

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gynecologic cancer

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To cite: Disis ML, Adams SF, Bajpai J, *et al.* Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of gynecologic cancer. *Journal for ImmunoTherapy of Cancer* 2023;**11**:e006624. doi:10.1136/jitc-2022-006624

Accepted 28 April 2023

ABSTRACT

Advanced gynecologic cancers have historically lacked effective treatment options. Recently, immune checkpoint inhibitors (ICIs) have been approved by the US Food and Drug Administration for the treatment of cervical cancer and endometrial cancer, offering durable responses for some patients. In addition, many immunotherapy strategies are under investigation for the treatment of earlier stages of disease or in other gynecologic cancers, such as ovarian cancer and rare gynecologic tumors. While the integration of ICIs into the standard of care has improved outcomes for patients, their use requires a nuanced understanding of biomarker testing, treatment selection, patient selection, response evaluation and surveillance, and patient quality of life considerations, among other topics. To address this need for guidance, the Society for Immunotherapy of Cancer (SITC) convened a multidisciplinary panel of experts to develop a clinical practice guideline. The Expert Panel drew on the published literature as well as their own clinical experience to develop evidence- and consensus-based recommendations to provide guidance to cancer care professionals treating patients with gynecologic cancer.

INTRODUCTION

Gynecologic cancer causes a significant global health burden for people assigned female at birth,¹ even with advances in prevention such as vaccination against the human papilloma-virus (HPV)—the main etiological agent of cervical, vaginal, and vulvar cancers.² Recurrent or metastatic gynecologic cancer, especially of the cervix, endometrium, or ovary, has historically been associated with poor prognosis and limited treatment options that often elicit significant toxicities.

In recent years, immune checkpoint inhibitors (ICIs) antagonizing programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) (collectively referred

to in this clinical practice guideline [CPG] as PD-(L)1) have improved outcomes in numerous cancers either as monotherapies or in combination with chemotherapy, tumor-targeted therapies, or other ICIs. These regimens disrupt suppressive signaling in the tumor microenvironment such that tumor antigen-specific T cells may efficiently eradicate cancer cells and initiate subsequent cycles of antigen presentation, T cell priming, trafficking and infiltration, and recognition of tumor antigens by effector cells.³

Many features of gynecologic cancer—including elevated PD-L1 expression, pathogenic mutations in DNA polymerase epsilon (*POLE*) with accompanying ultra-mutated tumor mutational burden (TMB), intercurrent HPV infections, presence of tumor infiltrating lymphocytes (TILs), and high penetrance of mismatch repair (MMR) deficiency (dMMR)—suggest the presence of pre-existing anti-tumor immunity that may be amenable to re-invigoration through immunotherapy.⁴ As such, ICIs have demonstrated clinical benefit in advanced cervical cancer⁵ and endometrial cancer.^{6,7} Not all gynecologic tumors respond to ICIs, however, and biomarkers are crucial to identify patients who may benefit.

Shared decision-making between patients and clinicians for an immunotherapy treatment plan for gynecologic cancer may require an understanding of biomarker testing and interpretation, treatment selection, special considerations for understudied patient populations, management of immune-related adverse events (irAEs), radiologic surveillance, patient education, and quality of life (QOL) support. To provide evidence- and



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consensus-based recommendations for clinicians treating gynecologic cancer, the Society for Immunotherapy of Cancer (SITC) convened a multidisciplinary panel of experts in the field to develop this CPG. The SITC CPGs are provided by SITC to assist providers in clinical decision-making and do not mandate a particular course of treatment or medical care. The CPGs are not intended to supplant sound judgment by the treating physician with respect to particular patients or special clinical situations and cannot always account for individual variations among patients. SITC considers adherence to the guidance to be voluntary, with the ultimate determination for the selected course of action to be made by the physician in light of each patient's individual circumstances.

GUIDELINE DEVELOPMENT METHODS

This CPG was developed by the SITC Gynecologic Cancer Immunotherapy Guideline Expert Panel, under the governance of the SITC Cancer Immunotherapy Guidelines Oversight Committee. The Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines were used as a model for guideline development.

Expert Panel composition

The guideline development group was multidisciplinary and balanced. Members were selected based on their expertise and experience in the field, including medical oncology, nursing, and patient advocacy, as well as other specialties as needed to support recommendation development.

Conflict of interest management

Disclosures of all financial relationships that might result in actual, potential, or perceived conflicts of interest were individually reported prior to the onset of manuscript development as well as at all key decision points during manuscript development. Those with significant financial connections that may compromise the ability to fairly weigh evidence (either actual or perceived) were not eligible to participate in guideline development. Any non-disqualifying conflicts of interests among members of the SITC Gynecologic Cancer Immunotherapy Guideline Expert Panel were managed as outlined in SITC's disclosure and conflict of interest resolution policies.

The financial support for the development of this guideline was provided solely by SITC. No commercial funding was received.

Recommendation development

Panel recommendations are based on literature evidence, where possible, and clinical experience, where appropriate. Literature searches in relevant databases were performed and publications were screened for inclusion in the evidence base for the guideline recommendations. Recommendations herein were developed based both on literature review and expert opinion presented

Box 1 Summary of 'The Oxford Levels of Evidence 2' (adapted from the Oxford Centre for Evidence-Based Medicine [OCEBM] Levels of Evidence Working Group).

Level 1

Systematic review or meta-analysis

Level 2

Randomized trial or observational study with dramatic effect

Level 3

Non-randomized, controlled cohort, or follow-up study

Level 4

Case series, case-control, or historically controlled study

Level 5

Mechanism-based reasoning

during open communication and scientific debate. Subsequently, recommendations were refined through a modified Delphi process as described by the RAND/UCLA Appropriateness Method, Expert Panel consensus discussions, and review and editing of manuscript drafts.

Evidence rating

The level of evidence (LE) for a given consensus recommendation is expressed in parentheses following the recommendation (eg, LE:1). Evidence supporting panel recommendations was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group 'The Oxford Levels of Evidence 2'. A summary of the OCEBM grading scale may be found in [box 1](#).

External review

A draft of this CPG was made publicly available to provide an opportunity for stakeholders potentially affected by guideline to review and comment on the content. All comments were evaluated by the Expert Panel and considered for inclusion into the final manuscript.

IMMUNOTHERAPY BIOMARKERS FOR GYNECOLOGIC CANCER

A number of the approved indications for ICIs in gynecologic cancer include biomarker-driven eligibility criteria for patient selection. Biomarker evaluation is paramount for developing an immunotherapy treatment plan, however, the recommended assays and their interpretation for guiding treatment decisions are heterogeneous across disease settings. This section provides an overview of validated and routinely used immunotherapy biomarkers for gynecologic cancer at the time of guideline publication, with additional organ site-specific requirements described in subsequent sections. [Figure 1](#) summarizes the prioritized and recommended biomarker tests for gynecologic cancers.

MMR deficiency/microsatellite instability

MMR proteins recognize and correct errors in DNA that arise during replication.⁸ The MMR machinery can become deficient through various mechanisms, including

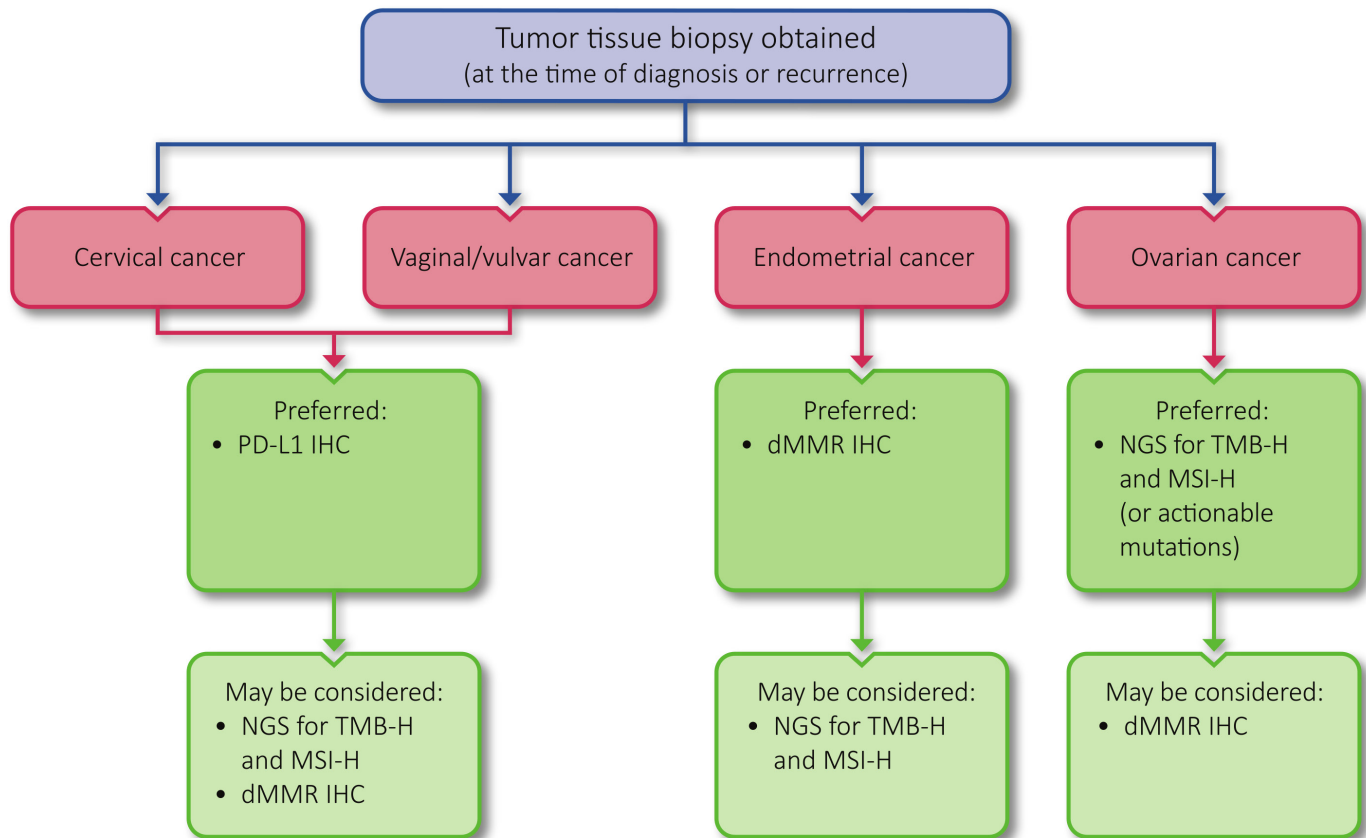


Figure 1 Immune biomarker testing for gynecologic cancer. The VENTANA MMR IHC assay is the FDA-approved companion diagnostic for determining MMR status for treatment with dostarlimab or pembrolizumab. The FoundationOne CDx is approved as a companion diagnostic for assaying MSI-H and TMB-H status for pembrolizumab treatment. The PD-L1 IHC 22C3 pharmDx assay is approved for measuring PD-L1 expression for the pembrolizumab indication in cervical cancer. dMMR, mismatch repair deficient; IHC, immunohistochemistry; MSI-H, high microsatellite instability; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; TMB-H, high tumor mutational burden.

loss of function in key MMR proteins (ie, MLH1, MSH2, MSH6, or PMS2) or silencing of expression due to *MLH1* promoter hypermethylation. Lynch syndrome is characterized by germline mutations in genes encoding MMR proteins and is present in approximately 2%–5% of endometrial cancers.^{9,10} One type of lesion repaired by MMR is expansions of short repetitive motifs called microsatellites, and a characteristic signature of dMMR is an accumulation of these expanded regions throughout the genome, which is referred to as high microsatellite instability (MSI-H). MSI-H is a hallmark of dMMR tumors (though each are distinct events) and both may lead to higher TMB and neoantigen expression.¹¹ MSI-H and dMMR both are associated with increased benefit with ICIs across many types of tumors¹² and are the basis of both tissue-agnostic and tissue-specific indications for ICIs.

Pembrolizumab, an anti-PD-1 ICI, received an accelerated approval for the treatment of patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options in May 2017.¹³ Efficacy was evaluated in a pooled analyses including 149 patients with MSI-H tumors enrolled in five non-randomized trials: KEYNOTE-016 (NCT01876511),

KEYNOTE-164 (NCT02460198), KEYNOTE-012 (NCT01848834), KEYNOTE-028 (NCT02054806), and KEYNOTE-158 (NCT02628067). The objective response rate (ORR) was 39.6% (95% CI 31.7% to 47.9%) and the median duration of response (DOR) was not reached with 78% of patients having DOR ≥6 months.¹⁴ This pooled analysis included 14 patients with endometrial cancer (an additional cohort of patients with endometrial cancer in KEYNOTE-158 is discussed in the **Recommended immunotherapy treatments for endometrial cancer** section), however no other gynecologic cancers were included in the registrational data.

Dostarlimab, another anti-PD-1 ICI, received accelerated approval for the treatment of patients with dMMR recurrent or advanced solid tumors that have progressed on or following prior treatment and who have no satisfactory alternative treatment options in August 2021.¹⁵ Approval was based on an ORR of 41.6% (95% CI 34.9% to 48.6%) in 209 patients in the GARNET trial (NCT02715284), which included a cohort of 103 patients with endometrial cancer (discussed in the **Recommended immunotherapy treatments for endometrial cancer** section). The median DOR was 34.7 months (range 2.6–35.8+), with 95.4% of patients with a DOR of ≥6 months. With the exception

of the endometrial cancer cohort, the only patients with gynecologic cancer in GARNET were two patients with ovarian cancer, one of whom had a partial response (PR) and the other stable disease (SD).¹⁵

Assessment of dMMR/MSI-H

Immunohistochemistry (IHC) nuclear staining for MMR proteins using a four-antibody panel is the most commonly used method to detect dMMR, however two-antibody IHC may also be used.¹⁶ Although the original US Food and Drug Administration (FDA) approval for pembrolizumab for the treatment of dMMR/MSI-H advanced solid tumors did not specify a companion diagnostic, the VENTANA MMR RxDx Panel assay was named as an IHC companion diagnostic for assessing dMMR to identify eligibility for both dostarlimab and pembrolizumab treatment in early 2022.¹⁵

MSI is most commonly assayed using next-generation sequencing (NGS).¹⁷ In the trials that led to the MSI-H tissue-agnostic approval for pembrolizumab, PCR-based MSI testing was used with no specific assay named as a companion diagnostic at the time of approval. In February of 2022, however, the FDA approved the FoundationOne CDx NGS assay as a companion diagnostic for determining MSI-H status. Overall, both PCR- and NGS-based assays for MSI-H are highly sensitive and concordant in some tumor types.¹⁸

It is important to note that MSI tests (PCR- and NGS-based) do not provide direct information on MMR proteins. Furthermore, these assays were developed and validated for use in colorectal cancer, and therefore have non-optimal performance in other tumor types, specifically endometrial cancer. For example, endometrial cancers have a significantly higher frequency of minimal microsatellite shifts, specifically tied to *MSH6* mutations,¹⁹ which may be missed by standard MSI testing.²⁰ Therefore, IHC for dMMR is preferred over MSI testing for non-colorectal cancers by the College of American Pathologists.^{4,21}

The selection of IHC or NGS assay for MSI and MMR assessment may have implications for treatment decisions. Pembrolizumab is FDA-approved for the treatment of both MSI-H and dMMR solid tumors, whereas the tissue-agnostic indication for dostarlimab includes only tumors that are dMMR. While MSI and MMR status are largely concordant, a small fraction of tumors may lose MMR protein expression while remaining microsatellite stable (MSS), and vice versa.²²

PD-L1 expression

PD-L1 expression on tumor cells (TCs) and/or immune cells (ICs) is prognostic in some tumors, and predictive of clinical benefit with ICIs in others. At the time of guideline publication, the only gynecologic cancer for which PD-L1 is used to identify eligibility for ICI treatment is cervical cancer (more details on outcomes by PD-L1 expression subgroups in registrational trials for ICIs in cervical cancer are provided in the **Recommended**

immunotherapy treatment for cervical cancer section). The utility of PD-L1 expression for patient selection and management for immunotherapy treatment is either unknown or non-existent for endometrial, ovarian, and other gynecologic malignancies.

Assessment of PD-L1 expression

A number of FDA-approved IHC PD-L1 companion diagnostics are available, using varying platforms, antibodies, positivity thresholds, and assessing only TCs, ICs, or both. All FDA-approved ICI indications in cervical cancer are for patients with tumors with a PD-L1 combined positive score (CPS) ≥ 1 , as measured by an FDA-approved test.¹³ CPS is measured as ratio of PD-L1-positive cells (TCs, lymphocytes, and macrophages) to the total number of TCs, multiplied by 100. In the registrational trials of pembrolizumab for the treatment of cervical cancer, PD-L1 expression was measured using an IHC assay based on the 22C3 antibody, and the PD-L1 IHC 22C3 pharmDx assay is the approved companion diagnostic for pembrolizumab use in cervical cancer.

Although limited data are available on PD-L1 assay and/or antibody concordance for gynecologic cancer specimens, studies from non-small cell lung cancer (NSCLC) and real world analyses including a variety of tumor types indicate that the 22C3, 28–8,^{23,24} and SP263²⁵ antibodies are largely interchangeable. Concordance may be inferior for staining of ICs compared with TCs, and additional studies are needed to confirm and validate PD-L1 assay concordance in cervical cancer, specifically. In addition, some studies in non-gynecologic tumors have shown good concordance with PD-L1 expression in tumor biopsy samples and fine-needle aspirates²⁶ or in decalcified bone,²⁷ but these are not yet validated.

Tumor mutational burden

Neoantigens can elicit a tumor-specific immune response. TMB is often used as a surrogate for neoantigen load, however, the correlation is not direct²⁸ as a raw count of mutations provides no information on whether the changes lead to epitopes that are presented by major histocompatibility complex (MHC) and elicit an immune response. Bioinformatics approaches for direct neoantigen load estimation via epitope and MHC binding prediction are not yet validated for routine clinical use. Although TMB and neoantigen load are not interchangeable, high-TMB (TMB-H) tumors may elicit antigen-specific T cell responses and thus are susceptible to immune rejection.²⁹

Pembrolizumab is currently FDA-approved in a tissue-agnostic indication for the treatment of metastatic or unresectable tumors that are TMB-H (defined as ≥ 10 mutations/megabase [mut/Mb] by an FDA-approved assay) that have progressed following prior treatment and that have no satisfactory alternative treatment options (table 1).¹³ The accelerated approval was granted in June 2020, based on a prospectively planned retrospective analysis from KEYNOTE-158, a multicohort phase II,

Table 1 Biomarkers for ICI patient selection in gynecologic cancer (adapted from Mills *et al*, *Modern Pathology*)⁴

Biomarker	Supporting trial(s)	Initial FDA approval year	FDA-approved agent(s)	Tumor type	Treatment setting	Definition of positivity
dMMR/MSI-H	KEYNOTE-016 KEYNOTE-164 KEYNOTE-012 KEYNOTE-028 KEYNOTE-158	2017	Pembrolizumab	Any solid tumor	Unresectable or metastatic tumors with disease progression following prior treatment and no satisfactory alternative treatment options	dMMR : Total loss of MMR protein expression in tumor nuclei by IHC* MSI-H : Instability at multiple sites by NGS or PCR†
	KEYNOTE-158	2022	Pembrolizumab	Endometrial cancer	Advanced tumors with disease progression following prior systemic therapy in any setting that are not candidates for curative surgery or radiation	
dMMR	GARNET	2021	Dostarlimab	Endometrial cancer	Advanced or recurrent tumors with disease progression on or after prior treatment with a platinum-containing regimen	Total loss of MMR protein expression in tumor nuclei by IHC*
		2021		Any solid tumor	Advanced or recurrent tumors with disease progression on or after prior treatment and no satisfactory alternative treatment options	
PD-L1	KEYNOTE-158	2018	Pembrolizumab	Cervical cancer	Recurrent or metastatic tumors with disease progression on or after chemotherapy	CPS _≥ 1‡
	KEYNOTE-826	2021	Pembrolizumab+platinum-based chemotherapy±bevacizumab	Cervical cancer	Persistent, recurrent, or metastatic tumors	
TMB-H	KEYNOTE-158	2020	Pembrolizumab	Any solid tumor	Unresectable or metastatic tumors with disease progression following prior treatment and no satisfactory alternative treatment options	≥10 mut/Mb by NGS§

*In 2021, the FDA approved the VENTANA MMR IHC assay as a companion diagnostic for determining MMR status for treatment with dostarlimab. Companion diagnostic status for assessing MMR status across solid tumors for treatment with pembrolizumab was granted in 2022.

†In 2022 the FoundationOne CDx assay was approved as a companion diagnostic for assaying MSI-H tumors for use with pembrolizumab.

‡In 2018 the FDA granted companion diagnostic status to the PD-L1 IHC 22C3 pharmDx assay for determining PD-L1-positive cervical tumors for use with pembrolizumab.

§In 2020, the FDA approved the FoundationOne CDx assay as a companion diagnostic for determining TMB-H tumors for use with pembrolizumab.

CPS, combined positive score; dMMR, mismatch repair deficiency; FDA, US Food and Drug Administration; ICI, immune checkpoint inhibitor; IHC, immunohistochemistry; MMR, mismatch repair; MSI-H, high microsatellite instability; Mut/Mb, mutations/Megabase; NGS, next-generation sequencing; PD-L1, programmed death-ligand 1; TMB-H, high tumor mutational burden.

non-randomized study including patients with a variety of solid tumors.³⁰ Among the 790 patients evaluable for TMB, 102 had TMB-H tumors. The overall ORRs were 29% (95% CI 21% to 39%) for TMB-H tumors and 6% (95% CI 5% to 8%) for TMB-low tumors.³⁰ While TMB-H for the FDA-approved pembrolizumab indication is defined as ≥ 10 mut/Mb, other studies indicate that a higher TMB cut-off may better predict response to ICIs. In the MyPathway (NCT02091141) phase IIA basket trial (n=121), the ORR for atezolizumab in patients with tumors with TMB ≥ 16 mut/Mb was 38.1%, and the ORR for patients with tumors with TMB ≥ 10 mut/Mb and TMB < 16 mut/Mb was 2.1%.³¹

Although the likelihood of clinical benefit with ICIs loosely correlates with increasing TMB in some tumors, TMB-H alone is not universally predictive.³² Somatic mutations may lead to neoantigens with sufficient homology to self-antigens as to be unrecognizable to the immune system. Additionally, other mechanisms including MHC silencing, resistance to interferon (IFN) signaling, and T cell exclusion may inhibit an effective anti-tumor response, even when suppression by immune checkpoints is alleviated by ICIs.³ Detailed discussions on the role of TMB-H as a predictive biomarker with ICIs across gynecologic disease settings are provided in the respective sections of this guideline. Overall, available evidence supports biomarkers other than TMB as preferred for guiding treatment decisions with ICIs, specifically, PD-L1 expression for cervical cancer and MMR/MSI for endometrial cancer.

Assessment of TMB

TMB is measured by the number of non-synonymous mutations per coding area of a tumor genome, which can be done by whole exome sequencing or a targeted panel of selected genes.³³ TMB was assessed in KEYNOTE-158 using the FoundationOne CDx assay, a 324-gene NGS panel that is FDA-approved as a companion diagnostic for the TMB-H indication for pembrolizumab. Retrospective analysis demonstrated good concordance between TMB-H assessed by whole exome sequencing and FoundationOne CDx.³⁴ Currently, TMB assessment is performed on tumor specimens, however, data are continuing to emerge on the use of blood-based assays to assess for TMB, including methods utilizing circulating-tumor DNA (ctDNA), as discussed in the **Biopsy and specimen considerations** section.

Biopsy and specimen considerations

At the time of guideline publication, all routinely used IHC-, NGS-, and PCR-based assays and companion diagnostics for assessing TMB, dMMR, MSI, and PD-L1 are validated for use on tumor biopsy tissue, and most assays are performed on formalin-fixed paraffin embedded tissue sections. Depending on sample availability, clinicians may need to select between specimens obtained from different anatomic locations or at different times during treatment for biomarker evaluation.

Primary versus metastatic tumor biopsies

In patients with metastatic disease at initial diagnosis or recurrence, clinicians may have the choice to assess biopsies from primary or metastatic lesions. Generally, most tumors tend to demonstrate somatic subclonal diversity from primary to metastatic sites,³⁵ yet the overall magnitude of genomic alterations and presence of driver mutations has relatively good concordance.³⁶

Data are lacking on whether MSI and dMMR status varies between primary and metastatic biopsies in gynecologic cancer. Germline dMMR mutations associated with Lynch syndrome should be present regardless of site. Data from colorectal cancer indicate that dMMR/MSI-H concordance in primary and metastatic tumors is high in some metastatic sites but has low concordance in others, and thus is largely organ-specific.³⁷

PD-L1 expression in cervical cancer may occasionally vary between primary and metastatic sites, although data are limited. One study of matched primary and metastatic lymph node biopsies from patients with squamous cell (n=96) and adenocarcinoma (n=31) cervical cancer found that PD-L1 expression on TCs in the primary tumor versus lymph node metastases varied 18%–31% depending on the histology, and metastases had increased levels of PD-L1 expressing ICs.³⁸ Data are lacking on whether this is true for non-lymph node metastases in cervical cancer. Another important consideration that may affect PD-L1 expression in metastatic lesions is the immunologic contexture of the metastatic site (eg, lung metastases may be immunologically ‘hot,’ whereas liver metastases may be immunologically ‘cold’).

Considerations for IHC on archived tissue biopsies

Data from lung cancer have demonstrated that PD-L1 expression on archived tumors samples > 3 years old may be diminished when assessed by IHC.³⁹ It is not clear if this is also true for dMMR proteins in archived tumor samples. Overall, fresh biopsies should be prioritized when possible and internal controls should be used to validate a negative result.

Liquid biopsy and ctDNA assessment

Data on the use of liquid-based assays to assess biomarkers in ctDNA are continuing to mature. NGS on ctDNA to assess TMB, MSI, and/or dMMR status has been shown to generally be concordant with tissue biopsies in a variety of solid tumors,⁴⁰ and specifically in endometrial cancer.⁴¹ Measurements of ctDNA may also provide dynamic information of tumor response to treatment before apparent radiographic change,^{42–43} but these approaches have not been validated to inform treatment decisions for any solid tumors at the time of guideline writing.

Liquid biomarker assessments have several theoretical advantages over traditional tissue biopsies, including the non-invasive nature and feasibility for longitudinal collection. An additional strategy that is being investigated in gynecologic cancer is obtaining fluid from ascites for analyses,⁴⁴ when available, which may contain information

on the immune microenvironment of tumors.^{45 46} This strategy may be especially promising in ovarian cancer, where ascites is more often available for sampling.

Emerging immune biomarkers

DNA *POLE* (a four-subunit complex encoded by the *POLE*, *POLE2*, *POLE3*, and *POLE4* genes) is the major replicative polymerase for leading-strand synthesis. Mutations in the catalytic or proofreading domains in *POLE* can lead to tumors with very high TMB.³⁴ *POLE* mutations have been found to be prognostic for better outcomes overall in solid tumors across treatment modalities.⁴⁷ Patients with *POLE*-mutated tumors treated with ICIs have further been found to have significantly higher clinical benefit rates, median overall survival (OS), and median progression-free survival (PFS) compared with patients with *POLE*-wild-type tumors.^{48 49} As such, *POLE* mutation status is an emerging biomarker for immunotherapy response, specifically in tumors that are more commonly *POLE*-mutated. *POLE* mutations are common in endometrial cancers, occurring at rates of roughly 10%, and are the defining feature of one of the molecular subtypes identified by The Cancer Genome Atlas (TCGA; see the **Histology, molecular subtypes, and immunotherapy biomarkers for endometrial cancer** section for more information).⁵⁰ Other biomarkers of response to immunotherapy, such as TIL density and gene expression profiling are active areas of investigation at the time of guideline publication.

Expert Panel recommendations

- ▶ For all patients with advanced or recurrent gynecologic cancer, MMR IHC should preferentially be performed as a first-line immunotherapy biomarker for dMMR (LE:1). MSI and NGS testing can be considered as second-line immunotherapy biomarker tests (LE:3).
- ▶ With the exception of cervical cancer (LE:2) (and possibly other HPV-related gynecologic cancers), PD-L1 IHC expression should not be used for clinical decision-making for patients with advanced or recurrent gynecologic cancers.
- ▶ For all patients with advanced or recurrent gynecologic cancers, NGS should be considered to assess for TMB-H eligibility for pembrolizumab treatment under the tissue-agnostic indication (LE:3).
- ▶ For all patients with gynecologic cancer, biomarker evaluation of recurrent lesions may be considered at the time of recurrence.

IMMUNOTHERAPY FOR THE TREATMENT OF CERVICAL CANCER

Cervical cancer was the fourth most common cancer in women globally in 2020,¹ with an estimated 14,100 new cases and 4,280 deaths estimated in the US in 2022.⁵¹ Major differences in incidence and death rates exist across geographic regions, attributed to disparities in access to preventative measures and early diagnosis. The primary etiological factor leading to cervical cancer is chronic or

persistent HPV infection, which is associated with 99.7% of invasive cervical cancers.⁵² The 9-valent HPV vaccine, which was approved in 2014 and is currently indicated for males and females ages 9–45,⁵³ offers protection against most of the 15 high-risk HPV types that are sexually transmitted and associated with cervical cancer. These types are also associated with other gynecologic cancers, including vaginal and vulvar cancer,⁵⁴ which are discussed in the **Vaginal and vulvar cancers** section.

HPV vaccination has dramatically reduced the incidence of cervical cancer in regions with widespread vaccine uptake.^{55 56} The HPV vaccine is a model of success in cancer prevention and reflects a vital immune component in HPV-related tumorigenesis, providing strong rationale for immunotherapy approaches for treatment of cervical cancer. Although therapeutic HPV vaccination was unable to achieve tumor rejection in advanced cervical cancer,^{57 58} some studies have shown a reduction in recurrence of cervical intraepithelial neoplasia (CIN) when patients were vaccinated after a loop electrosurgical excision procedure (LEEP).⁵⁹ Similarly, other studies have shown regression of vulvar intraepithelial neoplasia (another HPV-associated premalignancy) with therapeutic vaccination after resection.⁶⁰ HPV induces MHC downregulation, IFN resistance, and upregulation of PD-L1 expression in TCs,⁶¹ leading to an immunosuppressive tumor microenvironment. The advent of ICIs offered one strategy to overcome immunosuppression and render cervical tumors susceptible to eradication by antigen-specific T cells, and they are now the standard of care for PD-L1-positive cervical cancer.

Histology and immunotherapy biomarkers for cervical cancer

Currently, ICIs are only indicated for advanced/metastatic cervical cancer. However, ongoing studies are evaluating potential benefits in the resectable setting. Cervical cancer is typically diagnosed clinically by histologic evaluation of a cervical biopsy.^{62–64} Biomarker evaluation is another important component of the workup for advanced disease.

Cervical cancer histology

The most common histology of cervical cancer is squamous cell carcinoma, followed by adenocarcinoma and adenosquamous carcinoma, with other rare histological subtypes such as neuroendocrine, endometrioid, serous, and clear cell carcinomas also observed (some of which are discussed in the **Other rare gynecologic cancer variants** section). The indications for ICIs are inclusive of all histologies. Tumor size, extension, lymph node metastasis, and other factors assessed in staging generally have a greater impact on prognosis than histology.⁶⁵

Cervical cancer-specific immune biomarkers

At the time of guideline publication, PD-L1 expression is the only immune-related biomarker that predicts benefit with ICIs for patients with cervical cancer. The overall prevalence of PD-L1 expression above the CPS≥1

threshold for positivity in cervical cancers is high. Overall, 34.4%–96% of cervical cancers express PD-L1, with some of the variability potentially arising due to differences in antibodies, assays, and cut-off thresholds used across studies.^{5 66–69} Additionally, PD-L1 expression is more prevalent in squamous cell tumors compared with adenocarcinomas. More information on measuring PD-L1 expression can be found in the **Immunotherapy biomarkers for gynecologic cancer** section.

The presence or density of TILs has been associated with response to ICIs in other types of solid tumors⁷⁰ and specific subsets of infiltrating T cells have been associated with favorable prognosis trends in cervical tumors.^{71–73} High expression of PD-1 on cervical cancer TILs was associated with worse outcomes overall in patients who did not receive immunotherapy,⁷⁴ consistent with a role for immune suppression in poor prognosis. Data are currently lacking on whether the presence or density of specific TILs have prognostic value regarding response to ICIs.

The utility of TMB-H and MSI-H/dMMR as predictive biomarkers for patients with cervical cancer—a malignancy with a high prevalence of tumor-specific antigens due to presentation of HPV epitopes—is still unclear. Overall, TMB in cervical cancer is moderate; the median number of somatic mutations is between 1 mut/Mb and 10 mut/Mb,^{75 76} and the prevalence of TMB-H in all cervical cancers is between 10%–20%.^{30 77} Similarly, the overall prevalence of MSI-H in cervical cancers is fairly low, ranging from 2%–12%.^{78–80}

Expert Panel recommendations

- For patients with advanced/recurrent cervical cancer, PD-L1 testing is recommended (LE:2). MMR IHC and NGS for MSI and TMB can be considered (LE:3).

Recommended immunotherapy treatments for cervical cancer

At the time of guideline publication, the anti-PD-1 ICI pembrolizumab was approved in combination with chemotherapy with or without the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab for persistent, recurrent, or metastatic cervical cancer and as

a monotherapy for recurrent or metastatic cervical cancer that is chemotherapy-refractory. Both indications are for patients with a tumor CPS $\geq$ 1.¹³ The landmark trials and data leading to these approvals are provided in [table 2](#). In addition to the cervical cancer-specific approved immunotherapy indications, patients may be eligible for treatment with pembrolizumab or dostarlimab based the TMB or MSI/dMMR status of the tumor.

First-line immunotherapy for PD-L1-positive cervical cancer

In October 2021, the FDA granted regular approval to pembrolizumab in combination with platinum-based chemotherapy with or without bevacizumab in patients with persistent, recurrent, or metastatic PD-L1-positive (CPS $\geq$ 1) cervical cancer. Approval was based on the phase III, placebo-controlled, double-blind study KEYNOTE-826, which randomized patients to receive pembrolizumab (200mg every 3 weeks) or placebo plus platinum-based chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab. In total, 617 patients were enrolled, including 548 patients with tumors with PD-L1 CPS $\geq$ 1. The primary endpoints were PFS and OS. In the first planned interim analysis (median follow-up 22 months [range 15.1 to 29.4]), both endpoints were met demonstrating superiority with the addition of pembrolizumab to standard chemotherapy and anti-angiogenic therapy.⁶⁹ PFS was improved with the pembrolizumab combination compared with the placebo combination in the PD-L1 CPS $\geq$ 1 population ([table 2](#)), the PD-L1 CPS $\geq$ 10 population (10.4 months [95% CI 8.9 to 15.1] vs 8.1 months [95% CI 6.2 to 8.8]; hazard ratio [HR] 0.58 [95% CI 0.44 to 0.77]; $p<0.001$), and the intention to treat (ITT) population (10.4 months [95% CI 9.1 to 12.1] vs 8.2 months [95% CI 6.4 to 8.4]; HR 0.65 [95% CI 0.53 to 0.79]; $p<0.001$). Median OS was also improved with the pembrolizumab combination in all populations ([table 2](#)). Landmark OS estimates at 2 years were 53.0% (95% CI 46.0% to 59.4%) vs 41.7% (95% CI 34.9% to 48.2%) in the CPS $\geq$ 1 population, 54.4% (95% CI 45.5% to 62.4%) vs 44.6% (95% CI 36.3% to 52.5%) in the CPS $\geq$ 10 population, and 50.4% (95% CI 43.8% to 56.6%) vs 40.4% (95%

Table 2 Registrational trial data for ICIs for the treatment of cervical cancer

Trial info	Patients (n)	Agent(s) investigated	Primary endpoints	
ORR				
KEYNOTE-158 (NCT02628067) ⁵	77*†	Pembrolizumab	14.3% (95% CI 7.4% to 24.1%)‡	
PFS				
OS				
KEYNOTE-826 (NCT03635567) ^{13 69}	548*	Pembrolizumab+platinum-based chemotherapy±bevacizumab	HR for disease progression or death 0.62 (95% CI 0.50 to 0.77; p<0.001) Median PFS: 10.4 months (95% CI 9.7 to 12.3)	HR for death 0.64 (95% CI 0.50 to 0.81; p<0.001) Median OS: NR (95% CI 19.8 to NR)
		Placebo+platinum-based chemotherapy±bevacizumab	Median PFS: 8.2 months (95% CI 6.3 to 8.5)	Median OS: 16.3 months (95% CI 14.5 to 19.4)

*Patients whose tumors are PD-L1 CPS $\geq$ 1.

†Patients had received one or more lines of chemotherapy for recurrent or metastatic disease.

‡Data supporting original accelerated approval, which was subsequently converted to regular approval.

CI, confidence interval; CPS, combined positive score; HR, hazard ratio; ICI, immune checkpoint inhibitor; NR, not reached; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

CI 34.0% to 46.6%) in the ITT population. Secondary outcome measures for KEYNOTE-826 included ORR and DOR. In the PD-L1 CPS $\geq$ 1 group the ORR for the pembrolizumab combination was 68.1% compared with 50.2% in the placebo combination. DOR was also significantly longer in this group for those patients treated in the pembrolizumab combination arm, at 18.0 months vs 10.4 months in the placebo arm.

The treatment-related adverse events (TRAEs) in KEYNOTE-826 were consistent with known safety profiles. Grade 3–5 adverse events (AEs) occurred in 81.8% of patients in the pembrolizumab group and in 75.1% of patients in the placebo group, with the most common serious AEs in both groups being anemia, neutropenia, decreased neutrophil count, and hypertension. IrAEs were described in 33.9% (11.4% grade 3–5) of the patients in the pembrolizumab group and in 15.2% (2.9% grade 3–5) of those in the placebo group.⁶⁹ The most common irAEs experienced by patients receiving pembrolizumab in KEYNOTE-826 were hypothyroidism (18.2% any grade, 1.3% grade 3–5), hyperthyroidism (7.5% any grade, no grade 3–5 events), colitis (5.2% any grade, 1.6% grade 3–5), and severe skin reactions (4.6% any grade, 3.9% grade 3–5).

Immunotherapy for disease that progresses on or after chemotherapy

Accelerated approval for pembrolizumab monotherapy for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS $\geq$ 1) was granted in June 2018, based on results from the multicohort, non-randomized, open-label, phase II KEYNOTE-158 basket trial (table 2).⁵ The accelerated approval was converted to regular approval in October 2021. At median follow-up of 10.2 months (range 0.6–22.7) the ORR was 14.6% (95% CI 7.8% to 24.2%) in the 82 patients in the cohort with PD-L1-positive tumors. None of the 15 patients with PD-L1-negative tumors had responses by RECIST v.1.1. The best responses were three patients that achieved SD and the study was not powered to formally assess efficacy in the PD-L1-negative cohort. Median PFS in the PD-L1-positive cohort was 2.1 months (95% CI 2.1 to 2.3). Median OS was 9.4 months (95% CI 7.7 to 13.1) in the total population and 11 months (95% CI 9.1 to 14.1) in the PD-L1-positive population, and the estimated OS rates in the PD-L1-positive group at 6 months and 12 months were 80.2% and 47.3%, respectively.

Any-grade AEs were experienced in 65.3% of the total population, and 12.2% were grade 3–4. Investigator-assessed irAEs of any grade occurred in 25.5% of all treated patients, and 5.1% were grade 3–4. The most common irAEs were hypothyroidism (11.2%) and hyperthyroidism (9.2%).⁵

The accelerated approval for this indication was contingent on results of the confirmatory trial, KEYNOTE-826, which met its primary endpoints (see the **First-line immunotherapy for cervical cancer** section),⁶⁹ and in October

2021, the accelerated approval for this indication was converted to regular approval. The recommended immunotherapy treatments for patients with cervical cancer can be found in figure 2.

The anti-PD-1 ICI cemiplimab was granted priority review in the chemotherapy-experienced cervical cancer setting by the FDA in September 2021 after the phase III EMPOWER-Cervical 1 trial (NCT03257267) met its primary endpoint of improved median OS (compared with salvage chemotherapy)⁸¹ in patients with PD-L1-positive tumors (expression on $\geq$ 1% of TCs by the VENTANA PD-L1 (SP263) assay). However, the Supplemental Biologics License Application was withdrawn by the manufacturer after the company and FDA were not able to align on postmarketing studies. Importantly, while EMPOWER-Cervical 1 corroborates better responses and survival in patients with PD-L1 TC score $\geq$ 1% (ORR 18% [95% CI 11% to 28%]) treated with cemiplimab versus chemotherapy, a small number of responses to cemiplimab were also seen in patients with PD-L1 TC <1% (ORR 11% [95% CI 4% to 25%]), suggesting that more patients may respond to anti-PD-1 ICIs than are eligible for the current FDA indication for pembrolizumab. Importantly, while comparative data are lacking, anti-PD-1 ICIs are generally expected to have similar clinical efficacy.

TMB-H or MSI-H/dMMR cervical cancer

Patients with cervical cancer may also be eligible for immunotherapy under the tissue-agnostic indications for ICIs, depending on the TMB and/or MSI/MMR status of the tumor.^{13 15} For more details on tissue-agnostic approvals, see the **Immunotherapy biomarkers for gynecologic cancer** section. In KEYNOTE-158, response rates were numerically higher for the TMB-H cervical tumors (31% [95% CI 11% to 59%] in the TMB-H group vs roughly 12% of patients in the TMB-low group), however it is important to note that this arm of the trial was not designed to assess efficacy in specific disease settings.^{13 30} Although KEYNOTE-158 prespecified an additional post-marketing analysis on pan-tumor response rates by MMR status, the data on the six patients with cervical cancer included in the study were not presented.⁸² Additionally, neither of the efficacy analyses supporting the MSI-H/dMMR-based approvals for pembrolizumab or dostarlimab included patients with cervical cancer.

Expert Panel recommendations

- For patients with recurrent or metastatic cervical cancer that is PD-L1-positive (CPS $\geq$ 1) and has progressed on or after chemotherapy, pembrolizumab should be considered (LE:3).
- For patients with metastatic cervical cancer that is PD-L1-positive (CPS $\geq$ 1), pembrolizumab with chemotherapy with or without bevacizumab should be considered (LE:2).
- For patients with anti-PD-(L)1-resistant cervical cancer, currently there are no data to inform the

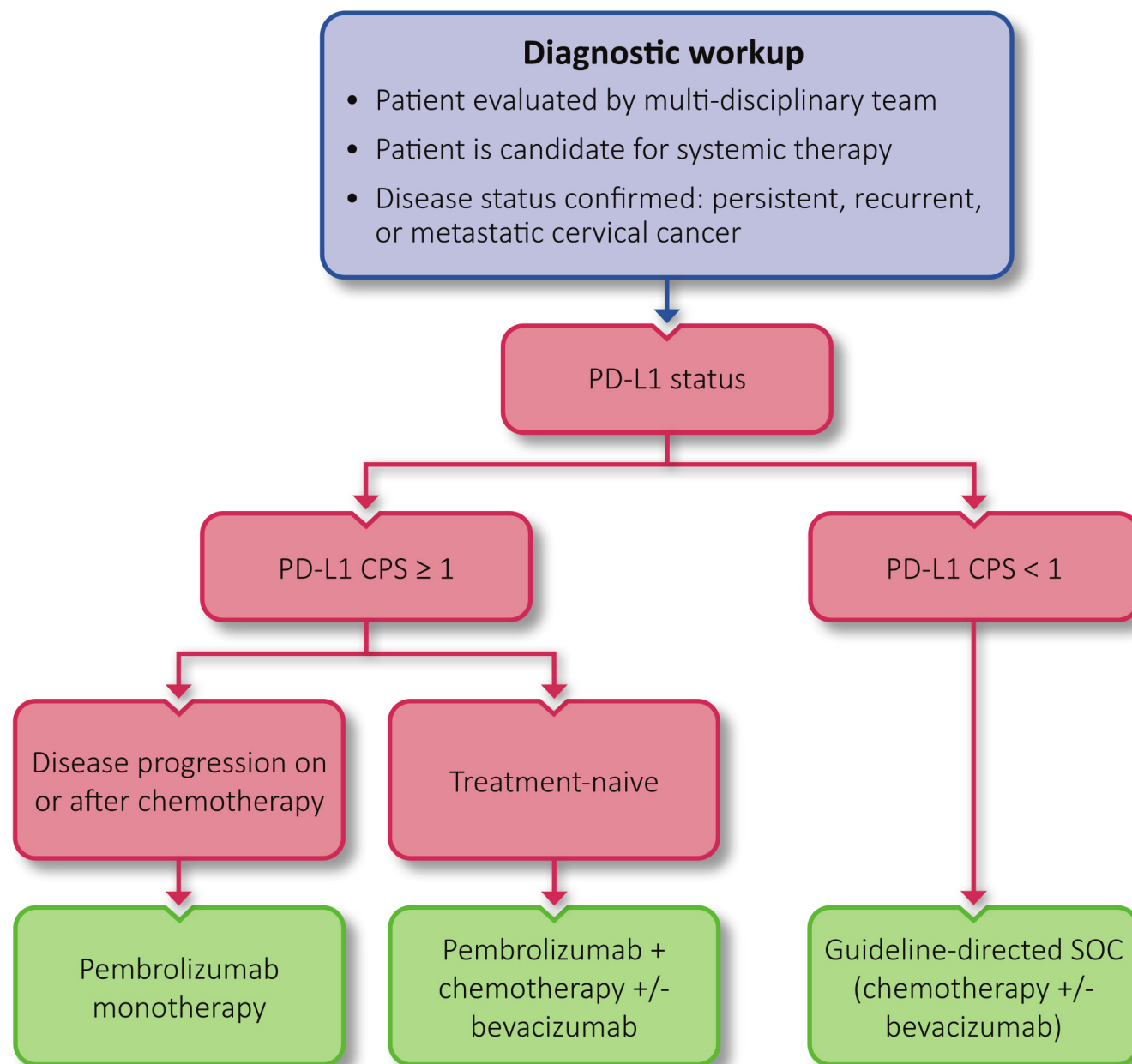


Figure 2 Advanced cervical cancer diagnostic workup and treatment algorithm. For all patients with cervical cancer, clinical trial enrolment should be encouraged, as feasible. CPS, combined positive score; PD-L1, programmed death-ligand 1; SOC, standard of care

sequencing of therapies and/or rechallenge with an ICI.

Emerging immunotherapy strategies for cervical cancer

Several investigational immunotherapy strategies were being evaluated in cervical cancer at the time of guideline publication, including ICI combinations, therapeutic vaccines, cell therapies, and other immunomodulating agents. Clinical trial enrollment should be offered and encouraged during a patient's treatment, to provide cutting-edge care and to continue to move the field forward.

ICI-based combinations for the treatment of cervical cancer

The combination of balstilimab (anti-PD-1) plus zalifrelimab (anti-cytotoxic T lymphocyte antigen-4

[CTLA-4]) met its ORR endpoint in a phase II single-arm trial (NCT03495882) with an ORR of 25.6% (95% CI 18.8% to 33.9%) in patients with recurrent and/or metastatic cervical cancer who relapsed after prior platinum-based therapy.⁸³ The phase I/II basket trial Checkmate358 (NCT02488759) has also reported positive results in patients with cervical cancer using ipilimumab (anti-CTLA-4) plus nivolumab (anti-PD-1), regardless of PD-L1 expression.⁸⁴

HPV infection has been associated with upregulation of transforming growth factor (TGF)- β signaling⁸⁵ motivating the investigation of inhibition of TGF- β signaling in combination with anti-PD-(L)1. Bintrafusp alfa (also known as M7824), the bifunctional fusion protein which

contains the extracellular domain of the TGF- β RII receptor (a TGF- β ‘trap’) fused to a mAb blocking PD-L1, resulted in an ORR of 28.2% and DOR of 11.7 months (range 1.4 to 41.2) in 39 patients with cervical cancer in pooled data from phase I and phase II trials (NCT02517398 and NCT03427411).⁸⁶ Bintrafusp alfa is also being combined with cytokines and HPV-targeting vaccines in other ongoing trials (NCT04287868; NCT04708470).

Radiation modulates the immune system via a number of mechanisms, including inducing type I IFN expression and antigen release to activate an adaptive immune response.⁸⁷ Several trials are investigating the combination of chemoradiation therapy (CRT) in combination with ICIs. The randomized phase III CALLA trial (NCT03830866), which compared CRT plus durvalumab to CRT alone for the treatment of high-risk locally advanced cervical cancer, did not reach its primary PFS endpoint.⁸⁸

Investigational immunotherapy strategies for the treatment of cervical cancer

Tumors evade immune eradication via multiple mechanisms beyond checkpoints.³ Augmenting the tumor-antigen-specific T cell repertoire via therapeutic vaccination is a strategy that has been well studied in cervical cancer.² Newer approaches are attempting to combine HPV-targeting vaccines with other treatments such as CRT and ICIs to overcome immune suppression in the tumor microenvironment. Axalimogene filolisbac (ADXS11-001) is a live-attenuated E7-producing *Listeria monocytogenes* vaccine that has reported results from phase II trials⁸⁹ and has progressed to phase III. Other vaccines being evaluated include ISA101, a synthetic long-peptide HPV-16 vaccine, which is being combined with nivolumab in a phase II trial (NCT02426892)⁹⁰ and the GX-188E DNA vaccine, which is being combined with pembrolizumab in the phase II trial KEYNOTE-567 (NCT03444376).⁹¹ The BVAC-C vaccine, a B cell-based and monocyte-based vaccine targeting E6 and E7, is being investigated in a phase II study (NCT02866006) as monotherapy or in combination with topotecan.⁹²

HPV-specific antigens can also be targeted using adoptive cell therapies (ACTs). Strategies to boost cell therapy HPV-specific cytotoxicity, including dendritic cell vaccines or viral gene delivery of E6 and/or E7, have proven to be effective in preclinical studies, and may improve clinical outcomes of these cell therapies in future studies.⁹³ Study C-145-04 (NCT03108495) is an ongoing, open-label, multicenter, phase II trial evaluating LN-145 TIL therapy in patients with advanced cervical cancer who have undergone prior chemotherapy. At a short follow-up of 3.5 months, in 27 patients the ORR was 44% and the disease control rate (DCR) was 89%,⁹⁴ supporting breakthrough therapy designation from the FDA in 2019. Additional cell therapy agents, such as T cell receptor (TCR)-engineered cell therapy, natural killer (NK) cell therapies, and chimeric antigen receptor (CAR) T cell therapy have also been employed in some small studies

in patients with cervical cancer, but limited data are available.

Expert Panel recommendations

- For all patients with cervical cancer, clinical trial enrollment should be offered, as feasible.
- Non-FDA-approved immunotherapy combination strategies should only be considered in the context of a clinical trial.

IMMUNOTHERAPY FOR THE TREATMENT OF ENDOMETRIAL CANCER

Endometrial cancer was the sixth most common cancer in women in 2020.¹ As the most common form of uterine cancer, incidence rates have been on the rise in the US for many years,^{95 96} with an estimated 65,000 new cases and 12,500 deaths in 2021.⁹⁷ In developed regions, diagnosis often occurs at an early/localized stage, which is associated with a favorable prognosis with the 5-year OS rates for The International Federation of Gynecology and Obstetrics (FIGO) stage IA and IB of 77%–90%.^{98 99} Advanced-stage endometrial cancer, however, has historically lacked effective treatments and the 5-year OS for stage IV disease is around 20%.⁹⁵ Metastatic or recurrent endometrial cancer has historically been treated with cytoreductive surgery, followed by systemic therapy, often multi-agent platinum plus taxane-based chemotherapy or endocrine therapy. Second- or later-line options for advanced disease have been limited to rechallenge, which generally offers moderate responses with low durability.^{100–102}

A percentage of endometrial tumors have high mutational burdens and IC infiltration, characteristics of immunologically ‘hot’ tumors. ICIs have significantly improved outcomes for other ‘hot’ tumors, such as melanoma and NSCLC, providing rationale for investigation of their efficacy in endometrial cancer as well.

Histology, molecular subtypes, and immunotherapy biomarkers for endometrial cancer

Endometrial tumors are commonly classified into two major histological subtypes: endometrioid, which is the most common and often lower-grade, and non-endometrioid, which includes serous, clear cell, carcinosarcoma, and others, all of which are classified as high grade.^{103 104} In addition to staging and histology, endometrial cancers can also be classified by molecular features, which has important implications for immunotherapy treatment.

Endometrial cancer molecular subgroups

Endometrial cancer is a heterogeneous disease. The most widely utilized molecular classification for endometrial cancer came from an analysis of 373 endometrial tumors by TCGA Research Network,⁵⁰ which delineates four molecular subgroups: (1) Ultra-mutated (often driven by mutations in *POLE*), (2) Hyper-mutated (driven by MSI), (3) High somatic copy-number alterations (SCNA) (often *TP53*-mutated and commonly serous histology), and (4) Low SCNA (commonly endometrioid histology). TCGA subgrouping is clinically informative, and methods have

been developed to improve feasibility as a standard assessment of biopsied samples, including the commonly used Proactive Molecular Risk classification tool for endometrial cancers (ProMisE).^{105 106} Furthermore, TCGA subgrouping may reveal tumors that are already eligible for ICI treatment due to dMMR/MSI-H and/or TMB-H status.

PD-L1 expression in endometrial cancer

The value of PD-L1 as a predictive biomarker for benefit with ICIs in endometrial cancer is limited. PD-L1 expression in endometrial cancer is heterogeneous, regardless of molecular subgroup, histology, or stage.^{107–110} Non-endometrioid and undifferentiated tumors tend to have higher PD-L1 expression.^{107 108 110 111} ORRs in early phase studies evaluating ICI monotherapy for previously treated endometrial carcinoma have been similar across PD-L1-positive and PD-L1-negative tumors.^{6 112 113} Some studies have reported higher PD-L1 expression on infiltrating lymphocytes of *POLE*-mutated and MSI-H tumors compared with MSS tumors, however little difference across subtypes was noted in PD-L1 expression on the TCs themselves.^{110 114 115} Other reports have observed a high degree of PD-L1 TC staining in MSS tumors with infrequent PD-L1 TC staining in *POLE*-mutated tumors.¹¹⁶ The prognostic significance of immune versus tumor PD-L1 staining in endometrial cancer is not known.

Mutation burden and dMMR/MSI in endometrial cancer

Endometrial cancers in the ultra-mutated or hyper-mutated TCGA groups are often dMMR/MSI-H, and therefore, eligible for ICI treatment under tissue agnostic and/or endometrial cancer-specific indications (see the **Recommended immunotherapy treatments for endometrial cancer** and the **Immunotherapy biomarkers for gynecologic cancer** sections for more detail on disease-specific indications and diagnostic testing for these biomarkers, respectively).¹³ Despite the high prevalence of dMMR in endometrial cancer, testing for dMMR/MSI-H is underutilized. One European study found that in 2018, less than 40% of patients with advanced recurrent endometrial cancer had any MSI/MMR screening.¹¹⁷

Ultra- or hyper-mutated endometrial cancers are typically TMB-H as well due to loss of proofreading in the replicative polymerase or lack of MMR, respectively. *POLE*-mutated endometrial cancers have the best prognosis compared with other molecular subgroups regardless of treatment used, largely attributed to high neoantigen burden. SNCA-high and SNCA-low subgroup tumors typically have a low mutation load.⁵⁰ Corresponding with the mutation frequencies, *POLE*-mutated endometrial tumors have the highest predicted neoantigen load (8,342 median predicted neoantigens per sample; range 628–20,440; $p < 0.001$) compared with MSI (541; range 146–8,063) and MSS tumors (70.5; range 7–1,877).¹¹⁴ *POLE*-mutated tumors also have higher degrees of CD8⁺ T cell infiltration as well as higher numbers of CD8⁺ and CD3⁺ TILs compared with other categories.^{114 115 118}

Exploratory analyses of responses to anti-PD-1-based regimens by TMB status have been reported from landmark trials assessing ICIs in previously treated endometrial cancer, GARNET and KEYNOTE-775. In GARNET, patients with TMB-H tumors had higher ORRs with dostarlimab treatment than patients with TMB-low tumors in both mismatch repair proficient (pMMR) (45.5% [95% CI 16.7% to 76.6%; $n = 5$ of 11] vs 12.1% [95% CI 7.2% to 18.6%; $n = 17$ of 141]) and dMMR subgroups (43.8% [95% CI 33.3% to 54.7%; $n = 39$ of 89] vs 21.4% [95% CI 4.7% to 50.8%; $n = 3$ of 14]).¹¹⁹ Similarly, in KEYNOTE-775, superior ORRs to pembrolizumab plus lenvatinib were observed in tumors with TMB above the cut-off threshold of >175 mutations/exome regardless of MSI status (77% for TMB-H group [$n = 10$ of 13] vs 33% for low TMB group [$n = 22$ of 66]) as well as in the small number of patients with tumors that were MSS and TMB-H (100% in the TMB-H group [$n = 4$ of 4] vs 34% in the low TMB group [$n = 22$ of 64]).¹²⁰ Despite these early and exploratory results, MMR status is the preferred biomarker over TMB to inform treatment selection in patients with previously treated endometrial cancer, where MMR status informs whether anti-PD-1 monotherapy and pembrolizumab plus lenvatinib combination therapy may be appropriate for patients with dMMR and pMMR tumors, respectively.

Expert Panel recommendations

- Tumor PD-L1 expression should not be used to guide immunotherapy treatment decisions in endometrial cancer (LE:2).
- For all patients with advanced or recurrent endometrial cancer, MMR IHC on tumor tissue should preferentially be performed as a first-line immunotherapy biomarker for dMMR (LE:1). MSI and NGS testing can be considered as second-line immunotherapy biomarker tests (LE:3).

Recommended immunotherapy treatments for endometrial cancer

ICIs have demonstrated benefit for biomarker-selected, previously treated endometrial cancers, as well as unselected, previously treated tumors when combined with the anti-angiogenic tyrosine kinase inhibitor (TKI) lenvatinib. ICIs combined with chemotherapy have also demonstrated benefit in patients with systemic therapy-naïve or first recurrent endometrial cancer, although these combinations were not FDA-approved at the time of guideline publication. Data leading to FDA approvals for ICIs for the treatment of endometrial cancer are summarized in [table 3](#).

Previously untreated stage III or IV or first recurrent endometrial cancer

While not FDA-approved at the time of guideline publication, two phase III randomized placebo-controlled trials have reported positive results with the use of anti-PD-1 ICIs in combination with carboplatin and paclitaxel in patients with previously untreated stage III or IV or first

Table 3 Landmark trials and registrational data for ICIs for the treatment of endometrial cancer

Trial info	Patients (n)	Agent(s) investigated	Primary endpoint(s)	
			PFS	OS
KEYNOTE-775* (NCT03517449) ^{13 125}	697†	Pembrolizumab+lenvatinib	HR versus chemotherapy 0.60 (95% CI 0.50 to 0.72; p<0.0001) Median PFS: 6.6 months (95% CI 5.6 to 7.4)	HR versus chemotherapy 0.68 (95% CI 0.56 to 0.84; p=0.0001) Median OS: 17.4 months (95% CI 14.2 to 19.9)
		Investigator's choice chemotherapy (paclitaxel or doxorubicin)	Median PFS: 3.8 months (95% CI 3.6 to 5.0)	Median OS: 12 months (95% CI 10.8 to 13.3)
			ORR	DOR
GARNET (NCT02715284) ⁷	71‡	Dostarlimab	42.3% (95% CI 30.6% to 54.6%)§	Median DOR: NR§
			ORR	
KEYNOTE-158 (NCT02628067) ¹³	90‡	Pembrolizumab	46% (95% CI 35% to 56%)	

*KEYNOTE-775 supported regular approval of pembrolizumab plus lenvatinib. Accelerated approval was based on KEYNOTE-146 (see the **pMMR endometrial cancer** section).
†Patients with tumors that are pMMR/MSS.
‡Patient with tumors that are dMMR.
§Data supporting original accelerated approval, which was subsequently converted to regular approval.
CI, confidence interval; dMMR, mismatch repair deficiency; DOR, duration of response; HR, hazard ratio; ICI, immune checkpoint inhibitor; MSS, microsatellite stable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pMMR, mismatch repair proficient.

recurrent endometrial cancer. In both studies, PFS was improved with the addition of an ICI to the standard of care chemotherapy regimen, regardless of MMR status.

The RUBY trial (NCT03981796) randomized 494 patients with primary advanced stage III or IV or first recurrent (systemic therapy-naïve or previously treated with neoadjuvant or adjuvant systemic therapy and had recurred or progressed ≥ 6 months after completion of treatment) endometrial cancer to receive dostarlimab (500mg) with carboplatin and paclitaxel or placebo with carboplatin and paclitaxel every 3 weeks for six cycles, followed by dostarlimab (1000mg) or placebo every 6 weeks for up to 3 years.¹²¹ Primary endpoints were PFS in both the dMMR/MSI-H and overall populations, and OS in the overall population. In patients with dMMR/MSI-H endometrial cancer (n=118; median follow-up 24.8 months [range 19.2–36.9]), the 2-year PFS rate was 61.4% (95% CI 46.3% to 73.4%) in the dostarlimab group and 15.7% (95% CI 7.2% to 27.0%) in the placebo group (HR for disease progression or death 0.28; 95% CI 0.16 to 0.50; p<0.001). In the overall population (median follow-up 25.4 months [range 19.2–37.8]), landmark PFS at 2 years was 36.1% (95% CI 29.3% to 42.9%) in the dostarlimab group and 18.1% (95% CI 13.0% to 23.9%; HR for disease progression or death 0.64; 95% CI 0.51 to 0.80; p<0.001) in the placebo group. The 2-year OS rates were 71.3% (95% CI 64.5% to 77.1%) with dostarlimab and 56.0% (95% CI 48.9% to 62.5%) with placebo (HR for death 0.64; 95% CI 0.46 to 0.87; p=0.0021). In subgroup analyses, the 2-year PFS rates for the pMMR/MSS population were 28.4% (95% CI 21.2% to 36.0%) with dostarlimab and 18.8% (95% CI 12.8% to 25.7%) with placebo (HR for disease progression or death 0.76; 95% CI 0.59 to 0.98), and 2-year OS rates were 67.7% (95% CI 59.8% to 74.4%) and 55.1% (95% CI 46.8% to 62.5%), respectively. In the overall population, grade ≥ 3 AEs occurred in 70.5% of patients in the dostarlimab group and 59.8% of patients in the placebo group, with the most common AEs (any grade) being

nausea (53.9% and 45.9%), alopecia (53.5% and 50.0%), and fatigue (51.9% and 54.5%). The most common irAEs to occur in the dostarlimab group were hypothyroidism (11.2%) and rash (6.6%).

The NRG-GY018 trial (NCT03914612) randomized 816 patients with stage III, IVA, or IVB or first recurrent (systemic therapy-naïve or previously treated with adjuvant chemotherapy and ≥ 12 months chemotherapy-free interval) endometrial cancer to receive either pembrolizumab (200mg) or placebo with carboplatin and paclitaxel every 3 weeks for six cycles, followed by pembrolizumab (400mg) or placebo every 6 weeks for up to 14 cycles.¹²² The primary endpoint was PFS. For the 225 patients with dMMR endometrial cancer, the 1-year PFS rates were 74% for patients in the pembrolizumab group and 38% for patients in the placebo group (median follow-up 12 months; HR 0.30; 95% CI 0.19 to 0.48; p<0.001). Median PFS was not reached (95% CI 30.6 to not reached) with pembrolizumab and was 7.6 months (95% CI 6.4 to 9.9) with placebo. In patients with pMMR endometrial cancer (n=588; median follow-up 7.9 months), the median PFS was 13.1 months (95% CI 10.5 to 18.8) with pembrolizumab and 8.7 months (95% CI 8.4 to 10.7) with placebo (HR 0.54; 95% CI 0.41 to 0.71; p<0.001). Grade ≥ 3 AEs occurred in 63.3% of patients who received pembrolizumab and in 47.2% of patients in the placebo group in the dMMR cohort, and 55.1% and 45.3%, respectively, in the pMMR cohort. Across all patient groups, some of the more common AEs at any grade included fatigue, peripheral sensory neuropathy, anemia, and nausea.

pMMR endometrial cancer

Pembrolizumab in combination with lenvatinib was granted accelerated approval for the treatment of patients with advanced endometrial carcinoma that is pMMR or not MSI-H and who have disease progression following

prior systemic therapy but are not candidates for curative surgery or radiation in September 2019. Accelerated approval was based on interim results of KEYNOTE-146, a phase Ib/II single-arm basket study in solid tumors. Of the 108 patients with previously treated endometrial cancer, 94 patients had tumors that were pMMR/MSS and 11 had tumors that were dMMR/MSI-H. At 24 weeks, the combination of pembrolizumab (200 mg intravenous every 3 weeks) plus lenvatinib (20 mg daily) showed anti-tumor activity regardless of MSI status. The ORR for patients with tumors not dMMR/MSI-H was 36.2% (95% CI 26.5% to 46.7%), the ORR for patients with dMMR/MSI-H tumors was 63.6% (95% CI 30.8% to 89.1%), and the ORR across subgroups was 38.0% (95% CI 28.8% to 47.8%).⁶

Accelerated approval was conditional pending results from KEYNOTE-775, a phase III, open-label trial in which patients were randomized to receive pembrolizumab plus lenvatinib or investigator's choice of doxorubicin or paclitaxel, which met its primary PFS and OS endpoints leading to conversion to regular approval in July 2021. In total, 827 patients (pMMR, n=697; dMMR, n=130) with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting were enrolled.^{13 123} In updated analyses (median follow-up [all comers] lenvatinib plus pembrolizumab group 18.7 months; chemotherapy group 12.2 months), in addition to continued PFS and OS benefit (HR 0.70 [95% CI 0.58 to 0.83]), more frequent and more durable responses were observed with pembrolizumab plus lenvatinib versus chemotherapy in the pMMR/MSS population (ORR 32.4% [95% CI 27.5% to 37.6%] vs 15.1% [95% CI 11.5% to 19.3%]; median DOR 9.3 months [range 1.6+ to 39.5+] vs 5.7 months [range 0 to 37.1+]). Similar efficacy outcomes were observed in the all-comers population as well.

Overall, AEs associated with pembrolizumab plus lenvatinib were consistent with known safety profiles for each agent. Any-grade TRAE rates were similar in both arms. Grade ≥ 3 TRAEs occurred in 90% of patients with pembrolizumab plus lenvatinib and in 74% of patients treated with chemotherapy.¹²³ Anti-angiogenic agents such as lenvatinib can create an increased risk for hemorrhage and hypertension,¹²⁴ both of which were observed in the lenvatinib plus pembrolizumab arm of KEYNOTE-775. Grade ≥ 3 hypertension occurred in 37.9% of patients receiving pembrolizumab plus lenvatinib, compared with 2.3% of patients who received chemotherapy.¹²⁵ The most common AE attributed to pembrolizumab treatment was hypothyroidism, which occurred in 57.6% (any grade) of patients who received pembrolizumab plus lenvatinib.

dMMR endometrial cancer

Endometrial tumors have among the highest rates of dMMR/MSI in solid tumors.^{12 50} Dostarlimab is approved for adult patients with dMMR recurrent or advanced endometrial cancer that has progressed on or following a prior platinum-containing regimen. The accelerated approval,

which was granted in April 2021, was based on GARNET, an open-label, phase I basket trial (table 3). Cohort A1 of GARNET included 71 patients with dMMR endometrial cancer, and the ORR and DOR endpoints were met at an interim analysis with a median follow-up of 11.2 months (range 0.03+ to 22.11+).⁷ The VENTANA MMR RxDx Panel, which was used to retroactively confirm MMR status in GARNET,¹⁵ was approved as the companion diagnostic for this indication. In February 2023, the accelerated approval was converted to regular approval. The reported ORR at the time of regular approval for patients with dMMR endometrial tumors (n=141) was 45.4% (95% CI 37.0% to 54.0%).¹⁵ The DOR was not reached (range 1.2+ to 52.8+ months) and the percentage of patients with response duration ≥ 12 months and 24 months was 85.9% and 54.7%, respectively.

At an additional interim analysis for GARNET, median PFS was 6.0 months (95% CI 4.1 to 18.0) for patients with dMMR/MSI-H tumors (median follow-up 27.6 months; n=143) and 2.7 months (95% CI 2.6 to 2.8) for patients with pMMR/MSS tumors (median follow-up 33 months; n=156), with estimated 36 month PFS rates of 40.1% and 6.8%, respectively.¹²⁶ Median OS was not reached for patients with dMMR/MSI-H tumors (95% CI 25.7 months to not reached; n=153) and 16.9 months (95% CI 13.0 to 21.8; n=161) for patients with pMMR/MSS tumors, with an estimated probability of survival at 36 months of 58.4% and 22.2%, respectively.

Patients with endometrial cancer that is dMMR or MSI-H who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation are also eligible for pembrolizumab monotherapy. Approval was granted in March 2022, based on Cohorts D and K of KEYNOTE-158 (table 3). At long-term follow-up (median 54.5 months; n=94), ORR was 50% (95% CI 39.5% to 60.5%), and the median DOR was 63.2 months (range 2.9 to 63.2).¹²⁷ Median PFS was 13.1 months (95% CI 4.3 to 25.7), with a 4-year estimated PFS rate of 37%. Median OS was 65.4 months (95% CI 29.5 to not reached), and the estimated OS rate at 4 years was 59%. The VENTANA MMR RxDx panel was approved as a companion diagnostic for assessing dMMR, and the FoundationOne CDx assay is FDA-approved as a companion diagnostic for assessing MSI-H. The recommended immunotherapy treatments for patients with endometrial cancer can be found in figure 3.

GARNET reported manageable toxicity for dostarlimab monotherapy, and no major safety differences were seen between patients with dMMR or pMMR tumors.¹¹⁹ Any grade TRAEs occurred in 67.6% of patients, and grade ≥ 3 TRAEs occurred in 16.6% of patients. The most common any-grade TRAEs were fatigue (17.6%), diarrhea (13.8%), and nausea (13.8%), and the most common grade ≥ 3 TRAE was anemia at 2.8%. Any-grade irAEs occurred in 23.1% of patients, the most common being hypothyroidism and diarrhea. Grade ≥ 3 irAEs occurred in 7.7% of patients.⁷ Similarly, no new safety signals were reported

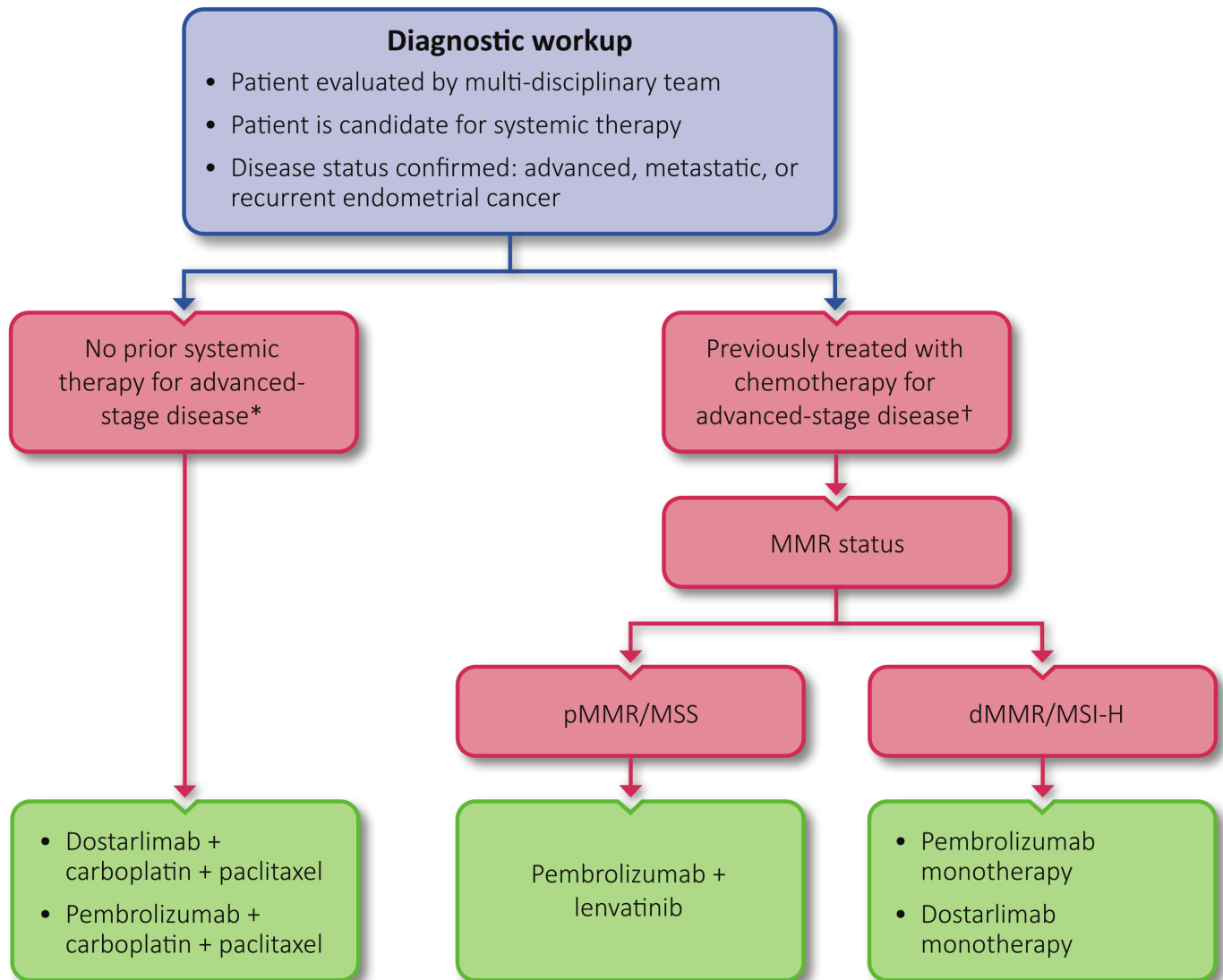


Figure 3 Advanced endometrial cancer diagnostic workup and treatment algorithm. For all patients with endometrial cancer, clinical trial enrolment should be encouraged, as feasible. For patients with HER2+ serous endometrial cancer, carboplatin plus paclitaxel and trastuzumab is also a treatment option. *Excluding prior chemotherapy given in the neoadjuvant or adjuvant setting; †Following prior systemic therapy in any setting including the neoadjuvant or adjuvant setting. dMMR, mismatch repair deficient; HER2, human epidermal growth factor receptor 2; MMR, mismatch repair; MSI-H, high microsatellite instability; MSS, microsatellite stable; pMMR, mismatch repair proficient.

with pembrolizumab monotherapy in KEYNOTE-158 (n=90). Any-grade TRAEs (investigator-identified) were reported in 76% of patients, and 12% were grade 3–4. The most common TRAEs were pruritus (24%), fatigue (21%), and diarrhea (16%). Infusion reactions or irAEs occurred in 28% of patients, and 7% were grade 3–4. The most common irAEs were hypothyroidism (14%) and hyperthyroidism (8%). Six patients (7%) discontinued treatment due to a TRAE, and there were no fatal TRAEs.

TMB-H endometrial cancer

The efficacy data leading to the accelerated approval of pembrolizumab for all solid tumors that are TMB-H are described in the **Immunotherapy biomarkers for gynecologic cancer** section. In the patients with TMB-H endometrial cancer (n=15) in KEYNOTE-158, the ORR with

pembrolizumab was 47% (95% CI 21% to 73%) and the response duration ranged from 8.4+ months to 33.9+ months.^{13 30} Responses were infrequent, however, in patients with endometrial cancer that was TMB-low, with only 4 of 67 patients responding.

Expert Panel recommendations

► For first-line treatment of recurrent or metastatic endometrial cancer, carboplatin plus paclitaxel with or without trastuzumab (if HER2+ serous endometrial cancer) was the standard of care at the time of guideline publication (LE:2). Anti-PD-1 ICI in combination with carboplatin plus paclitaxel demonstrated statistically significant and clinically meaningful improvements in PFS over chemotherapy alone for the treatment of previously untreated stage III or IV

or first recurrent (after prior neoadjuvant or adjuvant chemotherapy) endometrial cancer. The observed benefit was regardless of MMR status (LE:2), however, this combination was not FDA-approved at the time of guideline publication.

- For second-line treatment of patients with pMMR/MSS advanced or recurrent endometrial cancer, pembrolizumab plus lenvatinib is recommended, as indicated. For second-line treatment of patients with TMB-H/pMMR/MSS endometrial cancer (LE:2), pembrolizumab plus lenvatinib is the standard of care option (LE:2) however, anti-PD-1 monotherapy may also be an option (LE:3).
- For patients with dMMR/MSI-H advanced or recurrent endometrial cancer who have disease progression following prior systemic therapy in any setting and who are not candidates for curative surgery or radiation, pembrolizumab monotherapy is recommended (LE:3). For patients with dMMR/MSI-H advanced or recurrent endometrial cancer who have disease progression following prior platinum-containing regimen in any setting and who are not candidates for curative surgery or radiation, dostarlimab monotherapy is recommended (LE:3).

Emerging immunotherapy strategies for endometrial cancer

ICI monotherapies are effective for biomarker-selected patients with endometrial cancer, and trials are ongoing evaluating dual immunotherapy combinations such as anti-PD-(L)1 with anti-PVRG (a NK cell checkpoint protein) and anti-TIGIT (NCT04570839), IDO inhibition (NCT04106414), anti-CTLA-4 (NCT03015129; NCT05112601), and others. Many of the ICI combinations under investigation include novel ICI backbones, or agents approved in other regions outside of the US. Although comparative data are lacking, ICIs targeting the same pathway are generally expected not to differ in clinical efficacy.

KEYNOTE-146 and KEYNOTE-775 demonstrated that combining anti-PD-1 ICIs with VEGF(R) inhibition prolongs survival in patients with platinum-refractory endometrial cancer. The combination is now being assessed in the first-line setting for stage III, IV, or recurrent endometrial cancer in the phase III randomized LEAP-001 trial (NCT03884101). ICIs are also being combined with PARP inhibitors as dual therapies (NCT03016338), or as triplet therapies in combination with chemotherapy (DUO-E trial [NCT04269200]), and anti-VEGF(R) therapy (EndoBARR Trial [NCT03694262]¹²⁸). In addition, EndoMAP (NCT04486352) is an ongoing trial combining biomarker-selected targeted agents with atezolizumab for patients with recurrent or persistent endometrial cancer.

Several mechanisms beyond checkpoint activation likely contribute to endometrial cancer immune escape. Other strategies aimed at tipping the balance of the cancer immunity cycle to favor rejection include enhancing antigen presentation (eg, therapeutic cancer vaccines,

toll-like receptor [TLR]-agonists, etc), or increasing cytotoxic IC infiltration (eg, ACTs). Data supporting these approaches in endometrial cancer are extremely sparse, however, and few trials have advanced to late stages of development at the time of guideline writing.

Expert Panel recommendations

- For all patients with endometrial cancer, clinical trial enrollment should be encouraged, as feasible.
- Non-FDA-approved immunotherapy combination strategies should only be considered in the context of a clinical trial.

EMERGING IMMUNOTHERAPY STRATEGIES FOR THE TREATMENT OF OVARIAN CANCER

Ovarian cancer is the third most common gynecologic cancer. It is highly aggressive in advanced stages, with the highest mortality rate of gynecologic cancers.¹²⁹ The high mortality rate is partially attributed to a lack of effective screening methods to detect early stage disease. Moreover, in countries with limited resources, mortality is even higher.¹³⁰

There are a number of characteristics of ovarian cancer that, theoretically, make the disease a prime candidate for immunotherapy. PD-L1 expression has been reported in ovarian cancer and high expression is correlated with poor prognosis.¹³¹ Intratumoral T cell infiltration has been associated with improved OS in ovarian cancer in multiple analyses.^{132 133} However, clinical trials evaluating ICI therapy in ovarian cancer have reported very low response rates thus far. At the time of guideline publication, no immunotherapies were FDA-approved for the treatment of ovarian cancer, although a number of strategies are under investigation. Additionally, certain patients with ovarian cancer may be eligible for ICI treatment through tissue-agnostic indications (discussed in the **Immunotherapy biomarkers for gynecologic cancer** section) for TMB-H, MSI-H, or dMMR solid tumors. TMB in ovarian tumors is low, however, with a median of <5 mut/Mb.^{34 134} The expected frequency of MSI-H in epithelial ovarian tumors is estimated at 8%–17%, with over-representation in non-serous cancers.¹³⁵ Prospective, randomized data on the efficacy of ICI monotherapy in ovarian cancer that is TMB-H, MSI-H, or dMMR was lacking at the time of guideline publication.

Negative trials evaluating ICIs for the treatment of ovarian cancer

Enthusiasm for investigating ICIs for the treatment of recurrent ovarian cancer was high during the initial checkpoint blockade renaissance. Early phase clinical trials evaluated pembrolizumab (KEYNOTE-028 [NCT02054806]; KEYNOTE-100 [NCT02674061]), nivolumab, atezolizumab (NCT01375842), and avelumab (JAVELIN Solid Tumor [NCT01772004]) monotherapies, however, all reported low response rates, with ORRs ranging from roughly 8%–22%.¹³⁶ In one phase II randomized trial (NCT02498600), the addition of ipilimumab to

nivolumab resulted in higher responses than nivolumab monotherapy with an ORR of 31.4% (vs 12.2%; $p=0.034$). Higher response rates were seen for tumors with clear cell histology in both treatment arms. However, a greater magnitude of PFS benefit was seen with combination therapy versus ICI monotherapy for the patients with tumors with clear cell histology. Despite responses to the combination, however, durability was lacking, with a PFS of only 3.9 months.¹³⁷ No phase III trials evaluating dual immunotherapy for ovarian cancer were registered with ClinicalTrials.gov at the time of guideline publication.

KEYNOTE-100 found a trend towards increased efficacy of pembrolizumab with increasing PD-L1 CPS, with ORRs for patients with tumors with CPS<1, CPS≥1, and CPS≥10 of 5%, 10.2% and 17%,¹³⁸ respectively. However, other trials reported no difference in response rates across PD-L1 expression subgroups. Overall, underwhelming responses to ICI therapy indicate a need to target additional steps in the tumor-immunity cycle³ to overcome the immunosuppressed microenvironment in ovarian tumors, as well as a need for identifying predictive biomarkers.

In other solid tumors, such as triple negative breast cancer (TNBC)¹³⁹ the addition of chemotherapy to ICIs has improved survival outcomes possibly due to enhanced antigen release and induction of danger-associated molecular patterns (DAMPs) leading to an inflamed tumor microenvironment. Phase III trials in ovarian cancer evaluating chemotherapy plus ICI combinations, however, have not demonstrated improved outcomes compared with chemotherapy alone. The JAVELIN Ovarian 100 trial (NCT02718417), which was terminated for futility at the first interim analysis, compared avelumab in combination with investigator's choice of chemotherapy followed by avelumab maintenance, or chemotherapy followed by avelumab maintenance, versus chemotherapy alone for the first-line treatment of ovarian cancer. The chemotherapy induction followed by immunotherapy maintenance approach has become standard of care for the treatment of metastatic urothelial carcinoma,¹⁴⁰ yet no benefit over chemotherapy alone was seen in any immunotherapy-treated arm of the study. Additionally, the phase III IMagyn050 trial (NCT03038100) found no significant benefit with the addition of atezolizumab to a standard of care bevacizumab plus chemotherapy regimen in either the ITT or PD-L1-positive populations for patients who had undergone primary cytoreductive surgery resulting in gross residual disease or who were planned to receive neoadjuvant therapy followed by interval surgery.¹⁴¹ In the platinum-refractory setting, JAVELIN Ovarian 200 (NCT02580058) evaluated avelumab plus pegylated liposomal doxorubicin—a prototypical immunogenic cell death-inducing chemotherapy¹⁴²—for patients with disease progression after platinum-based chemotherapy also did not meet its primary endpoints.¹⁴³ Despite the negative results, lessons were learned from these trials, particularly in biomarker-selected subgroup analyses. While both JAVELIN trials found no improvements

compared with the control arms in patients with PD-L1-positive tumors treated with avelumab with or without chemotherapy, improved OS and PFS in patients with tumors that were positive for both PD-L1 (TCs ≥1% or ICs ≥5%) and CD8⁺ cells (cells within the tumor area ≥1%) were demonstrated in JAVELIN Ovarian 200. Prespecified exploratory analyses in IMagyn150 suggested a potential PFS benefit from atezolizumab in the subgroup of 260 patients with PD-L1 expression on ≥5% of ICs. Additional adequately powered and prospective studies will be needed to identify subsets of patients that may benefit from future immunotherapy-based combinations for the treatment of ovarian cancer.

Emerging immunotherapy strategies for ovarian cancer

Several trials were underway at the time of guideline publication investigating ICI-based combinations as well as other immunotherapy modalities for the treatment of ovarian cancer.

ICI-targeted therapy combinations for the treatment of ovarian cancer

Mutations in the DNA damage repair genes *BRCA1* and *BRCA2* are common in patients with ovarian cancer, with a prevalence of about 10%–15% overall and more frequently in tumors with serous (16%–18%) and high-grade serous (22.6%) histology.^{144–145} Tumors with *BRCA* mutations are sensitive to PARP inhibitors, which are currently approved in the front-line and recurrent maintenance setting for ovarian cancer. Tumors with *BRCA* mutations also have higher IC PD-L1 expression, predicted neoantigen expression, and TILs in high-grade serous ovarian tumors.¹⁴⁶ PARP inhibition may also be immunomodulating through upregulation of IFN signaling,¹⁴⁷ regulation of TGF-β signaling, and modulation of Tregs.¹⁴⁸ Preclinical evidence supports enhancement of stimulator of IFN genes (STING) dependent antitumor immune response via PARP inhibition and augmented therapeutic efficacy of checkpoint blockade even in the absence of *BRCA* mutations,¹⁴⁹ providing rationale for combination approach with ICIs. The phase I/II TOPACIO-KEYNOTE 162 trial (NCT02657889) assessed pembrolizumab with niraparib in patients with TNBC and recurrent ovarian cancer unselected by *BRCA* mutation status. An ORR of 18% (90% CI 11% to 29%) and a DCR of 65% (90% CI 54% to 75%) were reported in the ovarian cancer cohort ($n=60$). ORRs were consistent across tumor *BRCA* or homologous recombination deficiency (HRD) biomarker status.¹⁵⁰ An ORR of 71.9% (95% CI 53.25% to 86.25%) with a 28-week DCR of 65.6% (90% CI 49.6% to 79.4%) was reported in the phase I/II MEDIOLA trial (NCT02734004) in patients with *BRCA*-mutated, platinum-sensitive, relapsed ovarian cancer ($n=32$) treated with durvalumab plus olaparib.¹⁵¹

Triplet combinations are also being evaluated, including ICIs with PARP inhibitors and anti-VEGF(R) agents. The GINECO BOLD trial (NCT04015739) of durvalumab plus bevacizumab plus olaparib reported a

3-month DCR of 70% in patients with platinum-resistant relapsed ovarian cancer, and a 6-month DCR of 44% in the platinum-sensitive relapsed cohort.¹⁵² Pembrolizumab in combination with bevacizumab and oral metronomic cyclophosphamide is also being evaluated in a phase II randomized trial (NCT02853318), which reported an ORR of 47.5% and a median PFS of 10 months at an interim analysis.¹⁵³

Investigational immunotherapy strategies for the treatment of ovarian cancer

The presence of TILs in ovarian tumors indicates an anti-tumor response that is suppressed. However, the lack of benefit in the early ICI trials brings into question whether the abundance, differentiation status, or antigen specificity of TILs in ovarian cancer is inadequate to reject the tumor. Thus, strategies to augment the existing TILs, such as vaccines or ACT, are being evaluated. A wide variety of therapeutic vaccines have been tested in ovarian cancer, including dendritic cell vaccines, peptide-based, viral vector-based, and cancer testis antigen (CTA) targeting vaccines, and others.¹⁵⁴ However, efficacy has been limited,¹⁵⁵ as demonstrated in a recent meta-analysis of vaccine approaches in ovarian cancer. The pooled ORR estimate across 12 vaccine studies was 4% (95% CI 1% to 7%) and the reported ORRs from those studies ranged from 0%–33%, the estimated PFS was 13 months (95% CI 8.5 to 16.3) and the estimated median OS was 39 months (95% CI 31 to 49). However, more recent strategies to improve vaccine immunogenicity tailored to the specific type of vaccine, along with rational combinations or sequencing of vaccines with other therapies may increase efficacy.

ACT studies for ovarian cancer were first initiated in the 1990s. Since then, CAR T cells and TCR-engineered T cells, lymphodepletion, and combination regimens have been implemented to increase efficacy. Some of the tumor-specific targets for CAR T cell therapies used in ovarian cancer include MUC16, mesothelin, HER2, and folate receptor- α .^{156 157} Similar to other solid tumors, however, CAR T cell therapies have seen limited success in ovarian cancer.

Ongoing phase II trials are assessing measles virus-based therapy (NCT02068794; NCT02364713), adenovirus-based therapy (NCT03225989), and vaccinia virus-based therapy (VIRO-15; NCT02759588) for the treatment of ovarian cancer. Additional immunotherapy strategies under investigation include combining cell therapies with vaccines or oncolytic viruses, intraperitoneal delivery of chemoimmunotherapy, bispecific antibodies that bring ICs into close proximity to TCs, and others. Clinical trials evaluating immunotherapy approaches in ovarian cancer are abundant, and enrollment should be offered to patients, when appropriate.

Expert Panel recommendations

- For all patients with ovarian cancer, clinical trial enrollment should be offered, as feasible.

- NGS testing should be offered to all patients with newly diagnosed ovarian cancer (LE:2).
- For patients with recurrent TMB-H and/or MSI-H/dMMR ovarian tumors with no satisfactory alternative treatment options, treatment with ICIs should be considered (LE:3).
- Tumor PD-L1 expression should not be used to inform treatment decisions for ICI use in ovarian cancer (LE:2).

EMERGING IMMUNOTHERAPY STRATEGIES FOR THE TREATMENT OF RARE GYNECOLOGIC CANCERS

Vaginal and vulvar cancers

Vaginal and vulvar cancers are rare. Due to the difficulty in conducting randomized trials in patients with rare tumors, treatment paradigms for these cancers have largely been extrapolated from studies in cervical cancer, since both vaginal and vulvar cancers are also associated with persistent HPV infection, although at lower frequencies. Approximately 34% and 75% of vulvar and vaginal cancer have been found to be HPV-positive, respectively.^{158–160} Early stage disease is often treated with surgery with or without adjuvant radiation, and concurrent chemoradiation is the current standard of care for unresectable disease.^{161 162} Although no large-scale studies evaluating immunotherapy specifically for the treatment of vaginal and vulvar cancers were available at the time of guideline publication, some patients with these malignancies were included in basket trials or single-arm studies of checkpoint blockade.

The vaginal and vulvar cancer immune microenvironment

The presence of CD8⁺ and CD4⁺ TILs in vulvar tumors has been associated with a better prognosis overall regardless of the therapy administered.¹⁶³ PD-L1 expression on TCs is moderate (reported between 23%–33%),^{164 165} whereas it is much higher in infiltrating ICs (>90%).¹⁶⁵ Data are conflicting thus far on the prognostic utility of PD-L1 expression for vulvar tumors as well as on the association between checkpoint expression and HPV viral status.^{164 165} Metastases involving tumor-draining lymph nodes have been demonstrated to have an inflamed microenvironment with high expression of PD-1 and CTLA-4.¹⁶⁶ Data are lacking on the immune microenvironment of vaginal cancer specifically, however, HPV-positive vaginal cancer likely mimics the immunophenotype of other HPV-related cancers.¹⁶⁷

Immunotherapy outcomes in vaginal and vulvar cancers

Data on the efficacy of ICIs for the treatment of vulvar and vaginal cancer are sparse and limited to single-agent anti-PD-1 studies. The phase I/II CheckMate 358 trial (NCT02488759), which assessed nivolumab monotherapy in several virus-associated cancers, reported an ORR of 20.0% (95% CI 0.5% to 71.6%) and a DCR of 80.0% (95% CI 28.4% to 99.5%) in five patients with vaginal or vulvar cancer, four of whom had HPV-positive tumors.¹⁶⁸ OS rates at 12 months and 18 months were 40.0% (95%

CI 5.2% to 75.3%) and 20.0% (95% CI 0.8% to 58.2%), and the 6 months PFS rate was 40.0% (95% CI 5.2% to 75.3%). All of the four tumors evaluable for PD-L1 expression were PD-L1 TC $\geq$ 1%. Patients with vulvar cancer of unspecified HPV status (n=101) were also included as a cohort in the phase II KEYNOTE-158 trial, which evaluated pembrolizumab monotherapy for the treatment of multiple advanced solid tumors that progressed on standard of care therapy. The ORR in this cohort was 10.9% (95% CI 5.6% to 18.7%) with a median DOR of 20.4 months (range 2.1+ to 28.0). Median PFS for the vulvar cancer cohort in KEYNOTE-158 was 2.1 months (95% CI 2.0 to 2.1) and median OS was 6.2 months (95% CI 4.9 to 9.4).¹⁶⁹ A majority of patients (83.2%) had PD-L1-positive tumors (CPS $\geq$ 1), however responses were seen in both PD-L1-positive and PD-L1-negative populations. The safety profile for ICI monotherapy for vaginal and vulvar cancers in these small cohorts was generally consistent with other tumor types. Published data are lacking on the use of ICI-based combinations in vaginal and vulvar cancers.

HPV-targeting therapeutic vaccines have also been investigated for the treatment of vaginal and vulvar cancers. In patients with high-grade, HPV 16-positive vulvar intraepithelial neoplasia (n=19), vaccination against E6 and E7 peptides resulted in a 12-month clinical response rate of 79% (95% CI 54% to 94%), with nine complete responses (CRs; 47%), and the clinical response rate was maintained at 24 months.¹⁷⁰ Weak CD8⁺ T cell reactivity was associated with clinical non-response, providing rationale for a follow-up study that randomized 43 patients with high-grade vulvar and vaginal intraepithelial neoplasia to receive the ISA101 HPV 16-targeting vaccine with (n=22) or without the topical TLR7 agonist imiquimod (n=21).¹⁷¹ Responses to the vaccine were not improved with the addition of imiquimod, and the 12-month clinical response rate was 52% (95% CI 32.5% to 70.6%).¹⁷² Imiquimod, which is used as a topical 5% cream and is approved for genital and perianal wart and superficial basal cell carcinoma,¹⁷³ has however, been found to be effective in treating vaginal neoplasia, vulvar neoplasia, and CIN.¹⁷⁴

Other rare gynecologic cancer variants

Sparse data are available on the efficacy of ICIs for the treatment of gynecologic melanomas, sarcomas, and neuroendocrine tumors (NETs). Clinical trial enrollment is encouraged for all patients with these rare malignancies with an emphasis on combination immunotherapy strategies, in order to obtain the best possible treatments and continue to advance the field.

Gynecologic sarcomas

Overall, gynecologic sarcomas are rare, with uterine sarcoma being the most common.¹⁷⁵ The trials leading to FDA approvals for ICIs in the treatment of gynecologic cancers have predominantly included patients with carcinoma histologies. Data are emerging on the use of

ICIs in metastatic sarcomas, with mixed response rates across tumor types.¹⁷⁶ Unlike in uterine carcinomas where dMMR/MSI-H has been reported in up to 30% of tumors,^{119 177} dMMR prevalence in uterine sarcomas or leiomyosarcomas is low, up to 6%.¹⁷⁸ CD8⁺ T cell infiltration and PD-L1 expression on TCs and ICs in uterine leiomyosarcomas is also highly prevalent.¹⁷⁹ However, in a phase II trial investigating nivolumab monotherapy in a cohort of 12 patients with advanced uterine leiomyosarcoma (NCT02428192), no responses were reported.¹⁸⁰ The Alliance A091401 (NCT02500797) trial assessing nivolumab with or without ipilimumab in patients with varying sarcoma subtypes reported one response in a patient with uterine leiomyosarcoma treated with the ICI combination.¹⁸¹ Taken together, the data and use of ICIs in patients with gynecologic sarcomas is underwhelming and limited to very small patient numbers, and therefore the use of ICIs should only be considered based on immune biomarkers (ie, TMB and/or MMR/MSI).

Rare epithelial endometrial tumors

Epithelial endometrial tumors are most commonly endometrioid histology. More rare epithelial histologies such as clear cell, serous, carcinosarcoma, dedifferentiated, undifferentiated, and others, while less prevalent, are typically high grade.¹⁰⁴ Data are limited on efficacy of ICIs in treating these rare subtypes. However, in KEYNOTE-775 which included patients with clear cell, serous, and mixed histologies, subgroup analyses of PFS and OS favored the pembrolizumab plus lenvatinib combination over chemotherapy across all histological subtypes.¹²⁵

Gynecologic NETs

Gynecologic NETs include heterogeneous histologies and they can range from slow growing, well-differentiated tumors with low mutation burden to highly proliferative, poorly differentiated, highly mutated tumors.¹⁸² Extrapolating from basket trials that enrolled patients with various rare tumor types, NETs have low ORRs to ICI monotherapy of <10%.¹⁸² Dual ICI therapy (nivolumab plus ipilimumab) is being investigated in the DART trial (NCT02834013). Results have been reported in a cohort of patients with non-pancreatic NETs, including three patients with cervical NETs, in which one patient had a confirmed PR.¹⁸³

Gynecologic melanomas

Melanomas of the genitourinary tract are a rare subset of gynecologic malignancies. While these tumors have historically been classified as mucosal, recent molecular data indicate they may be distinct from both mucosal and cutaneous melanomas.^{184 185} Patients with vaginal and vulvar melanoma have an overall poor prognosis¹⁸⁵ and data on the immune microenvironment of gynecologic melanomas are scarce. Overall, the prevalence of PD-L1 expression is unclear, as reports have used inconsistent staining and scoring methodologies for measurement. However, high levels of CD8⁺ T cell infiltration have been

reported in vulvar melanomas, indicative of potential responsiveness to immunotherapy and a favorable prognosticator.¹⁸⁶ In case reports, the response rates to ICIs in gynecologic melanoma have been less remarkable than those seen in cutaneous melanoma. In one review including a total of 57 patients from various case reports and series with metastatic disease, there were 6 CRs and 13 PRs with anti-PD-1 monotherapy or in combination with anti-CTLA-4.¹⁸⁷ Concurrent ICI and radiotherapy has been shown to improve PFS, but not OS, in cutaneous melanoma in one meta-analysis,¹⁸⁸ and this strategy may also be appropriate for some patients with gynecologic melanoma. Neoadjuvant anti-CTLA-4 in combination with radiotherapy has also been reported in one small study (n=4), where among the three patients who underwent resection, one achieved pathologic complete response (pCR), and all three patients had local radiographic CR after surgery.¹⁸⁹ Recurrence was reported in two patients at 9 months and 10 months post-diagnosis, and the remaining two were disease-free at 20 months and 38 months. In addition, the use of combined dual checkpoint inhibition and high-dose and low-dose radiation after progression on dual ICIs alone was successful in one case report.¹⁹⁰

Gestational trophoblastic neoplasia

Gestational trophoblastic neoplasias (GTNs) are rare malignancies derived from placental trophoblasts and include malignant invasive mole, choriocarcinoma, and rare placental site trophoblastic and epithelioid trophoblastic tumors. Depending on the risk level of the GTN as determined by the FIGO risk score,¹⁹¹ standard treatments are chemotherapy and salvage chemotherapy for recurrent disease.¹⁹¹ GTNs are inherently immune-privileged through gestational immune tolerance, however, spontaneous tumor regression in metastatic disease has been reported.¹⁹² The finding that PD-L1 is ubiquitously expressed on GTNs^{193 194} suggests a role for immune checkpoints in maintenance of this immune tolerance, providing rationale for investigating ICIs in the subset of patients that have chemotherapy-refractory disease.

The phase II TROPHIMMUN study (NCT03135769) evaluated avelumab monotherapy in 15 patients with single-agent chemotherapy-resistant gestational trophoblastic tumors. Normalization of the disease biomarker human chorionic gonadotropin (hCG) was the primary endpoint, with secondary outcome measures including resistance-free survival (defined as a $\geq 20\%$ rise between two assays in three consecutive weekly hCG assays or plateau with $\leq 10\%$ decrease between two assays in four consecutive weekly hCG assays), PFS, and OS. Avelumab was given until serum levels of hCG normalized with an additional three consolidation cycles thereafter. At a median follow-up of 25 months, eight (53%) patients had hCG normalization and had discontinued avelumab, and no relapses were recorded after a median of 29 months of follow-up. All TRAEs were grade 1 or 2, and only three patients experienced an irAE (two with hyperthyroidism,

one with hypothyroidism).¹⁹⁵ An additional cohort of patients with unlimited previous lines of therapy was also included in this trial, however results were not reported at the time of guideline publication. In case reports, pembrolizumab treatment in patients with chemotherapy-resistant GTNs resulted in remission in two of two¹⁹⁶ and three of four¹⁹⁷ patients. Combination approaches have also been evaluated. One phase II trial (NCT04047017) that included 20 Chinese patients with GTN¹⁹⁸ demonstrated an ORR of 55% (95% CI 32% to 77%) with the combination of camrelizumab (an anti-PD-1 agent) and the VEGFR TKI apatinib. In this study, 60% of patients experienced a grade 3 TRAE, the most common being hypertension (25%) and rash (20%). Apatinib dose was reduced in five patients with grade 3 hypertension and was discontinued in one patient due to uncontrollable hypertension.

Expert Panel recommendations

Considerations of treatment options listed below are based on expert consensus (unless a LE is noted) as there are very few data for these rare tumors.

- For all patients with rare gynecologic malignancies, clinical trial enrollment should be offered, as feasible.
- For all patients with rare gynecologic malignancies, testing for TMB-H and MSI-H by NGS (preferred) and MMR by IHC (as an alternative) is recommended, for potential treatment under tissue-agnostic indications for ICIs (LE:3). For patients with rare gynecologic malignancies, testing for PD-L1 by IHC may be considered (LE:4).

Vaginal and vulvar cancers

- For previously treated patients with recurrent or metastatic vulvar or vaginal squamous cell carcinoma, second-line treatment with pembrolizumab (for patients with PD-L1-positive/TMB-H/MSI-H/dMMR tumors) or nivolumab (for patients with HPV-related tumors) should be considered (LE:3).
- For patients with unresectable/metastatic vulvar or vaginal melanoma, treatment can follow the standard of care treatment paradigms for cutaneous melanoma.
- For patients with locally advanced vulvar or vaginal melanoma with high risk of recurrence, adjuvant treatment with an anti-PD-1 ICI with or without an anti-CTLA-4 ICI may be considered.

Other rare gynecologic cancer variants

- For patients with uterine sarcoma who have exhausted other treatment options, biomarker-driven (ie, dMMR, TMB-H, or MSI-H) treatment with an anti-PD-1 ICI may be considered.
- For patients with previously treated rare epithelial endometrial tumors, second-line treatment with combination pembrolizumab plus lenvatinib should be considered.

Gestational trophoblastic neoplasia

- For patients with recurrent GTN with prior chemotherapy treatment, treatment with an anti-PD-(L)1 ICI may be considered (LE:3).

PATIENT SELECTION AND MANAGEMENT FOR GYNECOLOGIC CANCER

Many patients with gynecologic cancer have various pre-existing or intercurrent conditions that may require special considerations for the administration of ICIs and management of irAEs. In addition, optimal treatment duration and surveillance of response in patients receiving ICIs are open questions in the field. Overall, a multidisciplinary approach in the management of patients with pre-existing immunological comorbidities or other populations that have historically been excluded from clinical trials is strongly recommended whenever possible.

Special patient populations

While patients with active autoimmune disorders may have a greater risk of experiencing irAEs (either de novo or autoimmune flares) during ICI therapy, these toxicities are generally manageable. In studies including patients with NSCLC and melanoma with concurrent autoimmune disease, rates of autoimmune flares on treatment with ICIs ranged from 23%–38%.^{199–201} A majority were grade 1–2 and managed with corticosteroids or other immunosuppressants, and only 4%–14% of patients permanently discontinued the ICI therapy due to irAEs (including de novo and flares of pre-existing autoimmune disorders). Flares occurred more frequently in those with active symptoms than those with clinically inactive disease (60% vs 30%; $p=0.039$), and there was a trend towards more frequent flares in those on immunosuppressants at the start of ICI treatment compared with those who were not.²⁰¹ The overall rate of irAEs has been higher in patients with pre-existing autoimmune disorders, though response rates do not appear to be inferior.^{199–202} The type of autoimmune condition and whether it is active and/or requiring ongoing immunosuppression should be considered in a careful shared decision-making with the patient when considering ICI treatment. It is important to note that data are lacking on the impact of pre-existing autoimmune conditions specifically in patients with gynecologic malignancies, though increasing use of ICI therapy in these settings is expected to yield more information in the coming years.

The risk of developing HPV-related gynecologic cancers (including cervical, vulvar, and vaginal cancer) is higher in solid organ transplant (SOT) recipients compared with the general population, likely due to reactivation of viral replication while on immunosuppressants.²⁰³ In studies of ICI safety and efficacy in SOT recipients to date, allograft rejection occurred in roughly 28%–45% of patients,²⁰⁴ and rejection often occurred early.²⁰⁵ Tumor responses were seen in patients with (40%) and without (52%) graft rejection, though none had gynecologic cancer. Due to the relatively high rate of graft rejection in studies to date,

consultation with the transplant service is recommended and a very careful consideration of the relative risks and benefits should drive the decision to use ICIs in SOT recipients with gynecologic cancer.

Patients with HIV have higher rates of cervical cancer compared with the general population, and it is considered an AIDS-defining cancer.²⁰⁶ In a systematic review of patients with various cancers ($n=73$; NSCLC, melanoma, Kaposi sarcoma) and HIV treated with ICIs, HIV remained controlled in 93% of patients and CD4⁺ T cell counts increased.²⁰⁷ Grade ≥ 3 irAEs occurred in 8.6% and ORRs were 30% for NSCLC, 27% for melanoma, and 63% for Kaposi sarcoma. Overall, ICIs appear to have similar safety and efficacy in patients with well-controlled HIV compared with patients without HIV, although studies thus far have been mostly retrospective (prospective trials are ongoing) and have not included patients with gynecologic cancers. Data are limited on the use of ICIs in patients with uncontrolled HIV, and consultation with infectious disease specialists is encouraged.

Patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infection are frequently excluded from immunotherapy clinical trials due to concerns for potential viral reactivation with treatment.^{208–210} Available data indicate that ICIs are generally safe and effective for patients with HBV or HCV. In a systematic review including 198 patients with advanced cancer and HBV/HCV infections,²¹¹ ICIs were well tolerated with no new safety signals emerging. Any grade hepatic transaminase elevation (HTE) occurred in 13.5% of patients with HBV and 29.6% of patients with HCV. Although viral reactivation is uncommon,²¹² liver status, viral screening, and prophylactic antiviral therapy can be considered prior to administering ICIs.²¹³ Additionally, treatment of irAEs may require immunosuppression and increase the risk for viral reactivation, therefore caution is warranted and consultation with the hepatitis service is encouraged.

Patients with cancer are at increased risk for severe complications with influenza²¹⁴ and SARS-CoV-2²¹⁵ infections. Inactivated influenza vaccines²¹⁶ and mRNA or viral vectored SARS-CoV-2 vaccines do not compromise the safety or efficacy of ICIs and no increases in irAEs in vaccinated patients treated with ICIs has been reported.^{216–218} The benefits associated with vaccination against viral pathogens far outweigh the risks, and these vaccines should be encouraged.

Baseline corticosteroid use of ≥ 10 mg prednisone equivalent has been associated with worse OS and PFS in patients with NSCLC treated with ICIs compared with patients on 0 mg to <10 mg prednisone equivalents.^{219–220} However, PFS and OS were significantly shorter only among patients who received ≥ 10 mg prednisone for palliative reasons, and not for patients who received ≥ 10 mg prednisone for non-palliative indications.^{219–221} Early corticosteroid use (within the first cycle²²² or <2 months of starting ICIs²²³) has also been associated with lower efficacy. While more data are needed in gynecologic malignancies, if clinically feasible reducing corticosteroid use to <10 mg prednisone

equivalent and avoiding steroid use early in ICI treatment is recommended when administering ICIs. For patients with dermatologic conditions (pre-existing or treatment-related), local therapy may be considered to circumvent systemic steroid use, if appropriate. Glucocorticoid signaling has also been associated with chemoresistance in ovarian cancer.²²⁴ However, the effects of glucocorticoid signaling on immunotherapy in gynecologic cancer have not been determined.

The use of ICIs in the elderly is sometimes considered to be challenging due to frailty and possible immunosenescence associated with advanced age. Elderly patients treated with ICIs experience similar levels of toxicity as younger patients, with the exception of dermatologic toxicities, which are increased in elderly patients.^{225–226} One systematic review and meta-analysis found no difference in ICI efficacy in patients with NSCLC ≥ 65 years and < 65 years.²²⁷ Although some analyses have found worse outcomes with ICI therapy among patients > 75 years of age,^{228–229} others indicate that the safety and efficacy is comparable between older and younger populations.^{230–231} Studies on the impact of age on ICI therapy specifically in patients with gynecologic cancer were lacking at the time of guideline publication.

Limited data are available on the safety of ICIs in patients with severe organ dysfunction, such as those with cirrhosis, chronic kidney disease, history of idiopathic pulmonary fibrosis, and pneumonitis. Patients with significant organ dysfunction may have limited tolerability to irAEs, and management of irAEs may be challenging. Analyses of patients with hepatocellular carcinoma with Child-Pugh A and B cirrhosis have found that ICI monotherapy is generally safe, but patients with decompensated livers may be at increased risk of developing irAEs.²³² Patients with chronic or end-stage kidney disease on dialysis treated with ICIs had an irAE incidence rate of 49% in one retrospective review.²³³ While certain organ dysfunctions are not absolute contraindications to the use of ICIs, a frank risk-benefit discussion with the patient is required and careful monitoring for irAEs is needed.

Patients with gynecologic cancer, particularly ovarian cancer²³⁴ or cancer that has spread to the peritoneal cavity²³⁵ may have significant ascites, which is associated with worse survival. Studies are underway assessing the immune microenvironment of ascites, and there is evidence to suggest anti-VEGF targeted therapy may be an effective strategy in these patients.^{236–237} Although more data are needed in gynecologic cancer, increased incidence of anti-PD-(L)1-resistance has been documented in patients with gastrointestinal cancer and ascites.²³⁸ Therefore, treatment of patients with significant ascites may favor a more aggressive combination ICI treatment approach, specifically with anti-VEGF targeted agents. Indwelling pleural catheters (eg, PleurX) may be helpful in controlling significant ascites.²³⁹ Additionally, treatment with anti-PD-(L)1 therapy may result in pseudoprogression manifested as ascitic fluid accumulation due to the influx of activated T cells. Since worsening of

ascites is typically associated with disease progression, it is important to consider the possibility of pseudoprogression in such patients undergoing therapy with ICIs.

While rare in advanced gynecologic cancers where reproductive organs are often surgically removed, there may be instances where the safety of ICIs during pregnancy will need to be considered. Overall, clinical data are extremely limited on the use of ICIs during pregnancy. In seven case studies of patients with melanoma treated with ICIs during pregnancy, eight of the nine (88.9%) neonates were born prematurely, with a mean gestational age at delivery of 30.4 weeks (range 24–38), and complications during pregnancy occurred in 71.4% of patients.²⁴⁰ Patients who are pregnant may have limited treatment options if AEs occur, as certain agents commonly used to treat AEs, such as mycophenolate mofetil, have been shown to cause fetal malformation.²⁴¹ Due to these risks to the mother and fetus, ICI administration during pregnancy is discouraged.

Response monitoring

Responses to immunotherapy are often more delayed and more durable compared with chemotherapies and targeted agents. Atypical radiographic responses may occur in a small subset of patients. One atypical response associated with ICIs is pseudoprogression: initial apparent tumor growth on imaging followed by a response, which, in some cases may manifest as ascites. Additionally, in patients with metastatic disease, enlargement of lymph nodes can occur while other sites of disease may show a response or are stable. In cases of suspected pseudoprogression, the decision to continue or switch therapy depends on the patient's clinical status and symptoms. The vast majority of data available on pseudoprogression is in melanoma,^{242–243} with very little in gynecologic cancer. Importantly, pseudoprogression has not been described when immunotherapy is combined with a direct-acting cytotoxic or targeted agent. Nevertheless, clinicians should be aware of the possibility of atypical radiographic responses and repeat scans may be considered with apparent progressive disease (PD) to rule out pseudoprogression. Additionally, more delayed responses compared with the expected kinetics of other treatment modalities such as chemotherapy or targeted therapy are common with ICIs. This should be taken into account when lack of radiographic decrease in tumor size is noted early on in ICI treatment.

Responses to ICI therapies in patients with gynecologic cancers can be determined by radiologic evaluation, typically with CT or PET/CT. RECIST v.1.1²⁴⁴ is the most common response criteria used in solid tumor clinical trials, including immunotherapy clinical trials. However, conventional RECIST does not accommodate delayed responses and pseudoprogression. As such, immunotherapy-specific response criteria have been developed: immune-related response criteria (irRC),²⁴⁵ immune-related RECIST (irRECIST),²⁴⁶ immune-modified RECIST (imRECIST),²⁴⁷ and immune RECIST

(irRECIST).²⁴⁸ Overall, uptake of these immunotherapy-specific response criteria has been slow. Some gynecologic cancer clinical trials have incorporated irRECIST in the endpoint assessments, including KEYNOTE-146 which used irRECIST as the primary criteria for evaluating response, and the GARNET trial which used both irRECIST and RECIST v.1.1 in various cohorts. irRECIST combines the unidimensional measurement of RECIST v.1.1 with components of irRC, including that new lesions may not define PD, and confirmatory assessments should be performed at least 4 weeks after PD is suspected. It is important to emphasize, however, that formal response criteria are not routinely used outside of a clinical trial setting. In routine care, it is recommended to monitor responses via radiologic imaging every 2–3 months for the first 2 years, after which a risk-stratified reduction in imaging may be considered.

CA125 remains the only tumor marker routinely used in ovarian cancer despite limitations in its prognostic value.²⁴⁹ Data pertaining to the role of CA125 in the setting of ICIs are limited. It is conceivable that immune infiltration could lead to a rise in CA125. A retrospective review showed that patients achieving clinical benefit with ICIs experienced an increase in CA125 within 12 weeks of beginning therapy. This trend also occurred in patients with no clinical benefit from ICIs, however the magnitude of increase was significantly greater (195% vs 34%; $p=0.008$).²⁵⁰

Treatment duration

The optimal duration of ICI treatment is an unresolved question.²⁵¹ In melanoma, which has the most robust long-term data for ICIs, studies have reported that 76%–90% of patients who discontinue ICI therapy after attaining CR or PR experienced ongoing responses for as long as 5 years and beyond.^{252–253} Some patients who discontinue immunotherapy due to irAEs also experience long-term responses.^{254–255}

Postimmunotherapy treatment choice

Limited data are available to inform treatment selection for patients with disease that progresses on or after immunotherapy treatment. SITC has defined primary and secondary resistance scenarios to anti-PD-1 ICIs based on initial clinical benefit or lack thereof.²⁵⁶ Some mechanisms of resistance to anti-PD-(L)1 have been identified, including downregulation of antigen processing or presentation, defects in IFN signaling, attenuated effector functions, immune exclusion via β -catenin pathways, and other immunosuppressive checkpoints.^{257–258} The underlying mechanisms leading to anti-PD-(L)1 resistance are incompletely understood, however, and vary across tumor types. In gynecologic cancer, a gene expression pattern consistent with upregulation of TGF- β signaling has been linked to ICI non-response,²⁵⁹ and other mechanisms are likely involved as well. It is important to emphasize that there are no data to support benefit with switching ICIs targeting the same checkpoint/ligand pair after

resistance develops. For some patients rechallenge may be considered if disease progression occurs after discontinuation. Factors to take into consideration for this decision include the reason for discontinuation, the interval since discontinuation, and the patient's status and symptoms. If discontinuation was due to a severe irAE, rechallenge should include a careful risk-benefit discussion regarding the chance of developing the same or another irAE. Clinical trial enrollment in studies assessing options for patients with anti-PD-(L)1-resistant tumors is encouraged.

Toxicity

Through some of the same mechanisms that ICIs induce an antitumor immune response, ICIs may also cause irAEs. Unlike chemotherapy- or targeted therapy-related AEs that are often dose-dependent, occur quickly and during the time of treatment, and resolve rapidly when the agent is withdrawn, ICI-related irAEs can be delayed in onset and persistent, arising and continuing even months or years after exposure to ICI therapy.²⁶⁰

Overall, the frequency of irAEs reported in patients with gynecologic cancer is similar to the frequency of irAEs in other types of solid tumors. A retrospective real world study in women with gynecologic cancer ($n=129$) treated with ICIs reported the most common irAEs to be endocrine-related (29%), predominantly hypothyroidism, and gastrointestinal toxicities (38%) such as hepatitis and colitis.²⁶¹ Additionally, women treated with anti-CTLA-4 experienced greater rates of hypophysitis.²⁶²

Management of irAEs in patients with gynecologic cancer who have been treated with ICIs should follow general management principles for any solid tumor patient treated with ICIs, which can be found in SITC's ICI-related AE CPG.²⁶³ Importantly, ICI-related pneumonitis and COVID-19-related pneumonia can be clinically indistinguishable,²⁶⁴ and therefore testing to rule out COVID-19 should be included in the differential diagnosis.

Currently, two approved ICI combinations include anti-angiogenic agents: pembrolizumab plus chemotherapy with or without bevacizumab for cervical cancer and pembrolizumab plus lenvatinib for endometrial cancer. Anti-angiogenic agents can increase the risk of AEs such as hypertension, hemorrhage, varices, and increased alanine transaminase (ALT) and aspartate aminotransferase (AST), and therefore careful evaluation of the patient for their ability to tolerate an anti-angiogenic agent should be performed prior to administering those combination immunotherapy regimens.

Expert Panel recommendations

Special patient populations

- Patients with advanced gynecologic cancer living with controlled HIV infection should not be routinely excluded from receiving ICI therapy either on or off trials. The safety and efficacy of ICIs in patients with HIV who are compliant on highly active antiretroviral

therapy (HAART) are similar to those for the general population (LE:1).

- For patients with advanced gynecologic cancer and uncontrolled HIV infection, ICI therapy may still be considered and infectious disease consultation is recommended.
- Patients with advanced gynecologic cancer and chronic HBV/HCV infections can still be considered for ICI therapy (LE:1). Liver function should be checked at baseline and before every immunotherapy cycle for these patients and consultation with a hepatitis service should be considered.
- For patients with a history of active autoimmune disease requiring systemic immunosuppression (≥ 10 mg prednisone or equivalent, or biologics), the potential benefits of immunotherapy must be weighed against the ability to tolerate severe AEs (LE:4).
- For patients who have significant organ dysfunction due to progressive cancer or to intrinsic non-immune-related disease (eg, cirrhosis, chronic kidney disease, idiopathic pulmonary fibrosis or pneumonitis) the potential benefit of immunotherapy must be weighed against the potential for severe AEs as these individuals may have limited ability to tolerate irAEs.
- Patients with hypothyroidism, adrenal insufficiency, or insulin-dependent diabetes mellitus can generally be safely treated with immunotherapy in the setting of hormone replacement therapy and monitoring per the standard of care (LE:4).
- For patients on immunotherapy with pre-existing or immune-related adrenal insufficiency, physiologic replacement doses of steroids should be continued (LE:4).
- ICIs are generally contraindicated in SOT patients due to the high risk of allograft rejection (LE:1), but each case should be evaluated independently in consultation with the transplant service.

Response monitoring, management of radiologic progression, and toxicity

- For patients with gynecologic cancer, CA125 has limited utility in disease monitoring in patients undergoing ICI therapy (LE:4). Decisions to continue or change ICI therapy should be based on the overall clinical status of the patient and radiographic imaging.
- For patients with gynecologic cancer who attain clinical benefit with ICI therapy (ie, CR, PR or SD), routine imaging every 2–3 months for the first 2 years is recommended. Beyond 2 years, reduction in the frequency of imaging may be considered at the discretion of the physician.
- For patients with gynecologic cancer receiving ICI therapy, development of pleural effusions and/or ascites may sometimes represent pseudoprogression (LE:4), and this possibility should be considered in the context of the overall clinical picture in decisions to continue ICIs or switch therapy.

- For patients with gynecologic cancer receiving ICI therapy, a mixed response with enlargement of lymph nodes with stable or decreasing other sites of disease may sometimes represent pseudoprogression (LE:4), and this possibility should be considered in the context of the overall clinical picture in decisions to continue ICIs or switch therapy.
- For patients with gynecologic cancer and apparent radiologic progression on ICI therapy, continued treatment may be considered when the patient's overall clinical status and performance status are maintained and the clinician believes that clinical benefit of the therapy outweighs any treatment-related toxicities (LE:1).
- For patients with gynecologic cancer who initially had clinical benefit with ICI therapy and their disease recurred after ICI discontinuation, rechallenge may be considered (LE:1).
- For patients with gynecologic cancer receiving ICI therapy, baseline symptoms for systems commonly affected by irAEs (eg, bowel, endocrine, skin) should be reviewed and documented to facilitate early recognition and management of toxicity.
- For patients who have experienced severe irAEs due to immunotherapy, the potential benefit of resuming immunotherapy relative to the risk of subsequent severe AEs must be considered.
- Patients with a history of significant irAEs due to immunotherapy who are considered candidates for resuming immunotherapy should be stable on a corticosteroid dose of no more than 10 mg prednisone or equivalent daily.
- For patients with skin-related irAEs, optimizing local cutaneous therapy may be considered as an alternative to systemic steroids (LE:4). For patients who do not respond to topical steroids, systemic steroids with rapid taper should be considered.

PATIENT EDUCATION AND QOL SUPPORT

Providing patients with education on their treatment and resources to support their QOL is vital for all types of cancer therapy²⁶⁵ and immunotherapy is no exception. There are a number of aspects of immunotherapy, however, that are distinct from traditional cancer treatments and necessitate specific considerations for patient education as well as QOL support.

Patient education

Many patients may be unaware of the differences between immunotherapy and traditional treatment modalities such as chemotherapy and radiation. Therefore, describing how ICIs eliminate cancer, the expected types and timing of responses and side effects, and how side effects from ICIs are managed (ie, corticosteroid use, ICI withholding, ICI cessation),²⁶³ is especially important. Patients and caregivers should also be informed that an initial growth followed by a reduction in tumor size with immunotherapy, while rare, can occur. Caregivers are

also a vital component to the care team and should be educated on what to expect when a loved one is being treated with immunotherapy to help ease anxieties and instill confidence in the patient's well-being in between clinical visits.

Take-home educational resources on immunotherapy may also be given, including pamphlets, patient-focused guidelines, and/or plain-language summaries of clinical trial outcomes. Simple and easy to understand, user-friendly media such as mobile applications or videos (found through clinical- or patient-focused societies, agent manufacturers, etc) may be more effective for a wide variety of learning styles. Patients and caregivers should also carry information regarding their immunotherapy treatments with them at all times so that this can be shared with all medical personnel providing care for the patient, even in emergent scenarios. A wallet card, such as the Oncology Nursing Society (ONS) Immunotherapy Wallet Card, or having the information easily accessible on a mobile device is recommended.

Because some irAEs can be life-threatening,²⁶³ patient and caregiver education on early recognition of symptoms is vitally important and should include clear examples of symptoms of irAEs and/or TRAEs for the ICIs or ICI combination therapies given. Patients should also be aware that some irAEs may be delayed and/or permanent, such as immune-related endocrinopathies,²⁶⁶ and may require lifelong medication, such as thyroid hormone replacement for Hashimoto's thyroiditis or stress-dosing of steroids for adrenal insufficiency.²⁶⁷ Call parameters for when to contact providers should be given that include information on who specifically to contact in the patient care team in the event of symptoms. The xpert Panel recommendations for the **Patient education and QOL support** section include a summary of the recommended topics to cover when educating patients and caregivers on their immunotherapy treatment.

QOL support

Patients with gynecologic cancer may experience emotional, mental, and physical distress as a result of their diagnosis and treatment.²⁶⁸ Some of the physical and psychosocial effects of cancer can be addressed clinically through a multidisciplinary healthcare team. However, specialized support and advocacy groups offer patients resources and coping mechanisms beyond disease and symptom management. Additionally, incorporating mindfulness practices into daily routines, such as mindful meditation, has proven to have significant effects on reducing depression and anxiety in patients with cancer.²⁶⁹⁻²⁷⁰ Mindful meditation can be learned and practiced individually, or through local or online programs. Proactive referral to counseling, social workers, behavioral health, palliative care, and financial counseling is imperative to maintain QOL throughout treatment.

Cancer and its treatments affect patient QOL in multiple overlapping ways. Patients with cancer are burdened with uncertainty for their futures regardless of

the prognosis of their disease, leading to anxiety, depression, and anger. Patients with gynecologic cancer report feeling nervous (40%), worry (34%), fear (25%), sadness (21%), and loss of control (17%).²⁷¹ Importantly, 24% of patients reported needing someone to talk to and 57% reported needing help dealing with the psychosocial impacts of cancer. Overall, patients with gynecologic cancer who seek social support have better concurrent well-being.²⁶⁸ However, patients may be unaware of the availability of support groups and resources or hesitant to disclose challenges related to mental health. Frequent and active inquiring and screening by physicians²⁷² regarding their patients' mental well-being is important and an unmet need—as many as 73% of patients with gynecologic cancer have reported that they wanted the physician to ask if help was needed.

Inadequate control of disease- and treatment-related pain can be highly detrimental to QOL. Pain management may involve a multi-faceted palliative approach including judicious use of opioids, non-opioid pharmaceutical agents (eg, non-steroidal anti-inflammatory drugs [NSAIDs], antiepileptics/anticonvulsants, selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants, cannabinoids/medical marijuana, epidural anesthesia, etc), and non-pharmaceutical options (eg, acupuncture, hypnosis, cognitive behavioral therapy, neurostimulation, massage, etc).²⁷³ Early referral to palliative care is important to intervene before pain becomes intolerable.

Financial toxicity is also a major factor that negatively impacts QOL. Immunotherapy drugs are some of the most expensive on the market, and these agents are associated with additional costs beyond the price of the medications themselves, including hospital stays, travel to appointments for infusions, missing work, and others. Financial toxicity was reported in nearly half of patients with gynecologic cancer in one study that included 308 participants, with 14.9% reporting severe financial toxicity and 32.1% reporting moderate financial toxicity.²⁷⁴ Financial strain caused by cancer-related costs is associated with increased distress, anxiety, and a three times greater risk for depression.²⁷⁵ In addition, patients with financial strain may not have the ability to fill prescriptions, travel to necessary appointments, or buy food,²⁷⁴⁻²⁷⁶ which may affect their prognosis. Actively assessing a patient's ability to pay for cancer-related costs and referral to financial assistance through the hospital or advocacy groups may reduce this burden.

Gynecologic cancer-specific QOL considerations

Many patients receiving ICIs may have undergone prior surgical treatments which, depending on the extent, can be quite morbid for patients with gynecologic cancer. Patients may be coping with direct and indirect effects on sexual function, fertility, urinary and bowel function, physical changes and malformation, psychological and behavioral changes, menopausal symptoms, and other challenges.²⁷⁷ Management of physical and psychosocial

symptoms and referral to specialists, when appropriate, should continue while on ICIs. Some common irAEs may amplify the physical symptoms. For example, endocrine-related irAEs may further complicate hormonal dysfunction, and hormonal replacement therapy may be needed. In addition, patients experiencing a decrease in estrogen and androgens due to prior surgery (specifically, oophorectomy) are at an increased risk for urinary tract infections,²⁷⁷ which are also a common AE associated with ICIs.²⁷⁸ Finally, although most patients with advanced gynecologic cancer will have undergone previous surgeries to remove the affected organs, for patients who are still able to bear children, use of contraception and referral to an oncofertility specialist is encouraged.

Assessment of QOL and outcomes from landmark trials

QOL, health-related QOL (HRQOL), and/or patient-reported outcomes (PROs) are often formally assessed in clinical trials as secondary and exploratory endpoints. ICIs have generally demonstrated favorable tolerability in terms of HRQOL²⁷⁹ and prolongation of the time to symptomatic deterioration compared with chemotherapy.^{280,281} However, many of the formal assessment tools used in clinical trials were developed for cytotoxic or targeted therapy, and thus may not capture common irAEs.^{279,282} Although the formal assessment tools and questionnaires used in clinical trials are not practical for general clinical use, clinicians should frequently assess patients for treatment-related symptoms, in addition to physical and psychological functioning and well-being.

In gynecologic cancer, dostarlimab monotherapy in patients with MSI-H endometrial cancer in the GARNET trial²⁸³ was associated with improvements in pain, insomnia, and social and emotional functioning compared with baseline (assessed by the European Organization for Research and Treatment of Cancer (EORTC): Quality of Life Questionnaire-Core 30 [QLQ-C30] for global health status [GHS]/QOL). Additionally, appetite, nausea, vomiting, constipation, diarrhea, physical and role functioning, QOL, and GHS were maintained over the trial duration. In KEYNOTE-826, patients with cervical cancer treated with pembrolizumab had numerically improved QOL (assessed by QLQ-C30) compared with the placebo group, although the difference was not statistically significant.²⁸⁴ Pembrolizumab plus lenvatinib was associated with no significant difference in HRQOL between the pembrolizumab plus lenvatinib and physician's choice chemotherapy groups in KEYNOTE-775.²⁸⁵

Disparities in gynecologic cancer care

Disparities in access to care account for some of the global inequality in disease-specific survival for patients with gynecologic cancer. Global inequities in access to screening and preventative measures such as HPV vaccines result in sustained high mortality rates for several gynecologic cancers in countries with low healthcare resources, in contrast to the decreased incidence and mortality seen in higher-resource countries. In addition, due to the high

cost, the WHO does not deem immunotherapy agents as essential medicines,²⁸⁶ and therefore access to ICIs for patients with gynecologic cancer in low-resource countries is further limited.

Racial, ethnic, and geographic disparities for patients with gynecologic cancer also persist in high-resource countries including the US. Socioeconomic status as well as geographic location contribute to inequitable access to care among all patients with gynecologic cancer.²⁸⁷ These effect modifiers, however, cannot be interpreted without an awareness of systemic racism in the healthcare system and persistent marginalization of women of color, particularly Black women, in the US. Black women have significantly lower 5-year survival rates for ovarian, endometrial, and cervical cancer compared with white women.²⁸⁷ Many studies have demonstrated that Black patients with gynecologic cancer are less likely to receive care in line with evidence-based guidelines.^{288–290} Patients who are Black, on Medicaid, or have lower income are less likely to receive immunotherapy,²⁹¹ although data are lacking for gynecologic cancers specifically. Further amplifying these disparities, potential genetic, environmental, or physiological factors that may underpin some of the variance in disease outcomes or response to treatment are poorly understood because of inadequate representation of Black women in clinical trials.^{292,293}

Transgender patients are another population that experiences inequities in cancer care.²⁹⁴ Data are lacking on the overall incidence and screening for gynecologic cancer in transgender men, which will depend on surgical and hormonal status.²⁹⁵ However, transgender men have reported avoiding routine yearly gynecologic care (31.1%) due to fear of culturally incompetent care,²⁹⁶ which may lead to gynecologic cancer diagnoses at a later stage. Education on culturally sensitive and guideline-directed medical care of transgender patients is lacking outside of specialized treatment centers—surveys have found that 80% of gynecologists did not receive training on care for transgender patients in residency,²⁹⁷ and only 29% felt comfortable caring for transmasculine patients.²⁹⁸ Clinicians should proactively seek out training and resources on providing culturally and clinically competent care of patients with non-traditional genders, such as those offered by Health Professionals Advancing LGBTQ Equality (previously known as the Gay and Lesbian Medical Association [GLMA]) or the University of California San Francisco Center of Excellence for Transgender Health.

Continued efforts to extend equal access to cancer care for historically marginalized populations are of utmost importance. In addition, clinical research and clinical trials should prioritize enrolling diverse patient populations.

Expert Panel recommendations

- For all patients with gynecologic cancer, clinical trial enrolment should be offered, as feasible. Clinical

trials should be offered to all patients, including under-represented patient populations.

- For all patients with gynecologic cancer, a thorough review of symptoms should be performed and documented at initiation of treatment to help identify early irAEs.

Patient education

- For patients with gynecologic cancer receiving immunotherapy, prior to initiation and throughout treatment patient/family/caregiver education should highlight:
 - The unique mechanism of action of immunotherapy.
 - The unique side effects of immunotherapy, focusing on the early recognition of irAEs and the potential for these irAEs to become permanent or even appear after treatment has been completed.
 - That some of the more common toxicities have vague symptoms and therefore any change from baseline health should be reported.
 - That extreme fatigue, respiratory symptoms, rash, and increases in bowel movements can be early signs of irAEs and should prompt speedy notification of the treatment team.
 - That irAEs have unique management strategies that can include treatment with steroids and interruption of immunotherapy doses.
 - That combination regimens have the potential to cause additional serious AEs beyond those associated with ICIs (ie, hypertension with lenvatinib).
 - That measurable response to treatment can be delayed with immunotherapy compared with traditional cytotoxic treatments, and the evaluation criteria and timing for evaluation may be different.
 - The importance of alerting all treating providers, emergency department personnel, and first responders that the patient is on an immunotherapy with a diverse and unique range of side effects. This can be facilitated by encouraging the patient to carry information specific to their treatment and care team, such as the immunotherapy ONS wallet card, or having the information easily accessible on their phone.

QOL support

- For all patients with gynecologic cancer, holistic approaches to support QOL should be considered. This can include pharmacological management, mindfulness training programs, support groups, individualized therapy, and referral to specialists. A diverse offering increases the likelihood of meeting each patient's unique needs.
- All patients with gynecologic cancer and, when possible, care providers should be managed by a multi-disciplinary healthcare team to facilitate optimal QOL. This may include physicians, nurse practitioners/physician assistants, patient advocates, nurse navigators, oncology social workers, physical therapists,

palliative care providers, financial counselors, and complementary and integrative medicine providers such as acupuncturists or massage therapists.

CONCLUSION

ICIs, now approved as monotherapy or in combination with other agents for patients with cervical cancer, endometrial cancer, and in tissue-agnostic indications, are transforming the treatment landscape for these tumors and resulting in more frequent and durable responses compared with the previous standards of care. Despite these leaps forward, immunotherapy options are still lacking for many patients with other types of gynecologic cancer. Emblematic of this challenge is ovarian cancer, which has the highest mortality rate among gynecologic cancers.¹²⁹ Additional immunotherapy strategies beyond ICIs are needed, in addition to validated biomarkers for efficient patient selection. Finally, efforts to raise awareness of and alleviate the substantial disparities in access to treatment for patients with gynecologic cancer—including geographic, racial, gender identity, and others—are essential to provide adequate care for all patients.^{287 292} Immunotherapy is a dynamic and rapidly changing field that has the potential to improve outcomes for even more patients with gynecologic cancer as more data and approvals emerge. This CPG will be updated periodically as the field continues to evolve and updates will be available in SITC's CPG Mobile App.

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Correction notice This article has been corrected since it was first published online. The author Haider Mahdi's name was incorrectly spelt as Hader Mahdi.

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Acknowledgements The authors thank the SITC staff for their contributions including Emily Gronseth, PhD and Sam Million-Weaver, PhD for medical writing and Angela Kilbert and Nichole Larson for project management and assistance. The authors also thank SITC for supporting the manuscript development.

Contributors All authors served on the SITC Gynecologic Cancer Immunotherapy Guideline Expert Panel, drafted content, and provided critical review during the manuscript development. MLD and KO provided leadership as Chairs of the Expert Panel and provided guidance on the manuscript structure and content and thus are first and last authors; all other authors are listed alphabetically by last name. SAD was a patient representative. All authors have read and approved the final version of this manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SFA – Contracted Research: Astra Zeneca. JB – Contracted Research: (institutional financial interests for conducted research) Eli Lilly, Novartis, Roche, Samsung Bioepis co. Ltd, Sun Pharma, Paxman Coolers. MOB – Consulting Fees: Bristol-Myers Squibb, EMD Serono, GSK, Immunocore, Immunovaccine, Merck & Co., Novartis, Sanofi-Genzyme, Turnstone Biologics, Sun Pharma; Contracted Research: Merck, Takara Bio. TJC – Consulting Fees: Agenus, Xencor; Ownership Interest less than 5%: Agenus, Xencor. MLD – Fees for non-CE services: PER; Contracted Research: Pfizer, EMD Serono, Bavarian Nordisk, Precigen, Epithany, Veanna; Other: Editor-in-Chief, *JAMA Oncology*; Other Details: Compensation by JAMA. LD – Consulting: Pfizer. LAE – Consulting Fees: Genentech, F Hoffman La Roche, Chugai, GPCR, Gilead, Immune Onc, Immunet, Shionogi, Mersana; Consulting (no fees): Immunet; Contracted Research: Abbvie, AstraZeneca, Bolt Therapeutics, Bristol Myers Squibb, Compugen, Corvus, CytomX, EMD Serono, Genentech, F Hoffman La Roche, Immune Onc, Maxcyte, Merck, Next Cure, Silverback, Takeda, Tempst; Other: HeritX Incorporated, NSABP Foundation, Translational Breast Cancer Research Consortium, Breast Cancer Research Foundation, National Cancer Institute, Department of Defense, Johns Hopkins University, University of California San Francisco, Cornell University, Dana Farber Cancer Institute, Stand Up to Cancer (these are grants from non-industry entities). CFF – Consulting Fees: Bristol-Myers Squibb, Arch Oncology, Seagen, Aptitude Health, OncoLive, Aadi Biosciences/GOG Partners; Contracted Research: Genentech/Roche, Astra Zeneca, Bristol Meyers Squibb, Merck, Daiichi; Other: Merck, Genentech; Other Details: Scientific Advisory Board member (compensation waived). MEG – Consulting Fees: SeaGen (Tucatinib). MAG – Researcher: Fate Therapeutics, HCW Biologics; Consultant Advisor Speaker: Merck; NPI: 1265466809. AAJ – Consulting Fees: Nuprobe, Avenge Bio, BMS, Agenus, Instil Bio, GLG, Guidepoint, MacroGenics, Immune-Onc, Alkermes, EMD-Serono, Neo TILs, Genentech-Roche; Contracted Research: Iovance, AstraZeneca, BMS, Merck, Eli Lilly, Xencor, Immatics, Pfizer; Ownership Interest less than 5%: Avenge Bio. JBL – Contracted Research: Merck, Sanofi, AstraZeneca, Laekna, Sumitomo Dainippon Pharma Oncology, Harpoon Therapeutics, Precigen, Forty Seven. HM – Contracted Research: Puma Biotechnology. KO – Salary: The University of Chicago; IP Rights: PCT/US2014025673 “compositions and methods for use of recombinant T cell receptors for direct recognition of tumor antigen, PCT/US2014025456” enhancement of vaccines; Consulting Fees: GOG Foundation/Celsion, GSK, Daiichi-Sanyo; Contracted Research: Astra Zeneca research funding (grant), Tessaro Pharma research funding (grant). EZ – NPI: 1598921181. SAD, KCK, AM, VSJ – Nothing to disclose. SITC Staff – EG, AK, NL, SMW – Nothing to disclose.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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