At the Cervix of Change - Updates in Cervical Cancer

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Disclosures

- The following faculty speakers and/or planning committee members have disclosed the following:

Faculty Name	Name of Ineligible Companies	Nature of Relationship
Alex Wolff, BCOP, FHOPA	Syndax Pharmaceuticals	Oral menin inhibitor for acute myelogenous leukemia
Alex Wolff, BCOP, FHOPA	Bristol Myers Squibb	Idecabtagene vicleucel (Abcema®) CART in multiple myeloma

- The other planner(s) and speaker(s) have indicated that there are no relevant financial relationships with any ineligible companies to disclose. All of the relevant financial relationships listed for this individual have been mitigated.

Objectives

- Describe the epidemiology of cervical cancer, including affected populations, key risk factors, and current prevention strategies
- Explain cervical cancer staging and histologic subtypes
- Compare treatment strategies for localized, advanced, and metastatic or recurrent cervical cancer
- Identify supportive care considerations and common toxicity-management strategies in cervical cancer treatment

Abbreviations

- AUC: Area under the curve
- ADC: antibody drug conjugate
- AE: adverse effects
- ALT: alanine aminotransferase
- ASCO: American Society of Clinical Oncology
- AST: aspartate transaminase
- BG: blood glucose
- CBC: Complete blood count
- CID: Cervical intraepithelial dysplasia
- CIN: Cervical intraepithelial neoplasia
- CrCl: creatinine clearance
- CYP3A4: Cytochrome P450 3A4
- DNA: deoxyribose nucleic acid
- EBRT: external beam radiotherapy
- ECOG: Eastern Cooperative Oncology Group
- ESMO: European Society of Medical Oncology
- FIGO: International Federation of Gynecology and Obstetrics
- HER2: Human Epidermal Growth Factor Receptor 2
- HGB: hemoglobin
- HIV: Human immunodeficiency virus
- HPV: Human papilloma virus

Abbreviations

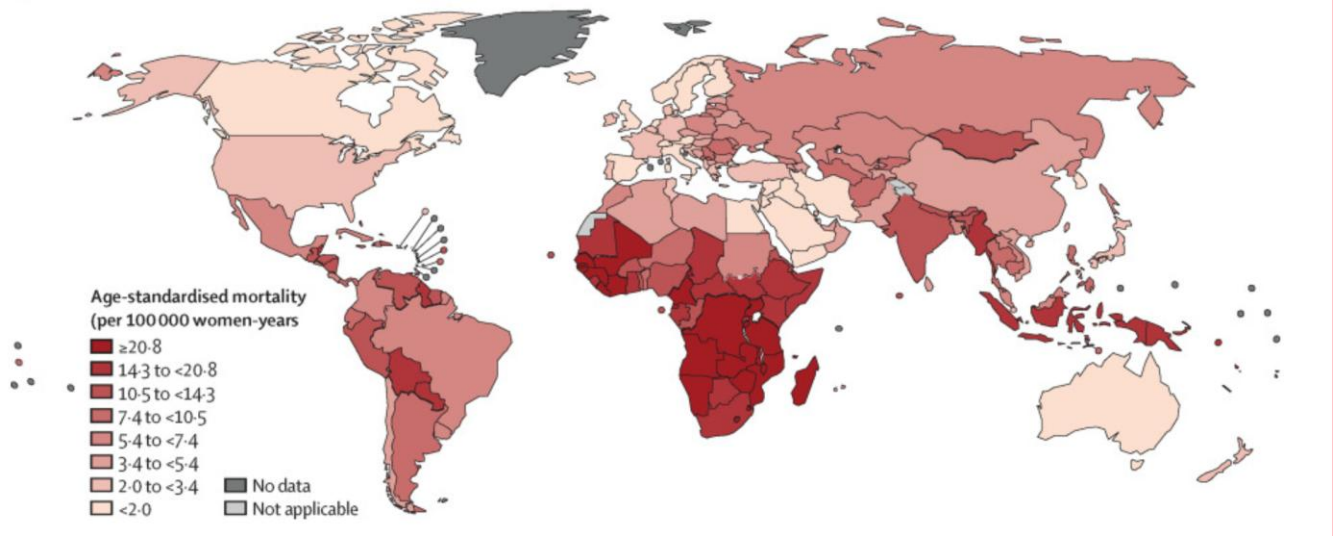
- HR: hazard ratio
- hrHPV: high-risk HPV
- IV: intravenous
- K: potassium
- LFT: liver function test
- MMR: Mismatch Repair
- MOA: mechanism of action
- MSI: Microsatellite
- Na: sodium
- NCCN: National Comprehensive Cancer Network
- NTRK: Neurotrophic tyrosine receptor kinase
- N/V: nausea and vomiting
- OS: overall survival
- PAP: Papaniculaou
- PDL-1: Program Death Ligand 1
- PFS: progression free survival
- PLT: platelets
- PO: oral
- QOL: quality of life
- RET: Rearranged during Transfection
- Scr: serum creatinine
- SLN: sentinel lymph node

Abbreviations

- STI: Sexually transmitted infection
- TF: tissue factor
- TMB: Tumor Mutational Burden
- TSH: thyroid stimulating hormone
- US: United States
- 5FU: 5-fluorouracil

Epidemiology

- Globally cervical cancer is the 4th most common cancer in women



Singh et al. *Lancet Glob Health.* 2023

Burden of Disease in the United States

- An estimated 13,360 new cases in 2025
- Accounts for 0.7% of all new cancer cases yearly
- 4,320 estimated deaths in 2025
- 5-year survival rate 68%
- Median age at diagnosis is 50 years old

Tewari et al. *N Eng J Med. 2025*

Risk Factors

- Early age for first intercourse
- Multiple sex partners
- Partners with multiple partners
- Lack of access to screening
- History of abnormal Papanicolaou (PAP) smears
- HPV infection
- Cervical dysplasia
- History of STIs
- Diagnosis of HIV

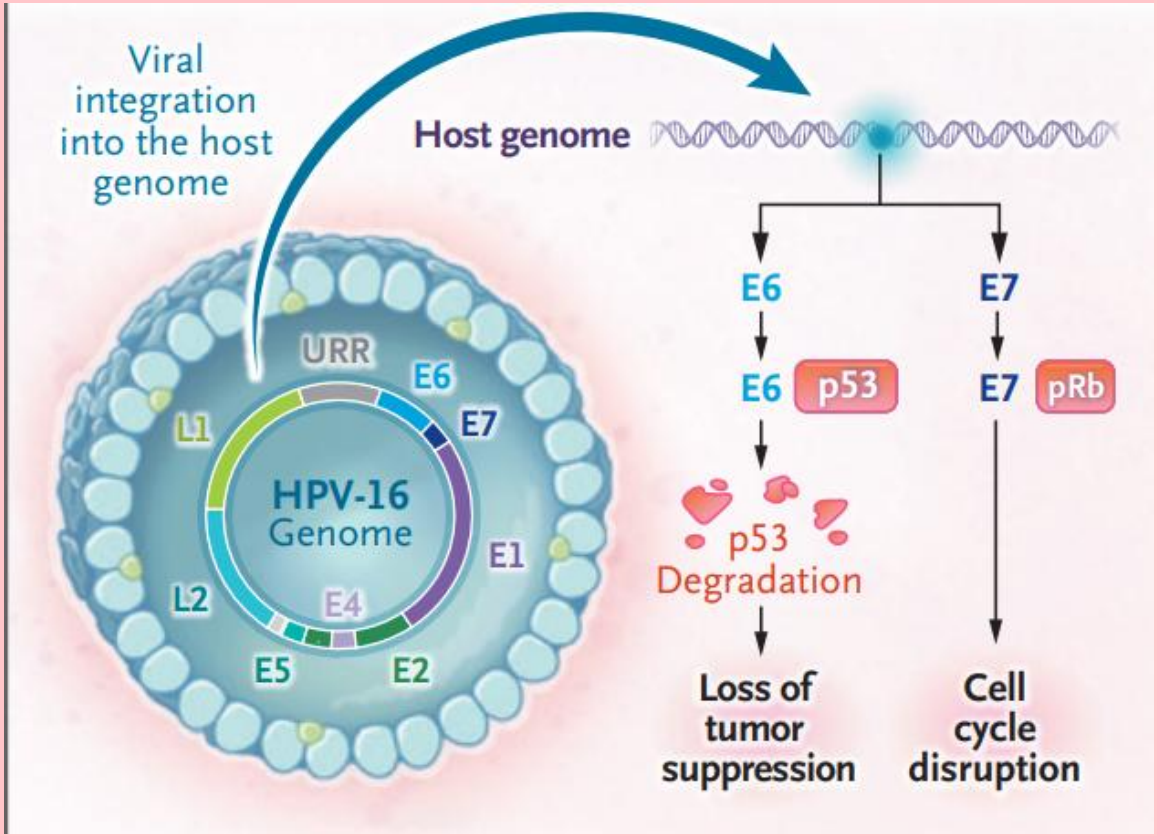
Shulman, et al. Prevention. 2025

Human Papilloma Virus

- Double-Stranded DNA Virus replicating as an episome within host cells
- High-risk HPV strains carry oncogenes that are normally regulated by the E2 protein
  - Disruption of E2 → uncontrolled oncogene expression → carcinogenesis
- Of the 448 HPV subtypes, ~15 are classified as high-risk (carcinogenic)
  - 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82
- Strain distribution in cervical cancer
  - HPV 16 → ~60% of cases
  - HPV 18 → ~15% of cases
  - And all other high-risk strains → 25% of cases

Tewari et al. N Eng J Med. 2025

Human Papilloma Virus Virology



Pathology

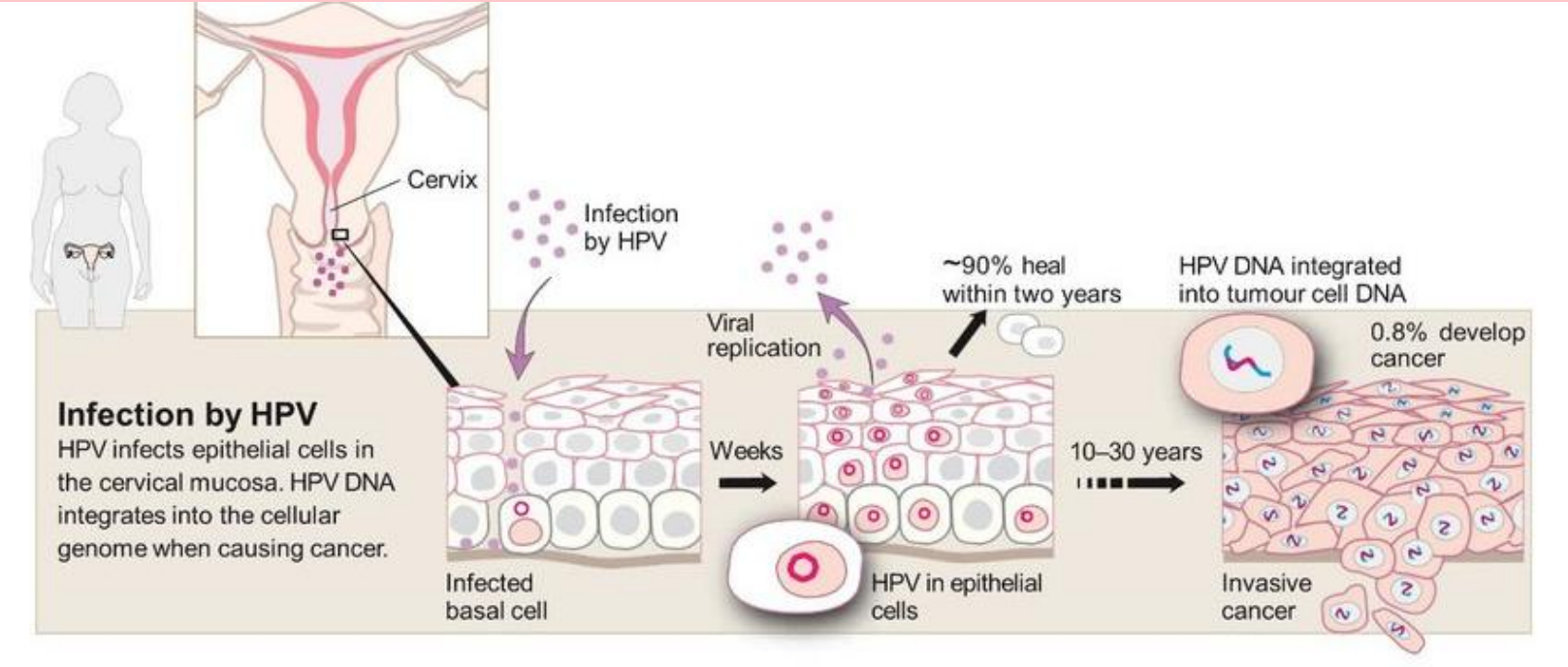


Image from Stark, et al. Acta Facultatis Medicae Naissensis 2018. Illustrator: Mattias Karlen

Prevention and Screening

HPV vaccine and PAP smears

"An ounce of prevention is worth a pound in cure"
- Benjamin Franklin

HPV Vaccine (Gardasil 9)

*Covers strains 6, 11, **16, 18,** 31, 33, 45, 52, and 58*

Ages 9-14 years

2-dose series
0 and 6-12 months

Ages 15-26 years

3 dose series
0, 1-2, and 6 months

Ages 27-45 years

Shared decision-making

CDC. Child and Adolescent Immunization by Age. 2025

Papanicolaou (PAP) Smear

- Screening procedure that collects cells from the cervix to detect early changes that could lead to cancer
  - Cytology: PAP smear which looks for abnormal cells
  - High-risk HPV testing (hrHPV): detects the presence of the HPV virus
- Possible results:
  - Normal: no abnormal cells were found
  - Unclear: cells look slightly different but may not be harmful
    - May need further testing
  - Abnormal: changes were found that may need to be watched more closely or treated
    - Atypical, precancerous, or cancerous cells

Pap Smear. UnitedHealth. 2025

Screening

Guidance from the US Preventive Services Task Force 2018

<21 years old

Do not screen

21-29 years old

Cytology every 3 years

30-65 years old

1. Cytology alone every 3 years
2. hrHPV testing every 5 years
3. Cytology and hrHPV testing every 5 years

>65 years old

No testing is needed if the earlier tests were negative

Hysterectomy

Do not screen

USPTF. JAMA. 2018
Bhalta, et al. Int J Gynaecol Obstet. 2021

Assessment Question 1

CJ is a 26-year-old female who is seeing her gynecologist for the first time since she was eighteen. She wants to know what screening she is due for and if there is anything she can do to prevent cervical cancer.

What are things that her doctor can talk to her about today? (select all that apply)

A. HPV vaccine

B. hrHPV testing

C. PAP smear

D. STI testing

Signs and symptoms

- **Often asymptomatic until later stages**
- Extreme fatigue
- Low appetite or unexplained weight loss
- Leg swelling or pain
- Mild pelvic discomfort
- Light bleeding or spotting between periods or after intercourse
- Unusual discharge
- HPV diagnosis
- Abnormal PAP test results

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCNGuidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

General Work up

- History and physical
- CBC
- Cervical biopsy
- Cone biopsy as indicated
- Imaging
- LFTs and renal function tests
- Smoking cessation
- Consider HIV testing
- Consider examination under anesthesia
- Consider referral to reproductive endocrinology and infertility specialist

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

Types of Cervical Cancer

Squamous Cell Carcinoma

- ~80%-90%

Endocervical Adenocarcinoma

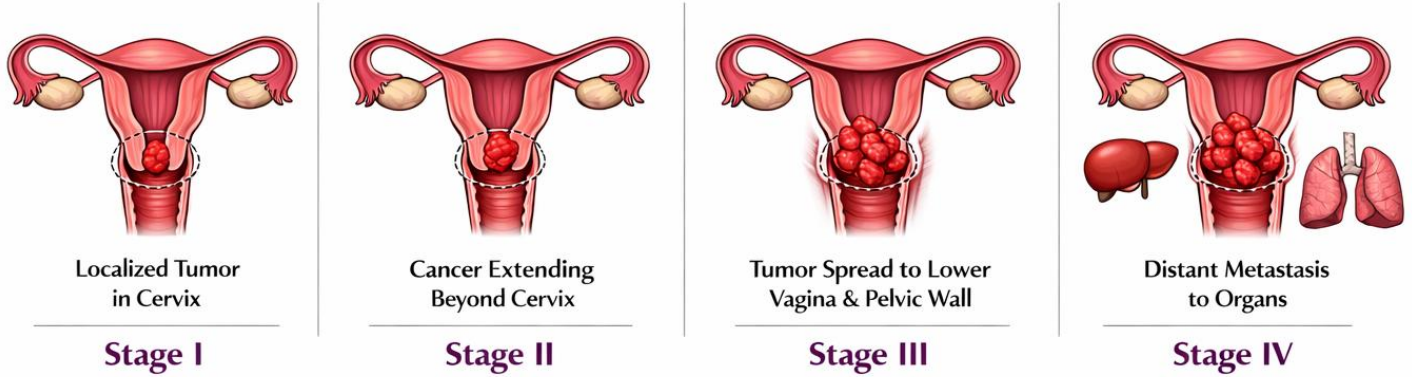
- ~20%

Adenosquamous Carcinoma

- ~5%-6%

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

2018 FIGO Staging



Pedersen, et al. Healthline. 2023
Image - Microsoft Copilot. Cervical cancer progression. 2026

Question 2

What is the most common type of cervical cancer which is also predominately caused by the HPV virus?

A. Squamous Cell Carcinoma

B. Endocervical Adenocarcinoma

C. Adenosquamous Carcinoma

D. Neuroendocrine Carcinoma

Treatment Evolution

1900s-1940s

Radical hysterectomy

1940s-1980s

PAP smear

1999

Shift to Chemoradiation with weekly cisplatin for Locally Advanced

2006

HPV vaccine approval

2014

Targeted therapy Bevacizumab for Metastatic/Recurrent

2018

Immunotherapy Pembrolizumab for Metastatic/Recurrent

2021

Antibody Drug Conjugate Tisotumab was approved for Metastatic/Recurrent

2024

Pembrolizumab approval for Locally Advanced

Treatment

Early Stage (IA-IIA1)

Locally Advanced (IB3, IIA2-IVA)

Metastatic (IVB)/Recurrent

Early Stage (IA-IIA1)

Early Stage (IA-IIA1)

- Surgery is the primary treatment, and the extent of surgery depends on whether the goal is fertility preservation and the extent of disease
  - Cone biopsy
  - Sentinel lymph node mapping
  - Trachelectomy and hysterectomy
- After surgery they look at the margins and lymph node involvement
  - Negative = surveillance
  - Positive = additional treatment
- Chemotherapy and radiation is added when there is more disease or surgery cannot be done

Rose et al., NEJM 1999

Locally Advanced
(Stage IB3, IIA2-IVA)

Locally Advanced (Stage IB3, IIA2-IVA)

Stage IB3 **Stage IIA2**	• Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy OR • Radical hysterectomy + pelvic lymphadencetomy ± para-aortic lymphadencetomy OR • Pelvic EBRT + concurrent platinum-containing chemotherapy + brachytherapy + selective completion hysterectomy
Stage IIB **Stage III** **Stage IVA**	<u>Negative for distant metastases</u> • EBRT + concurrent platinum-containing chemotherapy + brachytherapy ± pembrolizumab <u>Positive for distant metastases</u> • Systemic therapy ± individualized radiotherapy

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

Locally Advanced (Stage IB3, IIA2-IVA)

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)	
Preferred Regimens	**Other Recommended Regimens**

• Cisplatin + Pembrolizumab
  ○ Category 1: FIGO 2014 stage IIIA, IIIB, and IVA
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• Carboplatin + Pembrolizumab
• Cisplatin
• Carboplatin if cisplatin intolerant
	If single agent cisplatin and carboplatin are unavailable:
	• Capecitabine/Mitomycin
	• Gemcitabine
	• Paclitaxel
	
	Induction chemotherapy (followed by chemoradiation)
	• Carboplatin/Paclitaxel

All are in combination with radiation except induction chemotherapy

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Why Chemotherapy + Radiation?

- Concurrent chemoradiation is the standard of care for locally advanced cervical cancer
- Theoretically, chemotherapy and radiotherapy has a synergistic effect
    - Radiation provides local control while chemotherapy acts as a radiosensitizer
- What does it mean to be a radiosensitizer?
    - Radiation primarily works through DNA damage
    - Platinum agents intensify this damage by blocking DNA repair via DNA crosslinks
- Combining chemotherapy and radiation leads to more effective killing of cancer cells

Rose et al., NEJM 1999

Tangitgamol et al. Chochrane Database Syst Rev. 2024

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	Cisplatin	Carboplatin
Mechanism	Platinum based alkylating agent inhibits synthesis of DNA by forming crosslinks	Platinum analog of cisplatin causing DNA crosslinks
Dosing	CrCl ≥60: 40 mg/m^2 weekly	Dosed by AUC (Calvert Eq.) ▪ (CrCl +25) x AUC goal = dose(mg) • Weekly AUC goal = 2
Adverse effects	Renal toxicity • 1L pre and post infusion Ototoxicity Neuropathy High N/V • Pre-medicate	Myelosuppression Moderate neuropathy and ototoxicity Moderate to high N/V • Pre-medicate

Cisplatin (package insert). Pfizer; 2024, Carboplatin (package insert). Bristol Meyers Squibb; 2024.

Treatment Backbone

A Phase 3 Trial of Cisplatin-based Chemotherapy in Cervical Cancer (1999)	
Design	• Randomized phase III trial (N= 526)
Population	• Women with locally advanced cervical cancer (FIGO IIB, III, or IVA) without prior treatment
Comparison	• Group 1: Cisplatin 40 mg/m^2 per week x6 cycles + EBRT • Group 2: Cisplatin 50 mg/m^2 on days 1 and 29 followed by 5FU and hydroxyurea + EBRT • Group 3: Hydroxyurea 3g PO twice weekly for 6 weeks + EBRT
Results	• Risk of disease progression or death was 0.57 in group 1 and 0.55 in group 2 when compared to group 3 • OS rates were significantly higher in groups 1 and 2 (0.61 and 0.58)

Radiation and chemotherapy that contain cisplatin improve rates of OS and PFS among women with locally advanced cervical cancer

Rose et al., NEJM 1999

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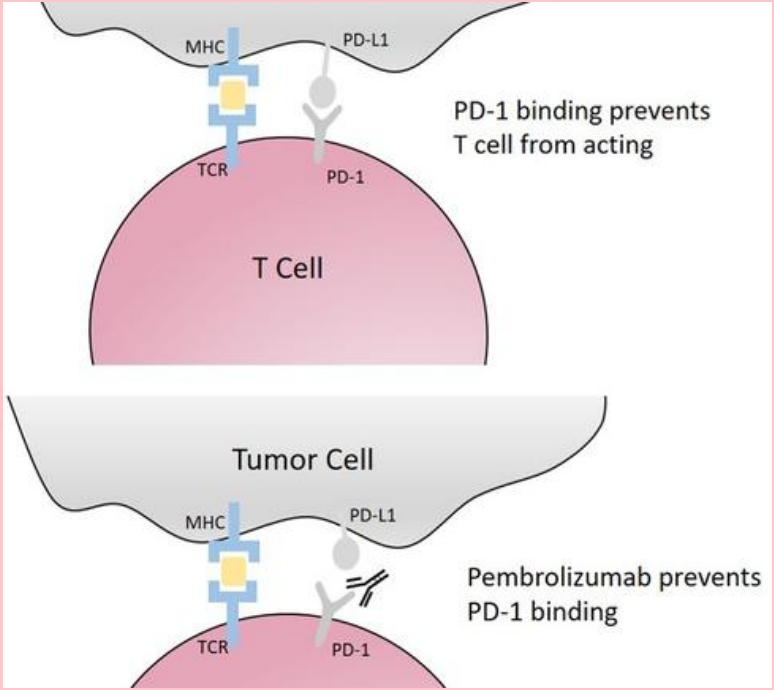
Pembrolizumab Mechanism of Action



Ross et al. Front Surg. 2022

Pembrolizumab

Mechanism	• Binds to PD-1 which blocks the interaction between PD-1 and PD-L1 which reactivates T-cells and leads to the death of tumor cells
Dosing	• 200 mg IV over 30 minutes every 3 weeks or 400 mg IV over 30 minutes every 6 weeks for up to 24 months, or until unacceptable toxicity or disease progression
Adverse effects	• Immune-medicated colitis, hepatitis, thyroiditis, pneumonitis, and rash
Monitoring	• Baseline and periodic TSH and liver function tests; manage adverse events per NCCN, ASCO, and ESMO guidelines with corticosteroids

Pembrolizumab (package insert). Merck & Co; 2026.

Keynote-A18

A Phase 3 Trial of Pembrolizumab in Cervical Cancer (2024)	
Design	• Randomized double blind phase III trial (N= 1,060)
Population	• Newly diagnosed high-risk (FIGO stage IB2-IIB with positive node disease or III-IVA), locally advanced disease without prior systemic therapy or radiation • ECOG 0-1 • 82%-85% had squamous cell cervical cancer and 15%-18% non-squamous cervical cancer
Comparison	• Investigational: Pembrolizumab 200 mg IV every 3 weeks (5 cycles) followed by 15 cycles of pembrolizumab 400 mg every 6 weeks • Control: matching placebo on the same schedule
Concurrent Backbone	• Weekly cisplatin 40 mg/m^2 for 5 cycles • EBRT followed by brachytherapy

Lorusso et al. Lancet. 2024

Keynote-A18

A Phase 3 Trial of Pembrolizumab in Cervical Cancer (2024)	
Safety	• Adverse events of grade 3 or higher were reported in 75% of patients in the pembrolizumab group and 69% in the standard group ○ Most common was anemia (19% with pembrolizumab vs. 16% with standard therapy) • Immune-mediated AEs were more frequent with pembrolizumab; most common were hypothyroidism (22.5% vs 6.8%) and hyperthyroidism (12.1% vs 2.8%) • No meaningful QoL differences

Lorusso et al. Lancet. 2024

Subgroup analysis

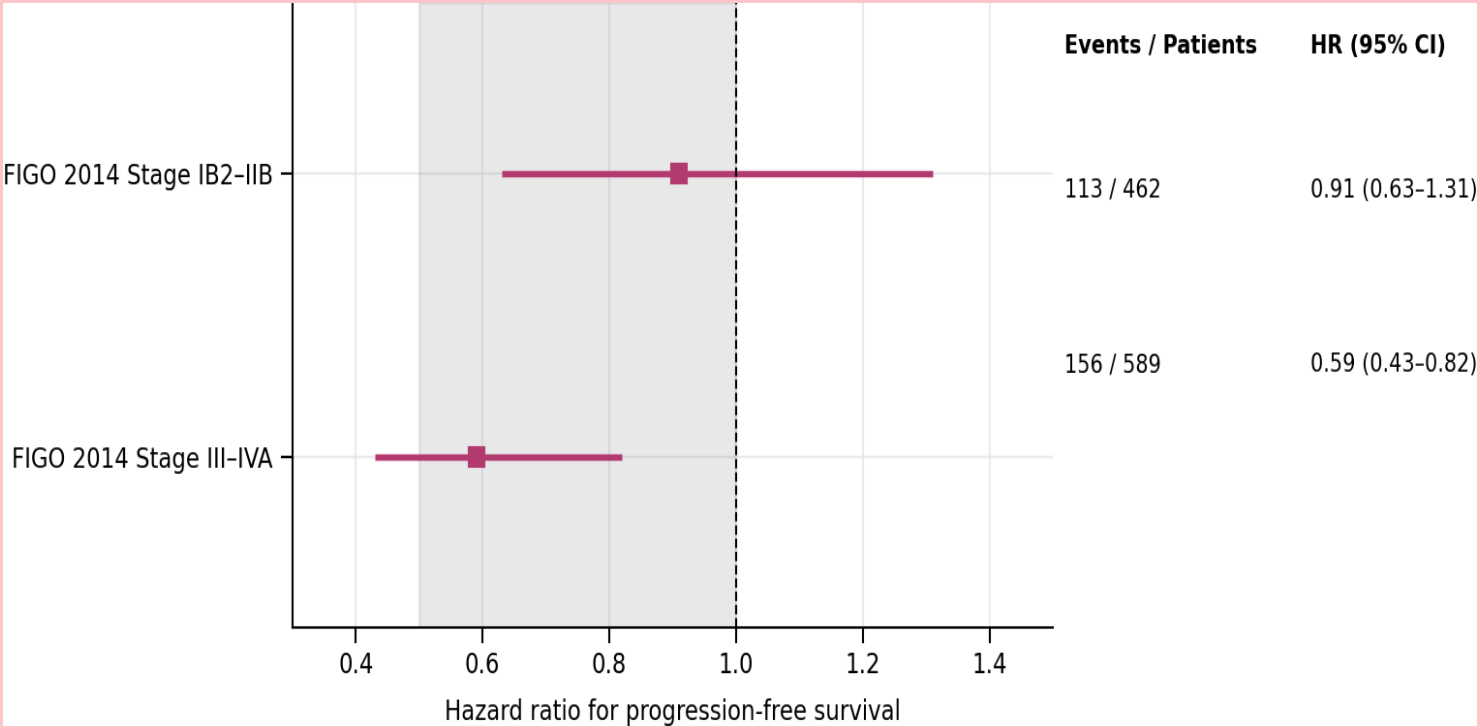


Image - Microsoft Copilot. Keynote A18 subgroup analysis. 2026

Lorusso et al. Lancet. 2024

Keynote-A18

A Phase 3 Trial of Pembrolizumab in Cervical Cancer (2024)			
	Pembrolizumab	**Placebo**	**Effect**
Median PFS	Not reached	Not reached	-
PFS at 24 months	68%	57%	HR for disease progression: 0.70
OS at 24 months	87%	81%	HR for death: 0.73

Pembrolizumab in combination with chemoradiotherapy significantly improved progression free survival in newly diagnosed, high-risk locally advanced cervical cancer

Lorusso et al. Lancet. 2024

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Paclitaxel

Mechanism of Action	Stabilizes the microtubules, inhibiting depolymerization, inhibiting cell replication which leads to apoptosis
Dosing	135 or 175 mg/m^2 every 3 weeks
Adverse effects	○ Hair loss ○ Peripheral neuropathy ○ Hypersensitivity reactions ▪ Premedicate all patients with diphenhydramine, famotidine, and dexamethasone ○ Myelosuppression

Paclitaxel (package insert). Pfizer; 2025

INTERLACE

Induction Chemotherapy + Standard Chemoradiation (2024)	
Design	• Randomized phase III trial (N= 500)
Population	• Newly diagnosed locally advanced cervical cancer
Comparison	• Induction chemotherapy (weekly carboplatin AUC 2 + paclitaxel 80 mg/m^2 x6 weeks) followed by standard cisplatin based chemoradiotherapy (40 mg/m^2 weekly x 5 weeks) • Standard cisplatin (40 mg/m^2 weekly x 5 weeks) based chemoradiotherapy alone
Results	• 5-year PFS: 72% vs 64% • 5-year OS: 80% vs 72% • Any grade 3 or greater AE: 59% vs 48% • Any hematological grade 3-4 event: 30% vs 13%

Short course induction chemotherapy followed by chemoradiotherapy significantly improves survival in patients with locally advanced cervical cancer but leads to more toxicity

McCormack et al. Lancet. 2024

Question 3 Patient Case

RD is a 46 y.o. female who initially presented to the hospital with a cervical mass concerning for cervical cancer. She underwent staging and was diagnosed with FIGO 2018 Stage IIIC2 cervical cancer.

Patient currently lives with her husband and 3 children. She done not currently use drugs, does not drink alcohol, and quit smoking about 13 years ago.

Labs: Na 134, K 3.9, BG 311, scr 0.57, AST 18, ALT 24, HGB 10.8 and PLT 453

She is scheduled to start radiation next week, what chemotherapy regimen is preferred?

A. Carboplatin/Paclitaxel

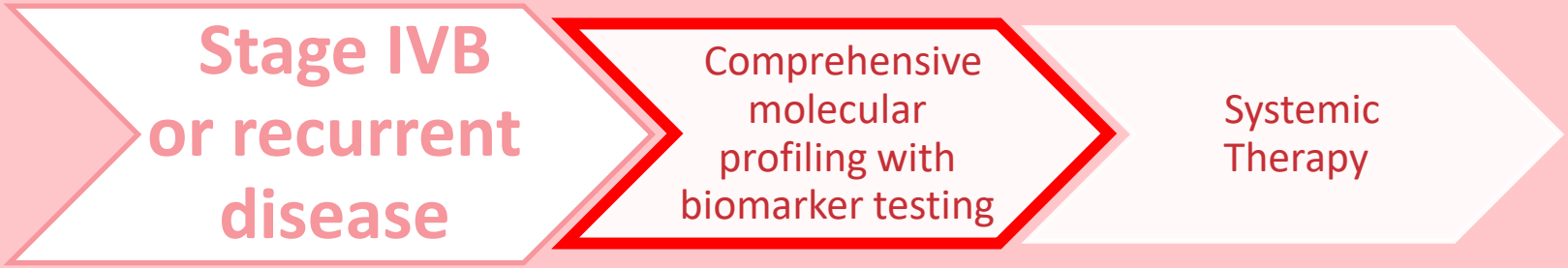
B. Cisplatin/Paclitaxel/Bevacizumab

C. Cisplatin/Pembrolizumab

D. Cisplatin/topotecan

Metastatic (Stage IVB) or Recurrent

Treatment Algorithm



Biomarker Testing in Stage IVB/Recurrent Disease

NCCN Guidelines recommend in all cases of metastatic or recurrent disease, the following comprehensive metabolic profiling be done

- Program Death Ligand 1 (PD-L1)
- HER2 Immunohistochemistry (IHC)
- Mismatch Repair (MMR)/Microsatellite Instability (MSI)
- Tumor mutational burden (TMB)
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- Rearranged during Transfection (RET)

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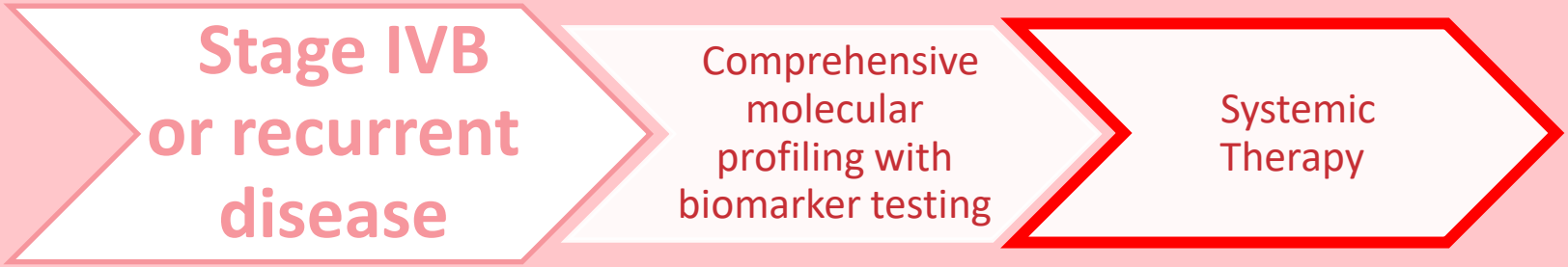
Primary objective with biomarkers: To guide patient-specific treatment and optimize their care

Treatment Algorithm



First Line Treatment

NCCN Guidelines	
Preferred Regimens	
Cisplatin/Paclitaxel/Bevacizumab	Category 1
Carboplatin/Paclitaxel/Bevacizumab	Category 2a
Atezolizumab + Bevacizumab + Cisplatin/Paclitaxel	Category 1
Atezolizumab + Bevacizumab + Carboplatin/Paclitaxel	Category 1
PD-L1-positive tumors (CPS ≥ 1) Pembrolizumab + cisplatin/paclitaxel ± bevacizumab Pembrolizumab + carboplatin/paclitaxel ± bevacizumab	Category 1

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Bevacizumab

Mechanism of Action	Inhibits vascular endothelial growth factor (VEGF) on the surface of endothelial cells, preventing cell proliferation and blood vessel formation
Dose	15 mg/kg IV every 3 weeks
When to Hold Doses	• An elective surgery in the next 28 days • Recently underwent major surgery in the last 28 days without adequate wound healing • Proteinuria ≥2 grams/24 hours
Adverse Drug Effects	Arterial thromboembolic events, **Gastrointestinal perforation and fistulas, Surgical and wound healing complications, Hemorrhage**, Congestive heart failure, Hypertension, Renal injury, and Proteinuria

. Bevacizumab (package insert). Genentech, Inc; 2016.

GOG 240: Bevacizumab Added to Chemotherapy

Trial Design	Phase III, randomized, open-label trial
Setting and Population	Patients with metastatic, persistent, or recurrent cervical carcinoma
Key Exclusion Criteria	• Recurrent disease amenable to cure via pelvic exenteration • Patients with nonhealing wounds, active bleeding conditions, or inadequately anticoagulated thromboembolism
Intervention Group	• Cisplatin 50 mg/m^2 + paclitaxel 135 or 175 mg/m^2 on day 1 of 21-day cycle OR • Topotecan 0.75 mg/m^2 on days 1 to 3 + paclitaxel 175 mg/m^2 on day 1 of 21-day cycle Plus • Bevacizumab: 15 mg per kilogram of body weight on day 1
Control Group	Either chemotherapy regimen without bevacizumab
Key Findings	The addition of bevacizumab improved: • Overall survival: 17.0 vs 13.3 months (HR 0.71; p=0.004) • Progression free survival: 8.2 vs 5.9 months (HR 0.67; p=0.002)
Safety	The addition of bevacizumab was associated with: • Grade ≥2 hypertension (25% vs 2%; P<0.001) • Grade ≥3 thromboembolic events (8% vs 1%; P=0.002) • Grade ≥3 GI–GU fistulae (3% vs 0%; P=0.001)

Tewari et al. N Engl J Med. 2014

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Control G	
Key Find	• Overall survival: 17.0 vs 13.3 months (HR 0.71; p=0.004) • Progression free survival: 8.2 vs 5.9 months (HR 0.67; p=0.002)
Safety	The addition of bevacizumab was associated with: • Grade ≥2 hypertension (25% vs 2%; P<0.001) • Grade ≥3 thromboembolic events (8% vs 1%; P=0.002) • Grade ≥3 GI–GU fistulae (3% vs 0%; P=0.001)

Conclusion: The addition of bevacizumab to combination chemotherapy in patients with recurrent, persistent, or metastatic cervical cancer was associated with an improvement of median overall survival.

Tewari et al. N Engl J Med. 2014

First Line Treatment

NCCN Guidelines	
Preferred Regimens	
Cisplatin/Paclitaxel/Bevacizumab	Category 1
Carboplatin/Paclitaxel/Bevacizumab	Category 2a
Atezolizumab + Bevacizumab + Cisplatin/Paclitaxel	Category 1
Atezolizumab + Bevacizumab + Carboplatin/Paclitaxel	Category 1
PD-L1-positive tumors (CPS ≥ 1) Pembrolizumab + cisplatin/paclitaxel ± bevacizumab Pembrolizumab + carboplatin/paclitaxel ± bevacizumab	Category 1

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

Atezolizumab

Mechanism of action	Programed death ligand-1 (PD-L1) inhibitor
Dosing	1200 mg on day 1 of every 3-week cycle
Adverse effects	Immune-mediated colitis, hepatitis, thyroiditis, pneumonitis, and rash
Monitoring	Baseline and periodic thyroid-stimulating hormone and liver function tests; manage adverse events per NCCN, ASCO, and ESMO guidelines with corticosteroids

Atezolizumab (package insert). Genentech, Inc; 2016.

BEATcc

Trial Design	Multi-center, phase III, investigator-initiated, randomized, open-label trial
Setting and Population	Patients with measurable metastatic (IVB), persistent, or recurrent cervical carcinoma not amenable to curative surgery or radiation
Key Exclusion Criteria	• Previous systemic therapy for metastatic, persistent, or recurrent disease • Ongoing disease of the bladder or rectum • Previous anti-VEGF therapy or immune checkpoint blockade • Patients with nonhealing wounds, active bleeding conditions, or inadequately anticoagulated thromboembolism
Intervention Group	• Standard therapy: cisplatin 50 mg/m² or carboplatin AUC of 5), IV paclitaxel 175 mg/m², and IV bevacizumab 15 mg/kg, all on day 1 of every 3-week cycle • + IV atezolizumab 1200 mg on day 1 of every 3-week cycle
Control Group	Standard therapy without atezolizumab
Key Findings	The addition of atezolizumab to standard therapy improved: • Overall survival: 32.1 vs 22.8 months (HR 0.68; p=0.0046) • Progression-free survival: 13.7 vs 10.4 months (HR 0.62; p<0.0001)
Safety	Incidence of grade ≥3 adverse event numerically higher in treatment group (79 vs 75%)

Oaknin, et al. Lancet. 2024

BEATcc

Trial Design	Multi-center, phase III, investigator-initiated, randomized, open-label trial
Setting and Population	Patients with measurable metastatic (IVB), persistent, or recurrent cervical carcinoma not amenable to curative surgery or radiation
Key Exclusion	…nt disease … inadequately
Intervention	…IV paclitaxel 175 …week cycle
Control Group	Standard therapy without atezolizumab
Key Findings	The addition of atezolizumab to standard therapy improved: • Overall survival: 32.1 vs 22.8 months (HR 0.68; p=0.0046) • Progression-free survival: 13.7 vs 10.4 months (HR 0.62; p<0.0001)
Safety	Incidence of grade ≥3 adverse event numerically higher in treatment group (79 vs 75%)

Conclusion: The addition of atezolizumab significantly improves the efficacy of first-line bevacizumab and chemotherapy for metastatic, persistent, or recurrent cervical cancer.

Oaknin, et al. Lancet. 2024

First Line Treatment

NCCN Guidelines	
Preferred Regimens	
Cisplatin/Paclitaxel/Bevacizumab	Category 1
Carboplatin/Paclitaxel/Bevacizumab	Category 2a
Atezolizumab + Bevacizumab + Cisplatin/Paclitaxel	Category 1
Atezolizumab + Bevacizumab + Carboplatin/Paclitaxel	Category 1
PD-L1-positive tumors (CPS ≥ 1) Pembrolizumab + cisplatin/paclitaxel ± bevacizumab Pembrolizumab + carboplatin/paclitaxel ± bevacizumab	Category 1

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

KEYNOTE-826

Trial Design	Phase III, randomized, multi-center, double-blind trial
Setting and Population	• Patients with metastatic, persistent, or recurrent cervical carcinoma • Not been treated with systemic chemotherapy and not amenable to curative treatment
Key Exclusion Criteria	• Recurrent Disease amenable to cure via pelvic exenteration • Patients with nonhealing wounds, active bleeding conditions, or inadequately anticoagulated thromboembolism
Intervention Group	• Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 or carboplatin AUC 5 mg/mL every 3 weeks for up to 6 cycles • Could receive bevacizumab 15 mg/kg every 3 weeks per investigator's discretion • Pembrolizumab 200 mg IV every 3 weeks for up to 35 cycles
Control Group	• Chemotherapy ± bevacizumab + placebo
Key Findings	Impact of pembrolizumab in intention-to-treat population: • Overall survival: 50.4% vs 40.4% at 24 months (HR 0.67; p<0.001) • Progression free survival: 10.4 vs 8.2 months (HR 0.65; p<0.001)
Safety	Grade 3-5 adverse events: • Pembrolizumab group: 81.8% • Placebo group: 75.1%

Colombo et al. N Engl J Med. 2021

KEYNOTE-826

Overall Survival				
	Pembrolizumab	Placebo	HR (95% CI)	P-Value
Intention-to-Treat	50.4%	40.4%	0.67 (0.54 – 0.84)	P < 0.001
CPS ≥ 1	53%	41.7%	0.64 (0.5 – 0.81)	P < 0.001
CPS ≥ 10	54.4%	44.6%	0.61 (0.44 – 0.84)	P = 0.001

Colombo et al. N Engl J Med. 2021

KEYNOTE-826

Trial Design	Phase III, randomized, multi-center, double-blind trial
Setting and Population	• Patients with metastatic, persistent, or recurrent cervical carcinoma with a PD-L1 combined positive score of ≥ 1 to curative treatment
Key Exclusio	inadequately
Intervention	5 mg/mL per minute igator's discretion
Control G	
Key Findings	Impact of pembrolizumab in intention-to-treat population: • Overall survival: 50.4% vs 40.4% at 24 months (HR 0.67; p<0.001) • Progression free survival: 10.4 vs 8.2 months (HR 0.65; p<0.001)
Safety	Grade 3-5 adverse events: • Pembrolizumab group: 81.8% • Placebo group: 75.1%

Conclusion: The addition of pembrolizumab to platinum-based chemotherapy significantly prolonged progression-free and overall survival in patients with persistent, recurrent, or metastatic cervical cancer with PD-L1 CPS ≥ 1

Kitagawa et al. J Clin Oncol. 2015

First Line Treatment

NCCN Guidelines	
Other recommended regimens	
Carboplatin/Paclitaxel • For patients who have already received cisplatin therapy	Category 1
Topotecan/paclitaxel/bevacizumab	Category 1
Topotecan/paclitaxel	Category 2a
Cisplatin/topotecan	Category 2a
Cisplatin	Category 2a
Carboplatin	Category 2a

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

JCOG0505

Trial Design	Multicenter, open-label, randomized phase III trial
Setting and Population	• Patients between 20-75 years of age with measurable metastatic (IVB), persistent, or recurrent cervical carcinoma not amenable to curative surgery or radiation.
Key Exclusion Criteria	• ≥ 1 platinum-based chemotherapy previously (including chemoradiation) • Prior chemotherapy with taxanes
Intervention Group	• Paclitaxel + cisplatin (TP): paclitaxel 135 mg/m^2 over 24 hours IV on day 1, followed by cisplatin 50 mg/m^2 IV on day 2 • Paclitaxel + carboplatin (TC): paclitaxel 175 mg/m2 over 3 hours IV on day 1, followed by a 1-hour IV infusion of carboplatin (AUC of 5 mg/mL) on the same day
Key Findings	• Median overall survival:18.3 months with TP vs 17.5 months with TC • HR of overall survival was 0.994 (90% CI, 0.79 to 1.25; noninferiority P .032) • Patients who had not previously received cisplatin: Overall survival was shorter with TC (13.0 vs 23.2 months; HR, 1.571; 95% CI, 1.06 to 2.32) • Mean proportions of Non-hospitalization periods was significantly longer with TC (P .001)

Kitagawa et al. J Clin Oncol. 2015

JCOG0505

Trial Design	Multicenter, open-label, randomized phase III trial
Setting and Population	• Patients between 20-75 years of age with measurable metastatic (IVB), persistent, or recurrent cervical carcinoma not amenable to curative surgery or radiation.
Key Exclusion	iation)
Intervention	V on day 1, followed IV on day 1, per minute) on the
Key Findings	TC) • HR of overall survival was 0.994 (90% CI, 0.79 to 1.25; noninferiority P .032) • Patients who had not previously received cisplatin: Overall survival was shorter with TC (13.0 vs 23.2 months; HR, 1.571; 95% CI, 1.06 to 2.32) • Mean proportions of Non-hospitalization periods was significantly longer with TC (P .001)

Conclusion: TC was noninferior to TP in overall survival and quality of life. However, there was a clinically meaningful reduction in overall survival among cisplatin-naïve patients treated with TC, suggesting that cisplatin should remain the preferred initial platinum agent

Kitagawa et al. J Clin Oncol. 2015

Second Line and Subsequent Therapy

NCCN Guidelines		
Preferred Regimens	**Other Recommended Regimens**	**Useful in Certain Circumstances**
• Tisotumab vedotin-tftv (Category 1) • Pembrolizumab for TMB-H, PDL-1-positive or MSI-H/dMMR tumors	• Bevacizumab • Paclitaxel • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Cemiplimab	PD-L1 positive tumors (either of the following): • Nivolumab • Tisotumab vedotin-tftv + pembrolizumab HER2-positive tumors: • Fam-trastuzumab deruxtecan-nxki HER2-mutant: • Neratinib RET gene fusion-positive tumors: • Selpercatinib NTRK gene fusion-positive tumors (any of the following): • Larotrectinib • Entrectinib • Repotrectinib

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

Second Line and Subsequent Therapy

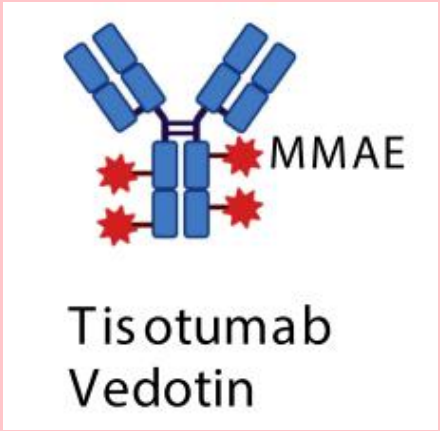
NCCN Guidelines

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
• Tisotumab vedotin-tftv (Category 1) • Pembrolizumab for TMB-H, PDL-1-positive or MSI-H/dMMR tumors	• Bevacizumab • Paclitaxel • Albumin-bound paclitaxel • Docetaxel • Fluorouracil • Gemcitabine • Pemetrexed • Topotecan • Vinorelbine • Irinotecan • Cemiplimab	PD-L1 positive tumors (either of the following): • Nivolumab • Tisotumab vedotin-tftv + pembrolizumab HER2-positive tumors: • Fam-trastuzumab deruxtecan-nxki HER2-mutant: • Neratinib RET gene fusion-positive tumors: • Selpercatinib NTRK gene fusion-positive tumors (any of the following): • Larotrectinib • Entrectinib • Repotrectinib

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology(NCCN Guidelines®): Cervical Cancer. NCCN. V.2.2026. Accessed January 30, 2026. https://www.nccn.org

Tisotumab vedotin (TV)

- **Human tissue factor direct antibody-drug conjugate (ADC) targeting cell surface-expressed tissue factor (TF)**
- **Conjugated with microtubule-disrupting agent monomethyl auristatin E (MMAE)**
- **Causes direct cytotoxicity and indirect death of adjacent cells (bystander effect)**



Tisotumab Vedotin binds to TF positive tumor cells → Undergoes liposomal degradation → MMAE is released within the tumor cell → Cell cycle arrest at G2/M phase → Apoptosis

Agostinelli et al. Cancer Manag Res. 2023

Tisotumab vedotin

Dose	2 mg/kg IV (Max dose: 200 mg) every 3 weeks
Dose Reduction	• First reduction: 1.3 mg/kg (max 130 mg) • Second reduction: 0.9 mg/kg (max 90 mg); If unable to tolerate then permanently discontinue
When To Avoid Use	AST > 3 times or total bilirubin > 1.5 times the upper limit of normal
Drug Interactions	Strong CYP3A4 Inducer
Adverse Drug Effects	Peripheral neuropathy, alopecia, hemorrhage, pneumonitis, increased serum creatinine, GI toxicity, **ocular toxicity**, rash

Tisotumab vedotin-tftv (package insert). Seagen Inc.; 2016.

Supportive Care

Ophthalmic Exam

- At baseline
- Before each cycle for first 9 cycles
- As clinically indicated thereafter

Cold Packs

- Applied to eyes following administration of the vasoconstrictive eye drops
- Keep in place throughout entirety of infusion

Corrective Lenses

- Avoid use throughout entirety of the treatment
- Discuss with optometrist

Eye Care

- Topical corticosteroid
  - 1 drop in each eye three times a day for 72 hours post infusion
- Topical ocular vasoconstrictor
  - 1 drop in each eye on infusion days
- Topical lubricating
  - Administer for duration of therapy and for 30 days from final dose

Seagen Inc. tisotumab vedotin-tftv (package insert). U.S. Food and Drug Administration; 2016. Accessed February 12, 2026

innovaTV 301

Trial Design	Phase III, randomized, multinational, open-label trial
Setting and Population	• Patients with recurrent or metastatic cervical cancer • Had disease progression during or after previous treatment with the standard-of-care systemic chemotherapy ± immunotherapy
Key Exclusion Criteria	• Patients with cancers that had primary neuroendocrine, lymphoid, sarcomatoid, or other histologic features • Patients with clinically significant bleeding, cardiovascular issues, or risks
Intervention Group	• Tisotumab vedotin 2 mg/kg IV every 3 weeks
Control Group	• Investigator's choice of IV chemotherapy
Key Findings	Tisotumab vedotin treatment arm: • Median overall survival: 11.5 vs 9.5 months (HR 0.70; p=0.004) • Progression-free survival: 4.2 vs 2.9 months (HR 0.67; p<0.001) • Risk of death: HR 0.70 (95% CI, 0.54 to 0.89; P=0.004) • Improvement in quality of life from baseline to cycle 5: 13.9% vs. 3.4%
Safety	Grade 3-5 adverse events: • Tisotumab vedotin group: 52% • Comparator group: 62.3%

Vergote et al. N Engl J Med. 2024

innovaTV 301

Trial Design	Phase III, randomized, multinational, open-label trial
Setting and Population	• Patients with recurrent or metastatic cervical cancer • Had disease progression during or after previous treatment with the standard-of-care
Key Exclusion	d, sarcomatoid, or , or risks
Intervention	
Control Gr	
Key Findi	• Progression-free survival: 4.2 vs 2.9 months (HR 0.67; p<0.001) • Risk of death: HR 0.70 (95% CI, 0.54 to 0.89; P=0.004) • Improvement in quality of life from baseline to cycle 5: 13.9% vs. 3.4%
Safety	Grade 3-5 adverse events: • Tisotumab vedotin group: 52% • Comparator group: 62.3%

Conclusion: Second or third line tisotumab vedotin had a significantly greater efficacy in recurrent cervical cancer when compared to standard of care

Vergote et al. N Engl J Med. 2024

Question 4 supportive care

CR is a 70 year old female with a past oncologic history of squamous cell carcinoma of the cervix (Stage IIIB, PD-L1 1%) that has continued to progress despite cisplatin/paclitaxel + pembrolizumab, and carboplatin/paclitaxel + pembrolizumab, who presented to clinic today to be evaluated for treatment with tisotumab vedotin.

Which of the following supportive care options are not recommended for patients receiving tisotumab vedotin?

A. Baseline eye exam and before the first 9 cycles

B. Cold packs applied to the eyes throughout the entirety of the infusion

C. Vasoconstrictive eye drops placed in both eyes on the day of infusion

D. IV diphenhydramine, IV famotidine, and IV dexamethasone 30 minutes to 1 hour prior to each infusion

Key Takeaways

Prevention of Cervical Cancer is paramount through HPV vaccination and guideline-directed screening

The treatment strategy is dependent on the stage of Cervical Cancer

Surgery is the primary treatment for Early Stage Cervical Cancer

Immunotherapy is now recommended in both the high-risk locally advanced and in the metastatic settings

Biomarker testing is recommended in recurrent/metastatic disease to optimize individualized treatment selection with immunotherapy, targeted oral agents, and antibody-drug conjugates

Questions?

Thank you for attending our presentation!

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