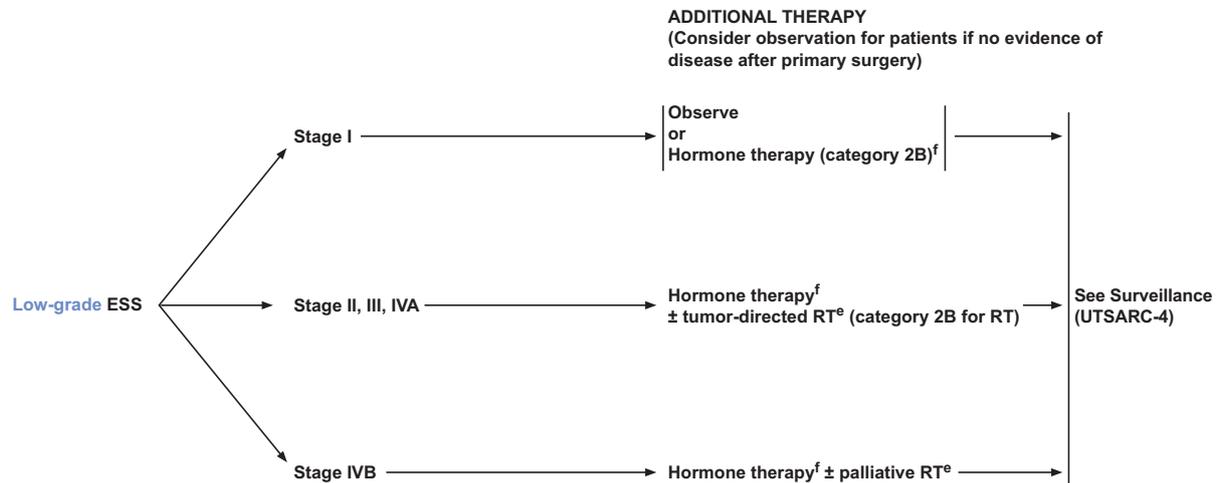
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<sup>e</sup>See Principles of Radiation Therapy (UN-A).

<sup>f</sup>See Systemic Therapy for Uterine Sarcoma (UTSARC-A).

<sup>g</sup>By definition, ESS has low-grade cytologic features. High-grade subtypes of endometrial sarcomas (undifferentiated endometrial sarcomas in WHO classification) are still being defined.

<sup>h</sup>See Uterine Sarcoma Classification (UTSARC-B).

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UTSARC-2

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**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

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**All recommendations are category 2A unless otherwise noted.**

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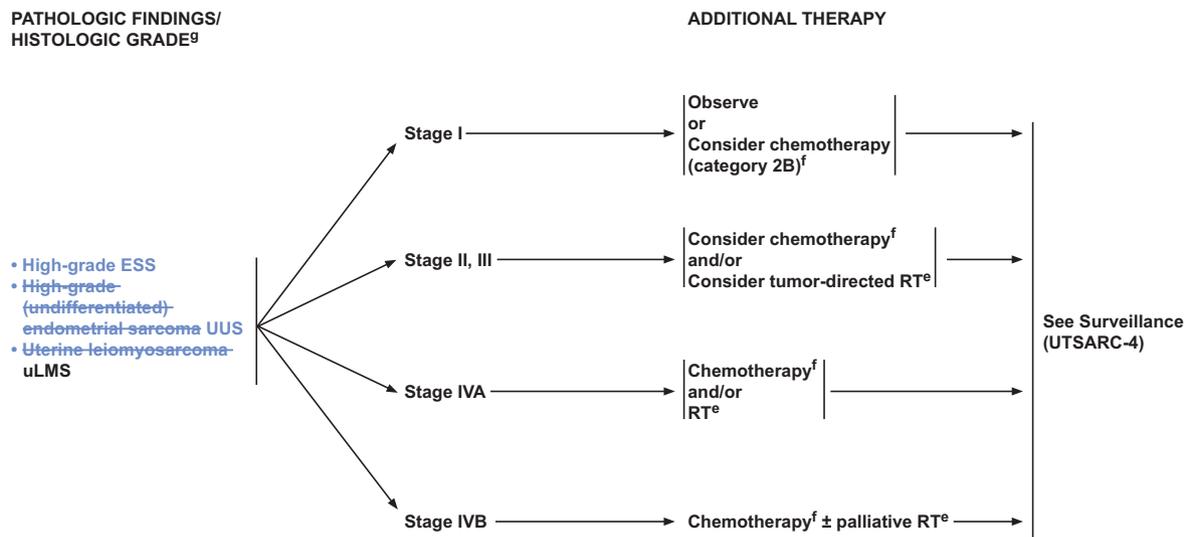
## Overview

The NCCN Uterine Neoplasms Panel is an interdisciplinary group of representatives from NCCN Member Institutions consisting of specialists in gynecologic oncology, medical oncology, radiation oncology, and pathology. The NCCN guidelines for Uterine Neoplasms include evidence-based recommendations for the assessment and management of uterine cancers. The panel updates the guidelines on an annual basis, with additional interim updates as appropriate. Notable recent updates include modified classifications of malignant mesenchymal neoplasms and updated systemic therapy recommendations for uterine sarcomas. The latest full version of these guidelines is available at NCCN.org.

## Uterine Sarcoma Background

In 2015, an estimated 54,870 diagnoses of uterine cancers are predicted in the United States, with

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<sup>f</sup>See Systemic Therapy for Uterine Sarcoma (UTSARC-A).

<sup>g</sup>See Uterine Sarcoma Classification (UTSARC-B).

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UTSARC-3

only 1,600 of these being uterine sarcomas.<sup>1</sup> Uterine sarcomas are malignant mesenchymal tumors that include endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS), and uterine leiomyosarcoma (uLMS). According to a 2012 systematic review of data from 1970 to 2011, uLMS was the most common subtype (63%), followed by ESS (21%) and less common subtypes such as UUS.<sup>2</sup> Even rarer subtypes of malignant mesenchymal tumors that can occur in the uterus include adenosarcoma, rhabdomyosarcoma, and perivascular epithelioid cell neoplasm (PEComa).<sup>3</sup> Carcinosarcomas were previously categorized and included in the sarcoma treatment algorithms until the mid-2000s, but are now considered and treated as high-grade epithelial tumors (carcinomas).<sup>4</sup>

Because uterine sarcomas are rare tumors that comprise only 3% of all uterine neoplasms,<sup>1</sup> randomized clinical trials are difficult to execute and data from this patient population are extremely limited.

Much of the existing evidence is derived from retrospective reviews, and treatment paradigms (eg, hormonal therapy for hormone receptor–positive uterine sarcomas) must often be developed on an empirical basis by extrapolating data from other disease types. As such, expert consensus and clinical experience are important factors in the development of these NCCN Guidelines for Uterine Sarcomas. This report summarizes the existing data and provides insight into the rationale for the 2016 updates to the guidelines.

### Changes to Mesenchymal Tumor Classification

Recent advances have expanded understanding of the molecular features of these tumors, leading to the identification of genetic signatures that characterize some of the uterine sarcoma subtypes. Currently, mesenchymal tumors are primarily diagnosed using

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<b>SYSTEMIC THERAPY FOR UTERINE SARCOMA<sup>1</sup></b> (Clinical trials strongly recommended)	
<b>CHEMOTHERAPY REGIMENS<sup>4</sup></b> (Clinical trials strongly recommended)	
<b>Combination regimens:</b> <ul style="list-style-type: none"> <li>• Docetaxel/gemcitabine (preferred for leiomyosarcoma)</li> <li>• Doxorubicin/ifosfamide</li> <li>• Doxorubicin/dacarbazine</li> <li>• Gemcitabine/dacarbazine</li> <li>• Gemcitabine/vinorelbine</li> </ul>	<b>Single-agent options:</b> <ul style="list-style-type: none"> <li>• Dacarbazine</li> <li>• Doxorubicin</li> <li>• Epirubicin</li> <li>• Eribulin</li> <li>• Gemcitabine</li> <li>• Ifosfamide</li> <li>• Liposomal doxorubicin</li> <li>• Pazopanib</li> <li>• Temozolomide</li> <li>• Vinorelbine (category 2B)</li> <li>• Docetaxel (category 3)</li> </ul>
<b>HORMONE THERAPY (ESS-only)</b> (For Low-grade ESS or Hormone Receptor Positive (ER/PR) uLMS <sup>5</sup> ):	
<ul style="list-style-type: none"> <li>• Medroxyprogesterone acetate (category 2B for ER/PR positive uLMS)</li> <li>• Megestrol acetate (category 2B for ER/PR positive uLMS)</li> <li>• Aromatase inhibitors<sup>2</sup></li> <li>• GnRH analogs (category 2B for low-grade ESS and ER/PR positive uLMS)</li> </ul>	

\*These hormonal therapies may be considered for patients with uLMS that is ER/PR positive, preferably with small tumor volume or an indolent growth pace.

<sup>1</sup>Liposomal doxorubicin and docetaxel may cause drug reactions. See NCCN Guidelines for Ovarian Cancer—Management of Drug Reactions [OV-C].

<sup>2</sup>Aromatase inhibitors for uLMS that are ER/PR positive.

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**Back to Recurrence**  
(UTSARC-4)

UTSARC-A

histopathologic criteria, and the results of molecular studies are not used in routine pathologic evaluation. However, molecular analysis (eg, identification of characteristic translocations) can help classify difficult cases and provide future therapeutic targets.

ESSs are composed of cells resembling the endometrial stroma in the proliferative phase.<sup>3,5</sup> ESS displays a heterogeneous mix of morphologic and genetic features. A significant proportion of these tumors (ie, up to half) harbor a *JAZF1-SUZ12* (formerly *JAZF1-JJAZ1*) gene fusion and present as lower-grade, earlier-stage tumors.<sup>6-9</sup> More recently, a higher-grade and more aggressively behaving ESS variant with a unique genetic rearrangement, *YWHAE-FAM22A/B*, also known as *YWHAE-NUTM2A/B*, was identified.<sup>10,11</sup> These findings provided support for subdividing ESS into distinct low- and high-grade entities based on histopathology, clinical behavior, and patient outcomes. In light of new information, the WHO released an updated (4th) edition of the *WHO Classification of Tumours of Female Reproductive Organs*.

The updated 2014 edition recognizes low-grade and high-grade ESS as distinct histopathologic entities.<sup>12</sup>

### Histopathology as a Prognostic Indicator

Research has demonstrated a strong association between histopathologic subtype and prognosis in uterine sarcoma. A review of 249 cases of uterine sarcoma revealed histopathologic subtype to be a significant independent prognostic factor for survival. Of the sarcoma types examined in this study, overall survival (OS) for low-grade ESS was not reached, whereas OS for high-grade ESS and uLMS was 16.5 and 21 months, respectively.<sup>13</sup> Patient outcomes were also examined through a multi-institutional review of 105 patients with low- versus high-grade ESS.<sup>8</sup> Patients with low-grade ESS were significantly more likely to present with uterine/cervix-confined disease (68% vs 39%;  $P=.002$ ) and survived longer than those with high-grade disease. Median OS was 53 months for high-grade ESS, and OS was not reached for low-grade ESS (88% of patients were

**UTERINE SARCOMA CLASSIFICATION<sup>1</sup>**

- Low-grade endometrial stromal sarcoma (ESS)<sup>2</sup>
- High-grade ESS<sup>3</sup>
- High-grade (undifferentiated)-endometrial sarcoma Undifferentiated uterine sarcoma (UUS)<sup>4</sup>
- Uterine leiomyosarcoma (uLMS)<sup>5</sup>

**Other Rare Uterine mesenchymal sarcoma Subtypes:**  
(see the NCCN Guidelines for Soft Tissue Sarcoma)

- Adenosarcomas
- PEComas
- Rhabdomyosarcoma

<sup>1</sup>Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO Classification of Tumours of the Female Reproductive Organs, Volume 6, 2014.

<sup>2</sup>Endometrial stromal sarcomas displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index. By definition, ESS is low-grade histology.

Low-grade endometrial stromal sarcomas (LGESS) are characterized by small cells with low-grade cytology and features resembling stromal cells in proliferative endometrium. Mitotic activity is usually low (<5 MF per 10 HPF) (LGESS)

<sup>3</sup>High-grade sarcomas showing pleomorphism or anaplasia greater than that seen in proliferative phase endometrial stroma or completely lacking recognizable stromal differentiation; mitotic index is almost always >10 mf/10 hpf.

High-grade endometrial stromal sarcomas (HGESS) are characterized by small cells with high-grade cytology, frequent necrosis, and brisk mitotic activity (>10 MF per 10 HPF). HGESS can contain areas of conventional LGESS.

<sup>4</sup>Undifferentiated uterine sarcomas (UUS) are characterized by cells with high-grade cytologic features lacking any resemblance to the stromal cells in proliferative endometrium or any other specific type of differentiation.

<sup>5</sup>Excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, diffuse leiomyomatosis; management in individual cases may be modified based on clinicopathologic prognostic factors, such as size (< or > 5 cm), mitotic activity (< or > 10 mf/10 hpf), age (< or > 50 years), and presence or absence of vascular invasion.

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UTSARC-B

alive at 80 months;  $P < .001$ ). Presence of residual disease after resection had a significant, negative impact on OS for patients with high- but not low-grade ESS.<sup>8</sup> High-grade ESS appears to carry an intermediate prognosis between that of low-grade ESS and UUS.<sup>14–16</sup> Generally, the prognosis for UUS is poor regardless of disease stage, and optimal standard treatment options are unclear.<sup>17–21</sup>

### NCCN Recommendations

In previous versions, the NCCN Guidelines defined ESS as “displaying morphologic features of proliferative phase endometrial stroma and showing any mitotic index. By definition, ESS is low-grade histology.” This description coincided with the then-current WHO classifications of ESS. However, a panel member brought to the panel’s attention recent changes within the 4th edition of the *WHO Classification of Tumours of Female Reproductive Organs*, published in 2014. A suggestion was made to update the tumor classifications in the NCCN Guidelines

to correspond with the most up-to-date terminology used by the WHO. Additional panel members supported this idea, emphasizing recent evidence that ESS variants harboring *YWHAE* rearrangements behave distinctly from low-grade ESS.<sup>10,11</sup> The panel differentiated between the indolent, typically hormone-sensitive nature of low-grade ESS and the more aggressive behavior of high-grade ESS, for which hormone sensitivity is less well defined.

The panel also discussed its collective experience with high-grade ESS cases, emphasizing variable hormone sensitivity and requirement for more aggressive therapy with cytotoxic agents. Several panel members also noted a limited ability to make evidence-based treatment recommendations for high-grade ESS, highlighting the developing nature of this disease classification. At this time, panel consensus was to treat this disease according to protocols for uLMS and UUS.

In light of the WHO reclassification of these tumors, tumor “definitions” were updated with input from both panel and select NCCN Member Insti-

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tution–affiliated pathologists. The guidelines now recognize and describe 2 distinct classes of ESS: low-grade and high-grade ESS (see UTSARC-B, page 1326). The algorithm states that low-grade ESS is characterized by small cells with low-grade cytology and features resembling stromal cells in proliferative endometrium, typically with low mitotic activity (usually <5 mitotic figures [MF] per 10 high-powered field [HPF]). Per this updated classification, the algorithm on UTSARC-2 now applies solely to low-grade ESS, rather than all ESS, as was the case in previous versions (see page 1323).

Previously, the guidelines referenced a single class of “undifferentiated” mesenchymal sarcoma, which was described as a high-grade sarcoma showing pleomorphism or anaplasia greater than that seen in proliferative phase endometrial stroma or completely lacking recognizable stromal differentiation. Characteristic mitotic index was typically in excess of 10 MF per 10 HPF. However, per the updated WHO system, descriptions of the newly designated high-grade ESS and UUS were incorporated into the NCCN Guidelines. The panel now describes high-grade ESS as a tumor characterized by small cells with high-grade cytology, frequent necrosis, and brisk mitotic activity in excess of 10 MF per 10 HPF. The panel also notes that high-grade tumors can contain areas of conventional low-grade ESS. An amended description of UUS refers to tumors characterized by cells with high-grade cytologic features lacking any resemblance to the stromal cells in proliferative endometrium or any other specific type of differentiation (see UTSARC-B, page 1326).

uLMS classification was unchanged in the WHO system, and the description of uLMS in the NCCN Guidelines remains unchanged, stating that uLMS “excludes smooth muscle tumors of uncertain malignant potential, epithelioid smooth muscle tumors, benign metastasizing leiomyomas, intravenous leiomyomatosis, diffuse leiomyomatosis,” and suggesting that management may be modified based on clinicopathologic prognostic factors such as tumor size (less than or greater than 5 cm), mitotic activity (less than or greater than 10 MF/10 HPF), age (older or younger than 50 years of age), and presence or absence of vascular invasion.

The treatment algorithm flow was updated to reflect new histopathologic classifications. For treating low-grade ESS, users are still directed to UTSARC-2.

For guidelines on treating high-grade ESS, users are now directed to UTSARC-3 (see page 1324), which provides combined recommendations for high-grade ESS, UUS, and uLMS. Previously, the treatment algorithms on this page applied only to high-grade undifferentiated endometrial sarcoma (now called UUS) and uLMS. Treatment recommendations for uLMS remain unchanged in the latest version of the NCCN Guidelines.

Finally, in the 2016 updates to the NCCN Guidelines, the panel opted to acknowledge rare mesenchymal tumor subtypes, such as adenosarcoma, PEComa, and rhabdomyosarcoma among the listed uterine sarcoma classifications (see UTSARC-B, page 1326). Currently, panel members do not believe adequate data and consensus exist to provide evidence-based treatment recommendations for these very rare uterine tumors, although they recognize these diseases as distinct entities. Guideline users are directed to the NCCN Guidelines for Soft Tissue Sarcoma for treatment recommendations (to view the most recent version of these guidelines, visit [NCCN.org](http://NCCN.org)).

### Updates to Systemic Therapy Recommendations for Uterine Sarcomas

Historically, several combination and single-agent cytotoxic regimens have been recommended in the guidelines. Gemcitabine/docetaxel is a well-studied combination therapy for treating uterine sarcomas, and is considered the preferred regimen for treating uLMS.<sup>22–31</sup> In addition to gemcitabine/docetaxel, other combination regimens included in the NCCN Guidelines are doxorubicin/ifosfamide, doxorubicin/dacarbazine, gemcitabine/dacarbazine, and gemcitabine/vinorelbine.<sup>31–34</sup> Single-agent considerations for treating advanced or metastatic disease include dacarbazine, doxorubicin, epirubicin, gemcitabine, ifosfamide, liposomal doxorubicin, pazopanib, temozolomide, vinorelbine, and docetaxel.<sup>3,5,25,26,32,34–51</sup> The aforementioned regimens remain part of the standard armamentarium and are included in the updated version of the guidelines (see UTSARC-A, page 1325). Additionally, the panel discussed potential novel applications of eribulin and hormonal therapy.

#### Addition of Eribulin as a Systemic Therapy Option

Eribulin is a microtubule binding agent that inhibits mitotic activity.<sup>52</sup> In 2011, results were published

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from a phase II trial examining eribulin for treating advanced or metastatic, intermediate or high-grade soft tissue sarcomas.<sup>52</sup> Four patient cohorts included 128 pretreated patients with adipocytic sarcoma, leiomyosarcoma, synovial sarcoma, or various other subtypes. The data indicated that eribulin was active in leiomyosarcoma and adipocytic sarcomas with 32% and 42% of patients, respectively, demonstrating progression-free survival at 12 weeks. Other soft tissue sarcoma histologies showed a response but did not reach prespecified efficacy criteria. A phase III trial followed up on these findings, comparing the survival benefit of eribulin and dacarbazine in 452 patients with advanced leiomyosarcoma or adipocytic sarcoma.<sup>53</sup> Median OS was 13.5 and 11.5 months for eribulin and dacarbazine, respectively (hazard ratio, 0.768; 95% CI, 0.618–0.954;  $P=.017$ ). Toxicity was as expected for both drugs.

### Hormonal Therapy

Most ESS and a subset of uLMS express estrogen and progesterone hormone receptors (ER/PR+), presenting a potential target for the armamentarium of existing endocrine therapies.<sup>54–56</sup> Therapies that reduce the levels or activity of endogenous estrogen provide a noncytotoxic alternative systemic therapy option for treating hormone-sensitive uterine sarcomas. Hormonal agents used in uterine sarcomas include aromatase inhibitors (AIs), progestins (eg, medroxyprogesterone acetate, megestrol acetate), and gonadotropin-releasing hormone (GnRH) analogues. Tamoxifen is not indicated for patients with uterine sarcomas, because an increased risk of developing endometrial cancer and uterine sarcoma was observed in patients taking tamoxifen for breast cancer risk reduction.<sup>57–59</sup>

Because uterine sarcomas are rare tumors, much of the data on hormonal therapy in ER/PR+ uterine sarcomas are from retrospective reviews and case series in small patient groups. In patients with operable disease, hormonal therapy has been used in the adjuvant setting to prevent recurrence. Hormonal agents have also been used to control disease in the setting of recurrent or metastatic sarcomas. Additionally, some studies provide evidence for the preoperative use of hormonal agents to render inoperable tumors amenable to resection.<sup>3,54,55</sup> For an overview of the data examining hormonal therapy for treating uLMS and ESS, see reviews by Amant et al,<sup>3</sup> Ioffe et al,<sup>56</sup> and Thanopoulou and Judson.<sup>54</sup>

Multiple single-institution retrospective analyses provide support for AI, progestin, or GnRH analogue efficacy for treating low-grade ESS.<sup>56,60–64</sup> A 2012 meta-analysis of the available data from retrospective studies and case reports suggested a 67% overall response rate of ESS to AIs.<sup>62</sup> More recently, studies have generated data to support the efficacy of hormonal therapies for treating hormone receptor-positive uLMS. Retrospective data from single-institution studies generally indicate some activity of AIs in uLMS.<sup>56,65,66</sup> However, other studies have demonstrated more limited response rates for AIs in uLMS, possibly because of the varying degree of hormone sensitivity in these tumors.<sup>62,67</sup>

### NCCN Recommendations

The guidelines now provide separate treatment recommendations for low-grade ESS and the collective grouping of higher-grade diseases, which includes high-grade ESS, uLMS, and UUS. Primary surgery is the mainstay of treatment for patients who are deemed suitable for primary surgery, with adjuvant therapy as indicated. For patients not suitable to receive primary surgery, primary treatment recommendations include systemic therapy and/or pelvic radiation therapy (RT) with or without brachytherapy. Systemic therapy is an important component of treatment for relapsed disease.

**Adjuvant Therapy for Low-Grade ESS:** Postoperative hormone therapy is recommended for stages I–IV ESS (category 2A for stages II–IV; category 2B for stage I). Adjuvant tumor-directed RT may be added for stages II–IVA (category 2B); palliative RT can be considered for stage IVB. Recommended hormonal agents include megestrol, medroxyprogesterone, and AIs (category 2A); GnRH analogues, (category 2B) are also an option. Hormone therapy is also recommended for ESS that has recurred or is unresectable. Tamoxifen is contraindicated and was previously removed from the NCCN Guidelines.

**Adjuvant Therapy for High-Grade Uterine Sarcomas (High-Grade ESS, uLMS, UUS):** Patients with stage I disease can be observed; consideration of chemotherapy is also an option (category 2B). For treating stage II–III disease, the panel recommends consideration of chemotherapy and/or tumor-directed RT. For stage IVA disease, chemotherapy and/or RT are recommended. Chemotherapy with or without palliative RT is an option for treating stage

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IVB disease. Systemic therapy, including hormonal agents for hormone-sensitive tumors, is recommended for recurrent disease.

**Updates to the Systemic Therapy Options:** The panel reviewed all existing systemic therapy recommendations and discussed new data for existing or novel agents. Upon review of the available evidence for the included combination chemotherapy regimens, the panel decided that insufficient evidence exists to promote one regimen over another at this time. As such, all combination regimens remain category 2A recommendations.

Upon reviewing the available evidence for single-agent systemic options, panel members discussed the evidence supporting trabectedin and eribulin for treating uterine sarcomas. The panel first reviewed the data on eribulin, which is a commercially available agent indicated for treating metastatic breast cancer, and found that data from a recent phase III trial<sup>53</sup> demonstrated a survival benefit for this agent over dacarbazine (an existing category 2A therapy recommendation for treating uterine sarcoma in the NCCN Guidelines). Accordingly, the panel voted on whether to recommend eribulin for off-label use in treating uterine sarcomas. A panel vote revealed 90% consensus to include eribulin among the single-agent treatment options (category 2A; see UTSARC-A, page 1325). Regarding trabectedin, the panel discussed data from a recent phase III trial comparing trabectedin with dacarbazine in 518 patients with advanced, pretreated uLMS (73%) or liposarcoma (27%). The trabectedin data were positive for disease control but nonsignificant for OS (analysis ongoing).<sup>68</sup> Because trabectedin is not yet approved for commercial use in the United States and is only available through clinical trials, the panel opted not to include this agent at this time, but will continue to monitor the FDA's consideration of this agent.

The panel also reconsidered its recommendations for hormone therapy for treating ER/PR+ ESS and uLMS. In previous iterations of the guidelines, recommended hormonal therapy options for ESS included medroxyprogesterone acetate, megestrol acetate, AIs, and GnRH analogues, (category 2B for GnRH analogues, category 2A for all others), and AIs were included as the appropriate option for treating ER/PR+ uLMS. Upon further consideration, the panel questioned whether all existing hormonal agents recommended for ESS should also be

considered for treating ER/PR+ uLMS. Accordingly, the panel voted on whether medroxyprogesterone acetate, megestrol acetate, and GnRH analogues, should be considered treatment options for uLMS in addition to the existing recommendation for AIs. Panel votes revealed 82% consensus to add the progestin agents (category 2A) and 71% consensus for adding GnRH analogues, (category 2B) as treatment options for ER/PR+ uLMS (see UTSARC-A, page 1325).

### Conclusions

Important recent updates to the NCCN Guidelines for Uterine Sarcoma are highlighted in this report. Relevant changes in the classification and treatment of specific uterine sarcoma subtypes were discussed, as well as updates to the recommended systemic therapy options. The NCCN Guidelines are updated at least annually and more often when new high-quality clinical data become available in the interim. The most up-to-date version of these continuously evolving guidelines is available at NCCN.org. The recommendations in the NCCN Guidelines are based on evidence from clinical trials, when available, combined with expert consensus of the NCCN panel. Independent medical judgment is required to apply these guidelines individually to provide optimal care. The physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the NCCN panel strongly encourages participation in prospective clinical trials.

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### Posttest Questions

1. A 56-year-old woman is diagnosed with stage III, hormone receptor–negative uLMS. Which systemic agent/regimen is recommended by the NCCN Guidelines?
  - a. Aromatase inhibitor
  - b. Docetaxel/gemcitabine
  - c. Bevacizumab
  - d. Cisplatin/eribulin
  - e. Megestrol acetate
2. True or False: ESS is broadly characterized by low-grade histology and nonaggressive clinical behavior.

3. Adjuvant cytotoxic chemotherapy should be considered for patients with:
  - a. Stage II high-grade, ER/PR-negative ESS
  - b. Stage II low-grade, ER/PR-positive ESS
  - c. Stage II uLMS
  - d. A and B
  - e. A and C
  - f. All of the above

