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Cervical cancer treatment update: A Society of Gynecologic Oncology clinical practice statement

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Author Contributions

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Understanding the Biology of Cervical Cancer

Cervical cancer is the fourth most commonly diagnosed cancer in women worldwide [1]. Although cervical cancer incidence has declined with increased screening and higher uptake of human papillomavirus (HPV) vaccination in high-income countries, it remains the second highest cause of cancer mortality among women in low- and middle-income countries. In the United States (US), there will be an estimated 13,960 new cases of and 4,310 deaths from cervical cancer in 2023 [2]. The FIGO staging for cervical cancer was updated in 2018 to incorporate pathologic as well as imaging results (Table 1). Understanding the molecular mechanisms that contribute to the pathogenesis of cervical cancer is crucial to improving treatment outcomes.

Persistent HPV infection is the main factor in the development of cervical cancer [3]. Risk factors that may account for persistence of HPV include smoking and immunosuppression. Several high-risk HPV variants, particularly types 16 and 18, play an important role in the pathogenesis and prognosis of cervical cancer. Integration of HPV DNA into the host genome leads to upregulation of two viral oncoproteins, E6 and E7. Once active in a cell, these proteins inhibit p53 and Rb, both tumor suppressor proteins, which directly and indirectly influence cellular pathways such as proliferation, growth, and apoptosis [3]. The level of HPV DNA integration has been shown to correlate with disease progression. Therefore, further understanding the mechanisms of integration and identifying HPV DNA integration hot spots in the human genome will provide further insight into HPV-induced carcinogenesis [4].

Driver mutations, such as *PIK3CA* (phosphatidylinositide 3-kinase catalytic subunit α), *KRAS* (Kirsten rat sarcoma viral oncogene homolog), and *EGFR* (epidermal growth factor receptor) are frequently seen in cervical cancer [5]. Activating mutations and amplifications of *PIK3CA* have been reported in up to 36% of cervical cancers [6–8], and most commonly occur in squamous cell carcinomas [9]. Some studies suggest that tumors with *PIK3CA* mutations are associated with higher rates of radiation resistance [10], and *PI3KCA* mutations may predict response to PI3K/AKT/mTOR inhibitors [11, 12]. *KRAS* mutations are more common in adenocarcinomas and are associated with HPV18 infection [13]. Mutations in *KRAS* may play an important role in the pathogenesis of cervical cancer through the RAS/RAF/MEK/ERK signaling pathway [13, 14]. Unfortunately, to date, trials of MEK inhibitors in cervical cancer have shown limited activity [15]. Further exploration will need an actionable biomarker.

Therapy by Treatment Setting

Locally Advanced Cervical Cancer

Locally advanced cervical cancer is defined as clinically visible tumor exceeding 4 cm or invading beyond the cervix, extending to the pelvic sidewalls, vagina, bladder, rectum, or involving pelvic and/or para-aortic lymph nodes. The current standard of care for locally advanced cervical cancer is external beam radiation therapy and concurrent weekly cisplatin, with the entire course of treatment completed within 56 days. Brachytherapy is integral for patients who undergo curative-intent treatment [16]. With a median follow-up of 4.3 years the EMBRACE-I study showed a local control rate of >90% in patients who received the standard of care.[17] Unfortunately, small, non-academic facilities are more likely to have incomplete or protracted radiation treatments.[18] Studies have demonstrated that cause-specific survival and overall survival (OS) are worse in patients who do not receive brachytherapy or if treatment extends beyond 56 days. [19] Black and Hispanic patients are less likely to receive brachytherapy, highlighting the urgent need to address socio-economic and racial inequities. [20] Patients should be referred to facilities with expertise and adequate resources to treat cervical cancer.

Several radiosensitizers have been evaluated in the treatment of locally advanced cervical cancer, including cisplatin, 5-fluorouracil (5-FU), hydroxyurea, gemcitabine, and mitomycin C. Across five initial studies, concurrent cisplatin-based chemoradiation reduced the risk of death between 30% and 50%, which led to a National Cancer Institute (NCI) clinical alert in 1999 and established the current standard for radiosensitization [21]. Chemotherapy is thought to augment the efficacy of radiation by cell-cycle specific cytotoxicity, cell synchronization to a more radiosensitive phase, decreasing tumor repopulation, and inhibiting repair of radiation-induced cell damage [22]. Ongoing research is focused on improving outcomes further by adding additional systemic agents to cisplatin and radiation. The addition of gemcitabine to cisplatin chemoradiotherapy followed by adjuvant gemcitabine/cisplatin chemotherapy was explored in a phase III study and showed improved survival outcomes with the addition of gemcitabine, but at the cost of increased toxicity [23]. The NRG-GY006 trial (NCT2466971) did not show a benefit with the addition of triapine, a ribonucleotide reductase inhibitor, in combination with cisplatin and radiation in locally advanced cervical cancer [24].

In an attempt to improve survival, the randomized phase III OUTBACK trial evaluated the addition of 4 cycles of carboplatin and paclitaxel following chemoradiation in patients with high-risk disease (lymph node-positive 2008 International Federation of Gynecology and Obstetrics [FIGO] stage IB1, IB2, II, IIIB, and IVA); patients with para-aortic nodal involvement above L3 or L4 were excluded [25]. Results demonstrated increased toxicity but no difference in 5-year OS with the addition of adjuvant chemotherapy.

Immunotherapy, when combined or sequenced with chemoradiation, may provide additional benefit in high-risk locally advanced cervical cancer [26]. The CALLA trial, a phase III randomized controlled trial, evaluated the role of concurrent and adjuvant durvalumab (a programmed death-ligand 1 [PD-L1] inhibitor) to standard chemoradiation therapy, and showed no improvement in progression-free survival (PFS), the primary endpoint [27].

Further exploration of biomarkers, including PD-L1, may help identify patients who are most likely to derive benefit from immunotherapy in the adjuvant setting. At this time, three additional checkpoint inhibitors are being explored in the primary and adjuvant settings in ongoing clinical trials: pembrolizumab (KEYNOTE-A18; NCT04221945) [28], atezolizumab (ATEZOLACC; NCT03612791) [29], and dostarlimab (ATOMICC; NCT03833479) [30]. An initial press release from a prespecified interim analysis of Keynote-A18 reported a statistically significant and clinically meaningful improvement in PFS with the addition of pembrolizumab to chemoradiotherapy following by maintenance pembrolizumab compared to chemoradiotherapy alone. The US Food and Drug Administration (FDA) has granted priority review with anticipated target decision date of January 20, 2024. The use of immune checkpoint inhibitors as a primer for chemoradiation has been recently explored in the NRG-GY017 trial, and findings demonstrated improved immunogenicity with neoadjuvant compared to concurrent administration of atezolizumab [26]. Therefore, differential sequencing of chemoradiation and immune checkpoint blockade requires further exploration.

Advanced/Recurrent Cervical Cancer, First Line

Historically, cisplatin has been the mainstay of treatment for metastatic cervical cancer, with response rates ranging from 18% to 38%. Previous use of cisplatin concurrent with radiation in the locally advanced setting, however, resulted in lower response rates for single-agent cisplatin when used for cervical cancer recurrence. In an effort to improve response rates in patients with recurrent or distant metastatic disease, the GOG 204 study examined different platinum-based combinations, pairing cisplatin with paclitaxel, vinorelbine, gemcitabine, or topotecan; response rates were 29%, 25.9%, 22.3%, and 23.4%, respectively [31]. The study closed early due to futility and established cisplatin and paclitaxel as the preferred regimen.

In 2017, the standard of care for first-line treatment of advanced, recurrent, or metastatic cervical cancer changed to cisplatin, paclitaxel, and bevacizumab based on results of the GOG 240 trial [32]. In this randomized phase III clinical trial, 452 patients with stage IVB or recurrent/persistent disease were randomized to either paclitaxel-cisplatin or the non-platinum doublet of paclitaxel-topotecan, with a second randomization to the addition of bevacizumab or placebo. The addition of bevacizumab to the cisplatin-paclitaxel chemotherapy doublet significantly prolonged OS, the primary endpoint, by a median of 2.5 months (17.5 vs 15 months; HR: 0.73; 95% CI: 0.54–0.99; P=.004) (Figure 1). In addition, the use of non-platinum doublets did not improve survival compared with cisplatin-paclitaxel, even in patients who were previously exposed to platinum. Patients with no prior radiation therapy benefited most from the addition of bevacizumab. Patients treated with bevacizumab had higher risks of grade ≥2 hypertension (25% vs 1.8%), grade 2 fistula (8.64% vs 0.9%), grade 3 fistula (5.9% vs 0.5%), and grade ≥3 thromboembolic events (12.7% vs 1.8%). In the bevacizumab group, all grade 3 fistulas occurred in patients who had received prior pelvic radiation.

The KEYNOTE-826 trial introduced checkpoint inhibitors to the first-line treatment of persistent, recurrent, or metastatic cervical cancer [33]. This double-blind, phase III, placebocontrolled trial randomized 548 patients to receive 200 mg of pembrolizumab or

intravenous (IV) placebo every 3 weeks for up to 35 cycles, in combination with platinum-based chemotherapy with or without bevacizumab, per investigator discretion. The dual primary endpoints of PFS and OS were each tested sequentially in patients with a PD-L1 combined positive score (CPS) ≥1, and in patients with a PD-L1 CPS ≥10. CPS was defined as the number of PD-L1-positive staining cells divided by the number of viable tumor cells, multiplied by 100.

The addition of pembrolizumab to chemotherapy significantly improved OS and PFS, regardless of histologic type, bevacizumab use, prior chemoradiotherapy, as well as among protocol-specified CPS ≥1 and CPS ≥10 populations (Table 2). Adding pembrolizumab to chemotherapy (paclitaxel plus cisplatin or carboplatin) with or without bevacizumab led to a 37%, 40%, and 42% reduction in the risk of death for all-comer, CPS ≥1, CPS ≥10 populations, respectively, establishing a new standard of care in the management of PD-L1-positive cervical cancer, with an improved quality of life (QOL) [34].

Ongoing trials of front-line treatment for metastatic or advanced cervical cancer are evaluating the addition of other checkpoint inhibitors to standard of care. The BEATcc trial (NCT03556839) is exploring the addition of atezolizumab to the GOG 240 protocol combination of platinum plus taxane and bevacizumab, and mandates use of bevacizumab [35]. FERMATA (NCT03912415), a European trial, is evaluating the addition of the PD-1 inhibitor, BCD-100, to chemotherapy [36]; bevacizumab is administered at the physician's discretion, similar to the KEYNOTE-826 trial.

Recurrent Cervical Cancer, Second/Third Line

Despite improvements in front-line therapies, some cervical cancers recur or progress. Few active single agents are available in the second-line or greater settings (Figure 2) [37–48]. Combination drugs elicit higher response rates, with older phase II trials of non-platinum-based doublets evaluating paclitaxel in combination with topotecan, as well as docetaxel in combination with gemcitabine, showing response rates of 54% and 29%, respectively [49, 50].

As single agents, checkpoint inhibitors yield a modest response rate. In KEYNOTE-158, a phase II basket trial, single-agent pembrolizumab was administered to 98 immunotherapy naïve patients with previously treated cervical cancer. The objective response rate was 12.2% (95% CI: 6.5%−20.4%), with 3 complete and 9 partial responses [51]. Most patients (84%) had PD-L1-positive tumors. The objective response rate was 14.6% in patients with PD-L1-positive tumors; no PD-L1-negative tumors exhibited a response. These results led to an accelerated approval of pembrolizumab by the US FDA in 2018, which was incorporated into the National Comprehensive Cancer Network (NCCN) guidelines as a preferred regimen for recurrent PDL1-positive tumors or the rare subset (<2%) of microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) tumors.

In the phase III, open-label, multicenter EMPOWER-Cervical 1 trial, 608 patients who had disease progression after first-line platinum-containing chemotherapy were randomly assigned to a PD-L1 inhibitor, cemiplimab (350 mg every 3 weeks), versus investigator's choice of single-agent chemotherapy (topotecan, pemetrexed, vinorelbine, gemcitabine, or

irinotecan) [52]. PD-L1 expression status was determined using the SP263 monoclonal antibody. Tumor cells with membranous staining for PD-L1 were considered positive, and the percentage of PD-L1-positive tumor cells in the overall tumor sections was evaluated. Cemiplimab was associated with significantly longer OS compared to chemotherapy in the intention-to-treat population (12.0 vs 8.5 months, HR: 0.69, 95% CI: 0.56–0.84). The objective response rate was 16.4% in the cemiplimab arm compared with 6.3% in the chemotherapy arms. Responses were seen regardless of PD-L1 expression status. The objective response rates for cemiplimab were 18% and 11%, for PD-L1 expression ≥1% and <1%, respectively. Although an inability to agree on post-marketing strategies for cemiplimab led to the withdrawal of the supplemental Biologics License Application in the US, cemiplimab is approved outside the US.

The hypothesis that dual checkpoint inhibitors enhance anti-tumor activity compared to PD-L1 inhibition alone was explored in several trials [53, 54]. Checkmate-358, a phase I/II clinical trial, evaluated two checkpoint inhibitors, ipilimumab (anti-CTLA-4 inhibitor) and nivolumab (a PD-L1 inhibitor), compared to monotherapy nivolumab, in patients with recurrent and/or metastatic cervical cancer with up to 2 prior lines of systemic therapy. The objective response rate was 26% with nivolumab alone, 31% with 3 mg/kg nivolumab plus 1 mg/kg ipilimumab, and 38% with 1 mg/kg of nivolumab plus 3 mg/kg ipilimumab. Notably, a significant proportion of patients in all arms did not receive any prior systemic therapy in the metastatic setting. As expected, the combination regimen had higher response rates than nivolumab alone. The responses were durable, regardless of PD-L1 status, across all treatment arms [53]. Another dual-targeted immunotherapy combination, was explored in a phase II trial using balstilimab (anti-PD-1 inhibitor) and zalifrelimab (anti-CTLA-4 inhibitor) in second-line treatment for patients with recurrent metastatic cervical cancer who relapsed after platinum-based therapy [54]. This population represented more heavily pre-treated patients with more diverse histologies. An objective response rate of 25.6% was noted, with enhanced benefit observed irrespective of PD-L1 tumor expression status. Responses were durable, with duration of response not reached at 21-month follow-up. The ongoing RaPiDS/GOG-3028 randomized phase II study will evaluate the safety and efficacy of balstilimab alone and in combination with zalifrelimab in the second-line setting for recurrent and/or metastatic cervical cancer (NCT03894215).

Tisotumab vedotin is the first antibody-drug conjugate (ADC) to be approved by the US FDA for gynecologic malignancies. This novel ADC targets tissue factor and contains a microtubule-disrupting payload, monomethyl auristatin E (MMAE). In the phase II, open-label, multi-center, single-arm innovaTV 204/GOG 3023/ENGOT-cx6 trial, 101 patients with previously treated (up to 2 prior systemic regimens) recurrent or metastatic cervical cancer received at least 1 dose of tisotumab vedotin (Figure 3) [55]. After a median follow-up of 10 months, the confirmed objective response rate was 24% (95% CI: 16%−33%), with 7 patients (7%) achieving complete responses and 17 patients (17%) achieving partial responses. While having a manageable toxicity profile, alopecia was common (38%) and some unique adverse events were seen, including conjunctivitis (26%), dry eye (23%) and epistaxis (30%). Mitigation strategies to manage ocular toxicity include ophthalmic exam at baseline and prior to each infusion, as well as use of 3 types of eye drops throughout the treatment: vasoconstriction eye drops prior to infusion, topical corticosteroid for 72

hours after infusion, and topical lubricating drops throughout treatment. In the event of ocular toxicity, prompt consultation with an eye specialist who is familiar with this agent is important.

Immunotherapy should be incorporated as early in the disease course as possible, and for second or later lines, patients could receive tisotumab vedotin or participate in a clinical trial. Recognizing that many community cancer programs may not have access to clinical trials, alternative recommended regimens include albumin-bound paclitaxel, bevacizumab, docetaxel, gemcitabine, pemetrexed, topotecan, and vinorelbine [21].

Cervical Cancer Quality of Life, Financial Toxicity and Disparities

Though many advances have been made in the diagnosis and treatment of cervical cancer, there are important consequences from the disease and its treatment among survivors, especially the impact on QOL. The deleterious effect on the QOL in patients with cervical cancer disturbingly begins prior to the diagnosis of the disease. Fear, self-blame, distress, and anxiety about cervical cancer are common in people who receive abnormal Papanicolaou test results or positive HPV DNA tests. These results negatively impact body image, self-esteem, and relationships with partners, and lead to sexual and reproductive issues, as well as an overall decrease of QOL [56]. A variety of functional disorders can occur following surgical therapies that involve the female genital anatomy, which may directly affect survivors' perceptions of body image and sexual function. Radiotherapy can damage the vaginal epithelium, while chemotherapy can induce various adverse effects like nausea, vomiting, diarrhea, constipation, mucositis, weight changes, and hormonal changes [57].

Furthermore, various psychological factors, including low self-esteem, changes in self-image, beliefs about the origin of cancer, relationship tensions, fears, and worries can affect patients' QOL [57–59]. Patients with cervical cancer tend to have an initial improvement in QOL after definitive treatment; however, this often deteriorates when mature follow-up data are acquired. Among patients treated with brachytherapy, 30% reported symptoms of acute stress disorder one week after treatment; this increased to 41% of patients with symptoms of post-traumatic stress disorder 3 months after treatment [60]. Additionally, 1 in 5 patients treated with curative intent with chemoradiotherapy were still taking opioids 12 months after treatment, indicating a component of chronic pain [61]. Five years after initial treatment, survivors of cervical cancer who were treated with radiotherapy had worse sexual function than those treated with radical hysterectomy and lymph node dissection [59]. In contrast, survivors of cervical cancer who are treated with surgery alone can expect overall QOL and sexual function similar to peers without a history of cancer.

Differences in QOL may reflect the intensity of treatment required for definitive treatment of more advanced disease; however, improving long-term QOL in this vulnerable population is an essential goal. For example, work is ongoing to improve sexual function postradiotherapy by limiting the dose to female erectile tissues, similar to what is done when treating prostate cancer [62]. Additionally, patients with cervical cancer are more likely than patients with

any other cancer to report participation in a support group as beneficial (96%); despite this, only 1.3% of patients report having been recommended to one by their physician [63].

Patients with cervical cancer are at increased risk for financial toxicity (ie, the personal economic burdens of cancer diagnosis and treatment), which can lead to downstream decreases in physical, financial, and cancer outcomes [64, 65]. Increased risk is thought to be caused by the intensity of curative treatment, decreases in QOL and functional status after treatment, and the unique population of survivors with high overlap for known risk factors of financial toxicity. This population includes younger patients, patients who identify as racial or ethnic minorities and are made vulnerable by structural racism, and patients with poor access to health care at baseline [66]. Additional risks for financial toxicity in survivors include frequent surveillance imaging and visits [67], and risk of unemployment and resulting insurance disruptions [68].

Potential solutions to financial toxicity exist at many levels in the healthcare system and should be driven by a multidisciplinary team [64]. Hospital-level solutions include implementing universal financial toxicity screening, financial navigation, and pharmacoequity in the prescription of generic or biosimilar medications [66, 69]. Cost-conscious clinical pathways should be used to continually re-evaluate the relative benefit and cost-effectiveness of multi-drug regimens [69]. For instance, restriction of pembrolizumab in the recurrent/metastatic setting to those with PD-L1 positive tumors [70]. Many oncologists are interested in decreasing financial toxicity, but few have received adequate training [71]. In reality, simple, practical solutions can decrease financial burdens on patients. These include streamlining clinics to reduce wait times or helping offset additional food or transportation/travel costs, which can be a material burden from cancer treatment and survivorship [72–74].

Underrepresentation of racial and ethnic minorities in gynecologic oncology clinical trials, particularly of Black and Latinx populations, further highlights the need for equitable representation in both clinical research and the medical workforce [75]. Concerted efforts are required to improve access to care and facilitate enrollment in clinical trials for marginalized communities by reducing geographic barriers to treatment centers and the provision of key resources and services [74, 75]. Collaborative and focused initiatives are urgently needed to bridge the significant divide and alleviate inequalities in the treatment of cervical cancer.

Future Directions

Cervical cancers harbor potentially targetable oncogenic alterations; optimizing tailored treatment strategies are an ongoing research focus to improve clinical outcomes. Ongoing clinical trials are listed in Table 3. Other therapeutic strategies to treat cervical cancer include immunologic vaccines, tumor-infiltrating lymphocytes, and genetically engineered T cells targeting HPV-associated proteins, ADCs, and poly (ADP-ribosyl) polymerase-1 (PARP) inhibitors.

Optimal treatment for recurrent cervical cancer remains an area of great unmet need. Given the overall limited response rates to novel agents, future directions will necessitate the exploration of rational, innovative treatment strategies, including combinations of immunotherapy, targeted agents, and/or ADCs. While a focus on finding treatments for patients with cervical cancer is a priority, our best hope for eliminating the significant burden of this disease is the eradication of high-risk HPV through vaccination. In the interim continued screening and prompt assessment of abnormal tests are essential. Finally, the development of effective therapies for cervical cancer must incorporate strategies to ensure universal equitable access to these treatments.

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Highlights

- Cervical cancer remains the second highest cause of cancer mortality among women in low- and middle-income countries.
- Immunotherapy may be most effective as a treatment for cervical cancer when used early in the disease course.
- Novel therapeutic approaches for cervical cancer include combinations of immunotherapy and targeted agents.
- Cervical cancer is associated with financial toxicity which can impair physical and cancer outcomes.

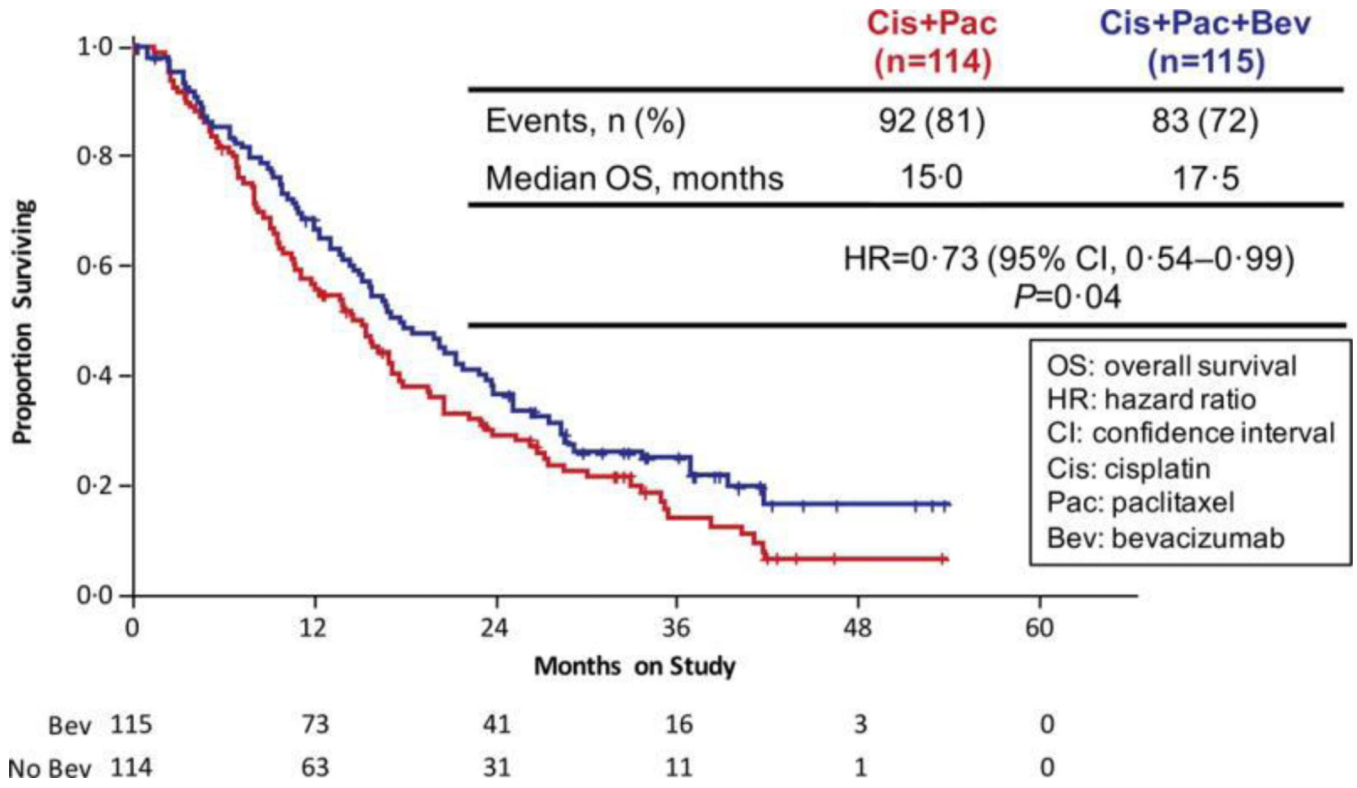

Figure 1:

Final overall survival results from the Gynecologic Oncology Group (GOG) protocol 240. Kaplan-Meier curves depicting the intent-to-treat final protocol-specified overall survival comparing cisplatin plus paclitaxel with and without bevacizumab.

OS: overall survival; HR: hazard ratio; CI: confidence interval; Cis: cisplatin; Pac: paclitaxel; Bev: bevacizumab

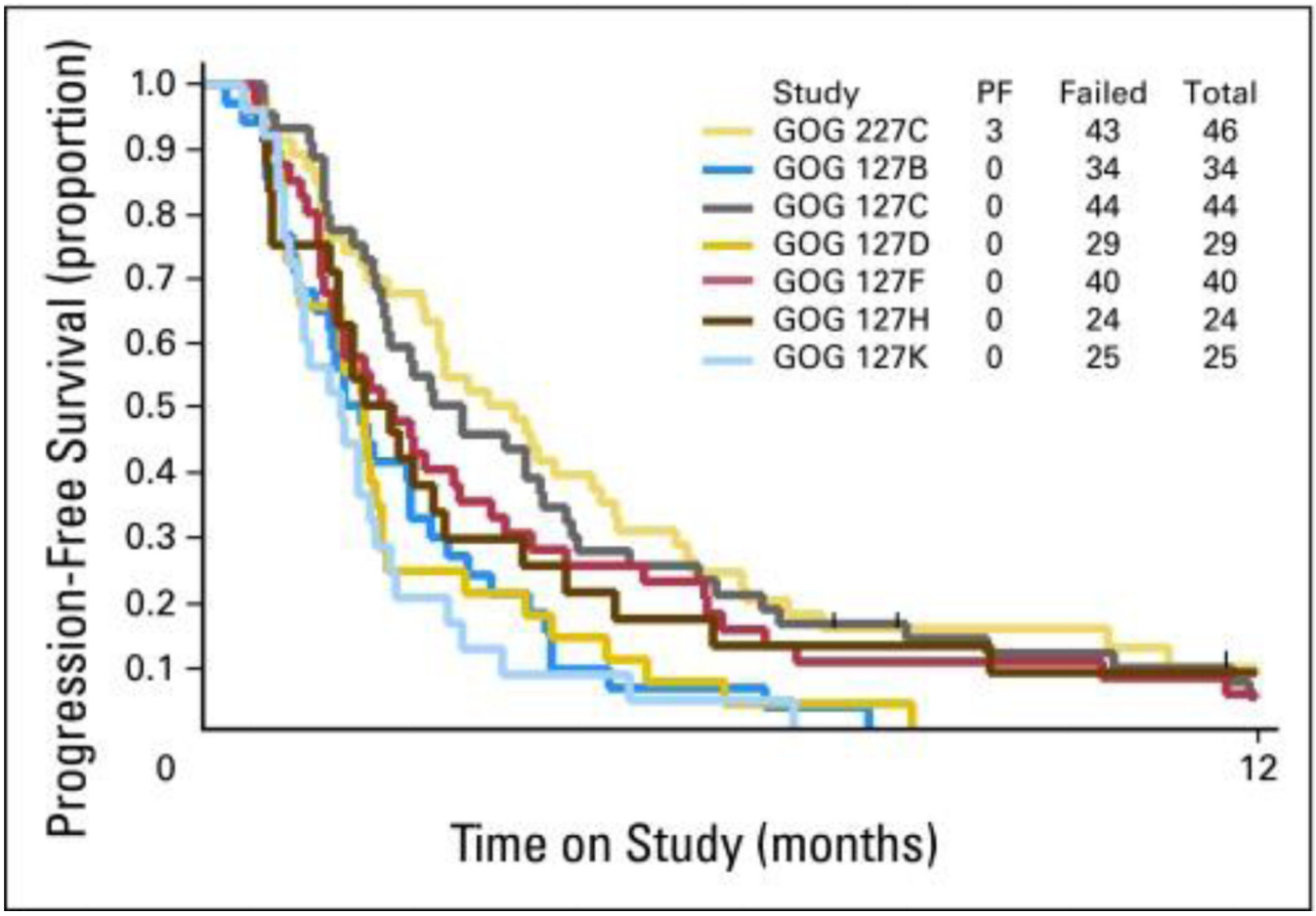

Figure 2:

Nonrandomized comparison of progression-free survival (PFS) among Gynecologic Oncology Group (GOG) studies using cytotoxic single-agent compounds (GOG 127B-K) and bevacizumab (GOG 227C) in recurrent metastatic cervical cancer.

PF: progression free

Reprinted from Journal of Clinical Oncology, Volume 27, Issue 7, Monk BJ, Sill MW, Burger RA, et al., Phase II trial of bevacizumab in the treatment of persistent or recurrent squamous cell carcinoma of the cervix: A Gynecologic Oncology Group study, Pages 1069–1074, Copyright (2009). Reprinted with permission from Wolters Kluwer Health, Inc.

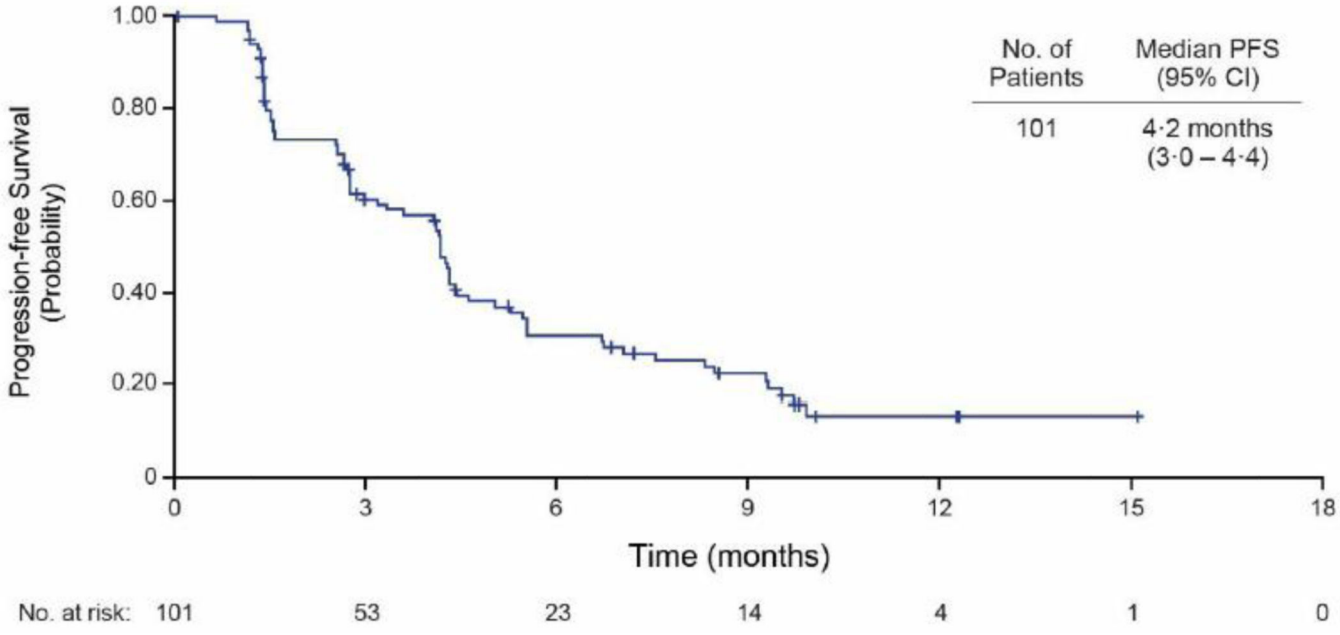

Figure 3:

Efficacy of tisotumab vedotin in patients with previously treated recurrent or metastatic cervical cancer. Progression-free survival was assessed by an independent review committee. PFS: progression-free survival; CI: confidence interval

Reprinted from Supplement to: The Lancet, Volume 22, Coleman RL, Lorusso D, Gennigens C, et al., Efficacy and safety of tisotumab vedotin in previously treated recurrent or metastatic cervical cancer (innovaTV 204/GOG-3023/ENGOT-cx6): a multicentre, open-label, single-arm, phase 2 study, Pages 609–619, Copyright (2021). Reprinted with permission from Elsevier.

Table 1.

The 2018 International Federation of Gynecology and Obstetrics (FIGO) staging classification of cervical cancer.

FIGO Stage	Description
Stage I	The carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)
IA	Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5 mm[a]
IA1	Measured stromal invasion <3 mm in depth
IA2	Measured stromal invasion ≥3 mm and <5 mm in depth
IB	Invasive carcinoma with measured deepest invasion ≥5 mm (greater than Stage IA), lesion limited to the cervix uteri[b]
IB1	Invasive carcinoma ≥5 mm depth of stromal invasion, and <2 cm in greatest dimension
IB2	Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
IB3	Invasive carcinoma ≥4 cm in greatest dimension
Stage II	The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall
IIA	Involvement limited to the upper two-thirds of the vagina without parametrial involvement
IIA1	Invasive carcinoma ≥4 cm in greatest dimension
IIA2	Invasive carcinoma ≥4 cm in greatest dimension
IIB	With parametrial involvement but not up to the pelvic wall
Stage III	The carcinoma involves the lower third of the vagina and/or extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney and/or involves pelvic and/or para-aortic lymph nodes
IIIA	The carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney (unless known to be due to another cause)
IIIC	Involvement of pelvic and/or para-aortic lymph nodes, irrespective of tumor size and extent (with r and p notations) [c]
IIIC1	Pelvic lymph node metastasis only
IIIC2	Para-aortic lymph node metastasis
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum (a bullous edema, as such, does not permit a case to be assigned to Stage IV)
IVA	Spread to adjacent pelvic organs
IVB	Spread to distant organs

When in doubt, the lower stage should be assigned.

[a] Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages.

[b] The involvement of vascular/lymphatic spaces does not change the staging. The lateral extent of the lesion is no longer considered.

[c] Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to Stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be Stage IIIC1r, and if confirmed by pathologic findings, it would be allocated to Stage IIIC1p. The type of imaging modality or pathology technique used should always be documented.

The staging updates are highlighted in the table in red with additional clarification in the boxes.

Table 2.

Progression-free survival and overall survival from KEYNOTE-826 trial

	PD-L1 CPS ≥1		All-Comer		PD-L1 CPS ≥10	
	Pembro + Chemo n = 273	**Pbo + Chemo n = 275**	**Pembro + Chemo n = 308**	**Pbo + Chemo n = 309**	**Pembro + Chemo n = 158**	**Pbo + Chemo n = 159**
OS, median, mo	28.6	16.5	26.4	16.8	29.6	17.4
24-mo OS rate, %	53.5	39.4	52.1	38.7	54.4	42.5
OS, HR (95% CI)	0.60 (0.49–0.74); *P*< 0.0001		0.63 (0.52–0.77); *P*< 0.0001		0.58 (0.44–0.78); *P*< 0.0001	
PFS,median, mo	10.5	8.2	10.4	8.2	10.4	8.1
12-mo PFS rate, %	45.6	33.7	44.7	33.1	44.7	33.5
PFS, HR (95% CI)	0.58 (0.47–0.71); *P*< 0.0001		0.61 (0.50–0.74); *P*< 0.0001		0.52 (0.40–0.68); *P*< 0.0001	

PFS: progression-free survival; OS: overall survival; PD-L1: programmed death-ligand 1; CPS: Combined Positive Score; CI: confidence interval; HR: Hazard Ratio

Reprinted with permission from J Clin Oncol 41, 2023 (suppl 16; abstr 5500) Monk B, Colombo N, Tewari K, et al. KEYNOTE-826: Final overall survival results from a randomized, double-blind, phase 3 study of pembrolizumab + chemotherapy vs placebo + chemotherapy for first-line treatment of persistent, recurrent, or metastatic cervical cancer.

Table 3.

Ongoing clinical trials

	Title	Study population	Phase	Treatment	Primary outcome	Secondary outcome
Advanced/ Induction	Pembrolizumab and Chemoradiation Treatment for Advanced Cervical Cancer [NCT02635360]	Locally advanced cervical cancer	II	Pembrolizumab with CRT	Change in immunologic markers, DLT	Metabolic response rate on PET/CT, incidence of distant metastasis, PFS, OS
	TSR-042 (Dostralimab) as Maintenance Therapy for Patients With High-risk Locally Advanced Cervical Cancer After Chemo-radiation (ATOMICC) [NCT03833479]	Stage IB/IIA/IIB/III/IVA cervical cancer with pelvic and para-aortic lymph nodes	II	CRT, maintenance dostarlimab	PFS	AE, OS
	Atezolizumab Before and/or With Chemoradiotherapy in Immune System Activation in Patients with Node Positive Stage IB2, II, IIIB, or IVA Cervical Cancer [NCT03738228]	Stage IB/II cervical cancer with PALN or IIB/III/IVA cervical cancer with pelvic or para-aortic lymph nodes	I	Atezolizumab with CRT, atezolizumab before CRT	DLT	DFS, AE, ORR, PFS
	Trial Assessing the Inhibitor of Programmed Cell Death Ligand 1 (PD-L1) Immune Checkpoint Atezolizumab (ATEZOLACC) [NCT03612791]	Locally advanced cervical cancer	II	Atezolizumab with CRT and adjuvant atezolizumab	PFS	
	Nivolumab-ipilimumab and Chemoradiation for Cervical Cancer [NCT05492123]	Stage IB2II-IB3 with positive nodes, or stage IIB-IVA	II	Nivolumab/ipilimumab induction with CRT	PFS	ORR, OS, HRQOL, AE, DOR
Recurrent/ Metastatic	Platinum Chemotherapy Plus Paclitaxel With Bevacizumab and Atezolizumab in Metastatic Carcinoma of the Cervix (BEATcc) [NCT03556839]	Metastatic/persistent/ recurrent	III	Platinum/taxane/ bevacizumab +/− atezolizumab	PFS, OS	ORR, DOR, AE, FST, PFS, HRQOL
	Efficacy and Safety of BCD-100 (Anti-PD-1) in Combination With Platinum-Based Chemotherapy With and Without Bevacizumab as First-Line Treatment of Subjects with Advanced Cervical Cancer (FERMATA) [NCT03912415]	Metastatic/persistent/ recurrent	III	BCD-100 (anti-PD-1) + platinum/taxane +/− bevacizumab	OS	PFS, ORR, DCR, TTR, DOR
	Niraparib in Combination With Dostarlimab in Patients With Recurrent or Progressive Cervix Cancer (STAR) [NCT04068753]	Recurrent/ progressive	II	Niraparib + dostarlimab	Proportion of patients with response	AE, DOR, PFS, OS
	Niraparib Combined With Brivanib or Toripalimab in Patients With Cervical Cancer (CQGOG0101) [NCT04395612]	Recurrent/ progressive	II	Niraparib + brivanib or toripalimab	ORR	PFS, DCR
	Bevacizumab and Rucaparib in Recurrent Carcinoma of the Cervix or Endometrium (Clovis-001) [NCT03476798]	Recurrent/ progressive	II	Rucaparib + bevacizumab	PFS	ORR, AE, OS
	Anti-PD-1 Independently or in Combination with Anti-CTLA-4 in Second-line Cervical Cancer (RaPiDS) [NCT03894215]	Recurrent/ progressive	II	Balstilimab + zalifrelimab	ORR	DOR, AE

CRT: chemoradiation; PALN: para-aortic lymph nodes; PFS: progression-free survival; AE: adverse event; OS; overall survival; DLT: dose limiting toxicity; ORR: objective response rate, DOR: duration of response; FST: first subsequent therapy; TTR: time to response; DCR: disease control rate; HRQOL: health-related quality of life; PET: positron emission tomography; CT: computed tomography; DFS: disease-free survival; PD-1: programmed cell death protein-1; CTLA-4: cytotoxic T-lymphocyte-associated protein 4.