

JULY 2025

An Educational Module for Healthcare Professionals

Optimizing Treatment Sequencing in
Recurrent/Metastatic Cervical Cancer
Immunotherapy, Targeted, and Molecular Therapies



King County Medical Society
COMMUNITY FOUNDATION

This educational initiative is supported by an independent
medical education grant from Pfizer and Genmab

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PART 1

Background and Disease Overview



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Introduction to the KCMS Cervical Cancer Educational Initiative

This educational program was developed as a direct deliverable of the Pfizer Independent Medical Education (IME) grant awarded to the King County Medical Society (KCMS).

KCMS began this project by conducting a comprehensive baseline survey across oncology, obstetrics/gynecology (OB/GYN), nursing, pharmacy, and care coordination specialties. Healthcare professionals identified critical barriers to care, including delays in prior authorization, referral inefficiencies, limited familiarity with guidelines, and systemic disparities affecting underserved populations.

All educational content was informed by these frontline insights and reviewed by a Tumor Board composed of gynecologic oncology, medical oncology, and patient-centered care experts.

Introduction to the KCMS Cervical Cancer Educational Initiative

This PowerPoint module specifically delivers:

- Case-based learning on sequencing immunotherapy and targeted therapies in recurrent/metastatic cervical cancer
- Clinical decision-making frameworks
- Patient case studies applying guideline recommendations to practice
- Evidence-based approaches to shared decision-making, survivorship care, and patient-centered treatment planning

In addition to this educational module, KCMS has developed a full suite of deliverables, including multilingual patient education resources, standardized referral checklists for OB-GYNs and PCPs, practical prior authorization toolkits, downloadable workflow guides, and short educational videos. These tools are designed to further reduce barriers to care and enhance provider knowledge.

Together, these initiatives fulfill the commitments outlined in the original grant proposal — advancing equitable, timely access to life-saving therapies for patients with recurrent/metastatic cervical cancer.

**Thanks to the support of Pfizer and Genmab,
KCMS is proud to make these resources freely available to the medical community.**

Cervical Cancer: Current Incidence, Mortality, and Emerging Trends 2023

Cervical cancer remains a significant public health concern, particularly for patients with recurrent or metastatic disease. This section reviews the latest incidence, mortality, and emerging biological trends that are shaping the current treatment landscape.

KEY POINTS

Estimated New Cases in the U.S.

About 14,000 women were expected to be diagnosed with invasive cervical cancer in 2023.¹

Estimated Deaths in the U.S.

Over 4,300 women were expected to die from cervical cancer in 2023.²

REFERENCES

¹ American Cancer Society, Cancer Facts & Figures 2023

² SEER Program, National Cancer Institute (NCI)

³ Centers for Disease Control and Prevention (CDC)

TRENDS

- Overall, cervical cancer incidence rates have dropped by more than 50% since the 1970s, primarily due to increased screening.³
- In recent years, incidence rates have remained stable overall, but there has been a 1.7% annual increase among women aged 30 to 44 from 2012 to 2019.²
- Advances in molecular and biomarker testing (e.g., PD-L1 expression, HER2 amplification, NTRK fusions, RET alterations, and tumor mutational burden) are expanding treatment options for patients with recurrent/metastatic cervical cancer.

Advances in Cervical Cancer Treatment Immunotherapy, Targeted Therapy, and Biomarker-Driven Care

Cervical cancer remains a significant public health concern, particularly for patients with recurrent or metastatic disease. This section reviews the latest incidence, mortality, and emerging biological trends that are shaping the current treatment landscape.

KEY POINTS

STANDARD TREATMENTS

Treatment options for cervical cancer depend on the stage and may include surgery, radiation therapy, chemotherapy, and immunotherapy.¹

Targeted therapies are now available for patients with specific molecular alterations.

IMMUNOTHERAPY

PD-1/PD-L1 inhibitors, such as pembrolizumab, are used in some instances, particularly for tumors expressing PD-L1.²

Additional agents and combinations (e.g., atezolizumab, an anti-PD-L1 therapy) are increasingly incorporated into clinical practice guidelines and ongoing research.

PREVALENCE

Studies suggest that a significant percentage of advanced cervical cancer cases express PD-L1 (Combined Positive Score [CPS] ≥ 1), which may influence treatment decisions.³

Molecular testing for other biomarkers such as HER2 amplification, NTRK fusions, RET alterations, and high tumor mutational burden (TMB) is also increasingly important in guiding treatment decisions.

CLINICAL TRIALS

Major clinical trials have evaluated the role of immunotherapy in PD-L1-positive cervical cancer, leading to its inclusion in treatment guidelines.⁴

Emerging trials are also evaluating novel antibody-drug conjugates and targeted therapies for biomarker-driven subsets of cervical cancer.

REFERENCES

¹NCCN Clinical Practice Guidelines in Oncology – Cervical Cancer. Available at: www.nccn.org

²KEYNOTE-158 & KEYNOTE-826 Clinical Trials – New England Journal of Medicine, 2021. DOI: 10.1056/NEJMoa2112435

³WHO Cancer Fact Sheets – Cervical Cancer. Available at: www.who.int

⁴European Journal of Gynaecological Oncology (EJGO) & Springer Link – Immunotherapy Research.

Impact of HPV Vaccination & Disparities in Cervical Cancer Outcomes

HPV Vaccination Success

Cervical cancer incidence rates have declined by 65% among women aged 20 to 24 from 2012 to 2019, the first cohort to receive the HPV vaccine¹. However, disparities in vaccination rates persist across different racial, ethnic, and socioeconomic groups, contributing to ongoing inequities in cervical cancer outcomes.

Current Vaccination Coverage

As of 2023, 76.8% of adolescents (ages 13–17) have received at least one dose of the HPV vaccine². Completion rates for the full vaccine series, however, remain lower, particularly among underserved populations.

REFERENCES

¹American Cancer Society (ACS) & ASCO Post – HPV vaccination impact on cervical cancer rates.

²Centers for Disease Control and Prevention (CDC) – HPV vaccination coverage, 2023. Available at: www.cdc.gov

³American Journal of Managed Care (AJMC) & Medical Xpress – Cervical cancer disparities.

Disparities in Cervical Cancer Outcomes: Rural vs. Urban Disparities

Women in rural areas of the U.S. experience higher cervical cancer incidence and mortality rates compared to urban residents³. Limited access to preventive services, such as HPV vaccination and regular screening (Pap/HPV co-testing), contributes significantly to these gaps.

Racial and Ethnic Disparities

Non-Hispanic Black women in rural areas face higher incidence and mortality rates, emphasizing the need to address healthcare inequities³. Additionally, Hispanic and American Indian/Alaska Native women experience disproportionately high cervical cancer burdens, necessitating culturally tailored interventions.

Optimizing Treatment Strategies for Recurrent/Metastatic Cervical Cancer

About this module

This educational module provides **practical, case-based guidance** to help clinicians optimize treatment strategies for patients with recurrent/metastatic cervical cancer.

You will learn to:

- Identify **appropriate patient selection criteria** for immunotherapy and targeted therapies
- **Apply biomarker-driven treatment pathways** using the latest clinical evidence
- Navigate **real-world challenges** such as prior authorization delays and referral gaps
- Integrate **comprehensive molecular profiling** (e.g., HER2 amplification, NTRK fusions, RET alterations, high tumor mutational burden) into treatment decisions



Learning Objectives

By the end of this module, you will be able to:

1. **Apply evidence-based guidelines** (NCCN, ESMO, ASCO) for sequencing immunotherapy and targeted therapies.
2. **Determine first-line and second-line treatment eligibility criteria** based on clinical and biomarker factors (**PD-L1, TMB, MSI, HER2 amplification, NTRK fusions, RET alterations**).
3. **Use biomarker-driven decision-making** to personalize treatment selection and improve patient outcomes.
4. **Identify barriers to treatment** access and implement practical strategies to enhance care delivery.
5. **Navigate insurance and prior authorization** challenges to improve patient access to care.
6. **Integrate case-based decision-making principles** into clinical practice to optimize outcomes.

Understanding PD-L1 and the Immune System

The interaction between tumors and the immune system plays a critical role in cervical cancer progression and treatment response.

This section reviews the role of PD-L1 in immune evasion, how immune checkpoint inhibitors (ICIs) work, the importance of PD-L1 testing, and why some tumors develop resistance.

A deeper understanding of these mechanisms helps inform treatment selection and sequencing strategies in recurrent/metastatic cervical cancer.

Biological Mechanism of PD-L1 and Immune Checkpoint Inhibitors

1. The Role of PD-L1 in Cancer Immune Evasion

- PD-L1 (Programmed Death-ligand 1) is a protein expressed on cancer cells and some immune cells.
- It binds to PD-1 (Programmed Death-1), a receptor on T-cells, turning off T-cell activity and preventing the immune system from attacking the tumor.
- While this mechanism prevents autoimmunity (immune tolerance), tumors exploit it to evade immune destruction.
- PD-L1 expression is just one mechanism of immune evasion; tumors may also use alternative pathways.

2. How Do Immune Checkpoint Inhibitors (ICIs) Work?

- Checkpoint inhibitors (like pembrolizumab and nivolumab) block PD-1 or PD-L1, preventing them from binding allowing T-cells to re-engage and attack cancer cells.
- Combination therapies involving ICIs and other agents are under investigation to improve outcomes.

3. Why PD-L1 Testing Is Important

- Not all tumors express high levels of PD-L1.
- Tumors with higher PD-L1 expression (CPS ≥ 1) are more likely to respond to ICIs.
- If PD-L1 is low, the tumor may escape immune detection, making ICIs less effective.
- Emerging biomarkers like tumor mutational burden (TMB) and microsatellite instability (MSI) may also guide immunotherapy decisions.

Biological Mechanism of PD-L1 and Immune Checkpoint Inhibitors

4. What Happens Inside the Tumor Microenvironment?

- Before Treatment:
 - Cancer cells express PD-L1, suppressing T-cell activity.
 - T-cells become exhausted and are unable to attack the tumor.
- After Treatment with an ICI:
 - The checkpoint inhibitor blocks PD-L1 or PD-1, preventing immune suppression.
 - T-cells are reactivated, allowing them to kill cancer cells.

5. Why Some Patients Don't Respond:

- Low PD-L1 tumors may not rely on the PD-1/PD-L1 pathway.
- Other immune escape mechanisms (such as T-cell exclusion or mutations in antigen presentation) may be at play.
- Some patients develop resistance by upregulating alternative immune suppression pathways.
- Understanding resistance mechanisms is critical to improving future treatment strategies.

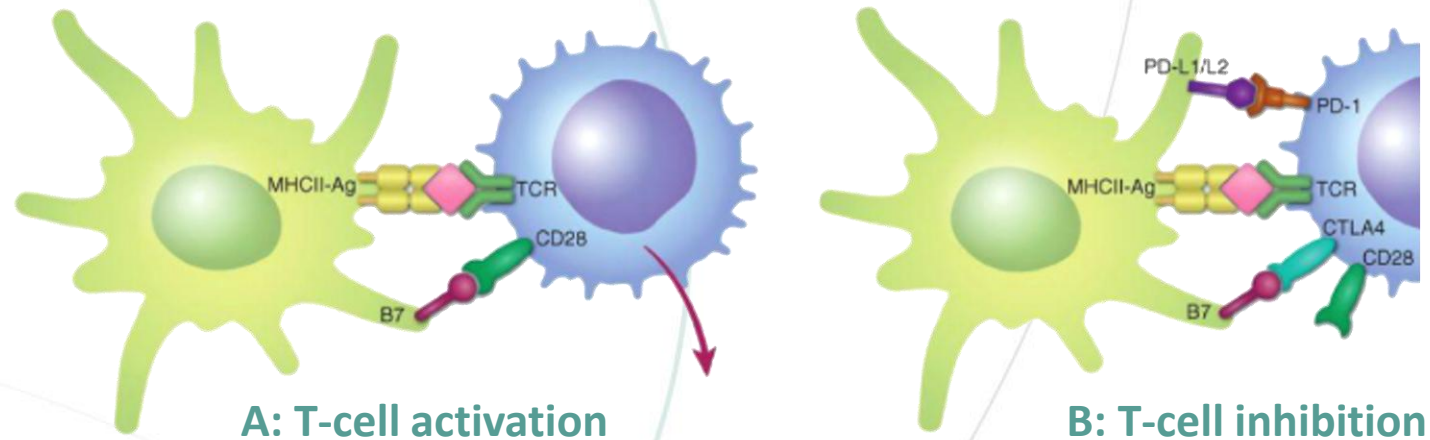
Summary of Biological and Clinical Relevance

Biomarker	Mechanism	Treatment Implications
PD-L1	Suppresses T-cell activation by binding to PD-1 on T-cells	High PD-L1 expression (CPS \geq 1) predicts better response to immune checkpoint inhibitors (ICIs) (e.g., pembrolizumab, nivolumab).
TMB	High mutational burden generates more neoantigens, leading to a stronger T-cell response	TMB \geq 10 mutations/Mb correlates with increased ICI responsiveness across multiple cancer types, independent of PD-L1 status.
MSI	Defective mismatch repair (MMR) leads to hypermutation, increasing neoantigen load.	MSI-H tumors are highly sensitive to ICIs, even with low PD-L1 expression, leading to FDA approvals for ICI therapy across multiple cancers.

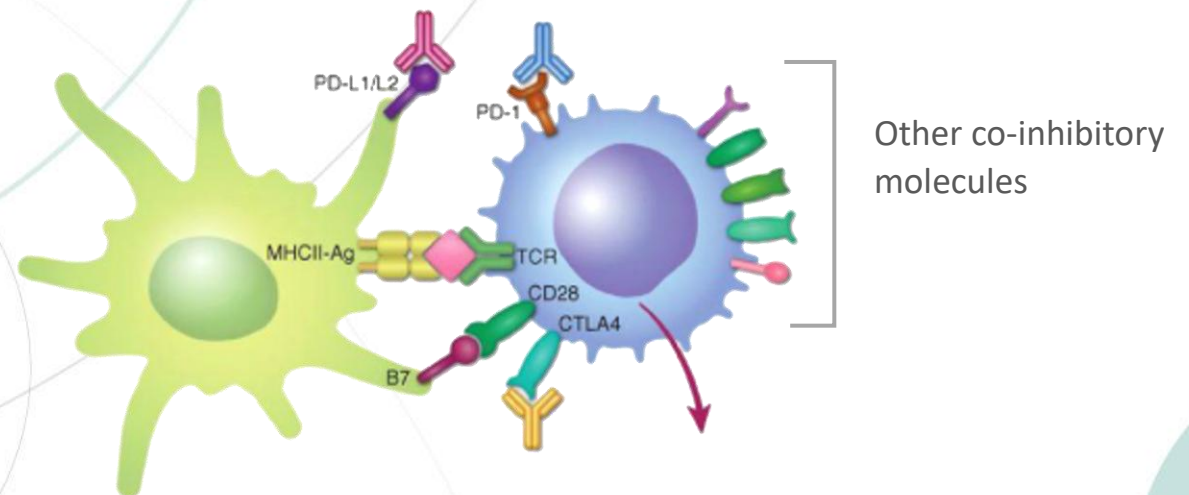
Now that we've covered how PD-L1, TMB, and MSI impact immune response, let's examine the molecular interactions that drive this process and how immune checkpoint inhibitors restore T-cell activity in the following slides.

T-cell Activation, Inhibition, and Reactivation by Immune Checkpoint Inhibitors

Checkpoint inhibitors restore T-cell activity by blocking PD-1/PD-L1 or CTLA-4-mediated suppression. This enables the immune system to attack cancer cells.



C: T-cell reactivation using immune checkpoint antibodies

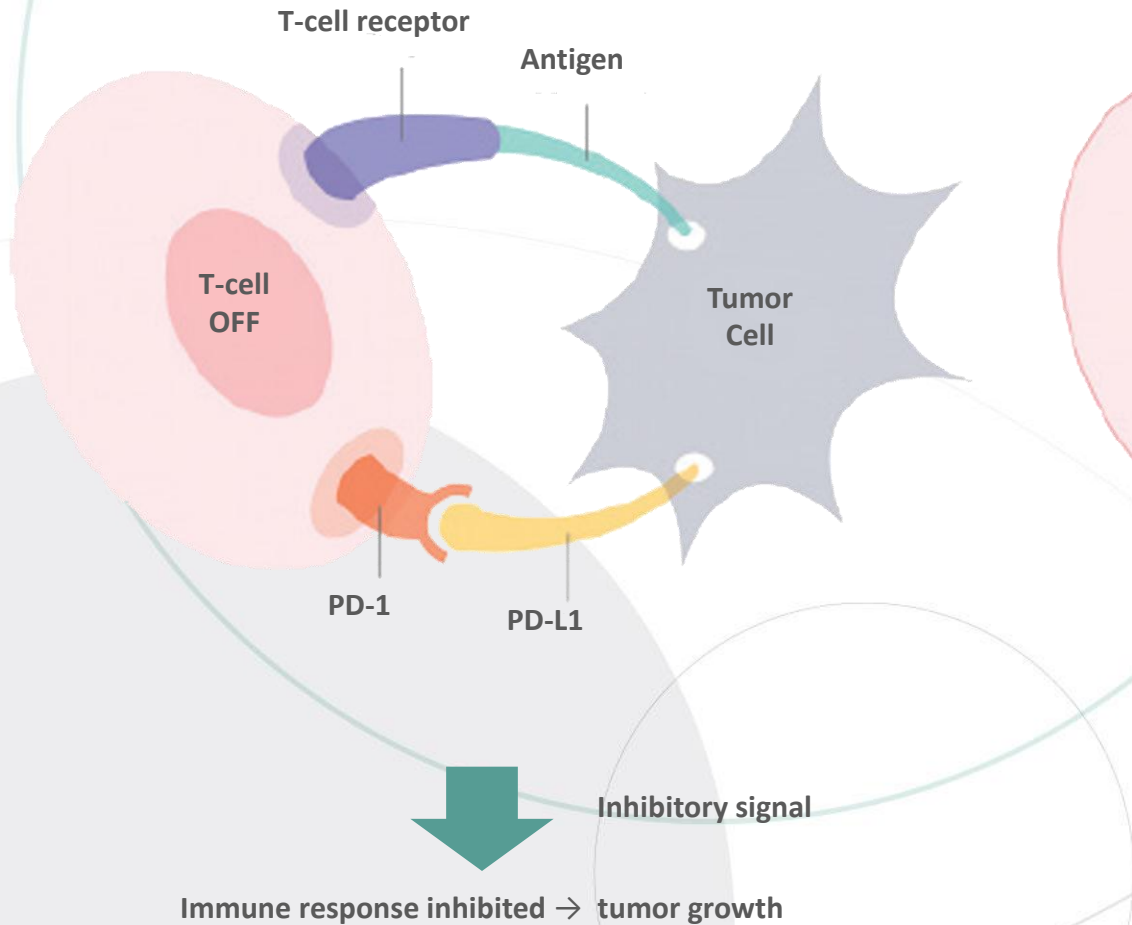


Frontiers¹ - Immune checkpoint inhibitors in advanced and recurrent/metastatic cervical cancer

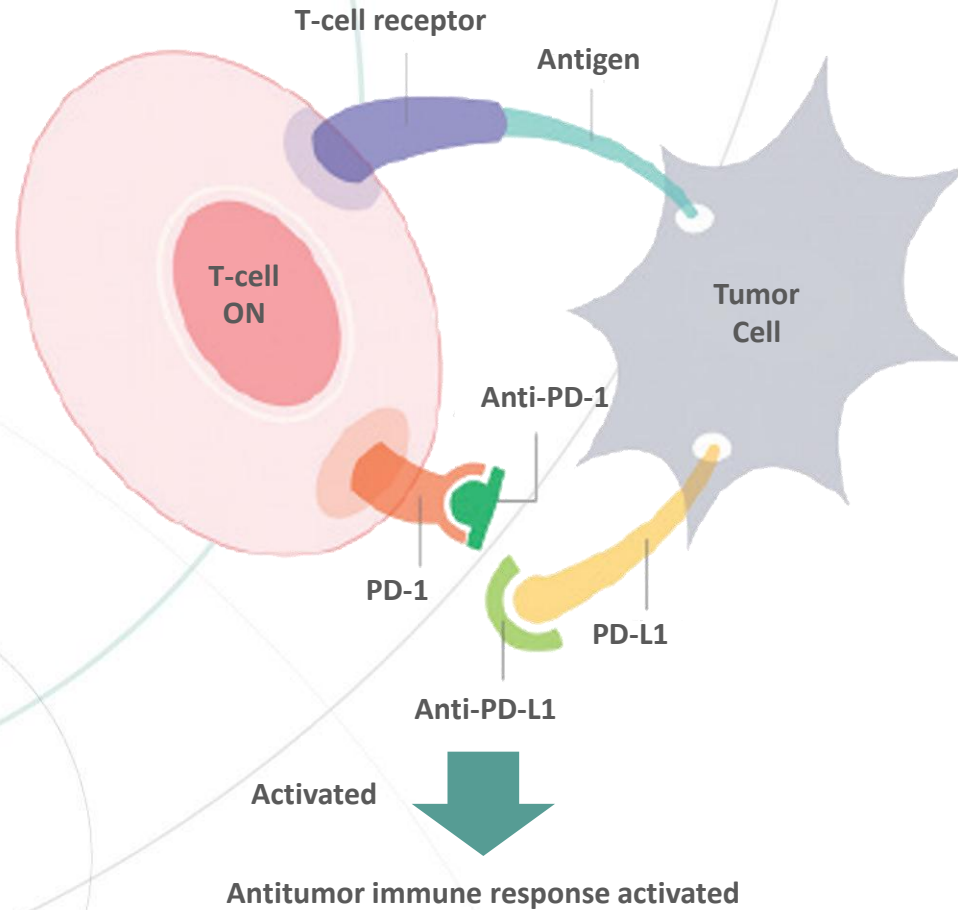
Research funded by **Pfizer** and **Genmab**

Rationale for PD-L1 Expression as a Biomarker in Immuno-Oncology

Binding of PD-1 to PD-L1 inhibits T-cell response, enabling tumor immune evasion.



Anti-PD-1 or anti-PD-L1 monoclonal antibodies (immune checkpoint inhibitors)^{1,2} block PD-1/PD-L1 binding, restoring antitumor immune response.



REFERENCES

¹ J Oncol Sci. 2018. *Rationale for PD-L1 Expression as a Biomarker in Immuno-Oncology*. 2018.

² PubMed Central. PMC6016855.

PART 2

Therapeutic Strategies and Clinical Decision-Making



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Standard First-Line Treatment Options

Based on NCCN, ESMO, & ASCO Guidelines in Treatment Sequencing

Platinum-Based Chemotherapy + Bevacizumab + Pembrolizumab

NCCN: National Comprehensive Cancer Network

ESMO: European Society for Medical Oncology

ASCO: American Society of Clinical Oncology

PD-L1: Programmed Death-Ligand 1

PD-L1: Positive tumors are more likely to respond to ICIs. If CPS ≥ 1 , the patient is eligible for pembrolizumab in first-line treatment.

VEGF: Vascular Endothelial Growth Factor

Treatment Selection in Recurrent/Metastatic Cervical Cancer

Effective treatment planning integrates biomarker testing, patient-specific factors, and clinical guidelines. While oncologists lead decision-making, a multidisciplinary team is crucial in treatment access, toxicity management, and care coordination.

Key Considerations in 1st-Line Treatment Selection

1. Programmed Death-Ligand (PD-L1) testing determines eligibility for immune checkpoint inhibitors (ICI).
2. Platinum-Based Chemotherapy Backbone is standard for most patients and typically combined with other agents to improve outcomes.
3. Bevacizumab (VEGF Inhibitor) is added if there are no contraindications, particularly bleeding risk.
4. Multidisciplinary teams play a key role in managing side effects and supporting treatment adherence.

Standard 1st-Line Treatment Recommendations: For PD-L1+ Tumors (CPS ≥ 1)

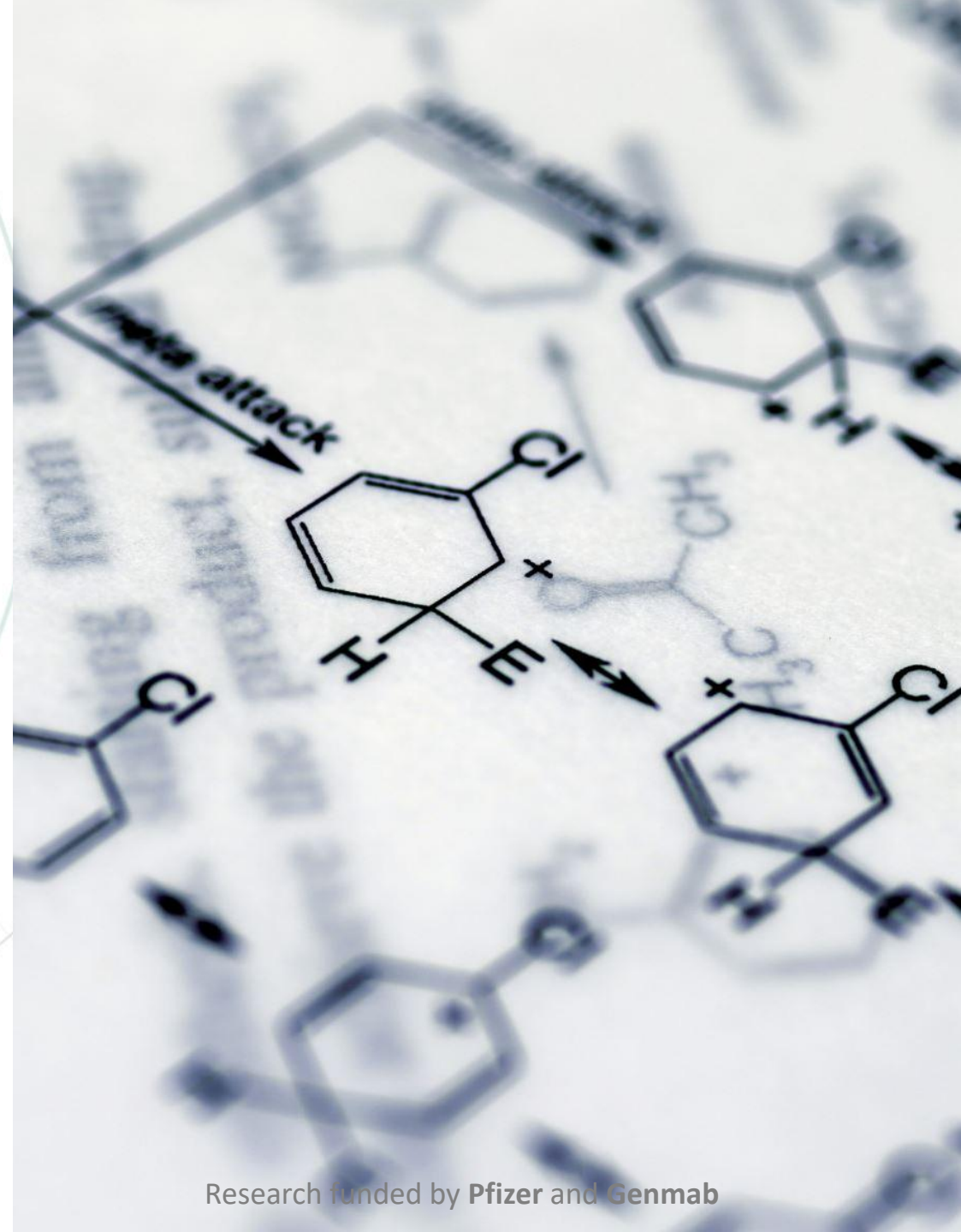
- Platinum-based chemotherapy plus bevacizumab (unless contraindicated) and pembrolizumab which may be continued for up to 24 months.

For PD-L1 Negative Tumors or Contraindications

- Platinum-based Chemotherapy Alone
- Consider biomarker-driven targeted therapies or clinical trials where appropriate.

Standard First-Line Treatment Options

- PD-L1 positive (CPS ≥ 1): Pembrolizumab + chemotherapy \pm bevacizumab.
- HER2 positive: Trastuzumab deruxtecan (after progression).
- RET fusion positive: Selpercatinib.
- NTRK fusion positive: Larotrectinib.
- Emerging option: Atezolizumab + bevacizumab + chemotherapy (clinical trials).
- Molecular profiling increasingly guides personalized therapy decisions.



Research funded by Pfizer and Genmab

First-Line Treatment Algorithm

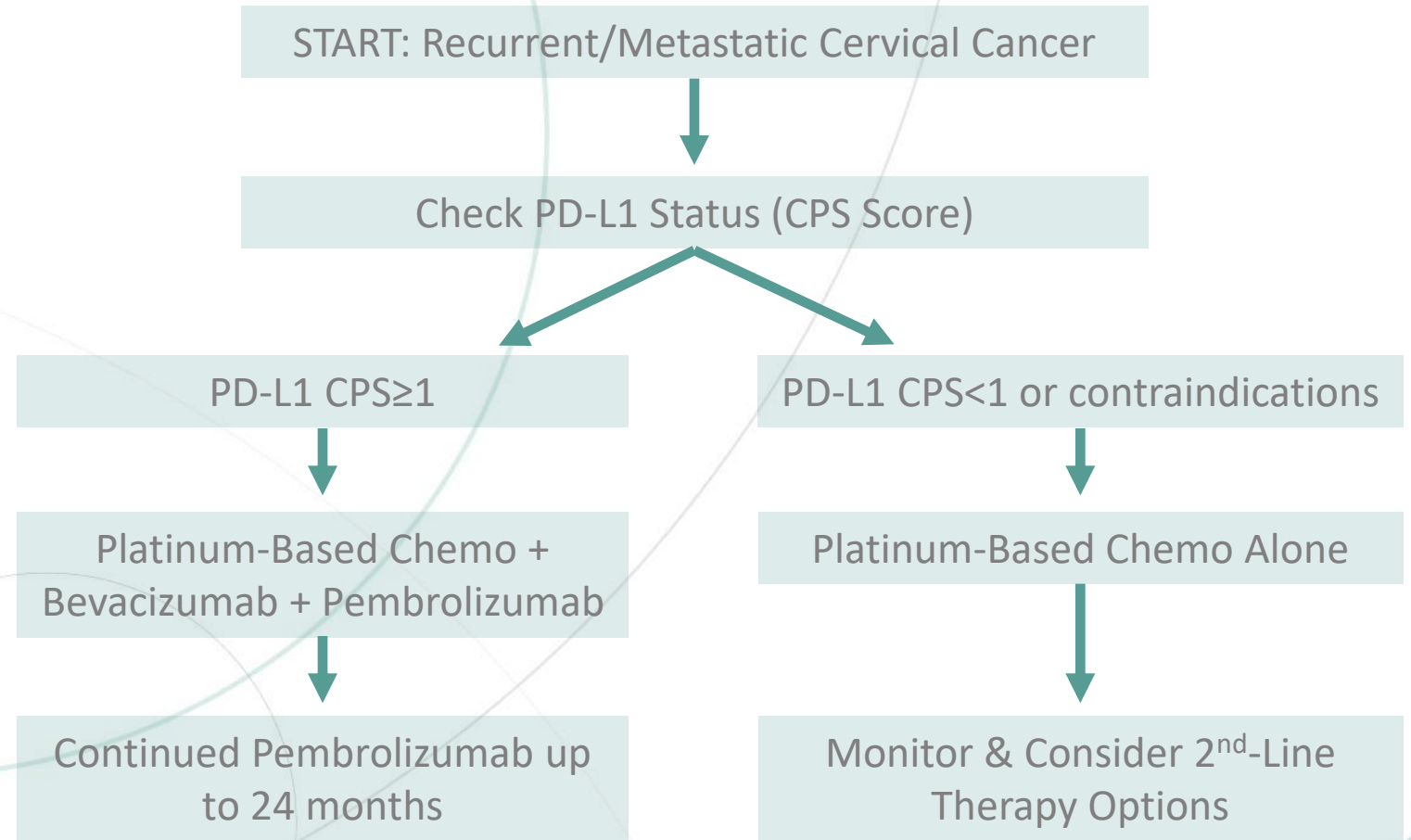
Is PD-L1 CPS ≥ 1 ?

Yes: Chemotherapy +
Bevacizumab +
Pembrolizumab

No: Chemotherapy alone

Monitor & evaluate for
2nd-line options if needed.

First-Line Treatment Algorithm: Recurrent/Metastatic Cervical Cancer



Treatment Decision Guide

When to Transition to Second-Line Treatment

Transitioning to Second-Line Therapy should be considered if a patient meets any of the following criteria:

- 1. Disease Progression:** Cancer advances despite completing first-line therapy.
- 2. Severe Toxicity or Treatment Intolerance:** Patient experiences significant side effects that limit continued use of first-line treatment.
- 3. Platinum-Resistant Disease:** Tumor progresses within 6 months of platinum-based chemotherapy, indicating low likelihood of further platinum treatment benefit.

Key Takeaway:

Second-line treatment should be initiated if a patient meets any of these criteria.

Second-Line Treatment

When and How to Choose the Next Step

Which Treatment Path is Best for Your Patient?

STEP 1: Review Prior Treatment

Did the patient receive platinum-based chemotherapy plus immunotherapy (e.g., pembrolizumab) as part of first-line treatment?

ANSWER:

Yes

- Consider **Antibody-Drug Conjugates (ADC) – tisotumab vedotin**
- Monitor for ocular toxicity, neuropathy, bleeding risks

No:

- Consider **Checkpoint Inhibitors (pembrolizumab/nivolumab)** if PD-L1 CPS ≥ 1
- Watch for immune-related adverse events (pneumonitis, colitis, endocrinopathies)

STEP 2: Assess Biomarkers & Disease Resistance PD-L1 CPS ≥ 1 ?

- ✓ **If checkpoint inhibitors** (pembrolizumab/nivolumab) **were NOT used** in 1st-line, consider adding them.
- ✗ **If already used**, proceed to ADC therapy or explore clinical trials.

Platinum-Resistant Disease?

Yes: Explore Clinical Trials & Emerging Treatments

- Investigational agents, novel immunotherapies, and combo approaches
- Early referral to academic centers or clinical trial networks is essential
- tisotumab vedotin (ADC) is the preferred option.
- Consider clinical trials for novel targeted therapies.

No: Consider additional chemotherapy or targeted therapy based on prior treatment response and patient-specific factors.

MSI-High (MSI-H) / TMB-High (>10 mut/Mb)?

If yes, consider checkpoint inhibitor monotherapy (nivolumab or pembrolizumab).

Final Considerations: Biomarkers & Treatment

Use biomarker testing and patient-specific risk factors to guide individualized treatment decisions.

Optimization

Still uncertain? → Takeaway: Personalized treatment decisions should consider prior treatment, PD-L1 expression, platinum resistance status, and patient-specific risks. Early clinical trial referral is key for platinum-resistant disease.

Second-Line Treatment Options

Treatment Category	Example Drugs	Patient Population/ Indication	Key Considerations
Antibody-Drug Conjugates (ADC)	tisotumab vedotin	For patients with disease progression after platinum-based chemotherapy	Monitor for ocular toxicity (may require prophylactic eye drops). Other adverse effect: peripheral neuropathy, bleeding risks. Regular ophthalmology assessments recommended.
Checkpoint Inhibitors (if not used in first-line)	pembrolizumab (PD-L1 CPS \geq or nivolumab	For patients who did not receive checkpoint inhibitors in first-line therapy	Watch for immune-related adverse event (irAEs), including pneumonitis, colitis, and thyroid dysfunction. Requires ongoing monitoring and multidisciplinary support.
Targeted Therapy (for select patients)	bevacizumab (if not used in first-line)	For recurrent/metastatic disease without prior exposure to bevacizumab	Assess for contraindications: recent surgery, high bleeding/thrombosis risk. Monitor for hypertension, proteinuria, and GI perforation risk. Blood pressure control is essential.
Clinical Trials & Emerging Therapies	Bispecific Antibodies, ADC + Checkpoint Inhibitors Combinations, and PARP Inhibitors (for biomarker-selected patients)	For patients with platinum-resistant disease or multiple prior treatments	Early referral to clinical trials is critical for expanding options. Potential barriers include insurance limitations and geographic access.

Second-Line Treatment Decision Guide

Key Question	Treatment Recommendation	Clinical Considerations
Platinum + Immunotherapy (e.g., pembrolizumab) in first-line?	Yes: ADC Therapy (tisotumab vedotin)	Monitor for ocular toxicity, neuropathy, bleeding risks. Works best in tumors with high TF expression.
	No: Checkpoint inhibitors (pembrolizumab/nivolumab), if PD-L1 CPS ≥ 1	Watch for immune-related adverse events (pneumonitis, colitis, endocrinopathies). Best in inflamed tumors.
Platinum-Resistant Disease?	Yes: Clinical trials and emerging therapies	Investigational agents, novel immunotherapies, TGF- β inhibitors, or checkpoint pathways (LAG-3, TIGIT).
	No: Chemo or targeted therapy based on prior response	Platinum rechallenge may be an option if response lasted ≥ 6 months.
PD-L1 CPS ≥ 1 ?	Yes: Add checkpoint inhibitors if not used in first-line	Investigational agents, novel immunotherapies, TGF- β inhibitors, or checkpoint pathways (LAG-3, TIGIT).
	No: Proceed to ADC Therapy (tisotumab vedotin) or clinical trials	Platinum rechallenge may be an option if response lasted ≥ 6 months.
MSI-H / TMB-High (>10 mut/Mb)?	Yes: Checkpoint inhibitor monotherapy (nivolumab or pembrolizumab)	Best response in high neoantigen load or deficient mismatch repair (dMMR) tumor

Recap: Identifying the need for Second-Line Therapy

When to Initiate Second-Line Therapy:

Disease Progression:

Tumor growth, new metastases, or worsening symptoms.

Treatment Toxicity:

Severe side effects limiting continuation of first-line therapy.

Platinum Resistance:

Disease recurrence within 6-months of platinum-based chemotherapy.

Key Decision Points for Therapy Selection:

Check prior therapy - Did the patient receive first-line platinum + immunotherapy?

Yes: Consider Antibody-Drug Conjugates (ADC) (e.g., tisotumab vedotin).

No: Evaluate for Checkpoint Inhibitors (pembrolizumab/nivolumab) if PD-L1 CPS ≥ 1 .

Assess Biomarker and Resistance Status - Platinum-Resistant Disease?

Yes: Prioritize tisotumab vedotin or refer for clinical trials.

No: Consider platinum rechallenge or targeted therapy based on prior response.

Do biomarkers support immune-based therapy?

PD-L1 CPS ≥ 1 : If checkpoint inhibitors were not used in first-line, consider adding them.

MSI-High (MSI-H) or TMB-High (>10 mut/Mb): Checkpoint inhibitor monotherapy may be an option.

Next Steps for Clinical Action:

- Ensure biomarker testing before finalizing second-line treatment.
- Refer early for clinical trial options in platinum-resistant disease.
- Monitor for toxicity risks, especially ocular (ADC) and immune checkpoint inhibitor (ICI) adverse events.

Takeaway:

Second-line therapy decisions should be personalized based on prior treatment, biomarker expression, and platinum resistance status. Early clinical trial referral is key for platinum-resistant cases.

Personalized Therapy: Biomarker-Driven Second-Line Treatment Decisions

Biomarker-Based Treatment Selection

PD-L1 Expression (CPS Score)

- CPS ≥ 1 → Consider pembrolizumab-based therapy
- CPS < 1 → Alternative approaches needed (e.g., ADCs, chemotherapy)

MSI (Microsatellite Instability) & MMR Status

- MSI-High (MSI-H) / dMMR → Higher response rates to checkpoint inhibitors (pembrolizumab, nivolumab)
- MSI-Stable (MSS) / pMMR → Limited benefit from immunotherapy

Tumor Mutational Burden (TMB)

- High TMB (>10 mutations/Mb) → May respond to checkpoint inhibitors
- Low TMB → Immunotherapy less likely to be effective

Key takeaway: Comprehensive biomarker testing guides treatment selection, determining the best path between immunotherapy, targeted therapy, or chemotherapy.

How biomarkers influence treatment decisions

Biomarker	Clinical Meaning	Treatment Implications
PD-L1 CPS ≥ 1	Tumor expresses PD-L1, increasing ICI sensitivity	Pembrolizumab-based therapy preferred
PD-L1 CPS < 1	Low/absent PD-L1 expression	Consider alternative therapies (e.g., ADCs or chemotherapy)
MSI-H/dMMR	High mutation burden due to faulty DNA repair	Checkpoint inhibitors highly effective
TMB-High (>10 mut/Mb)	Increased tumor mutations generate more neoantigens	Checkpoint inhibitors may be beneficial

Key Biomarkers for Immunotherapy Decision-Making in Second-Line Treatment

Key Biomarkers for Immunotherapy Decision-Making

PD-L1 Expression (CPS – Combined Positive Score)

Definition: Measures PD-L1 expression in tumor & immune cells to predict response to ICIs.

How It's Used:

- CPS ≥ 1 → Candidate eligible for pembrolizumab-based therapy
- CPS < 1 → May require ADCs therapy or chemotherapy instead.

Key Pitfall: PD-L1 positivity \neq guaranteed response. Some PD-L1+ tumors still evade immune attack.

MSI (Microsatellite Instability) & dMMR (Deficient Mismatch Repair)

Definition: Genomic instability caused by defective DNA repair.

How It's Used:

- MSI-High (MSI-H) / dMMR → High response rates to checkpoint inhibitors (pembrolizumab, nivolumab).
- MSS (Microsatellite Stable) / pMMR → Less likely to benefit from ICIs.

Key Pitfall: Some MSI-H tumors resist ICIs due to other immune escape mechanisms.

Tumor Mutational Burden (TMB)

Definition: Number of mutations per megabase (Mb) of tumor DNA.

How It's Used:

- TMB > 10 mut/Mb → More likely to respond to checkpoint inhibitors.
- TMB-low tumors → Typically require alternative treatments.

Key Pitfall: High TMB alone doesn't guarantee response—immune microenvironment matters.

Key takeaway: Biomarker testing should guide treatment selection early to optimize immunotherapy decisions.

Now that we have assessed patient eligibility and key clinical factors in Step 2, we move to Step 3: Selecting the most appropriate second-line treatment pathway.

Second-Line Treatment Step 3 – Treatment Selection Pathways

Once you have assessed the patient's eligibility and clinical factors in Step 2, move into treatment selection.

There are three primary pathways for second-line treatment, depending on the patient's prior therapy and disease status:

- 1. Pathway A:** Patients who received first-line immunotherapy + platinum-based chemotherapy
- 2. Pathway B:** Patients who did not receive immunotherapy in first-line treatment
- 3. Pathway C:** Patients with platinum-resistant or rapidly progressing disease

The following slides will outline treatment options for each of these pathways.

Second-Line Treatment: Step 3A

Step 3A: Second-Line Treatment for Patients Previously Treated with First-Line Immunotherapy + Platinum

Primary Treatment Option: Antibody-Drug Conjugates (ADC)

Drug of Choice: Tisotumab vedotin

Mechanism: Targets tissue factor (TF) to deliver a cytotoxic payload.

Why This Choice? After pembrolizumab exposure, immune checkpoint blockade may have limited efficacy, making ADC therapy the preferred strategy.

Key Considerations:

Ocular toxicity: Prophylactic eye drops required

Neuropathy: Monitor closely for early symptoms

Bleeding risk: Caution in patients with recent surgery or high-risk bleeding conditions

Dose adjustment: Consider delays or modifications for adverse events

Alternative Options:

Platinum rechallenge: If platinum-sensitive (progression ≥ 6 months after last platinum therapy)

Clinical trials: Investigational ADCs and novel combination therapies

Best Supportive Care: For patients with declining performance status

Second-Line Treatment: Step 3B

Treatment Pathway for Patients Who Did Not Receive Immunotherapy in First-Line

ADC (Antibody-Drug Conjugate) = Targeted cancer therapy combining:

- **Monoclonal antibody**
- **Cytotoxic drug**
- **Linker** (delivers drug precisely)

Example: tisotumab vedotin

Benefit: Targets tumors while reducing toxicity to normal cells.

Primary Treatment Option:

Primary Option: Checkpoint inhibitors (pembrolizumab/nivolumab if PD-L1 CPS ≥ 1)

Why? Delayed initiation of immunotherapy can yield clinical benefits in eligible patients.

Mechanism: Enhances T-cell activation to target and destroy cancer cells.

Key Considerations:

Immune-related adverse events (irAEs): Pneumonitis, colitis, endocrinopathies

Steroid management: follow established guidelines to avoid treatment interruptions.

Alternative Options:

- If PD-L1 CPS < 1 or immunotherapy is not tolerated: Prioritize ADC therapy (tisotumab vedotin) or chemotherapy based on prior treatments.
- Consider adding bevacizumab (VEGF inhibitor) to platinum-based chemotherapy if not previously used, especially in platinum-sensitive disease.
- **Clinical Trials:** Investigate novel immunotherapy combinations and emerging checkpoint inhibitors.
- **Chemotherapy-Based Regimens:** Single-agent or combination chemotherapy remains an option for PD-L1 non-expressors.
- **Best Supportive Care:** Early palliative referral is recommended for patients with declining performance status.

Second-Line Treatment

Management of Immunotherapy and Targeted Therapy Toxicities

Monitor closely for immune-related adverse events (irAEs).

Common toxicities/irAEs:

- rash,
- colitis,
- hepatitis,
- pneumonitis.

Key Management Principles for Immunotherapy:

- Early identification of symptoms.
- Initiate corticosteroids for Grade ≥ 2 toxicities.
- Hold or permanently discontinue immune-oncology therapy depending on severity.
- Multidisciplinary management is critical: consult specialists e.g., pulmonary, GI, dermatology based on toxicity type.

Targeted Therapy Considerations:

- Monitor for cardiac, pulmonary, and hepatic function for toxicities.
- Individualize monitoring based on the specific agent used.

Second-Line Treatment: Step C

Patients with Platinum-Resistant Disease or Rapidly Progressing Disease

Recommended Therapy:

Clinical Trials & Emerging Therapies

Why? Standard treatments provide limited benefit, making investigational options crucial.

Key Considerations:

Access Barriers:

- Insurance coverage, geographic limitations, and strict trial eligibility may impact trial enrollment.
- Early Referral: Direct patients to academic centers, clinical trial networks, or specialized oncology groups.

Combination Approaches to Consider:

- Bispecific antibodies targeting novel immune pathways
- Antibody-drug conjugates (ADCs) for targeted therapy
- Checkpoint inhibitors in novel combinations
- Next-gen immunotherapies targeting alternative resistance mechanisms

Alternative Treatment Considerations (if clinical trials are not an option):

- Chemotherapy-based regimens: topotecan, paclitaxel, ifosfamide
- Palliative and supportive care: Early integration improves symptom management and quality of life

Takeaway:

Clinical trials offer the best chance for meaningful outcomes, while standard regimens and supportive care remain important considerations.

Second Line Treatment

Streamlined Treatment Pathways Summary

Pathway	Primary Treatment	Rationale	Key Consideration	Alternative Options
A: Prior Immunotherapy + Platinum	Antibody-Drug Conjugate (ADC) – Tisotumab Vedotin	Limited immune-based options; ADC's deliver cytotoxic payload directly to tumor cells	<ul style="list-style-type: none"> • Ocular toxicity: Pre-treat with eye drops • Neuropathy: Monitor symptoms • Bleeding risk: Caution with recent surgery 	Clinical trials (investigational ADC's, novel combination therapies) Best supportive care for declining performance status
B. No prior immunotherapy	Checkpoint Inhibitors (Pembrolizumab if PD-L1 CPS \geq 1)	Late introduction of immunotherapy can still provide benefit in eligible patients	<ul style="list-style-type: none"> • Monitor for immune-related adverse events (pneumonitis, colitis, endocrinopathies) • May require steroid for management 	If PD-L1 CPS \leq 1 or immunotherapy not tolerated – proceed to ADC of chemotherapy. Consider adding Bevacizumab if not previously used.
C. Platinum-Resistant/Rapid Progression	Clinical Trials & Emerging Therapies	Patients with platinum-resistant disease have limited benefit from standard treatments, making investigational options critical	<ul style="list-style-type: none"> • Access barriers – insurance, geography, trial eligibility • Early referral to academic centers or trial networks recommended 	Chemotherapy-based regimes (Tototecen, Paclitaxel, Ifosfamide) for patients, ineligible for clinical trials. Early palliative & supportive care for symptom management

Second-Line Treatment

Moving from Pathways to Personalized Treatment

Now that we've identified the three main treatment pathways (A, B, & C), the next step is to refine treatment selection based on individual patient factors.

What's Next?

- We will now break down the best second-line treatment options for each group.
- Treatment choices depend on
 - Prior therapies,
 - Biomarker status, and
 - Patient-specific considerations.

Up Next:

Pathway A – Optimizing Treatment for Pathway A
– Patients Who Received First-Line Immunotherapy + Platinum

Second-Line Treatment

Optimizing Treatment: Managing Toxicities & Patient Adherence

Why is toxicity management critical?

- Ensures patients can stay on therapy, improving long-term outcomes.
- Reduces risk of treatment discontinuation due to side effects.
- Enhances quality of life and overall treatment efficacy.

Common Toxicities & Management Strategies

1. Antibody-Drug Conjugates (ADC Therapy - tisotumab vedotin)

- Ocular Toxicity: Pre-treatment eye drops, close monitoring.
- Neuropathy: Dose modifications, pain management strategies.
- Bleeding Risk: Monitor for hemorrhage, especially post-surgery.

2. Checkpoint Inhibitors (pembrolizumab/nivolumab)

- Immune-Related Adverse Events (irAEs) → Early recognition and corticosteroid intervention when needed.
- Taper steroid tapering as needed after initiating corticosteroids to prevent irAE flare-ups.
- Consider multidisciplinary management (e.g., pulmonary, GI consultation) based on toxicity type.
- Pneumonitis & Colitis: Frequent monitoring, discontinue if severe.

3. Chemotherapy-Based Regimens

- Hematologic Toxicities: Monitor neutropenia, anemia, thrombocytopenia.
- Nausea & Fatigue: Supportive medications, lifestyle interventions.

Takeaway:

Proactive side effect management is crucial to maximize patient benefits while minimizing risks.

Next up:

Best practices for long-term patient monitoring & follow-up care.

Second-Line Treatment

Best Practices for Long-Term Patient Monitoring and Follow-Up Care

Why is ongoing monitoring essential?

- Detects early disease progression and treatment resistance.
- Reducing long-term toxicities and enhancing treatment safety.
- Enhances patient quality of life through proactive management.

Key Components of Follow-Up Care

1. Disease Surveillance

- Routine Imaging (CT/MRI/PET scans): Every 8-12 weeks.
- Tumor Marker Monitoring: Evaluate trends in biomarkers if applicable.
- Clinical Exam & Symptom Review: Detect new metastases or worsening symptoms.

2. Treatment Side-Effect Monitoring

- **Ophthalmologic Exams:** ADC-related ocular toxicity.
- **Endocrine Panel:** Checkpoint inhibitor-related thyroid & adrenal dysfunction.
- **Neuropathy Assessments:** Monitor for sensory or motor impairment.

3. Chemotherapy-Based Regimens

- **Patient-Reported Outcomes & Supportive Care**
- **Assess Functional Status:** Performance scales (ECOG/Karnofsky).
- **Manage Pain & Fatigue:** Consider palliative interventions as needed.
- **Psychosocial & Mental Health Support:** Address treatment burden & emotional well-being.

Takeaway:

Long-term follow-up is not just about tracking the disease—it's about optimizing quality of life and ensuring the best possible patient outcomes.

Next up:

Case studies highlighting real-world treatment decisions and outcomes.

PART 3

Case-Based Learning



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This educational initiative is supported by an independent medical education grant from Pfizer and Genmab

Real-World Case Studies: Navigating Second-Line Treatment in Metastatic Cervical Cancer

Best Practices for Long-Term Patient Monitoring & Follow-Up Care

Why These Case Studies Matter:

- Provide real-world examples of managing different stages of metastatic cervical cancer.
- Key factors influencing treatment decisions include biomarker status (e.g., PD-L1 CPS), prior therapies, and performance status.
- Emphasize the importance of:
 - Early identification of disease progression
 - Optimal sequencing of therapies
 - Balancing treatment efficacy with quality-of-life considerations

Case Studies

Case Study 1

- Newly diagnosed metastatic cervical cancer — 1st-line therapy selection based on PD-L1 status.

Cases Study 2

- Disease progression after 1st-line therapy — transition to 2nd-line ADC therapy.

Case Study 3

- Platinum-resistant disease management — clinical trial referral, chemotherapy options, and supportive care.

Takeaway:

Real-world management requires a personalized, adaptable approach informed by evolving disease biology, patient needs, and emerging treatment options.

Next up:

Case Study 1: Newly Diagnosed Metastatic Cervical Cancer

Case Study 1: Newly Diagnosed Metastatic Cervical Cancer

Best Practices for Long-Term Patient Monitoring and Follow-Up Care

Why This Case Study Matters:

- Highlights first-line treatment selection based on biomarkers and patient factors.
- Demonstrates key decision points in sequencing systemic therapy.

Patient Overview

- **Age:** 47-year-old female
- **Diagnosis:** Stage IVB metastatic cervical cancer
- **Metastatic Sites:** Lung, para-aortic lymph nodes
- **ECOG Performance Status:** 1 (fully ambulatory, mild symptoms)

Diagnostic Workup & Biomarkers

- **PD-L1 CPS:** 15

Clinical Considerations

- No significant comorbidities
- Fully ambulatory, eligible for systemic therapy
- High PD-L1 expression suggests potential immunotherapy benefit

Next up:

First-Line Treatment Approach & Rationale

Case Study 1: Newly Diagnosed Metastatic Cervical Cancer Treatment Decision

Treatment Decision: First-Line Therapy Selection

Recommended Regimen: Platinum-Based Chemotherapy + Bevacizumab + Pembrolizumab

- **Chemotherapy Backbone:**
carboplatin + paclitaxel (platinum doublet)
- **VEGF Inhibitor:**
bevacizumab (unless contraindicated)
- **Checkpoint Inhibitor:**
pembrolizumab (for PD-L1 CPS ≥ 1 patients)

Rationale

- Maximizes survival benefit in PD-L1-positive metastatic cervical cancer.
- Enhances response rates by targeting both VEGF and immune pathways.
- Delays disease progression compared to chemotherapy alone.

Case Study 1: Newly Diagnosed Metastatic Cervical Cancer

Key Considerations in Treatment Monitoring

Immune-Related Adverse Events (irAEs): Pneumonitis, colitis, endocrinopathies require early recognition & intervention.

Bleeding Risk with Bevacizumab: Avoid in patients with recent surgery or risk of GI perforation.

Chemotherapy Toxicities: Neutropenia, fatigue, nausea requires supportive care.

Next up:

Treatment Follow-Up &
Next Steps

Case Study 1: Newly Diagnosed Metastatic Cervical Cancer

Follow-Up and Potential Next Steps

After 6 months of therapy, imaging shows stable disease.

What's next?

1. Continue pembrolizumab maintenance therapy (up to 24 months total).
2. Monitor for treatment-related toxicities and adjust dosing if necessary.
3. If disease progresses → Transition to second-line therapy (tisotumab vedotin or clinical trials).

Takeaway:

First-line treatment selections should be guided by PD-L1 status, disease burden, and patient fitness, with long-term outcomes dependent on toxicity management and sequencing.

Case Study 2: Progression After First-Line Therapy

Transition to Second-Line Treatment

Why These Case Studies Matter:

- Demonstrates timing and approach to second-line therapy
- Highlights challenges in managing treatment-resistant disease

Patient Profile:

- **Age:** 50-year-old female
- **Diagnosis:** Recurrent cervical cancer
- **Prior Treatment:** Carboplatin + Paclitaxel + Bevacizumab + Pembrolizumab
- **Time to Progression:** 9 months post-first-line treatment
- **ECOG Performance Status:** 1 (fully ambulatory, mild symptoms)

Diagnostic Workup & Biomarkers:

- **Imaging:** Confirms progressive disease
- **Residual Toxicities:** Mild neuropathy from prior platinum-based chemotherapy
- No new actionable biomarkers identified

Decision Point:

- **Recommended Treatment:** Tisotumab Vedotin (Antibody-Drug Conjugate Therapy).
- **Mechanism of Action:** Targets tissue factor to deliver a cytotoxic payload **directly to cancer cells.**
- **Rationale:**
 - Patient progressed post-platinum therapy, making ADC therapy the preferred option
 - Directly targets cancer cells while minimizing systemic toxicity
 - Shown to improve progression-free survival in recurrent cervical cancer

Case Study 2: Progression After First-Line Therapy

Transition to Second-Line Treatment

Key Considerations in Treatment Monitoring

- **Ocular Toxicity:** Requires pre-treatment eye drops and regular ophthalmologic evaluation
- **Neuropathy:** Monitor for worsening sensory/motor symptoms, adjust dose if needed
- **Bleeding Risk:** Increased risk in patients with recent surgery or coagulopathy

Follow-Up & Potential Next Steps

After 3 months on tisetumab vedotin, patient has stable disease. **What next?**

- Continue treatment with close toxicity monitoring
- Assess for additional biomarker-driven therapy options (e.g., MSI-H, TMB-high patients may still benefit from checkpoint inhibitors)
- If disease progresses → Consider chemotherapy, clinical trials, or best supportive care

Takeaway:

Effective second-line therapy requires balancing toxicity management with timely recognition of progression, and consideration of clinical trial options.

Case Study 3: Effective Management of Platinum-Resistant Disease

Transition to Second-Line Treatment

Why These Case Studies Matter:

- Addresses treatment challenges in platinum-resistant cervical cancer
- Explores when to shift from standard therapies to clinical trials or supportive care

Patient Profile:

- **Age:** 55-year-old woman
- **Diagnosis:** Recurrent/metastatic cervical cancer
- **Previous Treatments:**
 - **First-line therapy:** carboplatin + paclitaxel + bevacizumab + pembrolizumab
 - **Second-line therapy:** tisotumab vedotin (ADC Therapy)
 - **Disease Progression:** Within 6 months of starting ADC therapy → Platinum-resistant disease

Diagnostic Workup & Biomarkers:

- ECOG 2 (mild functional decline)
- Progressive disease on imaging
- Increasing fatigue, mild neuropathy

Takeaway:

Managing platinum-resistant disease requires recognizing progression early, evaluating functional decline, and preparing to transition to clinical trials or supportive care.

Case Study 3: Managing Platinum-Resistant Disease

Decision Point: Treatment Options in Platinum-Resistant Disease

Recommended Options:

- Clinical Trial Referral – Investigational agents (e.g., bispecific antibodies, novel ADCs, combination checkpoint inhibitors)
- Chemotherapy-Based Regimens Options include Topotecan, Paclitaxel, Ifosfamide
- Best Supportive Care & Palliative Referral – If performance status declines further

Key Considerations in Decision-Making

- Clinical Trials: Preferred due to limited benefit from standard therapies
- Chemotherapy: Less effective but may provide short-term disease control
- Palliative Care Referral: Early integration for symptom management & quality of life

Follow-Up & Potential Next Steps:

- After 2 months, the patient enrolls in a clinical trial testing a combination of ADC + immune therapy.
- If stable disease or response, continue trial therapy
 - If further progression, shift to supportive care and symptom management

Takeaway:

Effective management of platinum-resistant disease requires a tailored approach that balances aggressive treatment with quality-of-life considerations.

From Clinical Pathways to Personalized Patient-Centered Care

Now that we've explored real-world treatment pathways, it's important to recognize that treatment selection is not based on disease factors alone.

Patient preferences, values, and goals are crucial in guiding second-line treatment decisions — especially when multiple options exist.

Takeaway:

Patient-centered care requires incorporating patient preferences, values, and goals into treatment selection, especially when multiple second-line options exist.

Next Up:

Strategies for incorporating patient-centered care into clinical decision-making.

Incorporating Patient Preferences in Treatment Selection

Why It's Important:

- Align treatment choices with patient values, lifestyle, and goals.
- Incorporate shared decision-making to improve satisfaction and adherence.
- Use decision aids (e.g., NCCN, ASCO tools) to explain treatment options and side effects.
- Discuss goals of care early and consider patient-specific factors (clinical, cultural, financial).
- Encourage open communication and engage patients and families.

Takeaway:

Effective management aligns treatment with patient values and evidence-based guidelines to ensure care that balances outcomes with quality of life.

Guideline-Driven Treatment Approaches

Why It's Important:

Treatment should align with the latest evidence-based guidelines while allowing flexibility for real-world practice.

Current NCCN/ESMO/ASCO Guidelines Overview:

1. First-Line Treatment: Platinum-based chemo + immunotherapy ± Bevacizumab.
2. Second-Line Treatment:

Disease Type	Recommended Therapy
Platinum-Sensitive Disease	Consider re-challenge with platinum-based chemotherapy
Platinum-Resistant	Antibody-Drug Conjugate (ADC) Therapy (e.g., tisotuman vedotin)
Checkpoint Inhibitor-Sensitive	Defective mismatch repair (MMR) leads to hypermutation, increasing neoantigen load.
Clinical Trial Consideration	Investigational therapies (e.g., bispecific antibodies, novel ADCs)
Supportive Care Focus	Symptom management, palliative care referral

Takeaway:

Aligning patient values with evidence-based guidelines ensures treatments that balance optimal outcomes with high-quality care.

Translating Guidelines into Real-World Practice

Translating Guidelines into Real-World Practice

Why These Case Studies Matter:

- Not all patients fit neatly into guideline recommendations, requiring adaptation in real-world practice.

Real-World Challenges & Adaptations:

I. Access to Therapy:

- Insurance hurdles may limit ADC and checkpoint inhibitor use
- Drug availability differs between urban and rural settings

II. Community vs. Academic Center Disparities:

- Clinical trials often limited to large institutions.
- Access constrained by geography and socioeconomic factors.

III. Physician Experience Matters:

- Managing toxicities requires interdisciplinary coordination.
- Refer complex cases to tertiary centers when possible.

Takeaway:

Even with evidence-based guidelines, treatment decisions are complex due to clinical, logistical, and patient-centered challenges.

Common Challenges in Second-Line Treatment

What makes treatment decisions difficult?

- **Platinum-Resistant Disease:** Limited standard options, reliance on clinical trials.
- **Toxicity from Prior Treatment:** Neuropathy, immune-related adverse events (irAEs), renal dysfunction limit drug selection.
- **Access to Clinical Trials:** Geographic and insurance barriers; strict eligibility criteria.
- **Patient Preferences and Quality of Life Considerations:** Balancing aggressive treatment vs. supportive care.
- **Urgency of Disease Progression:** Rapid disease worsening can restrict evaluation and treatment windows.

Takeaway:

Even with the appropriate therapy, real-world barriers can limit access and compromise patient outcomes.

Systemic Challenges in Second-Line Treatment

Managing Immune-Related Adverse Events (irAEs)

- 10–20% of patients receiving ipilimumab experience severe and potentially fatal immunological adverse effects due to T-cell activation and proliferation.
- Common irAEs: pneumonitis, colitis, and endocrine dysfunction.

Challenges:

- Early detection and standardized management protocols.
- Coordination gaps often exist between oncology, endocrinology, & primary care teams.

Barriers to Multidisciplinary Care

- Limited communication between oncologists, PCPs, & palliative care teams.
- Underuse of patient navigators and case managers.
- Better sequencing of therapies and specialist referrals needed.

Takeaway:

Addressing systemic challenges requires early irAEs detection and stronger multidisciplinary communication to improve patient outcomes.

Key Takeaways: Optimizing Cervical Cancer Treatment

Personalized Treatment Selection

- Biomarker testing (PD-L1, TMB, MSI) is critical for guiding therapy.
- Align treatments with patient goals and real-world constraints.

Second-Line and Platinum-Resistant Disease

- ADC therapy and checkpoint inhibitors offer viable options post-platinum.
- Clinical trial enrollment should be considered early.

Addressing Barriers to Care

- Proactively tackle insurance, financial, and geographic limitations.
- Improve coordination among oncology, palliative, and primary care teams.

Strategic Treatment Sequencing

- Optimize referrals for multidisciplinary care and trial access.
- Standardize processes for appeals and financial assistance.

Final Thought:

The best outcomes come from evidence-based, patient-centered decisions that adapt to real-world clinical challenges.

Best Practices in Treatment Sequencing

Multidisciplinary Collaboration is Critical

- Strengthen referral protocols between oncologists, gynecologic surgeons, and palliative care teams.
- Conduct regular tumor board discussions to streamline decision-making.
- Promote shared decision-making between providers and patients.

Enhance Patient Education & Support

- Use ADC therapy and checkpoint inhibitors as viable options post-platinum.
- Consider clinical trial enrollment early.

Key Takeaway:

Early coordination, biomarker-guided decisions, and strong multidisciplinary teamwork optimize treatment sequencing and improve patient outcomes.

Key Takeaways Before We Test Your Knowledge

WHAT WE'VE COVERED:

- Determined second-line treatment eligibility.
- Understood three main second-line treatment pathways based on prior therapy.
- Optimized treatment sequencing using patient and disease-specific factors.
- Addressed real-world treatment challenges and patient preferences.

Up Next:

Self-Assessment!

Final Key Takeaways: Optimizing Second-Line Treatment for Recurrent Metastatic Cervical Cancer

- I. **Optimize treatment sequencing:** Base decisions on prior therapy, biomarkers, and platinum sensitivity. Use immunotherapy for PD-L1+ patients; ADC therapy for post-platinum progression.
- II. **Refer to clinical trial early:** Investigational therapies may improve long-term outcomes, especially for platinum-resistant disease.
- III. **Require PD-L1 testing before checkpoint inhibitors:** Ensure eligibility testing early to guide optimal treatment selection.
- IV. **Strengthen multidisciplinary care:** Coordination among oncologists, palliative care teams, and patient navigators to provide comprehensive clinical and financial support.
- V. **Proactively manage toxicity:** Monitor for immune-related adverse events (irAEs) and ADC-related side effects. Refer patients to an ophthalmologist for ADC-associated ocular toxicity. Early recognition and intervention improve adherence and overall treatment success.

PART 4

Knowledge Assessment and Key Takeaways



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Instructions

1. Test your understanding of second-line treatment strategies for recurrent/metastatic cervical cancer.
2. Choose the **best answer** for each question.
3. Correct answers will be revealed after all questions are completed.
4. This self-assessment will cover both **treatment selection** and **toxicity management strategies**.

This educational initiative is supported by an independent medical education grant from Pfizer and Genmab

Question 1

First-Line Treatment for PD-L1+ Recurrent/Metastatic Cervical Cancer

QUESTION:

What is the preferred first-line treatment for PD-L1+ r/m cervical cancer?

✓ **SELECT AN ANSWER**

- A. tisotumab vedotin
- B. platinum-based chemotherapy + pembrolizumab + bevacizumab
- C. nivolumab monotherapy
- D. radiation therapy

Question 1: Answer

First-Line Treatment for PD-L1+ Recurrent/Metastatic Cervical Cancer

CORRECT ANSWER:

B. Platinum-based chemotherapy + pembrolizumab + bevacizumab

Explanation

- The standard first-line therapy for PD-L1+ recurrent/metastatic cervical cancer is **platinum-based chemo + pembrolizumab + bevacizumab**.
- This combination improves overall survival and progression-free survival compared to chemotherapy alone.

Why the Other Options Are Incorrect

- **A:** tisotumab vedotin is used in second-line treatment after disease progression on platinum therapy.
- **C:** nivolumab monotherapy is not the standard first-line treatment; pembrolizumab is preferred in this setting.
- **D:** radiation therapy is essential for locally advanced disease, but systemic therapy is the standard for recurrent/metastatic cases.

Key Takeaway

For PD-L1+ r/m cervical cancer, platinum-based chemotherapy + pembrolizumab + bevacizumab is the optimal first-line treatment. This combination significantly improves survival outcomes in PD-L1+ patients.

Question 2

Treatment After Platinum Progression

QUESTION:

A 48-year-old woman with metastatic cervical cancer previously received **carboplatin/paclitaxel + bevacizumab + pembrolizumab**. Nine months later, her disease progressed. She has no significant neuropathy but reports mild dry eyes and occasional epistaxis. Management strategies must consider early toxicity intervention to preserve treatment efficacy and patient quality of life.

What is the most appropriate next step in management?

SELECT AN ANSWER

- A. Repeat platinum-based chemotherapy
- B. tisotumab vedotin (ADC therapy)
- C. Switch to single-agent nivolumab
- D. Observe for further progression

Question 2: Answer

Treatment After Platinum Progression

CORRECT ANSWER:

B. Tisotumab vedotin (ADC Therapy)

Explanation

- Tisotumab vedotin is the preferred second-line therapy for platinum-resistant metastatic cervical cancer.
- Why? The patient progressed within 12 months of first-line platinum therapy, indicating platinum resistance. ADC therapy is preferred in this setting.

Why the Other Options Are Incorrect

- **A:** Platinum rechallenge is not recommended, as progression within 12 months suggests resistance. Rechallenge is unlikely to be effective.
- **C:** Single-agent checkpoint inhibitors Nivolumab is not standard after prior pembrolizumab exposure.
- **D:** Observation: Active disease progression requires intervention. Delaying treatment risks further deterioration.

Key Considerations

Monitor for ocular toxicity: Requires prophylactic eye drops and ophthalmologic monitoring.

Assess bleeding risk: Given the history of epistaxis, use caution.

Neuropathy surveillance: Though not present initially, it requires close monitoring due to ADC-related risks.

Key Takeaway

For platinum-resistant metastatic cervical cancer, Tisotumab vedotin (ADC therapy) is the preferred second-line option. Careful toxicity management is essential to minimize ocular and bleeding risks.

Question 3

Biomarkers and Immunotherapy

QUESTION:

What is the most common biomarker used to determine eligibility for immunotherapy in recurrent/metastatic cervical cancer?

SELECT AN ANSWER

- A. BRCA1/2 Mutations
- B. HER2 Expression
- C. PD-L1 CPS score
- D. KRAS Mutation

Question 3: Answer

Biomarkers and Immunotherapy

CORRECT ANSWER:

C. PD-L1 CPS score

Explanation

- The PD-L1 CPS score is essential for determining checkpoint inhibitor eligibility (e.g., **pembrolizumab**). Patients with CPS ≥ 1 benefit the most from immunotherapy.

Why the Other Options Are Incorrect

- **A: BRCA1/2 Mutations:** These are primarily associated with homologous recombination deficiency (HRD) and sensitivity to PARP inhibitors, which are used in ovarian and breast cancer, not cervical cancer.
- **B: HER2 Expression:** HER2 is relevant in breast and gastric cancers (e.g., **trastuzumab**) but does not guide immunotherapy in cervical cancer.
- **D: KRAS Mutation:** KRAS mutations are most relevant in colorectal and lung cancers, they do not predict immunotherapy response in cervical cancer.

Key Takeaway

Always check PD-L1 CPS score when evaluating immunotherapy for cervical cancer. Other biomarkers may guide treatment in different cancers but do not determine checkpoint inhibitor eligibility in this setting.

Question 4

Immunotherapy Eligibility

QUESTION:

Which is the key determinant of eligibility for checkpoint inhibitors (e.g., pembrolizumab) in second-line treatment of recurrent/metastatic cervical cancer?

SELECT AN ANSWER

- A. Prior exposure to chemotherapy
- B. PD-L1 expression (CPS ≥ 1)
- C. Age of the patient
- D. ECOG performance status

Question 4: Answer

Immunotherapy Eligibility

CORRECT ANSWER:

B. PD-L1 expression (CPS \geq 1)

Explanation

- PD-L1 CPS \geq 1 is the primary biomarker guiding eligibility for pembrolizumab in recurrent/metastatic cervical cancer.
- Checkpoint inhibitors (e.g., pembrolizumab) require PD-L1 testing.
- Patients with CPS \geq 1 are more likely to benefit from immune checkpoint inhibitors (ICIs) in cervical cancer treatment.

Why the Other Options Are Incorrect

- **A:** Prior exposure to chemotherapy: While many patients receiving second-line immunotherapy have had prior chemotherapy, it is not the key eligibility factor for pembrolizumab.
- **C:** Age of the patient: Age alone is not a deciding factor for immunotherapy. Eligibility is biologically driven (PD-L1 expression) rather than age-dependent.
- **D:** ECOG performance status: While ECOG 0-1 is preferred for initiating treatment, it does not determine PD-L1-based eligibility for checkpoint inhibitors.

Key Takeaway

Checkpoint inhibitor eligibility in cervical cancer is driven by PD-L1 CPS, not chemotherapy history, age, or performance status. Early PD-L1 testing ensures timely treatment decisions.

Question 5

Clinical Trial Referral

QUESTION:

Which factor is most important when determining referral of a clinical trial patient with recurrent/metastatic cervical cancer?

SELECT AN ANSWER

- A. Geographic proximity to trial site
- B. PD-L1 expression (CPS \geq 1)
- C. ECOG performance status
- D. Prior exposure to checkpoint inhibitors

Question 5: Answer

Clinical Trial Referral

CORRECT ANSWER:

A. Geographic proximity to trial site

Explanation:

- Enrollment in clinical trials for recurrent/metastatic cervical cancer often depends on the patient's ability to access a trial site.
- Geographic proximity and feasibility of travel are frequently the most practical and limiting determinants of referral.
- While PD-L1 expression and ECOG performance status are important for treatment decisions, they are not the primary barrier for trial enrollment.

Why the Other Options Are Incorrect

B: PD-L1 expression (CPS \geq 1): Relevant for immunotherapy eligibility, but not the key determinant for clinical trial referral.

C: ECOG performance status: Important for trial eligibility, but secondary to feasibility and logistics of referral.

D: Prior exposure to checkpoint inhibitors: May influence trial eligibility criteria but is not the central factor in deciding referral.

Key Takeaway

For clinical trial referral in recurrent/metastatic cervical cancer, **geographic proximity and patient access to the trial site** are often the most decisive factors. Early referral improves opportunities for enrollment and potential outcomes.

Question 6

Managing Toxicity in Second-Line Therapy

QUESTION:

A patient on tisotumab vedotin reported worsening dry eyes and grade 1-2 neuropathy.

What is the most appropriate management strategy?

SELECT AN ANSWER

- A. Continue treatment without changes
- B. Dose reduction and/or ophthalmology referral
- C. Stop treatment immediately
- D. Switch to platinum-based chemotherapy

Question 6: Answer

Managing Toxicity in Second-Line Therapy

CORRECT ANSWER:

B. Dose reduction or ophthalmology referral

Explanation

- Tisotumab vedotin toxicity management includes dose adjustments and early ophthalmology involvement to prevent severe ocular complications.
- Dry eyes and neuropathy are common side effects that are typically manageable without stopping treatment.
- Patients should receive prophylactic ophthalmology referral, and eye drops and neuropathy monitoring to prevent worsening symptoms.

Why the Other Options Are Incorrect

- **A:** Continue treatment without changes: This is inappropriate if symptoms worsen. Dose modifications and supportive care are needed.
- **C:** Stop treatment immediately: Discontinuation is only needed for severe (Grade 3/4) toxicity. Most mild to moderate toxicities can be managed with supportive care .
- **D:** Switch to platinum-based chemotherapy: Platinum-based chemotherapy is not the preferred second-line option after ADC therapy unless the disease progresses, or toxicity is unmanageable.

Key Takeaway

Tisotumab vedotin requires proactive toxicity management with ophthalmologic monitoring and dose modifications as needed. Discontinuation should be reserved for severe cases.

Question 7

Treatment for PD-L1 Negative Patients

QUESTION:

What is the preferred second-line treatment for a PD-L1-negative patient with platinum-resistant cervical cancer?

SELECT AN ANSWER

- A. Checkpoint inhibitor (pembrolizumab)
- B. Chemotherapy or ADC therapy (*tisotumab vedotin*)
- C. Targeted therapy (bevacizumab alone)
- D. Radiation therapy

Question 7: Answer

Treatment for PD-L1 Negative Patients

CORRECT ANSWER:

B. Chemotherapy or ADC therapy (*tisotumab vedotin*)

Takeaway
for Answer
7 and 8 are
the same

Explanation

- PD-L1 negative patients with platinum-resistance cervical cancer, ADC therapy (*tisotumab vedotin*) or chemotherapy is the preferred second-line option.
- *Tisotumab vedotin* (ADC therapy) is FDA-approved for platinum-resistant cervical cancer, regardless of PD-L1 status.
- ADC therapy does NOT require PD-L1 expression.
- Chemotherapy (e.g., topotecan, paclitaxel, or gemcitabine) remains a standard option, but ADC therapy is often preferred due to improved efficacy.

Why the Other Options Are Incorrect

- **A:** Checkpoint inhibitors (pembrolizumab): Pembrolizumab is only effective in PD-L1 CPS ≥ 1 patients and is not recommended for PD-L1 negative cases.
- **C:** Targeted therapy (bevacizumab alone): Bevacizumab is combined with chemotherapy but is not a standalone second-line treatment.
- **D:** Radiation therapy: Used for localized cervical cancer but not for systemic, platinum-resistant disease.

Key Takeaway

For PD-L1 negative patients with platinum-resistant cervical cancer, ADC therapy (*tisotumab vedotin*) or chemotherapy is the preferred second-line approach.

Question 8

Sequencing Therapies Based on Prior Treatment

QUESTION:

A patient received platinum-based chemotherapy 18 months ago.

Which second-line therapy is most appropriate?

SELECT AN ANSWER

- A. Rechallenge with platinum-based chemo
- B. Immediate *tisotumab vedotin* initiation
- C. Immunotherapy alone
- D. No treatment necessary

Question 8: Answer

Sequencing Therapies Based on Prior Treatment

CORRECT ANSWER:

A. Rechallenge with platinum-based chemotherapy

Takeaway
for Answer
7 and 8 are
the same

Explanation

- Since the patient received platinum-based chemotherapy 18 months ago, this suggests a platinum-sensitive disease (defined as progression occurring more than 6 months after prior platinum therapy).
- Platinum rechallenge is preferred in this setting as patients with a longer platinum-free interval are more likely to respond to re-treatment.

Why the Other Options Are Incorrect

- **B:** Immediate *tisotumab vedotin* initiation: ADC therapy (like *tisotumab vedotin*) is recommended for platinum-resistant disease but is not platinum-sensitive.
- **C:** Immunotherapy alone: While immunotherapy (e.g., pembrolizumab) can be used in PD-L1+ patients, platinum-sensitive patients often benefit more from chemotherapy-based approaches first.
- **D:** No treatment necessary: This patient has recurrent/metastatic disease and requires active management. Observation without intervention is not appropriate.

Key Takeaway

For patients with platinum-sensitive recurrent cervical cancer (progression > 6 months after prior platinum), rechallenge with platinum-based chemotherapy is the preferred second-line approach.

PART 5

Conclusion and Clinical Resources



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Next Steps in Clinical Practice

Incorporate Biomarker Testing Early

- Ensure PD-L1, MSI, and TMB testing at diagnosis
- Personalize treatment selection based on results

Facilitate Clinical Trial Access

- Implement standardized trial screening protocols
- Leverage trial-matching platforms for eligible patients
- Utilize digital matching tools and institutional databases to optimize timely clinical trial enrollment

Strengthen Multidisciplinary Collaboration

- Establish clear referral pathways for supportive and palliative care
- Promote shared decision-making with patients and caregivers

Enhance Toxicity Management

- Implement early screening protocols for ocular, bleeding, and immune-related toxicities
- Coordinate care with ophthalmology, endocrinology, and palliative specialists
- Provide patient education on side effect management

Key Resources for Clinical Practice & Patient Care

Evidence-Based Clinical Guidelines

- **NCCN Cervical Cancer Guidelines (2024):** Up-to-date, evidence-based recommendations for treatment sequencing and patient management
- **ASCO & ESMO Treatment Recommendations:** Best practices for second-line therapy and supportive care

Clinical Trials and Research

- **ClinicalTrials.gov:** A comprehensive database of ongoing and upcoming clinical trials in recurrent/metastatic (r/m) cervical cancer
- **Gynecologic Oncology Group (GOG) Trials:** Cutting-edge research, investigator-led trials, and patient enrollment details
- **Society of Gynecologic Oncology (SGO):** Updates on new investigational therapies and best practices

Patient and Caregiver Support

- **Pharmaceutical Assistance Programs:** Co-pay support, free drug programs, and financial aid for underinsured patients
- **Palliative and Supportive Care Networks:** Guidance on pain management, symptom control, and holistic care
- **Survivorship and Mental Health Resources:** Emotional and practical support for patients and caregivers, including peer support and counseling
- **Early Palliative Integration:** Improves quality of life and treatment outcomes

Thank You for Your Attention

Key Takeaways

- Use early biomarker testing to guide treatment and improve outcomes.
- Refer patients to clinical trials promptly to expand options.
- Manage toxicities proactively to preserve quality of life.
- Foster multidisciplinary collaboration for optimal care.
- Work together to improve survival and quality of life in recurrent/metastatic cervical cancer patients.

Thank You



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