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