NCCN Continuing Education

Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

Accreditation Statements

In support of improving patient care, National Comprehensive Cancer Network (NCCN) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Physicians: NCCN designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses: NCCN designates this educational activity for a maximum of 1.0 contact hour.

Pharmacists: NCCN designates this knowledge-based continuing education activity for 1.0 contact hour (0.1 CEUs) of continuing education credit. UAN: JA4008196-0000-23-012-H01-P

PAs: NCCN has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 1.0 AAPA Category 1 CME credit. Approval is valid until December 10, 2024. PAs should only claim credit commensurate with the extent of their participation.

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: (1) review the educational content; (2) take the posttest with a 66% minimum passing score and complete the evaluation at **https://education.nccn.org/node/92953**; and (3) view/print certificate.

Pharmacists: You must complete the posttest and evaluation within 30 days of the activity. Continuing pharmacy education credit is reported to the CPE Monitor once you have completed the posttest and evaluation and claimed your credits. Before completing these requirements, be sure your NCCN profile has been updated with your NAPB e-profile ID and date of birth. Your credit cannot be reported without this information. If you have any questions, please email education@nccn.org.

Release date: December 10, 2023; Expiration date: December 10, 2024

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Cervical Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Cervical Cancer

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients.

Individuals Who Provided Content Development and/or Authorship Assistance:

The faculty listed below have no relevant financial relationship(s) with ineligible companies to disclose.

Catheryn M. Yashar, MD, Panel Vice Chair
Nicole R. McMillian, MS, CHES, Senior Guidelines Coordinator, NCCN
Shaili Aggarwal, PhD, Oncology Scientist/Medical Writer, NCCN
Sara Espinosa, PhD, Oncology Scientist, Medical Writer

The faculty listed below have the following relevant financial relationship(s) with ineligible companies to disclose. All of the relevant financial relationships listed for these individuals have been mitigated.

Nadeem R. Abu-Rustum, MD, Panel Chair, has disclosed receiving grant/research support from GRAIL.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

This activity is supported by educational grants from AstraZeneca; Exact Sciences; Novartis; and Taiho Oncology, Inc. This activity is supported by an independent educational grant from Daiichi Sankyo. This activity is supported by independent medical education grants from Illumina, Inc. and Regeneron Pharmaceuticals, Inc.

Cervical Cancer, Version 1.2024

Featured Updates to the NCCN Guidelines

Nadeem R. Abu-Rustum, MD[1,*]; Catheryn M. Yashar, MD[2,*]; Rebecca Arend, MD[3]; Emma Barber, MD[4]; Kristin Bradley, MD[5]; Rebecca Brooks, MD[6]; Susana M. Campos, MD, MPH, MS[7]; Junzo Chino, MD[8]; Hye Sook Chon, MD[9]; Marta Ann Crispens, MD[10]; Shari Damast, MD[11]; Christine M. Fisher, MD, MPH[12]; Peter Frederick, MD[13]; David K. Gaffney, MD, PhD[14]; Stephanie Gaillard, MD, PhD[15]; Robert Giuntoli II, MD[16]; Scott Glaser, MD[17]; Jordan Holmes, MD, MPH[18]; Brooke E. Howitt, MD[19]; Jayanthi Lea, MD[20]; Gina Mantia-Smaldone, MD[21]; Andrea Mariani, MD[22]; David Mutch, MD[23]; Christa Nagel, MD[24]; Larissa Nekhlyudov, MD, MPH[7]; Mirna Podoll, MD[10]; Kerry Rodabaugh, MD[25]; Ritu Salani, MD, MBA[26]; John Schorge, MD[27]; Jean Siedel, DO, MS[28]; Rachel Sisodia, MD[29]; Pamela Soliman, MD, MPH[30]; Stefanie Ueda, MD[31]; Renata Urban, MD[32]; Emily Wyse[33]; Nicole R. McMillian, MS, CHES[34,*]; Shaili Aggarwal, PhD[34,*]; and Sara Espinosa, PhD[34,*]

ABSTRACT

The NCCN Guidelines for Cervical Cancer provide recommendations for all aspects of management for cervical cancer, including the diagnostic workup, staging, pathology, and treatment. The guidelines also include details on histopathologic classification of cervical cancer regarding diagnostic features, molecular profiles, and clinical outcomes. The treatment landscape of advanced cervical cancer is evolving constantly. These NCCN Guidelines Insights provide a summary of recent updates regarding the systemic therapy recommendations for recurrent or metastatic disease.

J Natl Compr Canc Netw 2023;21(12):1224–1233
doi:10.6004/jnccn.2023.0062

[1]Memorial Sloan Kettering Cancer Center; [2]UC San Diego Moores Cancer Center; [3]O'Neal Comprehensive Cancer Center at UAB; [4]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [5]University of Wisconsin Carbone Cancer Center; [6]UC Davis Comprehensive Cancer Center; [7]Dana-Farber/Brigham and Women's Cancer Center; [8]Duke Cancer Institute; [9]Moffitt Cancer Center; [10]Vanderbilt-Ingram Cancer Center; [11]Yale Cancer Center/Smilow Cancer Hospital; [12]University of Colorado Cancer Center; [13]Roswell Park Comprehensive Cancer Center; [14]Huntsman Cancer Institute at the University of Utah; [16]Abramson Cancer Center at the University of Pennsylvania; [17]City of Hope National Medical Center; [18]Indiana University Melvin and Bren Simon Comprehensive Cancer Center; [19]Stanford Cancer Institute; [20]UT Southwestern Simmons Comprehensive Cancer Center; [21]Fox Chase Cancer Center; [22]Mayo Clinic Comprehensive Cancer Center; [23]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [24]The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute; [25]Fred & Pamela Buffett Cancer Center; [26]UCLA Jonsson Comprehensive Cancer Center; [27]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [28]University of Michigan Rogel Cancer Center; [29]Mass General Cancer Center; [30]The University of Texas MD Anderson Cancer Center; [31]UCSF Helen Diller Family Comprehensive Cancer Center; [32]Fred Hutchinson Cancer Center; [15]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [33]Patient Advocate; and [34]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

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

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

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

SYSTEMIC THERAPY FOR CERVICAL CANCER[a]

Squamous Cell Carcinoma, Adenocarcinoma, or Adenosquamous Carcinoma		
Chemoradiation[b]	**Recurrent or Metastatic Disease**	
	First-line Therapy[b,d]	**Second-line or Subsequent Therapy[i]**
Preferred Regimens • Cisplatin • Carboplatin if patient is cisplatin intolerant **Other Recommended Regimens[c] (if cisplatin and carboplatin are unavailable)** • Capecitabine/mitomycin[1] • Gemcitabine[2] • Paclitaxel[3,4]	**Preferred Regimens** • PD-L1–positive tumors ▸ Pembrolizumab + cisplatin/paclitaxel ± bevacizumab (category 1)[e,f,g,h,5] ▸ Pembrolizumab + carboplatin/paclitaxel ± bevacizumab (category 1)[e,f,g,h,5] • Cisplatin/paclitaxel/bevacizumab[e,h,6] (category 1) • Carboplatin/paclitaxel/bevacizumab[e,h] **Other Recommended Regimens** • Cisplatin/paclitaxel (category 1)[7,8] • Carboplatin/paclitaxel[9,10] (category 1 for patients who have received prior cisplatin therapy) • Topotecan/paclitaxel/bevacizumab[e,h,6,11] (category 1) • Topotecan/paclitaxel[11] • Cisplatin/topotecan[11] • Cisplatin[8] • Carboplatin[12,13]	**Preferred Regimens** • Pembrolizumab for TMB-H tumors[f,j] or PD-L1–positive[g] or MSI-H/dMMR tumors[f,14] • Tisotumab vedotin-tftv[15] • Cemiplimab[f,16] **Other Recommended Regimens** • Bevacizumab[e] • Paclitaxel[13,17] • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan **Useful in Certain Circumstances** • PD-L1–positive tumors ▸ Nivolumab[f,g,18] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[19] • RET gene fusion-positive tumors ▸ Selpercatinib • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

Footnotes on CERV-F 1A of 3

Continued

References

Overview

An estimated 13,960 new cases of carcinoma of the uterine cervix (ie, cervical cancer) will be diagnosed in the United States in 2023, and an estimated 4,310 people will die of the disease.[1] Overall, cervical cancer rates are decreasing in the United States, although incidence remains high among Hispanic/Latino, Black, and Asian populations.[2–5] In 2020, the global new cases of and deaths from cervical cancer were estimated to be 604,127 and 341,831, respectively.[6] It is the fourth most common cancer in individuals assigned female at birth worldwide,[7,8] with 85% of cases occurring in developing countries, where cervical cancer is a leading cause of cancer death in individuals assigned female at birth.[6,9] Squamous cell carcinoma (SCC), adenocarcinoma (AC), and adenosquamous carcinoma (ASC) are the 3 common histologies of cervical cancer. SCC accounts for approximately 80% of all cervical cancers and AC accounts for approximately 20%. In developed countries, the substantial decline in incidence and mortality of SCC of the cervix is presumed to be the result of effective screening and higher HPV vaccination coverage, although racial, ethnic, and geographic disparities exist.[2,3,10–12] However, AC and ASC of the cervix have increased over the past 3 decades, probably because cervical cytologic screening methods are less effective for AC/ASC because the lesions are located deeper than the ectocervix.[13–17] The ASC subtype is rare and accounts for approximately 5% to 6% of all cervical carcinomas. Presently, there is no difference in treatment between SCC and AC/ASC cervical cancer subtypes, although the clinical features and prognosis of disease vary considerably between these subtypes.

Persistent HPV infection is a major factor in the development of cervical cancer.[18,19] The incidence of cervical cancer appears to be related to the prevalence of HPV in the population. In countries with a high incidence of cervical cancer, the prevalence of chronic HPV is approximately 10% to 20%, whereas in low-incidence countries it is 5% to 10%.[7] Screening methods using HPV testing may increase detection of adenocarcinoma. Vaccination with HPV vaccines may also decrease the incidence of both SCC and AC.[15,20] Although most studies report that most cervical cancers are caused by HPV, approximately 5% of the tumors are reported as HPV-independent tumors.[21,22] In 2020, the WHO updated the Female Genital Tumors classification of cervical cancer by subdividing the cervical cancer lesions into HPV-associated and HPV-independent tumors based on new pathologic findings.[23]

SYSTEMIC THERAPY FOR CERVICAL CANCER[a]
FOONOTES FOR CERV-F 1 OF 3

[a] Cisplatin, carboplatin, docetaxel, and paclitaxel may cause drug reactions (See NCCN Guidelines for Ovarian Cancer–Management of Drug Reactions [OV-D]).
[b] Cost and toxicity, especially when using extended field RT, should be carefully considered when selecting an appropriate regimen for treatment.
[c] These agents may be considered when cisplatin and carboplatin are unavailable.
[d] If not used previously, these agents can be used as second-line or subsequent therapy as clinically appropriate.
[e] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[f] NCCN Guidelines for the Management of Immunotherapy-Related Toxicities.
[g] Recommended in patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory.
[h] Checkpoint inhibitors and/or monoclonal antibodies included in this regimen may be continued as maintenance therapy. Refer to the original study protocol for maintenance therapy dosing schedules.
[i] Additional references for second-line therapy are provided in the Discussion.
[j] For the treatment of patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors, as determined by an FDA-approved assay, or a validated test performed in a CLIA-certified laboratory, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Continued
References
CERV-F
1A OF 3

Among these subtypes, HPV-associated SCC is the most prevalent, with very rare occurrences of HPV-independent SCC. The HPV-independent AC subtype has a less favorable prognosis compared with HPV-associated AC. The NCCN Cervical Cancer Panel acknowledges that although the prior versions of the WHO classification discussed these tumors based on morphologic features, the integration of the immunohistochemical and molecular profiles has led to a better classification system, which is now adapted in the 2020 WHO Classification of Female Genital Tumors for cervical cancer.[23]

Regardless of cancer subtype and HPV infection status, primary treatment with curative intent for patients with cervical cancer typically consists of surgery, chemoradiation, or a combination of these treatments; options vary by cancer stage. These NCCN Guidelines Insights highlight the recent updates to the systemic therapy options for the treatment of cervical cancer.

Systemic Therapy Recommendations for Cervical Cancer

Chemoradiation for Locally Advanced Cervical Cancer

Concurrent chemoradiation, using platinum-containing chemotherapy (cisplatin alone [preferred] or cisplatin/fluorouracil), is the treatment of choice for stages IB3, II, III, and IVA disease based on the results of randomized clinical trials.[24–29] These trials have shown that the use of concurrent chemoradiation results in a 30% to 50% decrease in the risk of death compared with radiotherapy (RT) alone. Long-term follow-up of 3 trials has confirmed that concurrent cisplatin-containing chemoradiation improves progression-free survival (PFS) and overall survival (OS) when compared with RT with (or without) hydroxyurea.[30–32] In the NCCN Guidelines, cisplatin remains the preferred radiosensitizing agent in the primary treatment of patients with locally advanced cervical cancer when used concomitantly with external-beam RT. The guidelines recommend carboplatin as a preferred radiosensitizing agent for patients who are cisplatin-intolerant.[33] The NCCN Cervical Cancer Panel recently included alternative radiosensitizing agents that could be considered for use only when cisplatin and carboplatin are unavailable (see CERV-F 1 of 3, above). The options of capecitabine/mitomycin, gemcitabine, and paclitaxel were added under "Other Recommended Regimens" as radiosensitizers based on a few early-phase studies that have shown their efficacy and tolerability when administered concomitantly with radiation.[34–36]

A phase III randomized trial enrolling 926 patients with locally advanced cervical cancer of stage II–IVA

evaluated the efficacy of RT + concurrent chemotherapy consisting of oral 5-fluorouracil/mitomycin compared with RT only, RT + adjuvant chemotherapy (5-fluorouracil), or RT + concurrent chemoradiotherapy + adjuvant chemotherapy.[34] Although acute side effects were more prevalent in the concurrent arm and the OS was not significant between the arms, the RT + concurrent chemotherapy arm showed the least locoregional recurrence and the highest 5-year disease-free survival (DFS) when compared with the other arms. In particular, the differences in DFS and OS rates were highly significant when comparing the concurrent chemoradiation arm with the RT-only arm (P=.0001). Several studies have shown that although 5-fluorouracil/mitomycin combined with RT was effective, the combination is also associated with relatively higher toxicity rates and should be used with caution.[37,38] The efficacy and safety of gemcitabine combined with pelvic radiation was tested in 19 patients with chemotherapy-naïve, advanced stage IIIB cervical cancer and showed a complete response (CR) of 89.5% and partial response (PR) of 5.3%, for an overall response rate (ORR) of 94.7%. The OS at a median follow-up time of 19.9 months was 100%, with a DFS of 84.2%. Due to gemcitabine's high potency as a radiosensitizer, it requires reduced dosing when used concurrently with radiation to avoid radiation toxicity.[35] In a comparative study, the disease control and toxicity profile were found to be similar between cisplatin and gemcitabine.[39] The benefit of paclitaxel alone as a radiosensitizer has not been extensively studied in the literature and there are only a few known preclinical or early-phase studies of its efficacy. In a pilot study to evaluate paclitaxel with RT, CR was achieved by 8 of 13 patients with locally advanced cervical cancer and by 4 of 6 patients treated with a recurrent disease.[40] Although chemoradiation is tolerated, acute and long-term side effects have been reported.[41–43] Due to significant toxicity concerns associated with these agents, the panel continues to prefer cisplatin or carboplatin as preferred agents over other nonplatinum chemoradiation regimens. The NCCN panel has noted for all chemoradiation agents that the cost and toxicity profiles of these radiosensitizing agents should be considered when selecting an appropriate regimen for treatment, and has strongly expressed that this is especially critical when these regimens are being used for extended-field RT where toxicities may be more severe (CERV-F 1A of 3, page 1228).

First-Line Systemic Therapy Options for Recurrent or Metastatic Cervical Cancer

The estimated 5-year survival rate for patients with early-stage cervical cancer is >90%, whereas the curative options for advanced-stage disease are limited.[44] Systemic therapy with or without radiation forms the basis of treatment for patients with recurrent or metastatic disease.

Chemotherapy as First-Line Therapy

Cisplatin has been considered the most effective agent for metastatic cervical cancer. However, most patients who develop metastatic disease have received concurrent cisplatin/RT as primary treatment and may no longer be sensitive to single-agent platinum therapy.[45,46] The combination of platinum-based chemotherapy (cisplatin or carboplatin)/paclitaxel/bevacizumab has been extensively investigated in clinical studies, and these combinations are among the preferred, first-line treatment options for patients with recurrent/metastatic cervical cancer in the NCCN Guidelines. In addition, the panel has continued to recommend other platinum-containing combination regimens, such as cisplatin/paclitaxel (category 1), carboplatin/paclitaxel (category 1), topotecan/paclitaxel/bevacizumab (category 1), topotecan/paclitaxel, and cisplatin/topotecan as appropriate alternate options for certain patients in the "Other Recommended Regimens" category.[45–50] The panel also recommends single-agent cisplatin and carboplatin as other recommended regimens. In previous versions of the guidelines, cisplatin appeared in the "Preferred, First-Line Single-Agent" category. However, based on the panel's clinical judgement, as more effective treatment options are increasingly being available in the first-line setting, platinum-based single-agent chemotherapy has been reserved as alternate options under "Other Recommended Regimens."

Pembrolizumab Plus Chemotherapy With or Without Bevacizumab as First-Line Therapy

Over the years, systemic therapy options for cervical cancer have undergone a paradigm shift due to the growing number of newer treatment options available with meaningful improvement in survival rates. In addition, because the importance of testing for the presence of certain biomarkers in advanced disease is well recognized, the availability of several agents targeting these specific biomarkers has led to improved outcomes in patients. Several new biomarker-based immune-oncologic agents have been added to the guidelines for the management of recurrent/metastatic cervical cancer in recent years. Currently, the guidelines include 2 immunotherapy-based regimens as preferred, first-line therapy options for the treatment of PD-L1–positive recurrent or metastatic cervical cancer. Pembrolizumab combined with chemotherapy, with or without bevacizumab, is the preferred, category 1 treatment option based on the results of the KEYNOTE-826 study.[51] In the primary analysis of the phase III KEYNOTE-826 trial, which enrolled 617 patients (548 with PD-L1–positive combined positive score [CPS] ≥1 tumors; 317 with CPS ≥10) with previously untreated persistent, recurrent, or metastatic cervical cancer, the addition of pembrolizumab to chemotherapy with or without bevacizumab improved PFS and OS compared with the placebo group (PFS: 10.4 vs 8.2 months, respectively; hazard ratio

[HR], 0.65; 95% CI, 0.53–0.79; $P<.001$, and OS at 24 months: 50.4% vs 40.4%, respectively; HR, 0.67; 95% CI, 0.54–0.84; $P<.001$). The ORR was significantly higher in the pembrolizumab arm compared with the placebo group among the patients with PD-L1–positive (CPS ≥1) tumors (68.1% vs 50.2%). Based on the results of the KEYNOTE-826 trial, the FDA approved pembrolizumab in combination with chemotherapy, with or without bevacizumab, for patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1). In the final, updated analysis of the trial presented at the 2023 ASCO Annual Meeting, the addition of pembrolizumab to chemotherapy with or without bevacizumab continued to show significant survival benefits in patients with PD-L1–positive (CPS ≥1) tumors at a median follow-up of 39.1 months, with median OS and PFS of 28.6 and 10.5 months versus 16.5 and 8.2 months in the pembrolizumab + chemotherapy arm versus the placebo + chemotherapy arm, respectively (HR, 0.60; 95% CI, 0.49–0.74; $P<.0001$).[52] The NCCN panel continues to recommend pembrolizumab for patients whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved assay or a validated test performed in a CLIA-certified laboratory. The panel revised the language for the assays used in the determination of specific biomarkers by including tests that are either approved by the FDA or are validated tests performed in CLIA-certified laboratories (CERV-F 1A of 3, page 1228).

Second-Line/Subsequent Systemic Therapy Options for Recurrent or Metastatic Cervical Cancer

The treatment options for patients who experience disease progression after first-line therapies have mostly been of limited effect, with low response rates to second-line and subsequent chemotherapies and a median PFS of approximately 3 to 6 months.[53,54]

Chemotherapy as Other Recommended, Second-Line/ Subsequent Therapy

During the Version 1.2023 updates of the NCCN Guidelines, the panel reevaluated the list of single-agent chemotherapies included as second-line/subsequent therapy options in the "Other Recommended Regimens" category by revoting on each of these agents for their efficacy and use based on panel members' clinical experience and judgement. The panel agreed to include the following options as second-line/subsequent treatment: bevacizumab, paclitaxel, albumin-bound paclitaxel, docetaxel, fluorouracil, gemcitabine, pemetrexed, topotecan, vinorelbine, and irinotecan. All agents were added as category 2A options, except irinotecan. Single-agents ifosfamide and mitomycin were no longer recommended by the panel as options for second-line/subsequent therapies in Version 1.2023. Furthermore, irinotecan, which was previously a category 2B option, was changed to category 2A, other recommended option, in the recently updated Version 1.2024 (CERV-F 1 of 3, page 1227).

Immunotherapy as Preferred, Second-Line/ Subsequent Therapy

Increasingly available data from several prospective studies have demonstrated the effectiveness of immunotherapies or specific biomarker-based therapies in the setting of disease progression and has significantly transformed the management of cervical cancer. In addition, many biomarker-specific therapies have demonstrated meaningful clinical efficacy and durability regardless of the underlying tumor type leading to an increase in tumor-agnostic regulatory approvals.

Pembrolizumab as a Preferred, Second-Line/ Subsequent Therapy

Pembrolizumab is an FDA-approved therapy for patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy for PD-L1–positive tumors (CPS ≥1). It is also approved for unresectable or metastatic microsatellite instability–high/mismatch repair–deficient (MSI-H/dMMR) or tumor mutational burden–high (TMB-H) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options. In the NCCN Guidelines, pembrolizumab monotherapy is the preferred, second-line therapy option for recurrent/metastatic MSI-H/dMMR or TMB-H or PD-L1–positive tumors based on results from KEYNOTE-028 (phase Ib) and KEYNOTE-158 (phase II) trials.[55–57]

Tisotumab Vedotin-tftv as a Preferred, Second-Line/ Subsequent Therapy

Tisotumab vedotin-tftv is an antibody–drug conjugate directed against tissue factor that is aberrantly expressed across multiple solid tumors and is associated with poor clinical outcomes and an increase in metastatic potential. Studies have indicated that tissue factor is highly prevalent in cervical cancer and might have a role in disease progression and poor patient outcome in the clinic.[58] The phase I/II, innovaTV 201 trial enrolled 147 patients with pretreated advanced or metastatic solid tumors, including 34 patients with advanced cervical cancer, in the dose expansion phase of the study to evaluate the safety and durability of tisotumab vedotin-tftv.[59,60] The ORR was 15.6% (95% CI, 10.2%–22.5%) with a median duration of response (DoR) of 5.7 months (95% CI, 3.0–9.5 months), and the median PFS was 3 months (range, 2.8–4.1 months). Among the patients with cervical cancer, an overall response was achieved by 9 of 34 (ORR, 26.5%; 95% CI, 12.9%–44.4%). The study protocol was further amended to include additional patients in the cervical cancer expansion cohort. Among a total of 55 patients enrolled in the

cervical cancer cohort, a confirmed overall response was achieved in 22% (95% CI, 12%–35%), with a median DoR of 6.0 months (95% CI, 1.0–9.7 months) and median PFS of 4.1 months (range, 1.7–6.7 months). This study was followed by the innovaTV 204 trial, a phase II single-arm study that evaluated the efficacy of tisotumab vedotin-tftv in 102 patients with recurrent or metastatic cervical cancer who experienced disease progression on previous systemic therapy.[61] At the median follow-up of 10 months, the confirmed ORR was 24% (95% CI, 16%–33%) which included 7% CR and 17% PR, and the median DoR was 8.3 months (95% CI, 4.2 months–not reached). Following the results from innovaTV 201 and innovaTV 204 trials that showed clinically meaningful and durable activity of tisotumab vedotin-tftv against pretreated recurrent/metastatic cervical cancer, the FDA approved it as a therapy for adult patients with recurrent or metastatic cervical cancer who experienced disease progression on or after chemotherapy.[62] In the ongoing phase III, randomized, innovaTV 301 trial, the efficacy and safety of tisotumab vedotin-tftv are being evaluated in 502 patients with pretreated advanced/metastatic cervical cancer, compared with an investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) (ClinicalTrials.gov identifier: NCT04697628). The interim analysis of the study has shown significant improvement in OS compared with chemotherapy.[63] The NCCN Guidelines recommend tisotumab vedotin-tftv as a preferred therapy option for the treatment of recurrent/metastatic cervical cancer with disease progression on or after chemotherapy regardless of biomarker status. It was included under "Other Recommended Regimens" in previous versions of the guidelines and was moved to "Preferred Options" in Version 1.2023 (CERV-F 1 of 3, page 1227).

Cemiplimab as a Preferred, Second-Line/ Subsequent Therapy

Cemiplimab is a PD-1–blocking monoclonal activity shown to have antitumor activity against cervical cancer. The phase III, randomized, EMPOWER-Cervical 1 clinical trial evaluated the efficacy of cemiplimab or investigator's choice of chemotherapy (topotecan, vinorelbine, gemcitabine, irinotecan, or pemetrexed) in patients with recurrent or metastatic cervical cancer whose disease had progressed on prior therapy.[64] The trial enrolled 608 patients who had previously received ≥1 lines of systemic therapy for recurrence, and randomized them to receive either cemiplimab or chemotherapy. The median OS and PFS were significantly longer in the cemiplimab arm versus the control arm (12.0 vs 8.5 months; HR, 0.69; 95% CI, 0.56–0.84; $P<.001$, and 2.8 vs 2.9 months; HR, 0.75; 95% CI, 0.63–0.89; $P<.001$, respectively).[65] A total of 16.4% of the patients in the cemiplimab arm achieved an objective response (95% CI, 12.5%–21.1%) compared with 6.3% (95% CI, 3.8%–9.6%) in the chemotherapy arm. Among patients with SCC cervical cancer, the median OS was 11.1 in the cemiplimab versus 8.8 months in the chemotherapy arm (HR, 0.73; 95% CI, 0.58–0.91), and was 13.3 versus 7.0 months (HR, 0.56; 95% CI, 0.36–0.85), respectively, for those with AC/ASC cervical cancer, indicating that there is an OS benefit irrespective of histology. In a subanalysis of the study,[66] samples from 254 patients were evaluated for PD-L1 expression to test the efficacy of cemiplimab in tumors with PD-L1 expression of ≥1%. The median OS of cemiplimab-treated PD-L1–expressed tumors (CPS ≥1) versus chemotherapy was 13.9 vs 9.3 months (HR, 0.70; 95% CI, 0.48–1.01), whereas the OS benefit for tumors with low PD-L1 expression (CPS <1) was comparable in the 2 arms; however, the authors of the study noted that due to smaller size of the subgroup population, reliable assessment of the benefits could not be made. In a 1-year follow-up analysis of this study, cemiplimab efficacy in PD-L1–positive (CPS ≥1) tumors was further tested by evaluating samples from 371 patients. Median OS in patients with PD-L1–positive (CPS ≥1) tumors was 12.1 versus 7.7 months (HR, 0.61; 95% CI, 0.45–0.83) in the cemiplimab versus chemotherapy arms, respectively, whereas in patients with PD-L1 CPS <1 tumors, OS was 10.8 versus 7.0 months (HR, 0.65; 95% CI, 0.43–0.98), respectively, indicating that cemiplimab has continued to show meaningful clinical benefits in both populations.[66] In Version 1.2024 of the NCCN Guidelines, cemiplimab was added as a preferred, second-line/subsequent therapy option (CERV-F 1 of 3, page 1227).

Biomarker-Directed, Useful in Certain Circumstances, Second-Line/Subsequent Therapy

The NCCN Guidelines for Cervical Cancer have included a list of biomarkers with their associated targeted treatments as second-line/subsequent therapies under "Useful in Certain Circumstances" options. The pathology section of the guidelines provides recommendations for individual biomarkers that should be evaluated for targeted therapy.

Nivolumab for PD-L1–Positive Tumor

Nivolumab, a checkpoint inhibitor, has shown efficacy in patients with recurrent/metastatic cervical cancer who received at least one prior chemotherapy regimen. The CheckMate 358, phase I/II single-arm trial evaluated 19 patients with advanced, pretreated, PD-L1–positive (CPS ≥1) cervical tumors.[67] The ORR was 26.3% (95% CI, 9.1%–51.2%) and the disease control rate (DCR) was 68.4% (95% CI, 43.4%–87.4%). The 12-month OS rate was 77.5% (95% CI, 50.5%–91.0%). The phase II NRG-GY002 trial showed low antitumor activity of nivolumab in 25 patients with pretreated persistent/recurrent cervical cancer; 36% of the patients had stable disease (90% CI, 20.2%−54.4%) as the

best response with a median duration of 5.7 months, and the PFS and OS at 6 months were 16% and 78.4%, respectively.[68,69] In Version 1.2023 of the NCCN Guidelines, the panel moved nivolumab from being a preferred, second-line or subsequent therapy option to the "Useful in certain Circumstances" category for PD-L1–positive tumors, and continues to recommend nivolumab in the same category in Version 1.2024.

Selpercatinib for RET *Gene Fusion–Positive Tumors*

RET gene fusions most commonly occur in thyroid and non–small cell lung cancers and are observed in <1% of patients with other solid tumors. In this small subset of patients, the prognosis of disease is poor in those who have experienced disease progression while on or after prior systemic therapy. The phase I/II LIBRETTO-001 multicenter, open-label trial evaluated the efficacy of selpercatinib in 806 patients with *RET*-mutant advanced solid tumors.[70] This interim analysis of the trial in a tumor-agnostic population, the efficacy and safety of selpercatinib was investigated in 41 patients with *RET* fusion–positive solid tumors across 14 tumor types who have experienced disease progression on or after previous systemic therapies or who had no satisfactory therapeutic options. The ORR was 43.9% (95% CI, 28.5%–60.3%), with median DoR of 24.5 months (95% CI, 9.2 months–not evaluable). Selpercatinib received tumor-agnostic approval by the FDA for patients with solid tumors with a *RET* gene fusion who have experienced disease progression on or after prior systemic treatment or who have no satisfactory alternative treatment options. The NCCN panel recommends selpercatinib as a biomarker-directed second-line/subsequent therapy in the "Useful in Certain Circumstances" category for *RET* gene fusion–positive tumors, given its efficacy in tumor-agnostic population. The panel also specified in the "Principles of Pathology" section of the guidelines that *RET* gene fusion testing may be considered for patients with locally advanced or metastatic cervical cancer.

TRK Inhibitors for NTRK *Gene Fusion–Positive Tumors*

In addition to selpercatinib, other targeted therapy regimens included in the NCCN Guidelines as biomarker-directed second-line/subsequent therapies that have been approved in a tumor-agnostic population are the tropomyosin receptor kinase (TRK) inhibitors, larotrectinib and entrectinib. Larotrectinib targets the TRK proteins that are encoded by the genes *NTRK1*, *NTRK2*, and *NTRK3*. *NTRK* gene fusions are found in approximately 1% of all solid tumors. In a primary analysis, the efficacy and safety of larotrectinib was reported in 55 patients enrolled in 3 clinical studies who had locally advanced or metastatic tumors with *NTRK* gene fusions and had experienced disease progression on standard chemotherapy received previously.[71] The 3 clinical studies included a phase I dose-finding study in adults, phase I/II dose-finding study in pediatric population, and a phase II single-arm basket trial. The ORR of larotrectinib in these 55 patients was 75% (95% CI, 61%–85%), with 13% CRs and 62% PRs; the median DoR and PFS had not been reached at the time. In a long-term follow-up analysis, of 153 patients, 121 had an objective response (79%; 95% CI, 72%–85%), with 16% having a CR, 63% having a PR, and 12% with stable disease.[72] The median DoR was 35.2 months (22.8 months–not estimable) and the median PFS was 28.3 months. Similarly, entrectinib showed a durable and clinically meaningful response in 54 patients with advanced/metastatic *NTRK* gene fusion tumors enrolled in 3 phase I/II clinical trials, with a 57.4% ORR, 10.4-month median DoR, and 11.2-month median PFS.[74] In a long-term efficacy and safety analysis in 121 patients at a median follow-up of 25.8 months, 61.2% had a CR or PR, with a median DoR of 20 months (95% CI, 13.0–38.2).[74] Both larotrectinib and entrectinib are FDA-approved for *NTRK* gene fusion–positive solid tumors for patients who have experienced disease progression after treatment or have no satisfactory standard therapy. The NCCN Guidelines recommend larotrectinib and entrectinib as a second-line/subsequent, useful in certain circumstances option for *NTRK* gene fusion–positive tumors and have changed the category of evidence from category 2B to category 2A (CERV-F 1 of 3, page 1227).

Trastuzumab Deruxtecan for HER2-Positive Tumors

Another tumor-agnostic study evaluated the durability and clinically meaningful response of trastuzumab deruxtecan across multiple HER2-expressing (immunohistochemistry [IHC] 3+ or 2+) advanced solid tumor types in patients who have experienced disease progression on prior therapy or who have no satisfactory alternative treatment options. HER2 expression is observed in a wide range of solid tumors and is an established prognostic biomarker for breast, gastric, and colorectal cancers. Cervical cancer has shown a HER2 positivity rate of approximately 2% to 6% in the literature.[75–77] The panel recommends HER2 IHC testing (with reflex to HER2 fluorescence in situ hybridization [FISH] for equivocal IHC) for advanced, metastatic, or recurrent cervical carcinoma in the "Principles of Pathology" section of the NCCN Guidelines (see CERV-A 1 of 7 in the full version of these guidelines at NCCN.org). Trastuzumab deruxtecan is an antibody–drug conjugate that contains the humanized anti-HER2 monoclonal antibody trastuzumab attached to the topoisomerase inhibitor deruxtecan.[78] In an interim analysis of DESTINY-PanTumor02, a phase II trial that enrolled 267 patients with locally advanced, unresectable, or metastatic HER2-expressing (IHC 3+ or 2+) solid tumors (including 40 patients with cervical cancer), the ORR was 37.1% (n=99; 95% CI, 31.3–43.2); median DoR was 11.3 months (95% CI, 9.6–17.8); median PFS was 6.9 months

(95% CI, 5.6–8.0); and median OS was 13.4 months (95% CI, 11.9–15.5).[79] In patients with cervical cancer, the confirmed ORR was 50% (95% CI, 33.8–66.2; 5% CR, 45% PR); median DoR was 14.2 months (95% CI, 4.1–NR); median OS was 13.6 months (95% CI, 11.1–NR); and DCR at 12 weeks was 67.5%. Version 1.2024 of the NCCN Guidelines include fam-trastuzumab deruxtecan-nxki as a category 2A, useful in certain circumstances, second-line/subsequent therapy option for HER2-positive tumors (IHC 3+ or 2+) (CERV-F 1 of 3, page 1227).

Summary

These NCCN Guidelines Insights focus on revisions and updates related to the systemic therapy options for patients with locally advanced or advanced/metastatic or recurrent cervical cancer. For a complete list of the recent updates, see Version 1.2024 of the NCCN Guidelines for Cervical Cancer at www.nccn.org.

To participate in this journal CE activity, go to https://education.nccn.org/node/92953

References

1. Siegel RL, Miller KD, Wagle NS, et al. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17–48.
2. Barnholtz-Sloan J, Patel N, Rollison D, et al. Incidence trends of invasive cervical cancer in the United States by combined race and ethnicity. Cancer Causes Control 2009;20:1129–1138.
3. Wang SS, Carreon JD, Gomez SL, et al. Cervical cancer incidence among 6 Asian ethnic groups in the United States, 1996 through 2004. Cancer 2010;116:949–956.
4. Howe HL, Wu X, Ries LA, et al. Annual report to the nation on the status of cancer, 1975-2003, featuring cancer among U.S. Hispanic/Latino populations. Cancer 2006;107:1711–1742.
5. Sherman ME, Wang SS, Carreon J, et al. Mortality trends for cervical squamous and adenocarcinoma in the United States. Relation to incidence and survival. Cancer 2005;103:1258–1264.
6. Global Cancer Observatory. Cancer over time. Accessed October 25, 2023. Available at: https://gco.iarc.fr/overtime/en/dataviz/tables?hide_tab_age_specific_numbers=1&mode=population&years=2012
7. Parkin DM, Bray F, Ferlay J, et al. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74–108.
8. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24:2137–2150.
9. Jemal A, Bray F, Center MM, et al. Global cancer statistics. CA Cancer J Clin 2011;61:69–90.
10. Bray F, Loos AH, McCarron P, et al. Trends in cervical squamous cell carcinoma incidence in 13 European countries: changing risk and the effects of screening. Cancer Epidemiol Biomarkers Prev 2005;14:677–686.
11. Watson M, Saraiya M, Benard V, et al. Burden of cervical cancer in the United States, 1998-2003. Cancer 2008;113(10 Suppl):2855–2864.
12. de Martel C, Georges D, Bray F, et al. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Health 2020;8:e180–190.
13. Bray F, Carstensen B, Møller H, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 2005;14:2191–2199.
14. Wang SS, Sherman ME, Hildesheim A, et al. Cervical adenocarcinoma and squamous cell carcinoma incidence trends among white women and black women in the United States for 1976-2000. Cancer 2004;100:1035–1044.
15. Castellsagué X, Díaz M, de Sanjosé S, et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. J Natl Cancer Inst 2006;98:303–315.
16. Sasieni P, Castanon A, Cuzick J. Screening and adenocarcinoma of the cervix. Int J Cancer 2009;125:525–529.
17. Stolnicu S, Barsan I, Hoang L, et al. International Endocervical Adenocarcinoma Criteria and Classification (IECC): a new pathogenetic classification for invasive adenocarcinomas of the endocervix. Am J Surg Pathol 2018;42:214–226.
18. Kjær SK, Frederiksen K, Munk C, et al. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. J Natl Cancer Inst 2010;102:1478–1488.
19. Rodríguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. J Natl Cancer Inst 2010;102:315–324.
20. Dahlström LA, Ylitalo N, Sundström K, et al. Prospective study of human papillomavirus and risk of cervical adenocarcinoma. Int J Cancer 2010;127:1923–1930.
21. Schiffman M, Doorbar J, Wentzensen N, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Primers 2016;2:16086.
22. Burk RD, Chen Z, Saller C, et al. Integrated genomic and molecular characterization of cervical cancer. Nature 2017;543:378–384.
23. Höhn AK, Brambs CE, Hiller GGR, et al. 2020 WHO classification of female genital tumors. Geburtshilfe Frauenheilkd 2021;81:1145–1153.
24. Keys HM, Bundy BN, Stehman FB, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154–1161.
25. Morris M, Eifel PJ, Lu J, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137–1143.
26. Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606–1613.
27. Whitney CW, Sause W, Bundy BN, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 1999;17:1339–1348.
28. Rose PG, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144–1153.
29. Thomas GM. Improved treatment for cervical cancer—concurrent chemotherapy and radiotherapy. N Engl J Med 1999;340:1198–1200.
30. Rose PG, Ali S, Watkins E, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:2804–2810.
31. Eifel PJ, Winter K, Morris M, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. J Clin Oncol 2004;22:872–880.
32. Stehman FB, Ali S, Keys HM, et al. Radiation therapy with or without weekly cisplatin for bulky stage 1B cervical carcinoma: follow-up of a Gynecologic Oncology Group trial. Am J Obstet Gynecol 2007;197:503.e1–e6.
33. Nam EJ, Lee M, Yim GW, et al. Comparison of carboplatin- and cisplatin-based concurrent chemoradiotherapy in locally advanced cervical cancer patients with morbidity risks. Oncologist 2013;18:843–849.
34. Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-fluorouracil, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. Int J Radiat Oncol Biol Phys 2003;55:1226–1232.
35. Pattaranutaporn P, Thirapakawong C, Chansilpa Y, et al. Phase II study of concurrent gemcitabine and radiotherapy in locally advanced stage IIIB cervical carcinoma. Gynecol Oncol 2001;81:404–407.

36. Candelaria M, Garcia-Arias A, Cetina L, et al. Radiosensitizers in cervical cancer. Cisplatin and beyond. Radiat Oncol 2006;1:15.
37. Christie DR, Bull CA, Gebski V, et al. Concurrent 5-fluorouracil, mitomycin C and irradiation in locally advanced cervix cancer. Radiother Oncol 1995;37:181–189.
38. Rakovitch E, Fyles AW, Pintilie M, et al. Role of mitomycin C in the development of late bowel toxicity following chemoradiation for locally advanced carcinoma of the cervix. Int J Radiat Oncol Biol Phys 1997;38:979–987.
39. Verma AK, Arya AK, Kumar M, et al. Weekly cisplatin or gemcitabine concomitant with radiation in the management of locally advanced carcinoma cervix: results from an observational study. J Gynecol Oncol 2009;20:221–226.
40. Cerrotta A, Gardan G, Cavina R, et al. Concurrent radiotherapy and weekly paclitaxel for locally advanced or recurrent squamous cell carcinoma of the uterine cervix. A pilot study with intensification of dose. Eur J Gynaecol Oncol 2002;23:115–119.
41. Vale C, Tierney JF, Stewart LA, et al. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. J Clin Oncol 2008;26:5802–5812.
42. King M, McConkey C, Latief TN, et al. Improved survival after concurrent weekly cisplatin and radiotherapy for cervical carcinoma with assessment of acute and late side-effects. Clin Oncol (R Coll Radiol) 2006;18:38–45.
43. Tan LT, Zahra M. Long-term survival and late toxicity after chemoradiotherapy for cervical cancer—the Addenbrooke's experience. Clin Oncol (R Coll Radiol) 2008;20:358–364.
44. Tabatabaei FS, Saeedian A, Azimi A, et al. Evaluation of survival rate and associated factors in patients with cervical cancer: a retrospective cohort study. J Res Health Sci 2022;22:e00552.
45. Moore DH, Blessing JA, McQuellon RP, et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. J Clin Oncol 2004;22:3113–3119.
46. Long HJ 3rd, Bundy BN, Grendys EC Jr, et al. Randomized phase III trial of cisplatin with or without topotecan in carcinoma of the uterine cervix: a Gynecologic Oncology Group Study. J Clin Oncol 2005;23:4626–4633.
47. Moore DH. Chemotherapy for advanced, recurrent, and metastatic cervical cancer. J Natl Compr Canc Netw 2008;6:53–57.
48. Tao X, Hu W, Ramirez PT, et al. Chemotherapy for recurrent and metastatic cervical cancer. Gynecol Oncol 2008;110Suppl 2):S67–71.
49. Monk BJ, Sill MW, McMeekin DS, et al. Phase III trial of four cisplatin-containing doublet combinations in stage IVB, recurrent, or persistent cervical carcinoma: a Gynecologic Oncology Group study. J Clin Oncol 2009;27:4649–4655.
50. Tewari KS, Sill MW, Penson RT, et al. Bevacizumab for advanced cervical cancer: final overall survival and adverse event analysis of a randomised, controlled, open-label, phase 3 trial (Gynecologic Oncology Group 240). Lancet 2017;390:1654–1663.
51. Colombo N, Dubot C, Lorusso D, et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. N Engl J Med 2021;385:1856–1867.
52. Monk BJ, Colombo N, Tewari KS, 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. J Clin Oncol 2023;41(Suppl):Abstract 5500.
53. Regalado Porras GO, Chávez Nogueda J, Poitevin Chacón A. Chemotherapy and molecular therapy in cervical cancer. Rep Pract Oncol Radiother 2018;23:533–539.
54. Boussios S, Seraj E, Zarkavelis G, et al. Management of patients with recurrent/advanced cervical cancer beyond first line platinum regimens: where do we stand? A literature review. Crit Rev Oncol Hematol 2016;108:164–174.
55. Frenel JS, Le Tourneau C, O'Neil B, et al. Safety and efficacy of pembrolizumab in advanced, programmed death ligand 1-positive cervical cancer: results from the phase Ib KEYNOTE-028 trial. J Clin Oncol 2017;35:4035–4041.
56. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the phase II KEYNOTE-158 study. J Clin Oncol 2020;38:1–10.
57. Maio M, Ascierto PA, Manzyuk L, et al. Pembrolizumab in microsatellite instability high or mismatch repair deficient cancers: updated analysis from the phase II KEYNOTE-158 study. Ann Oncol 2022;33:929–938.
58. Cocco E, Varughese J, Buza N, et al. Expression of tissue factor in adenocarcinoma and squamous cell carcinoma of the uterine cervix: implications for immunotherapy with hI-con1, a factor VII-IgGFc chimeric protein targeting tissue factor. BMC Cancer 2011;11:263.
59. de Bono JS, Concin N, Hong DS, et al. Tisotumab vedotin in patients with advanced or metastatic solid tumours (innovaTV 201): a first-in-human, multicentre, phase 1–2 trial. Lancet Oncol 2019;20:383–393.
60. Hong DS, Concin N, Vergote I, et al. Tisotumab vedotin in previously treated recurrent or metastatic cervical cancer. Clin Cancer Res 2020;26:1220–1228.
61. 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. Lancet Oncol 2021;22:609–619.
62. Heitz N, Greer SC, Halford Z. A review of tisotumab vedotin-tftv in recurrent or metastatic cervical cancer. Ann Pharmacother 2023;57:585–596.
63. Vergote IB, Gonzalez Martin A, Fujiwara K, et al. innovaTV 301/ENGOT-cx12/GOG-3057: a global, randomized, open-label, phase III study of tisotumab vedotin vs investigator's choice of chemotherapy in 2L or 3L recurrent or metastatic cervical cancer. Ann Oncol 2023;34(Suppl 2):S1276–1277. Abstract LBA9.
64. Oaknin A, Monk BJ, Vergote I, et al. EMPOWER Cervical-1: effects of cemiplimab versus chemotherapy on patient-reported quality of life, functioning and symptoms among women with recurrent cervical cancer. Eur J Cancer 2022;174:299–309.
65. Tewari KS, Monk BJ, Vergote I, et al. Survival with cemiplimab in recurrent cervical cancer. N Engl J Med 2022;386:544–555.
66. Oaknin A, Monk BJ, Polastro L, et al. Phase III EMPOWER-Cervical 1/GOG-3016/ENGOT-cx9 trial of cemiplimab in recurrent or metastatic (R/M) cervical cancer: long-term survival analysis. Ann Oncol 2022;33(Suppl 7):Abstract 519MO.
67. Naumann RW, Hollebecque A, Meyer T, et al. Safety and efficacy of nivolumab monotherapy in recurrent or metastatic cervical, vaginal, or vulvar carcinoma: results from the phase I/II CheckMate 358 Trial. J Clin Oncol 2019;37:2825–2834.
68. Yoshimoto D, Taguchi A, Tanikawa M, et al. Recurrent cervical cancer with PD-L1 amplification treated with nivolumab: a case enrolled in the BELIEVE trial. J Obstet Gynaecol Res 2022;48:2010–2014.
69. Santin AD, Deng W, Frumovitz M, et al. Phase II evaluation of nivolumab in the treatment of persistent or recurrent cervical cancer (NCT02257528/NRG-GY002). Gynecol Oncol 2020;157:161–166.
70. Subbiah V, Wolf J, Konda B, et al. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol 2022;23:1261–1273.
71. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731–739.
72. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol 2020;21:531–540.
73. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271–282.
74. Demetri GD, De Braud F, Drilon A, et al. Updated integrated analysis of the efficacy and safety of entrectinib in patients with NTRK fusion-positive solid tumors. Clin Cancer Res 2022;28:1302–1312.
75. Yan M, Schwaederle M, Arguello D, et al. HER2 expression status in diverse cancers: review of results from 37,992 patients. Cancer Metastasis Rev 2015;34:157–164.
76. Chavez-Blanco A, Perez-Sanchez V, Gonzalez-Fierro A, et al. HER2 expression in cervical cancer as a potential therapeutic target. BMC Cancer 2004;4:59.
77. Itkin B, Garcia A, Straminsky S, et al. Prevalence of HER2 overexpression and amplification in cervical cancer: a systematic review and meta-analysis. PLoS One 2021;16:e0257976.
78. Cai ZL, Yang HT, Huang T, et al. Efficacy and safety of trastuzumab deruxtecan in patients with solid tumors: a systematic review and meta-analysis of 3 randomized controlled trials. Am J Cancer Res 2023;13:3266–3274.
79. Meric-Bernstam, Makker V, Oaknin A, et al. Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: primary results from the DESTINY-PanTumor02 phase II trial. J Clin Oncol. Published online October 23, 2023. doi:10.1200/JCO.23.02005