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REVIEW

A Narrative Review of the Clinical, Humanistic, and Economic Value of Pembrolizumab-Based Immunotherapy for the Treatment of Breast and Gynecologic Cancers

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ABSTRACT

Breast and gynecologic cancers are common across the world and are associated with substantial societal and economic burden. Pembrolizumab was among the first immune checkpoint inhibitors targeting programmed cell death protein 1 to be approved for the treatment of patients with triple-negative breast cancer, cervical cancer, and endometrial cancer. Recent clinical trials have established pembrolizumab regimens as a standard of care treatment for these tumor types. Clinical data are further supported by patient-reported outcome, cost-effectiveness, and real-world evidence. Pembrolizumab monotherapy and combination regimens do not negatively influence health-related quality of life and are cost-effective relative to comparators. Ongoing phase 3 studies with pembrolizumab will expand the current understanding of its use in breast and gynecologic cancers. Several of these studies are in patients with early-stage disease with the hope of curing patients. The main objective of this review is to summarize the clinical, humanistic, and economic value of pembrolizumab in these settings and to describe the future challenges for patients, caregivers, clinicians, and payers.

Keywords: Breast cancer; Cervical cancer; Cost-effectiveness analysis (health services research); Ovarian cancer; Patient-reported outcomes (quality of life); Uterine cancer

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Key Summary Points

We review the clinical, humanistic, and economic value of pembrolizumab monotherapy and combination therapies in the treatment of patients with breast and gynecologic cancers.

Recent clinical trials have established pembrolizumab regimens as a standard of care treatment for triple-negative breast cancer, cervical cancer, and endometrial cancer.

Patient-reported outcomes, cost-effectiveness analysis, and real-world evidence support the clinical data.

Several ongoing phase 3 studies are evaluating pembrolizumab regimens in patients with triple-negative breast cancer (1 trial), HR+/HER2– breast cancer (2 trials), endometrial cancer (3 trials), cervical cancer (1 trial), and ovarian cancer (3 trials), with the goal of improving the lives of patients and potentially providing a cure for patients with early-stage disease.

Results from these ongoing studies of pembrolizumab will expand the current understanding of its use in breast and gynecologic cancers.

INTRODUCTION

Breast and gynecologic cancers are among the tumor types with the highest global incidence rates in women and are among the most common causes of cancer-related death [1]. The 2020 GLOBOCAN report estimated that breast cancer accounted for 24.5% of all new cancer cases (~2.3 million patients) and 15.5% of cancer-related deaths (~685,000 patients) among women worldwide. Breast cancer can also occur in men, with incidence rates ranging from 1.3 to 1.9 per 100,000 in the USA and Europe [2, 3]. In an analysis of the Surveillance, Epidemiology, and End Results database, cumulative mortality rates due to male breast cancer were 2.23% at 1 year, 7.56% at 3 years, and 13.10% at 5 years [4]. Gynecologic cancers, including endometrial, cervical, and ovarian cancers, accounted for 14.5% of all new cancer cases (~1.3 million patients) and 14.6% of cancer-related deaths (~646,000 patients). In 159 of the 185 countries included in the 2020 GLOBOCAN estimates, breast cancer was the most commonly diagnosed cancer among women; in 23 of the remaining 26 countries, cervical cancer was the most commonly diagnosed cancer [1].

Breast and gynecologic cancers are associated with substantial economic burden [5–14]. Direct medical costs increase with more advanced disease and subsequent lines of therapy [7, 11, 12, 14]. In a large systematic literature review, for example, estimates of annual direct medical costs to treat triple-negative breast cancer (TNBC) in the USA, Canada, and France ranged from $20,000 to $100,000 in 2021 US dollars (USD) per patient for stage I to III disease and from $100,000 to $300,000 USD (or higher) per patient for stage IV disease [12]. More rapid disease progression (i.e., ≤12 months vs >12 months from initiating first-line chemotherapy) has also been shown to increase direct medical costs in patients with ovarian cancer [5]. Hospitalizations typically account for the majority of the direct medical costs associated with breast and gynecologic cancers, whereas systemic anticancer treatment typically contributes between 5% and 30% [8, 9, 11, 12]. Indirect costs are also common in these patients (e.g., productivity loss because of absenteeism and disability, early retirement) and may increase with advancing disease or recurrence [6, 12–14].

In addition to the financial impact of breast and gynecologic cancers, social well-being and health-related quality of life (HRQoL) are also likely to be negatively affected. Women with cancer, including breast and gynecologic cancers, have been shown to experience greater impairment than men in their relationships with others [15]. Patients may experience more limitations (e.g., physical, social, activity), greater cognitive impairment, and worse general health than control patients without cancer [6, 8, 16–18], and further deterioration in HRQoL may accompany disease progression or recurrence [19, 20]. Some of the detriment in HRQoL

associated with these cancers can be attributed to the toxicities caused by systemic anticancer treatment, particularly chemotherapy [12, 20, 21]. An unmet need exists for therapeutic agents that improve outcomes, including HRQoL, and have manageable toxicity in patients with breast and gynecologic cancers [22–29].

Immunotherapy has emerged as a promising therapeutic approach for the treatment of multiple tumor types [30]. The monoclonal antibody pembrolizumab was among the first immune checkpoint inhibitors targeting programmed cell death protein 1 (PD-1) [30]. Pembrolizumab is approved for the treatment of certain patients with TNBC, endometrial cancer, and cervical cancer, with multiple regulatory approvals across these settings (Table 1) [31, 32]. Additionally, pembrolizumab continues to be studied in a broad clinical development program in breast and gynecologic cancers. The main objective of this review is to summarize the clinical, humanistic, and economic value of pembrolizumab monotherapy and combination therapies in these settings and to discuss the future challenges for patients, their families, clinicians, and payers. The poly(ADP-ribose) polymerase (PARP) inhibitor olaparib [33, 34], which has an important role in the treatment of breast and ovarian cancers, is briefly discussed as the agent is part of the same clinical development program as pembrolizumab. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CLINICAL, HUMANISTIC, AND ECONOMIC VALUE OF PEMBROLIZUMAB

Clinical Trial Evidence

The specific indications of pembrolizumab for the treatment of breast and gynecologic cancers are detailed in Table 1. Chemotherapy has been a standard of care treatment in these settings, but unprecedented progress has been made with pembrolizumab in the last 5 years, including eight approvals in the USA and five approvals in Europe. Efficacy results from clinical trials of pembrolizumab in patients with breast and gynecologic cancers are briefly summarized in the following sections. More detailed efficacy and safety findings from the clinical trials that led to the approval of pembrolizumab in these settings are presented in Table 2.

Breast Cancer

TNBC TNBC is diagnosed in 10–15% of patients with breast cancer [35, 36]. The 4-year survival rate for TNBC is 77%; rates are higher for stage I (95%) and stage II (84%) disease compared with stage III (53%) and stage IV (11%) disease [37]. Patients with TNBC are also more likely to experience disease recurrence, which tends to occur earlier than with other breast cancer subtypes [38–41].

Pembrolizumab is the first immunotherapy approved in the early-stage TNBC setting. Before approval of pembrolizumab in this setting, standard therapy for early-stage TNBC included a variety of chemotherapy regimens [42, 43]. Approval for pembrolizumab in early-stage TNBC was based on results from the KEYNOTE-522 trial, in which neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab demonstrated statistically significant and clinically meaningful improvements in pathologic complete response [pCR; 65% vs 51%; estimated treatment difference, 13.6 percentage points (95% CI 5.4–21.8); $P<0.001$] and event-free survival (EFS; events occurred in 16% of patients vs 24%; estimated EFS at 36 months, 85% vs 77%) versus neoadjuvant placebo plus chemotherapy followed by adjuvant placebo in patients with previously untreated, high-risk, early-stage TNBC. Benefits were observed regardless of tumor programmed cell death ligand 1 (PD-L1) status [44, 45]. Recently, positive overall survival results for KEYNOTE-522 were reported [46].

In the late-stage setting, approval was based on results from the KEYNOTE-355 trial, in which the addition of pembrolizumab to chemotherapy demonstrated statistically significant and clinically meaningful improvements

Table 1 Indications of pembrolizumab and olaparib for the treatment of breast and gynecologic cancers in the USA and Europe

	US FDA [31, 33]	EMA [32, 34]
Pembrolizumab approvals		
Breast cancer	For the treatment of patients with high-risk, early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥ 10) as determined by an FDA-approved test	In combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced or early-stage TNBC at high risk of recurrence In combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic TNBC in adults whose tumors express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease
Endometrial cancer	As a single agent, for the treatment of patients with advanced endometrial carcinoma that is MSI-H or dMMR, as determined by an FDA-approved test, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation In combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is pMMR as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation In combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent, for the treatment of patients with primary advanced or recurrent endometrial carcinoma	Monotherapy for the treatment of MSI-H or dMMR tumors in adults with advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation In combination with lenvatinib, for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation
Cervical cancer	As a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test In combination with chemotherapy, with or without bevacizumab, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test In combination with chemoradiotherapy, for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer	Not approved as a single agent for cervical cancer In combination with chemotherapy with or without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumors express PD-L1 with a CPS ≥ 1

Table 1 continued

	US FDA [31, 33]	EMA [32, 34]
Olaparib approvals		
Breast cancer	Adjuvant treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative, high-risk early breast cancer who have been treated with neoadjuvant or adjuvant chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza Treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative metastatic breast cancer who have been treated with chemotherapy in the neoadjuvant, adjuvant, or metastatic setting. Patients with HR-positive breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza	Monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline *BRCA1/2* mutations who have HER2-negative, high-risk early breast cancer previously treated with neoadjuvant or adjuvant chemotherapy Monotherapy for the treatment of adult patients with germline *BRCA1/2* mutations who have HER2-negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patients with HR-positive breast cancer should also have progressed on or after prior endocrine therapy or be considered unsuitable for endocrine therapy
Ovarian cancer	Maintenance treatment of adult patients with deleterious or suspected deleterious germline or somatic *BRCA*-mutated advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza Maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy In combination with bevacizumab, for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and whose cancer is associated with HRD-positive status defined by either a deleterious or suspected deleterious *BRCA* mutation and/or genomic instability. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza	Maintenance treatment of adult patients with advanced (FIGO stages III and IV), *BRCA1/2*-mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy Maintenance treatment of adult patients with platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are inresponse (complete or partial) to platinum-based chemotherapy In combination with bevacizumab, for the maintenance treatment of adult patients with advanced (FIGO stages III and IV), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with HRD-positive status defined by either a *BRCA1/2* mutation and/or genomic instability

Table 1 continued

CPS combined positive score, *dMMR* mismatch repair deficient, *EMA* European Medicines Agency, *FIGO* International Federation of Gynecology and Obstetrics, *HER2* human epidermal growth factor receptor 2, *HR* hormone receptor, *HRD* homologous recombination deficiency, *MSI-H* microsatellite instability-high, *PD-L1* programmed cell death ligand 1, *pMMR* mismatch repair proficient, *TNBC* triple-negative breast cancer, *US FDA* United States Food and Drug Administration

in progression-free survival (PFS) and overall survival (OS) versus chemotherapy alone in patients with previously untreated, locally recurrent unresectable or metastatic TNBC whose tumors expressed PD-L1 (combined positive score [CPS] ≥ 10; PFS hazard ratio [HR] 0.65 [95% CI 0.49–0.86], one-sided $P = 0.0012$; OS HR 0.73 [95% CI 0.55–0.95]) [47, 48].

Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer The most common breast cancer subtype, hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) breast cancer, accounts for about 70% of all breast cancer cases [37, 49–52]. An estimated 17% of patients with early-stage HR+/HER2– breast cancer will experience disease recurrence within 5 years of initiating endocrine therapy [53].

Pembrolizumab is not currently approved for the treatment of patients with HR+/HER2– breast cancer. Several studies have evaluated pembrolizumab, alone or in combination with other agents, in the early-stage [54] and late-stage [55–63] settings. Although some patients derived benefit, the sample sizes in these studies were small and no definitive conclusions could be made. Two phase 3 trials are ongoing in patients with HR+/HER2– breast cancer (see Ongoing Phase 3 Trials).

Gynecologic Cancers

Five-year survival rates for patients with newly diagnosed gynecologic cancers are estimated to be 49% for ovarian cancer, 66% for cervical cancer, and 81% for endometrial cancer across all disease stages [64]. However, in patients with metastatic disease, 5-year survival rates are only 18% for endometrial and cervical cancer and 30% for ovarian cancer. Approximately 50% of patients with ovarian cancer, 15% with cervical cancer, and 9% with endometrial cancer have metastatic disease at the time of diagnosis [64]. Disease recurrence is common despite curative intent surgery with or without adjuvant therapy [65–68].

Endometrial Cancer Pembrolizumab monotherapy and the combination of pembrolizumab

Table 2 Clinical trial evidence resulting in approval of pembrolizumab in patients with breast and gynecologic cancers

Indication	Trial name	Regulatory approval	Trial setting	Treatments	Total *N*	Efficacy	AEs
TNBC	KEYNOTE-522 [44–46]	Yes (Jul 2021 in USA; May 2022 in EU)	Previously untreated, high-risk, early-stage (stage II–III)	Pembrolizumab + chemotherapy (neo-adjuvant) followed by pembrolizumab (adjuvant) vs placebo + chemotherapy (neoadjuvant) followed by placebo (adjuvant)	1174	pCR (pembrolizumab vs placebo): 64.8% vs 51.2%; $P < 0.001$ in ITT population EFS: HR (95% CI) pembrolizumab vs placebo, 0.63 (0.48–0.82; $P < 0.001$) in ITT population OS: weighted hazard ratio, 0.66; $P = 0.002$ Results generally consistent across subgroups, including PD-L1 status	Treatment-related AEs (pembrolizumab vs placebo): 98.9% vs 99.7% Grade ≥ 3 treatment-related AEs: 77.1% vs 73.3% Immune-related AEs: 33.5% vs 11.3%
TNBC	KEYNOTE-355 [47, 48]	Yes (Nov 2020 in USA; Oct 2021 in EU)	Previously untreated, late-stage (locally recurrent inoperable or metastatic)	Pembrolizumab + chemotherapy vs placebo + chemotherapy	847	PFS: HR (95% CI) pembrolizumab vs placebo PD-L1 CPS ≥ 10: 0.65 (0.49–0.86; $P = 0.0012$) PD-L1 CPS ≥ 1: 0.74 (0.61–0.89; NS) ITT: 0.82 (0.69–0.97; not tested) OS: HR (95% CI) pembrolizumab vs placebo PD-L1 CPS ≥ 10: 0.73 (0.55–0.95; $P = 0.0185$) PD-L1 CPS ≥ 1: 0.86 (0.72–1.04; NS) ITT: 0.89 (0.76–1.05; not tested) Results generally consistent across subgroups	Treatment-related AEs (pembrolizumab vs placebo): 96.3% vs 95.0% Grade ≥ 3 treatment-related AEs: 68.1% vs 66.9% Immune-related AEs: 26.5% vs 6.4%
Endometrial cancer	KEYNOTE-158 [71]	Yes (Mar 2022 in USA; Apr 2022 in EU)	Previously treated, advanced MSI-H/dMMR	Pembrolizumab	90	ORR (95% CI): 48% (37–60%) < 2 lines of prior therapy: 53% (36–69%) ≥ 2 lines of prior therapy: 44% (28–60%)	Treatment-related AEs: 76% Grade ≥ 3 treatment-related AEs: 12% Immune-related AEs and infusion reactions: 28%
Endometrial cancer	KEYNOTE-775 [72]	Yes (Jul 2021 in USA; Nov 2021 in EU)	Previously treated, advanced, recurrent, or metastatic	Pembrolizumab + lenvatinib vs chemotherapy	827	PFS: HR (95% CI) pembrolizumab + lenvatinib vs chemotherapy pMMR: 0.60 (0.50–0.72; $P < 0.001$) All comers: 0.56 (0.47–0.66; $P < 0.001$) OS: HR (95% CI) pembrolizumab + lenvatinib vs chemotherapy pMMR: 0.68 (0.56–0.84; $P < 0.001$) All comers: 0.62 (0.51–0.75; $P < 0.001$) Results generally consistent across subgroups Continued efficacy benefit with extended follow-up [73]	Treatment-related AEs (pembrolizumab + lenvatinib vs chemotherapy): 97.3% vs 93.8% Grade ≥ 3 treatment-related AEs: 77.8% vs 59.0% Immune-related AEs: not reported No new safety signals with extended follow-up [73]

Table 2 continued

Indication	Trial name	Regulatory approval	Trial setting	Treatments	Total *N*	Efficacy	AEs
Endometrial cancer	NRG-GY018 [74]	Yes (Jun 2024 in USA)	Advanced or recurrent (most previously untreated)	Pembrolizumab + chemotherapy followed by maintenance pembolizumab vs placebo + chemotherapy followed by maintenance placebo	816	PFS: HR (95% CI) pembrolizumab + chemotherapy vs placebo + chemotherapy dMMR: 0.30 (0.19–0.48; $P < 0.001$) pMMR: 0.54 (0.41–0.71; $P < 0.001$)	AEs (pembrolizumab + chemotherapy vs placebo + chemotherapy) dMMR: 98.2% vs 99.1% pMMR: 93.5% vs 93.4% Grade ≥ 3 AEs dMMR: 63.3% vs 47.2% pMMR: 55.1% vs 45.3% Immune-mediated AEs dMMR: 38.5% vs 26.4% pMMR: 33.3% vs 19.7%
Cervical cancer	KEYNOTE-158 [77]	Yes (Jun 2018 in USA)	Recurrent or metastatic (most previously treated)	Pembrolizumab	98	ORR (95% CI): 12.2% (6.5–20.4%) All PD-L1 positive: 14.6% (7.8–24.2%) Previously treated, PD-L1 positive: 14.3% (7.4–24.1%) PD-L1 negative: 0% (0–21.8%)	Treatment-related AEs: 65.3% Grade ≥ 3 treatment-related AEs: 12.2% Immune-mediated AEs: 25.5%
Cervical cancer	KEYNOTE-A18 [79, 80]	Yes (Jan 2024 in USA)	Newly diagnosed, high-risk, locally advanced cervical cancer	Pembrolizumab + chemoradiotherapy vs placebo + chemoradiotherapy	1060 patients	PFS: HR (95% CI) 0.68 (0.56–0.84) OS: HR (95% CI) 0.67 (0·50–0.90; one-sided $P = 0·0040$)	Grade ≥ 3 treatment-related AEs: 69% vs 61%
Cervical cancer	KEYNOTE-826 [78]	Yes (Oct 2021 in USA; Apr 2022 in EU)	Previously untreated, persistent, recurrent, or metastatic	Pembrolizumab + chemotherapy vs placebo + chemotherapy	617	PFS: HR (95% CI) pembrolizumab vs placebo PD-L1 CPS ≥ 1: 0.62 (0.50–0.77; $P < 0.001$) ITT: 0.65 (0.53–0.79; $P < 0.001$) PD-L1 CPS ≥ 10: 0.58 (0.44–0.77; $P < 0.001$) OS: HR (95% CI) pembrolizumab vs placebo PD-L1 CPS ≥ 1: 0.64 (0.50–0.81; $P < 0.001$) ITT: 0.67 (0.54–0.84; $P < 0.001$) PD-L1 CPS ≥ 10: 0.61 (0.44–0.84; $P = 0.001$) Results generally consistent across subgroups	Treatment-related AEs (pembrolizumab vs placebo): 97.1% vs 97.1% Grade ≥ 3 treatment-related AEs: 68.4% vs 64.1% Immune-mediated AEs: 33.9% vs 15.2%

AE adverse event, *CPS* combined positive score, *dMMR* mismatch repair deficient, *EFS* event-free survival, *EU* European Union, *HR* hazard ratio, *ITT* intention to treat, *MSI-H* microsatellite instability-high, *NS* not significant, *ORR* objective response rate, *OS* overall survival, *pCR* pathologic complete response, *PD-L1* programmed cell death ligand 1, *PFS* progression-free survival, *pMMR* mismatch repair proficient, *TNBC* triple-negative breast cancer

plus lenvatinib are standard of care treatments for patients with endometrial cancer [69, 70]. Full approval of pembrolizumab monotherapy was based on results from the KEYNOTE-158 trial, in which pembrolizumab provided robust and durable antitumor activity with an objective response rate (ORR) of 48% (95% CI 37–60%) in patients with advanced microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) endometrial cancer following prior systemic therapy [71]. Approval of pembrolizumab plus lenvatinib was based on results from the KEYNOTE-775 trial, in which the combination provided statistically significant and clinically meaningful improvements in PFS [HR, mismatch repair proficient (pMMR) population: 0.60 (95% CI 0.50–0.72); $P<0.001$; overall population: 0.56 (95% CI 0.47–0.66); $P<0.001$], OS [HR, pMMR population: 0.68 (95% CI 0.56–0.84); $P<0.001$; overall population: 0.62 (95% CI 0.51–0.75); $P<0.001$], and ORR (pMMR population: 30.3% vs 15.1%; overall population: 31.9% vs 14.7%) versus chemotherapy alone in patients with advanced, recurrent, or metastatic endometrial cancer following prior systemic therapy [72]. Continued clinical benefit of combination therapy was observed with extended follow-up [73].

More recently, results of the NRG-GY018 trial were published [74]. In this collaborative study with the National Cancer Institute and NRG Oncology, the combination of pembrolizumab plus chemotherapy demonstrated statistically significant and clinically meaningful improvement in the primary endpoint of PFS versus chemotherapy alone in patients with previously untreated, advanced or recurrent endometrial cancer. The HR for PFS was 0.30 (95% CI 0.19–0.48; $P<0.001$) in the dMMR population and 0.54 (95% CI 0.41–0.71; $P<0.001$) in the pMMR population. Based on results from the NRG-GY018 trial, the regimen was recently approved in this setting and the National Comprehensive Cancer Network guidelines list it as a preferred option for endometrial cancer that is stage III or IVA with measurable disease or stage IVB with or without measurable disease [69].

At present, the only other immunotherapy-based combination that has received approval by the US Food and Drug Administration (FDA) is the combination of dostarlimab plus carboplatin and paclitaxel followed by single-agent dostarlimab in patients with primary advanced or recurrent endometrial cancer that is dMMR, as determined by an FDA-approved test, or MSI-H [75]. This approval was based on results from the randomized, double-blind, phase 3 RUBY study, in which the addition of dostarlimab to carboplatin and paclitaxel significantly improved PFS in patients with primary advanced stage III or IV or first recurrent dMMR endometrial cancer (HR 0.28 [95% CI 0.16–0.50]; $P<0.001$) [75].

Cervical Cancer Pembrolizumab monotherapy and the combination of pembrolizumab plus chemotherapy are standard of care treatments for patients with cervical cancer [76]. Approval of pembrolizumab monotherapy was based on results from the KEYNOTE-158 trial, in which pembrolizumab provided durable antitumor activity in patients with recurrent or metastatic, PD-L1-positive (CPS ≥ 1) cervical cancer following prior systemic therapy [77]. Approval of pembrolizumab plus chemotherapy, with or without bevacizumab, was based on results from the KEYNOTE-826 trial, in which this regimen provided statistically significant and clinically meaningful improvements in PFS and OS versus chemotherapy, with or without bevacizumab, in patients with previously untreated, persistent, recurrent, or metastatic cervical cancer [78]. Benefits were seen in the PD-L1 CPS ≥ 1, all-comer, and PD-L1 CPS ≥ 10 populations [78]. More recently, in the locally advanced setting, pembrolizumab with chemoradiotherapy (CRT) has been approved for patients with FIGO 2014 Stage III-IVA cervical cancer. This is based on the results of the KEYNOTE-A18 study, which recently reported positive OS results [79, 80].

In addition to pembrolizumab, the anti-PD-1 monoclonal antibody cemiplimab has also demonstrated benefit in patients with cervical cancer. In the EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 study, OS was significantly improved among patients with previously treated recurrent cervical cancer who received cemiplimab compared with those who received chemotherapy (HR 0.69 [95% CI 0.56–0.84]; two-sided $P<0.001$) [81].

Ovarian Cancer Pembrolizumab, alone or as part of combination therapy, is not currently approved for the treatment of patients with ovarian cancer. Results from several trials (KEYNOTE-100, KEYNOTE-028, and KEYNOTE-158) demonstrated modest antitumor activity with pembrolizumab monotherapy in patients with advanced ovarian cancer [82–84], including increased response rates with higher tumor PD-L1 expression [82]. Modest antitumor activity has also been reported in trials evaluating the combination of pembrolizumab with niraparib (KEYNOTE-162/TOPACIO) [85], nemvaleukin alfa (ARTISTRY-1) [86], and lenvatinib (LEAP-005) [87]. Several ongoing trials are assessing pembrolizumab combination therapies in patient populations with high unmet need, including KEYLYNK-001 in primary advanced, *BRCA1/2*-nonmutated disease and KEYNOTE-B96 in platinum-resistant disease (see Ongoing Phase 3 Trials).

Safety

A pooled analysis of data from 31 clinical trials evaluated the safety profile of pembrolizumab monotherapy across multiple tumor types. Among 8937 patients in the pooled safety dataset, 96.6% of patients who received pembrolizumab experienced at least one AE of any cause. The most frequently reported AEs were fatigue (29.7%), nausea (20.4%), and decreased appetite (20.3%). Any-grade immune-mediated AEs and infusion reactions were reported by 23.7% of patients. The most frequently occurring immune-mediated AEs and infusion reactions were hypothyroidism (10.5%), pneumonitis (4.2%), and hyperthyroidism (4.0%) [88].

Patient-Reported Outcome Evidence

Patient-reported outcome (PRO) results associated with pembrolizumab, administered alone or in combination with other agents, are summarized in the following sections and detailed in Table 3.

Breast Cancer

TNBC The KEYNOTE-522 trial assessed PROs in patients with previously untreated, high-risk, early-stage TNBC [89]. PROs based on the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (QLQ-C30) and the EORTC Breast Cancer-Specific Quality of Life Questionnaire (QLQ-BR23) were prespecified secondary objectives, and those based on the EuroQol 5-Dimension questionnaire (EQ-5D) were exploratory objectives. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab did not adversely impact HRQoL compared with neoadjuvant chemotherapy alone. The findings were consistent across all questionnaires assessed in both the neoadjuvant and adjuvant phases [89].

The KEYNOTE-355 trial assessed PROs in patients with previously untreated, locally recurrent unresectable or metastatic TNBC [90]. The same questionnaires as described for the KEYNOTE-522 trial were used as prespecified secondary and exploratory objectives. In the PD-L1 CPS ≥ 10 population, HRQoL findings were similar for patients who received pembrolizumab plus chemotherapy or chemotherapy alone, suggesting that combination therapy did not compromise HRQoL in this population [90]. A separate analysis of data from the KEYNOTE-355 trial used the Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TwiST) method, which incorporates efficacy, toxicity, symptom palliation, and HRQoL in assessing the value of anticancer therapy [91]. Pembrolizumab plus chemotherapy provided statistically significant and clinically meaningful improvements in Q-TwiST versus chemotherapy alone [91].

Gynecologic Cancers

Endometrial Cancer The KEYNOTE-158 [92] and KEYNOTE-775 [93] trials assessed PROs in patients with endometrial cancer. In the KEYNOTE-158 trial in patients with previously treated, advanced MSI-H/dMMR endometrial cancer, PROs based on the QLQ-C30 and EuroQol 5-Dimension 3-Level questionnaire (EQ-

Table 3 Patient-reported outcome evidence with pembrolizumab in patients with breast and gynecologic cancers

Indication	Trial name	Trial setting	Treatments	Instrument	Total *N*	PRO
TNBC	KEYNOTE-522 [89]	Previously untreated, high-risk, early-stage (stage II–III)	Pembrolizumab + chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) vs placebo + chemotherapy (neoadjuvant) followed by placebo (adjuvant)	EORTC QLQ-C30 and EORTC QLQ-BR23 (secondary objectives) EQ-5D (exploratory)	Neoadjuvant PRO full analysis set (1145 for EORTC QLQ-C30, 1141 for EORTC QLQ-BR23, and 1146 for EQ-5D) Adjuvant PRO full analysis set (847 for EORTC QLQ-C30, 844 for EORTC QLQ-BR23, and 850 for EQ-5D)	Neoadjuvant difference (95% CI) in LS mean score change from baseline to week 21[a] (pembrolizumab vs placebo) − 1.04 (− 3.46 to 1.38) for EORTC QLQ-C30 GHS/QoL, − 0.69 (− 3.13 to 1.75) for Emotional Functioning, and − 2.85 (− 5.11 to − 0.60) for Physical Functioning − 0.13 (− 1.92 to 1.65) for EORTC QLQ-BR23 Breast Symptoms − 1.61 (− 3.87 to 0.64) for EQ-5D VAS Adjuvant difference (95% CI) in LS mean score change from baseline to week 24[a] (pembrolizumab vs placebo) − 0.41 (− 2.60 to 1.77) for EORTC QLQ-C30 GHS/QoL, − 0.60 (− 2.99 to 1.79) for Emotional Functioning, and − 1.57 (− 3.36 to 0.21) for Physical Functioning 0.29 (− 2.05 to 2.63) for EORTC QLQ-BR23 Breast Symptoms − 0.59 (− 2.40 to 1.23) for EQ-5D VAS

Table 3 continued

Indication	Trial name	Trial setting	Treatments	Instrument	Total *N*	PRO
TNBC	KEYNOTE-355 [159]	Previously untreated, late-stage (locally recurrent inoperable or metastatic)	Pembrolizumab + chemotherapy vs placebo + chemotherapy	EORTC QLQ-C30 and EORTC QLQ-BR23 (secondary objectives) EQ-5D (exploratory)	317 for PD-L1 CPS ≥ 10 PRO analysis set	Difference (95% CI) in LS mean score change from baseline to week 15[a] (PD-L1 CPS ≥ 10, pembrolizumab vs placebo) − 1.81 (− 6.92 to 3.30) for EORTC QLQ-C30 GHS/QoL, − 1.43 (− 7.03 to 4.16) for Emotional Functioning, and − 1.05 (− 6.59 to 4.50) for Physical Functioning 0.18 (− 5.04 to 5.39) for EQ-5D VAS Similar between-group differences in LS mean change from baseline to week 15[a] in EORTC QLQ-BR23 functional (body image, sexual functioning, sexual enjoyment, and future perspective) and symptom (systemic therapy side effects, breast symptoms, arm symptoms, and upset by hair loss) scales/items

Table 3 continued

Indication	Trial name	Trial setting	Treatments	Instrument	Total *N*	PRO
TNBC	KEYNOTE-355 [91]	Previously untreated, late-stage (locally recurrent inoperable or metastatic)	Pembrolizumab + chemotherapy vs placebo + chemotherapy	Q-TWiST	323	Difference (95% CI) in mean Q-TWiST (PD-L1 CPS ≥ 10, pembrolizumab vs placebo) 3.7 (1.0–6.3) mo at 44 mo and 4.3 (1.0–7.3) mo at 52 mo corresponding to gains of 18% ($P = 0.003$) and 20% ($P = 0.004$), respectively
Endometrial cancer	KEYNOTE-158 [92]	Previously treated, advanced MSI-H/dMMR	Pembrolizumab	EORTC QLQ-C30 and EQ-5D-3L (exploratory)	63 for overall cohort and 35 for CR/PR cohort	Mean (95% CI) improvement from baseline to week 9[b] (overall cohort) 6.08 (0.71–11.46) for EORTC QLQ-C30 GHS/QoL 6.00 (2.25–9.75) for EQ-5D-3L VAS Mean (95% CI) improvement from baseline to week 9[b] (CR/PR cohort) 11.67 (5.33–18.00) for EORTC QLQ-C30 GHS/QoL 9.11 (5.24–12.98) for EQ-5D-3L VAS

Table 3 continued

Indication	Trial name	Trial setting	Treatments	Instrument	Total *N*	PRO
Endometrial cancer	KEYNOTE-775 [93]	Previously treated, advanced, recurrent, or metastatic	Pembrolizumab + lenvatinib + vs chemotherapy	EORTC QLQ-C30 GHS/QoL (secondary) EORTC QLQ-C30 (other scales), EORTC QLQ-EN24, and EQ-5D-5L (exploratory)	752 for PRO full analysis set	Difference (95% CI) in LS mean change from baseline to week 12[a] (pembrolizumab + lenvatinib vs chemotherapy) 1.01 (− 2.28 to 4.31) for EORTC QLQ-C30 GHS/QoL and − 0.09 (− 3.08 to 2.90) for Physical Functioning − 2.29 (− 5.03 to 0.45) for EORTC QLQ-EN24 Urological Symptoms 2.35 (− 0.44 to 5.14) for EQ-5D-5L VAS

Table 3 continued

Indication	Trial name	Trial setting	Treatments	Instrument	Total *N*	PRO
Cervical cancer	KEYNOTE-826 [94]	Previously untreated, persistent, recurrent, or metastatic	Pembrolizumab + chemotherapy vs placebo + chemotherapy	EORTC QLQ-C30 GHS/QoL (secondary) EORTC QLQ-C30 (other scales), EORTC QLQ-CX24, and EQ-5D-5L (exploratory)	566 for PRO full analysis set	Difference (95% CI) in LS mean change from baseline to week 30[a] (pembrolizumab vs placebo) 1.0 (− 2.7 to 4.7) for EORTC QLQ-C30 GHS/QoL and − 2.1 (− 6.0 to 1.8) for Physical Functioning 1.8 (− 1.6 to 5.1) for EQ-5D-5L VAS Similar between-group differences in LS mean change from baseline to week 30[a] in EORTC QLQ-CX24 symptom experience, sexual worry, peripheral neuropathy, menopausal symptoms, and lymphedema Median time to deterioration in EQ-5D-5L VAS not reached with pembrolizumab vs 7.7 mo with placebo (HR 0.75 [95% CI, 0.58–0.97)

5D-3L 5-Dimension 3-Level, *5D-5L* 5-Dimension 5-Level, *CPS* combined positive score, *CR* complete response, *dMMR* mismatch repair deficient, *EORTC* European Organisation for Research and Treatment of Cancer, *EQ* EuroQol, *GHS/QoL* global health status/quality of life, *HR* hazard ratio, *LS* least squares, *mo* months, *MSI-H* microsatellite instability-high, *PD-L1* programmed cell death ligand 1, *PR* partial response, *PRO* patient-reported outcome, *QLQ-BR23* Breast Cancer-Specific Quality of Life Questionnaire, *QLQ-C30* Quality of Life Questionnaire–Core 30, *QLQ-CX24* Quality of Life Questionnaire–Cervical Cancer, *QLQ-EN24* Quality of Life Questionnaire–Endometrial Cancer, *Q-TWiST* Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment, *TNBC* triple-negative breast cancer, *VAS* visual analogue scale

[a]The prespecified primary PRO analysis time point of interest was defined as the latest time at which there was ≥ 60%/80% completion/compliance

[b]Prespecified time point of interest

5D-3L) were prespecified exploratory endpoints [92]. Pembrolizumab monotherapy improved or maintained HRQoL, with the greatest benefit seen in patients who achieved a complete or partial response [92]. In the KEYNOTE-775 trial in patients with previously treated, advanced, recurrent, or metastatic endometrial cancer, the QLQ-C30 global health status/quality of life (GHS/QoL) score was a prespecified secondary objective, and PROs based on the QLQ-C30 (other than GHS/QoL), the EORTC endometrial cancer module (QLQ-EN24), and the EuroQol 5-Dimension 5-Level questionnaire (EQ-5D-5L) were exploratory objectives [93]. Patients treated with either pembrolizumab plus lenvatinib or chemotherapy alone experienced deterioration in HRQoL over time, and declines were generally similar in both treatment groups, although some differences were seen on individual scales. Taken together with the efficacy and safety findings, an overall positive benefit/risk profile was demonstrated in this study [93].

Cervical Cancer The KEYNOTE-826 trial assessed PROs in patients with previously untreated, persistent, recurrent, or metastatic cervical cancer [94]. The GHS/QoL score of the QLQ-C30 was a prespecified secondary objective, and PROs based on the QLQ-C30 (other than GHS/QoL) and on the EORTC cervical cancer module (QLQ-CX24) and EQ-5D-5L were exploratory objectives. The addition of pembrolizumab to chemotherapy, with or without bevacizumab, did not negatively affect HRQoL and median time to deterioration in EQ-5D-5L visual analogue scale was better than in the control arm [94].

Cost-effectiveness Evidence

Cost-effectiveness results associated with pembrolizumab monotherapy and combination therapies are summarized in the following sections and detailed in Table 4. All results are from a US third-party payer perspective.

Breast Cancer

TNBC A multistate transition model was developed to assess the cost-effectiveness of neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab compared with neoadjuvant chemotherapy alone in the early-stage TNBC setting [95]. Data were derived from the KEYNOTE-522 trial in patients with previously untreated, high-risk, early-stage TNBC. The pembrolizumab-based regimen improved quality-adjusted life years (QALY) and life years (LY). The incremental cost per QALY gained was below willingness-to-pay thresholds defined by the Institute of Clinical and Economic Review and World Health Organization criteria [95].

A partitioned-survival model was developed to assess the cost-effectiveness of pembrolizumab plus chemotherapy compared with chemotherapy alone in the late-stage TNBC setting [96]. Data were derived from the KEYNOTE-355 trial in patients with previously untreated, locally recurrent unresectable or metastatic TNBC. In the PD-L1 CPS ≥ 10 population, combination therapy improved QALY and LY and was cost-effective compared with chemotherapy alone. The authors also found pembrolizumab plus nab-paclitaxel to be cost-effective versus atezolizumab plus nab-paclitaxel based on a network meta-analysis. Data for the atezolizumab plus nab-paclitaxel arm were from the PD-L1 CPS ≥ 10 population in the IMpassion130 trial [96].

Gynecologic Cancers

Endometrial Cancer A partitioned-survival model was developed to assess the cost-effectiveness of pembrolizumab compared with chemotherapy in patients with endometrial cancer [97]. Data for pembrolizumab were derived from the KEYNOTE-158 trial in patients with previously treated, advanced MSI-H/dMMR endometrial cancer, and those for chemotherapy were derived from published literature in patients with previously treated, advanced endometrial cancer and unknown MSI-H/dMMR status. Pembrolizumab improved QALY and LY and was cost-effective compared with chemotherapy [97]. Secondly, the cost-effectiveness of pembrolizumab in combination with chemotherapy compared with chemotherapy alone was assessed using a Markov model that simulated the receipt of pembrolizumab plus chemo-

Table 4 Cost-effectiveness evidence with pembrolizumab in patients with breast and gynecologic cancers

Indication	Trial name	Country	Treatments	QALY gain	Incremental cost	ICER (per QALY)	WTP threshold (per QALY)
TNBC	KEYNOTE-522 [95]	USA	Pembrolizumab + chemotherapy (neoadjuvant) followed by pembrolizumab (adjuvant) vs placebo + chemotherapy (neoadjuvant) followed by placebo (adjuvant)	2.90	$79,046	$27,285	Up to $200,000
TNBC	KEYNOTE-355 [96]	USA	Pembrolizumab + chemotherapy vs placebo + chemotherapy Pembrolizumab + nab-paclitaxel (data from KEYNOTE-355) vs atezolizumab + nab-paclitaxel (data from IMpassion130)	0.70[a] 0.61[a]	$127,706[a] $26,867[a]	$183,732[a] $44,157[a]	Up to $200,000
Endometrial cancer	KEYNOTE-158 and literature review [97]	USA	Pembrolizumab (data from KEYNOTE-158) vs chemotherapy (data from published literature; MSI-H/dMMR status unknown)	3.80	$220,934	$58,165	Up to $200,000
Endometrial cancer	NRG-GY018 [98]	USA	Pembrolizumab + carboplatin and paclitaxel vs chemotherapy	dMMR: 4.05 pMMR: 0.93	dMMR: $167,224 pMMR: $83,661	dMMR: $41,305.09 pMMR: $90,284.80	Up to $150,000
Endometrial cancer	Study 309-KEYNOTE-775 [99]	USA	Lenvatinib + pembrolizumab vs chemotherapy	–	–	$163,735	–
Cervical cancer	KEYNOTE-826 [100]	USA	Pembrolizumab + chemotherapy vs placebo + chemotherapy	1.42	$203,700	$142,996	Up to $200,000

CPS combined positive score, *ICER* incremental cost-effectiveness ratio, *PD-L1* programmed cell death ligand 1, *QALY* quality-adjusted life years, *TNBC* triple-negative breast cancer, *WTP* willingness to pay

[a]Data reported for PD-L1 CPS ≥ 10 population

therapy or chemotherapy alone by patients with previously untreated advanced endometrial cancer from the NRG-GY018 trial. The combination of pembrolizumab with chemotherapy was cost-effective compared with chemotherapy alone for patients with advanced or recurrent endometrial cancer, regardless of dMMR or pMMR status [98]. A cost-effectiveness analysis from the KEYNOTE-775/Study-309 study of pembrolizumab plus lenvatinib compared with chemotherapy in patients with recurrent pMMR endometrial cancer after platinum-based therapy has recently been published. In this USA-based analysis, a Markov decision model was used to create a hypothetical clinical trajectory for women with recurrent pMMR endometrial cancer who had failed carboplatin and paclitaxel and had received either pembrolizumab plus lenvatinib or chemotherapy. The incremental cost-effectiveness ratio for pembrolizumab plus lenvatinib versus chemotherapy was $163,735/QALY [99].

Cervical Cancer A multistate transition model was developed to assess the cost-effectiveness of pembrolizumab plus chemotherapy with or without bevacizumab compared with chemotherapy with or without bevacizumab in patients with cervical cancer [100]. Data were derived from the KEYNOTE-826 trial in patients with previously untreated, persistent, recurrent, or metastatic cervical cancer. The pembrolizumab-based regimen improved QALY and LY and was cost-effective compared with chemotherapy with or without bevacizumab [100].

Real-World Evidence and Network Meta-analyses

Breast Cancer

TNBC In the absence of randomized comparative trials, two fixed-effects Bayesian network meta-analyses/indirect treatment comparisons assessed the efficacy of pembrolizumab-based therapies compared with other available treatments for patients with early-stage [101] and late-stage [102] TNBC. In the early-stage setting, the KEYNOTE-522 regimen (i.e., neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab) provided statistically or numerically higher pCR rates compared with neoadjuvant paclitaxel plus carboplatin followed by adjuvant anthracycline plus cyclophosphamide [odds ratio (OR) 1.36 (95% CI 1.06–1.73)], neoadjuvant docetaxel plus carboplatin followed by adjuvant anthracycline plus cyclophosphamide [OR 1.37 (95% CI 0.61–3.14)], neoadjuvant nab-paclitaxel followed by adjuvant anthracycline plus cyclophosphamide [OR 1.19 (95% CI 0.61–2.30)], neoadjuvant paclitaxel followed by adjuvant anthracycline plus cyclophosphamide [OR 3.12 (95% CI 2.04–4.85)], neoadjuvant paclitaxel plus bevacizumab followed by adjuvant anthracycline plus cyclophosphamide plus bevacizumab [OR 1.89 (95% CI 1.07–3.30)], and neoadjuvant paclitaxel plus carboplatin plus veliparib followed by adjuvant anthracycline plus cyclophosphamide [OR 1.42 (95% CI 0.92–2.21)] [101]. Neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab also improved EFS relative to neoadjuvant paclitaxel plus carboplatin followed by adjuvant anthracycline plus cyclophosphamide [HR 0.63 (95% CI 0.48–0.82)], neoadjuvant docetaxel plus carboplatin followed by adjuvant anthracycline plus cyclophosphamide [HR 0.54 (95% CI 0.14–2.09)], neoadjuvant nab-paclitaxel followed by adjuvant anthracycline plus cyclophosphamide [HR 0.58 (95% CI 0.28–1.17)], neoadjuvant paclitaxel followed by adjuvant anthracycline plus cyclophosphamide [HR 0.36 (95% CI 0.21–0.61)], and neoadjuvant paclitaxel plus carboplatin plus veliparib followed by adjuvant anthracycline plus cyclophosphamide [HR 0.57 (95% CI 0.34–0.95)] [101].

In the late-stage setting, the KEYNOTE-355 regimen (i.e., pembrolizumab plus nab-paclitaxel) was shown in a network meta-analysis/indirect treatment comparison to be numerically or statistically superior for OS to atezolizumab plus nab-paclitaxel [HR 0.82 (95% CI 0.46–1.44)], carboplatin [HR 0.41 (95% CI 0.21–0.83)], docetaxel [HR 0.35 (95% CI 0.19–0.67)], and nab-paclitaxel [HR 0.63 (95% CI 0.39–1.02)] [102]. Similar results were reported for PFS, with corresponding HRs of 0.90 (95% CI 0.54–1.51), 0.74 (95% CI 0.39–1.41), 0.77 (95% CI 0.42–1.41),

and 0.64 (95% CI 0.41–1.01), respectively. Benefits were also observed with the combination of pembrolizumab plus paclitaxel (or gemcitabine/carboplatin) versus most comparators [102].

Gynecologic Cancers

Endometrial Cancer Real-world evidence is available on the use of pembrolizumab monotherapy [103] and the combination of pembrolizumab plus lenvatinib in patients with endometrial cancer. Endometrial Cancer Health Outcomes (ECHO) was a retrospective chart review study of outcomes in patients with advanced MSI-H/dMMR endometrial cancer who experienced treatment failure following previous systemic therapy [103]. Median PFS was 29.0 months (95% CI 18.0 months–not reached) among 91 patients treated with pembrolizumab monotherapy, 4.0 months (95% CI 2.0–9.0 months) among 21 patients treated with chemotherapy (with or without bevacizumab), and 2.0 months (95% CI 2.0–9.0 months) among 12 patients treated with doxorubicin or doxorubicin liposomal monotherapy [103].

The Endometrial Dosing in Real World (ENDOW) study was a retrospective assessment of utilization and dosing patterns of pembrolizumab plus lenvatinib in patients with previously treated endometrial cancer using IQVIA claims data [104]. The median time on treatment for the combination was 5.1 months in the second-line setting and 5.8 months in later settings. Most patients initiated treatment with lenvatinib at the label-recommended dose (20 mg daily), including 71% of patients in the second-line setting and 64% of patients in later settings, and 48% and 47% of patients, respectively, remained on the same lenvatinib dose for the treatment duration [104].

Cervical Cancer One study provided real-world evidence on the use of chemotherapy, targeted therapy, and immunotherapy in patients with recurrent cervical cancer [105, 106]. A total of 959 patients were included in the analysis. The most common treatments at first recurrence were platinum-based chemotherapy combinations (64%), nonplatinum cytotoxic agents (17%), single platinum agents (15%), bevacizumab (6%), and pembrolizumab (3%). Among patients treated with nonplatinum agents, use of targeted therapy tended to increase over time and use of immunotherapy was highest in the most recent years [105, 106]. A study conducted in patients with high-risk locally advanced cervical cancer across four continents (North America, South America, Europe, and Asia) in different healthcare systems provided evidence that patients most frequently seek information on the disease state and treatment options/side effects [107, 108]. Notably, primary motivators for seeking information varied across the four continents, as did satisfaction with the information received; these differences could be attributed to varying social and cultural differences in these countries that could influence treatment options and treatment preferences. With the exception of patients in the USA, patients reported more negative feelings than positive in their search for information. Patients may also defer or avoid searching for information when they suffer from fear, anxiety, depression, stress, and confusion, which indicates a high unmet need for seeking information on cervical cancer in these four continents. A recent Delphi study showed that in addition to patient suffering, 51% of family caregivers experience anxiety/worry, 66% have financial difficulties, and 12–18% have different types of spiritual suffering [109]. These results indicate the importance of taking into account family caregivers when establishing policy support for patients with cervical cancer.

OLAPARIB IN BREAST AND OVARIAN CANCERS

The specific indications of the PARP inhibitor olaparib for the treatment of breast and ovarian cancers are detailed in Table 1. Efficacy and safety results from phase 3 clinical trials of olaparib are summarized in the following sections.

Breast Cancer

Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer

Two phase 3 trials evaluated olaparib in patients with early-stage [110, 111] and late-stage [112] HER2– breast cancer. The OlympiA trial enrolled patients with high-risk, early-stage HER2– disease with a germline *BRCA1* or *BRCA2* mutation [110, 111]. All patients had received local treatment and neoadjuvant or adjuvant chemotherapy and were then randomized (1:1) to receive adjuvant olaparib 300 mg orally twice daily or placebo. Endocrine therapy was administered concurrently with study medication for patients with HR+ tumors. Treatment with olaparib provided statistically significant improvements in invasive disease-free survival (primary endpoint) [110], distant disease-free survival [110], and OS [111] versus placebo.

The OlympiAD trial enrolled patients with HER2– metastatic breast cancer with a germline *BRCA1* or *BRCA2* mutation [112]. All patients had received ≤ 2 previous chemotherapy regimens for metastatic disease. Patients were randomized (2:1) to receive olaparib 300 mg orally twice daily or physician's choice chemotherapy (capecitabine, eribulin, or vinorelbine). Treatment with olaparib provided statistically significant improvement in PFS (primary endpoint) versus chemotherapy [112]. In both phase 3 trials [110–112], the safety profile of olaparib was consistent with that of previous studies.

Gynecologic Cancers

Ovarian Cancer

Two phase 3 trials evaluated first-line maintenance therapy with olaparib alone [113] or in combination with bevacizumab [114] in patients with ovarian cancer. The SOLO1/GOG-3004 trial enrolled patients with newly diagnosed, advanced ovarian cancer with a *BRCA1* or *BRCA2* mutation [113]. All patients had achieved a partial or complete response after platinum-based chemotherapy and were then randomized (2:1) to receive olaparib 300 mg orally twice daily or placebo. Treatment with olaparib provided statistically significant improvement in PFS (primary endpoint) versus placebo. The safety profile of olaparib was consistent with that of previous studies [113].

The PAOLA-1 trial enrolled patients with newly diagnosed, advanced ovarian cancer regardless of *BRCA* mutation status [114]. All patients had achieved a complete or partial response after platinum-taxane chemotherapy and were then randomized (2:1) to receive olaparib 300 mg orally twice daily plus bevacizumab 15 mg/kg every 3 weeks or placebo plus bevacizumab (same dose). The addition of olaparib to bevacizumab provided statistically significantly improvement in PFS (primary endpoint) versus bevacizumab alone. Benefits were seen in patients with tumors positive for homologous recombination deficiency (HRD), including those without a *BRCA* mutation. The safety profile of combination therapy was consistent with those of the individual agents [114].

Results of a phase 3 study in patients with platinum-sensitive, relapsed ovarian cancer with a *BRCA1* or *BRCA2* mutation also demonstrated clinical benefit with olaparib 300 mg twice daily. In the SOLO2/ENGOT-Ov21 trial [115], maintenance therapy with olaparib led to statistically significant improvement in PFS (primary endpoint) compared with placebo.

ONGOING PHASE 3 TRIALS OF PEMBROLIZUMAB

Ten phase 3 trials of pembrolizumab are ongoing in breast (three trials) and gynecologic (seven trials) cancers. Many of these trials are being conducted in collaboration with the European Network of Gynaecological Oncological Trial Groups (ENGOT) and GOG. The planned patient populations and endpoints are summarized in Table 5. Ongoing non-registrational basket trials, which are evaluating various pembrolizumab combination therapy approaches, are not summarized here.

Table 5 Ongoing phase 3 trials of pembrolizumab in patients with breast and gynecologic cancers

Indication	Trial name	Trial setting	Treatments	Total *N* (estimated)	Primary endpoints	Key secondary endpoints
TNBC	KEYNOTE-242/S1418/BR006 [116]	Early-stage with residual invasive cancer or positive lymph nodes after neoadjuvant chemotherapy	Pembrolizumab (adjuvant) vs observation	1155	Invasive disease-free survival Severity of fatigue Physical function	OS Distant recurrence-free survival Safety
HR+/HER2− breast cancer	KEYNOTE-756[a] [117, 118]	High-risk, early-stage	Pembrolizumab + chemotherapy (neoadjuvant) followed by pembrolizumab + endocrine therapy (adjuvant) vs placebo + chemotherapy (neoadjuvant) followed by placebo + endocrine therapy (adjuvant)	1240	pCR (ypT0/Tis ypN0) EFS	OS pCR (other definitions) EFS and OS in PD-L1 CPS ≥ 1 Safety HRQoL
HR+/HER2− breast cancer	KEYNOTE-B49 [120, 121]	Late-stage (locally recurrent inoperable or metastatic), PD-L1 CPS ≥ 1	Pembrolizumab + chemotherapy vs placebo + chemotherapy after progression on prior endocrine therapy	800	PFS (BICR) in PD-L1 CPS ≥ 10 and ≥ 1 OS in PD-L1 CPS ≥ 10 and ≥ 1	PFS (investigator), ORR (BICR), DCR (BICR), and DOR (BICR) in PD-L1 CPS ≥ 10 and ≥ 1 Safety HRQoL
Endometrial cancer	KEYNOTE-B21/ENGOT-en11/GOG-3053[b] [122]	Newly diagnosed, high-risk (stage 1/II nonendometrioid, stage III/IVA, p53 abnormality)	Pembrolizumab + chemotherapy ± radiotherapy (adjuvant) vs placebo + chemotherapy ± radiotherapy (adjuvant) following surgery with curative intent with no postoperative evidence of disease	990	DFS (investigator) OS	DFS (BICR) DFS (investigator) and OS by biomarker status (PD-L1 and TMB) Safety HRQoL

Table 5 continued

Indication	Trial name	Trial setting	Treatments	Total *N* (estimated)	Primary endpoints	Key secondary endpoints
Endometrial cancer	KEYNOTE-C93/ GOG-3064/ ENGOT-en15 [124]	Previously untreated, dMMR, advanced (stage III–IV) or recurrent	Pembrolizumab vs chemotherapy	350	PFS (BICR) OS	ORR, DCR, and DOR (all BICR) PFS (investigator) PFS after subsequent-line treatment (investigator) Safety HRQoL
Ovarian cancer	KEYLYNK-001/ ENGOT-ov43/ GOG-3036 [127]	Advanced (stage III–IV), *BRCA1/2*-nonmutated	Pembrolizumab + chemotherapy followed by pembrolizumab + olaparib vs pembrolizumab + chemotherapy followed by pembrolizumab + placebo vs placebo + chemotherapy followed by placebo	1367	PFS (investigator) OS	PFS (BICR) PFS after subsequent-line treatment (investigator) Safety HRQoL
Ovarian cancer	KEYNOTE-B96/ ENGOT-ov65 [128]	Platinum-resistant	Pembrolizumab + paclitaxel (± bevacizumab) vs placebo + paclitaxel (± bevacizumab)	616	PFS (investigator) in PD-L1 CPS ≥ 1 and all patients	OS in PD-L1 CPS ≥ 1 and all patients PFS (BICR) in PD-L1 CPS ≥ 1 and all patients Safety HRQoL
Ovarian cancer	ARTISTRY-7 [129]	Platinum-resistant	Pembrolizumab + nemvaleukin alfa vs chemotherapy (PLD, paclitaxel, topotecan, or gemcitabine)	376	PFS (investigator)	ORR (investigator) OS DCR, DOR, and TTR (all investigator) Safety

Table 5 continued

BICR blinded independent central review, *CPS* combined positive score, *CR* complete response, *DCR* disease control rate, *DFS* disease-free survival, *ENGOT* European Network of Gynaecological Oncological Trial groups, *dMMR* mismatch repair deficient, *DOR* duration of response, *EFS* event-free survival, *GOG* GOG Foundation, Inc., *HER* human epidermal growth factor receptor 2,*HR* hormone receptor, *HRQoL* health-related quality of life, *ORR* objective response rate, *OS* overall survival, *pCR* pathologic complete response, *PD-L1* programmed cell death ligand 1, *PFS* progression-free survival, *PLD* pegylated liposomal doxorubicin, *pMMR* mismatch repair proficient, *TMB* tumor mutational burden, *TNBC* triple-negative breast cancer, *TTR* time to response

[a]Positive results from the first interim analysis demonstrating a significant improvement in pCR were reported at the European Society for Medical Oncology (ESMO) Congress in 2023 [119]. A full description of the trial results is expected in future publications

[b]Results from an interim analysis were recently published [123]. The study did not meet its primary endpoint in all-comers; however, prespecified subgroup analysis based on the study's stratification factors suggested clinically relevant improvement for patients with dMMR tumors

Breast Cancer

TNBC

One phase 3 trial is ongoing in patients with early-stage TNBC. The KEYNOTE-242 trial is evaluating adjuvant pembrolizumab versus observation in patients with residual invasive cancer or positive lymph nodes after neoadjuvant chemotherapy [116].

Hormone Receptor-Positive/Human Epidermal Growth Factor Receptor 2-Negative Breast Cancer

Two phase 3 trials are ongoing in patients with HR+/HER2– breast cancer. In the early-stage setting, the KEYNOTE-756 trial is evaluating neoadjuvant pembrolizumab plus chemotherapy followed by adjuvant pembrolizumab plus endocrine therapy versus neoadjuvant chemotherapy followed by adjuvant endocrine therapy in patients with high-risk disease [117, 118]. Positive results from the first interim analysis demonstrating a significant improvement in pCR rate among patients in the pembrolizumab group were reported at the European Society for Medical Oncology (ESMO) Congress in 2023 [119]. A full description of the trial results is expected in future publications. In the late-stage setting, the KEYNOTE-B49 trial is assessing pembrolizumab plus chemotherapy versus chemotherapy after progression on previous endocrine therapy in patients with locally recurrent inoperable or metastatic disease whose tumors express PD-L1 (CPS ≥ 1) [120, 121].

Gynecologic Cancers

Endometrial Cancer

Three phase 3 trials are ongoing in patients with endometrial cancer. The KEYNOTE-B21/ENGOT-en11/GOG-3053 trial is evaluating adjuvant pembrolizumab plus chemotherapy (with or without radiotherapy) versus adjuvant chemotherapy (with or without radiotherapy) in patients with newly diagnosed endometrial

cancer with a high risk of recurrence [122]. Results from an interim analysis were recently published [123]. The study did not meet its primary endpoint of disease-free survival in all-comers; however, prespecified subgroup analysis based on the study's stratification factors suggested clinically relevant improvement for patients with dMMR tumors. The other trials are being conducted in the first-line setting in patients with advanced or recurrent endometrial cancer. The KEYNOTE-C93/GOG-3064/ENGOT-en15 trial is assessing pembrolizumab versus platinum-doublet chemotherapy in patients with MSI-H/dMMR tumors [124], and the LEAP-001/ENGOT-en9 trial is evaluating pembrolizumab plus lenvatinib versus platinum-doublet chemotherapy in both the MSI-H/dMMR and non-MSI-H/pMMR populations [125]. Results from the final analysis were reported at the European Congress on Gynaecological Oncology (ESGO) in 2024 [126]. The study did not meet the prespecified statistical criterion for PFS or OS; however, the study confirmed that pembrolizumab plus lenvatinib is an active combination and important treatment option. A full description of the trial results is expected in future publications.

Ovarian Cancer

Three phase 3 trials are ongoing in patients with ovarian cancer. The KEYLYNK-001/ENGOT-ov43/GOG-3036 trial is evaluating first-line pembrolizumab plus chemotherapy (with or without bevacizumab), with or without olaparib maintenance, in patients with *BRCA*-nonmutated, advanced disease [127]. The other trials are being conducted in patients with platinum-resistant disease. The KEYNOTE-B96/ENGOT-ov65 trial is assessing pembrolizumab plus paclitaxel (with or without bevacizumab) versus paclitaxel (with or without bevacizumab) [128], and the ARTISTRY-7 trial is evaluating pembrolizumab plus the interleukin-2 agonist nemvaleukin alfa versus investigator's choice chemotherapy [129].

CONTINUED CHALLENGES IN BREAST AND GYNECOLOGIC CANCERS

Simultaneous with the development of treatments that improve outcomes for patients with breast and gynecologic cancers, efforts are also ongoing to reduce the incidence of these cancers. At a population level, these efforts include the development of risk assessment tools and identification of risk factors and high-risk populations. Global attempts to establish screening and immunization programs for human papillomavirus (HPV) have provided a glimpse into the potential successes and challenges likely to be met by such measures [130, 131]. Although screening and HPV immunization, for example, have been shown to substantially reduce rates of cervical cancer in many countries [132–136], low- and middle-income countries (LMICs) in particular may have financial and infrastructural barriers that limit implementation of these programs [131]. There remains a need to increase the availability of these important tools so that broader populations of patients affected by breast and gynecologic cancers will have greater access [130, 133, 137]. In the case of ovarian cancer, screening and preventive programs have been proposed, but as of yet, no specific and reliable method exists to detect this cancer type [138]. Access to anticancer therapies and reimbursement may pose additional difficulties [139, 140]. One multicountry analysis showed that the mean time between regulatory approval of anticancer therapies and a health technology assessment reimbursement decision was 321 days, with a range of 182 days (Australia) to 547 days (England) [139].

Genetic testing can help guide optimal treatment of breast and gynecologic cancers, yet rates of implementation vary widely by region. For example, MSI/MMR status is tested in nearly all patients with advanced endometrial cancer in the USA [28] but in only 36% of patients in Europe [141]. Although about half of cases of high-grade serous ovarian cancer exhibit HRD, which has demonstrated prognostic and predictive value in this setting, there is no uniformly accepted gold standard for HRD assessment

[142]. *BRCA* testing is not performed systematically in patients with advanced ovarian cancer, with survey results indicating variable rates ranging from 45% in Italy to 73% in the USA [143].

Treatment options for breast and gynecologic cancers have improved over time. PARP inhibitors, for example, are now commonly used to treat *BRCA1/2*-mutated cancers, including breast and ovarian cancer. However, many patients eventually develop resistance to these agents [144–146], thereby posing an obstacle to their prolonged use. Further research into the mechanisms involved and strategies to overcome treatment resistance are needed. Several phase 3 trials are currently investigating whether combining pembrolizumab and olaparib could be a potential strategy (see Ongoing Phase 3 Trials).

Other challenges relate to gender inequalities. Transgender individuals may encounter discrimination from healthcare providers and/or an inadequate offering of services [147]. Transgender men have high rates of cigarette and alcohol use (risk factors for cervical and vulvar neoplasia and mucinous epithelial ovarian cancer) [147], yet many do not receive regular Pap smears for fear of discrimination [148]. Screening for breast and gynecologic cancers is essential in this population, and recommendations should follow those for cisgender women [149]. Further data are needed to better understand the prevalence and outcomes of breast and gynecologic cancers in the transgender community [147, 149].

Racial and ethnic inequalities are also a concern. A greater proportion of Black versus white women are diagnosed with metastatic TNBC or metastatic endometrial cancer in the USA, and 5-year survival rates across all stages of these cancers are lower in Black women [64, 150]. Black women are less likely than white women to undergo *BRCA* testing [151] and to receive guideline-recommended therapy [152]. Black women with endometrial cancer have shorter survival times than white women, even in the context of equal access to healthcare [153]. Potentially relevant factors could include comorbidities, tumor histology, delays in treatment initiation, and adherence to therapy [150, 152, 153]. In the USA, women of Asian, Black, and Hispanic origin are underrepresented in precision oncology trials of gynecologic cancers [154], and the Asian population has been consistently underrepresented in clinical trials in general (vs census data) regardless of therapeutic area [155]. Greater efforts must be made to represent minority populations in clinical trials. Toward this end, the US FDA has published draft guidance for sponsors of investigational medical products, intended to increase the enrollment of underrepresented populations and improve the generalizability of results [156].

There is a lack of literature on the socioeconomic burden of patients with cervical cancer and their caregivers in LMICs. In the context of LMICs, innovative approaches such as distributional cost-effectiveness analysis (DCEA) could provide valuable information on the equity impacts of heath technologies and trade-offs [157]. The DCEA approach is useful in compensating for equity issues lacking in conventional cost-effectiveness data that do not consider the distributional breakdowns and equity weighting analyses based on variables that may include ethnicity, socioeconomic status, and geographical region. Consistent application of DCEA by health technology assessment (HTA) agencies would enable comparison of equity impacts across diseases and their interventions [158]. However, lack of consistency in the equity characteristics and quality of data collected or reported are the key challenges for robust analyses at the time of HTA [158].

CONCLUSIONS

Breast and gynecologic cancers affect patients, their families, caregivers, and communities globally, with high morbidity and mortality despite advancements in prevention and treatment. Extensive clinical, humanistic, and economic data are now available to support pembrolizumab monotherapy and combination therapy for patients with TNBC, endometrial cancer, and cervical cancer. Pembrolizumab has significantly improved patient outcomes and is now a standard of care therapy for these

cancers. Several phase 3 studies are ongoing in these and other tumor types with the goal of further improving the lives of patients and potentially providing a cure for patients with early-stage disease.

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Declarations

Conflict of Interest. Matthew J. Monberg, Steve Keefe, Vassiliki Karantza, Konstantinos Tryfonidis, Sarper Toker, Jaime Mejia, Robert Orlowski, Amin Haiderali, Vimalanand S. Prabhu and Gursel Aktan are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and stockholders in Merck & Co., Inc., Rahway, NJ, USA. Pembrolizumab is manufactured by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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