Southeastern Multidisciplinary Approaches to Cancer Symposium

Moving the Needle in GYN Malignancies- Incorporating Novel Therapeutics in Cervical and Endometrial Cancers

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Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Learning Objectives

- ★ Identify the latest phase III data that changed standards of care.
- ★ Use biomarkers to select immunotherapy, HER2-directed therapy, and ADC trials.
- ★ Translate clinical-trial endpoints into sequencing decisions.
- ★ Discuss toxicities of novel agents.

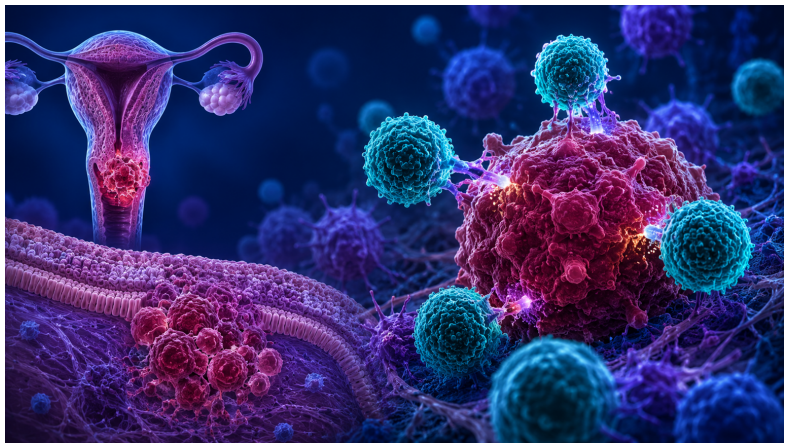
Why this topic matters now

13,490

estimated U.S. cervical cancer cases in 2026

4,200

estimated U.S. cervical cancer deaths in 2026



68,270

estimated U.S. endometrial / uterine corpus cases in 2026

14,450

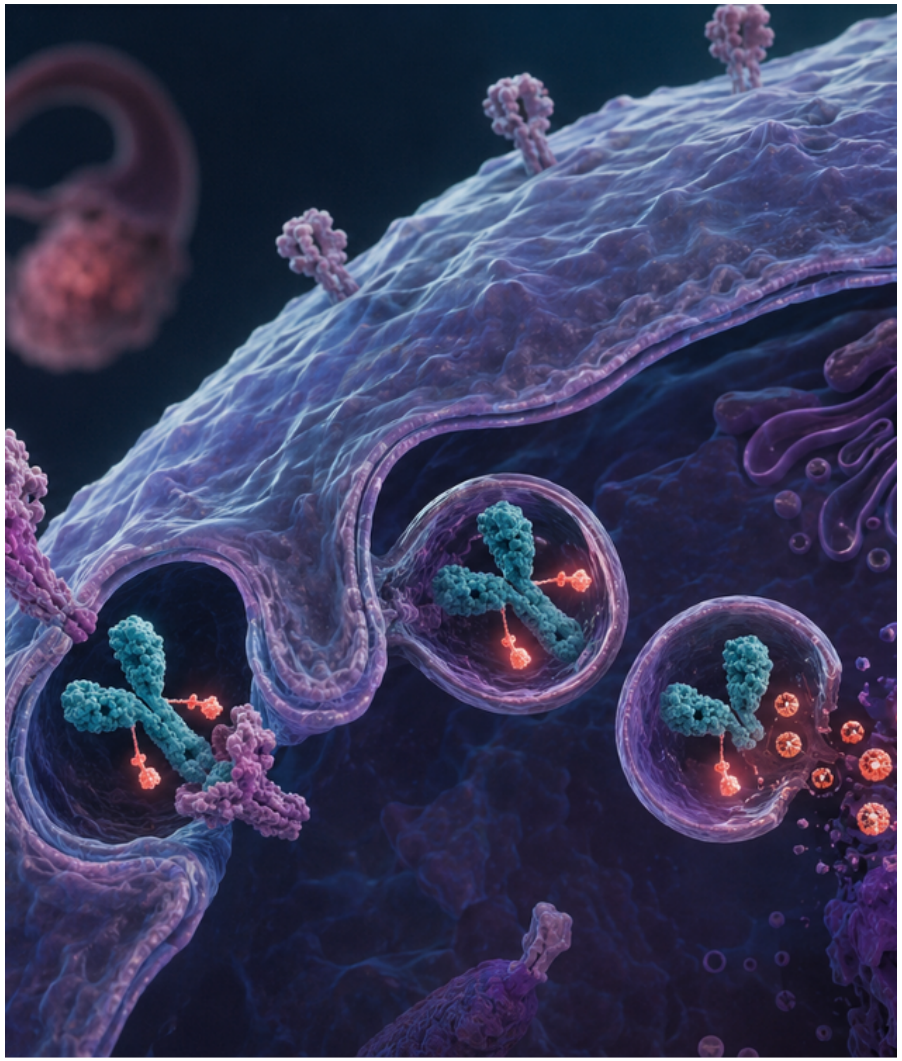
estimated U.S. endometrial / uterine corpus deaths in 2026

*Uterine Cancer is one of the few cancers with an increasing incidence and decreasing survival outcome

Sources: ACS Cancer Facts & Figures 2026; SEER Cancer Stat Facts 2026.

The therapeutic landscape is converging around 4 modalities

- **Checkpoint blockade**- PD-1 / PD-L1 agents
- **Anti-angiogenic therapy**- VEGF agents
- **Antibody-drug conjugates**- Tissue factor, TROP2, and HER2 ADCs deliver cytotoxic payloads with target-linked toxicity profiles.
- **HER2 / molecular targets**- HER2, MMR/MSI, TMB, NTRK, POLE, p53, ER/PR increasingly route therapy and trial options.



Biomarkers: treat the biopsy as the therapeutic gateway

Testing should be front-loaded so trial and treatment options are not missed later

Cervical Cancer

- ➔ PDL-1
- ➔ HER2
- ➔ For metastatic or recurrent disease- comprehensive molecular profiling by FDA approved assay looking for MMR, MSI, TMB, HER2, NTRK, RET

Endometrial Cancer

- ➔ MMR/MSI is mandatory for prognosis and systemic therapy routing.
- ➔ HER2 IHC/ISH for serous/p53-abnormal disease;
- ➔ ER/PR informs endocrine combinations.

Sources: NCCN cervical cancer v2.2026; ESMO endometrial cancer guideline; FDA drug labels.

Operational rule: order reflex MMR/MSI + p53/POLE context + HER2 where histology indicates; bank tissue for trial-directed targets.

Cervical Cancer

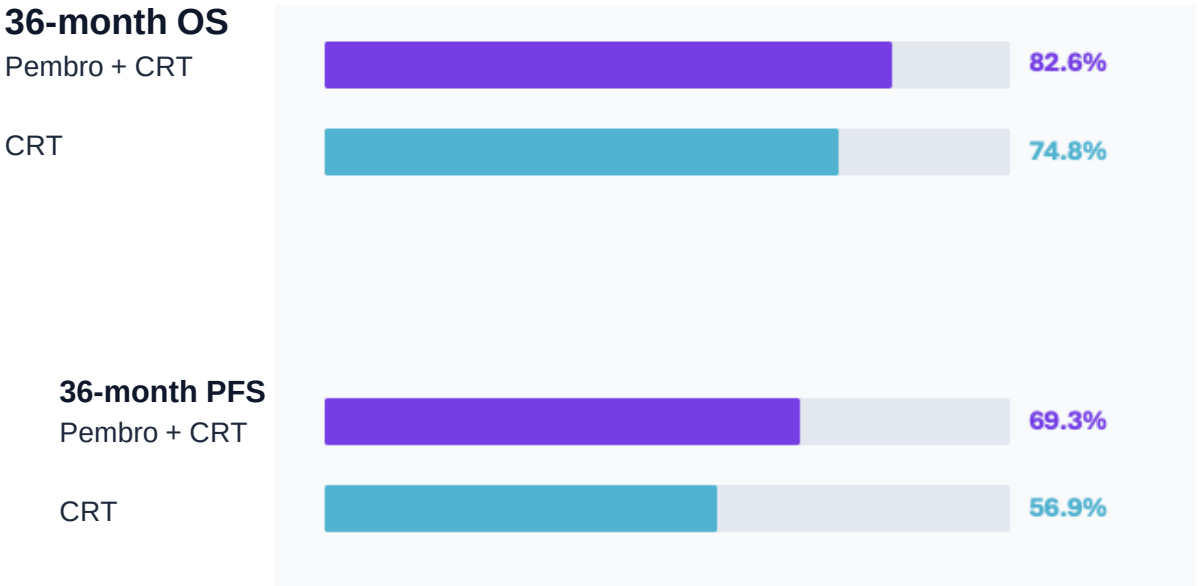
Use of immunotherapy in combination with ChemoRadiation

KEYNOTE-A18 / ENGOT-cx11 / GOG-3047: pembrolizumab + concurrent CRT → pembrolizumab maintenance.

High-risk locally advanced cervical cancer • Phase III • N=1,060

Pembrolizumab + CRT significantly improved 36-month OS and PFS versus CRT alone; FDA approval covers FIGO 2014 stage III–IVA disease.

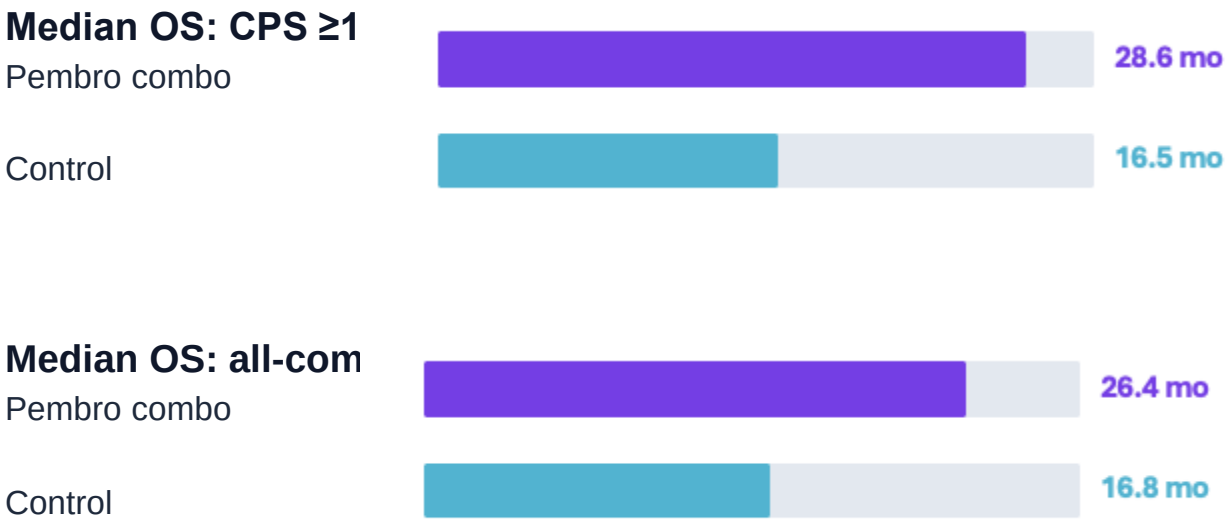
HR OS 0.67 • HR PFS 0.68



Cervical cancer:

Immunotherapy for first-line metastatic/recurrent disease

KEYNOTE-826 established pembrolizumab + platinum/taxane ± bevacizumab for PD-L1 CPS ≥1 disease.



phase 3 trial
patients with persistent, recurrent, or metastatic cervical cancer
randomly assigned

OS HR 0.60 in CPS ≥1 **OS HR 0.63 in all-comers**

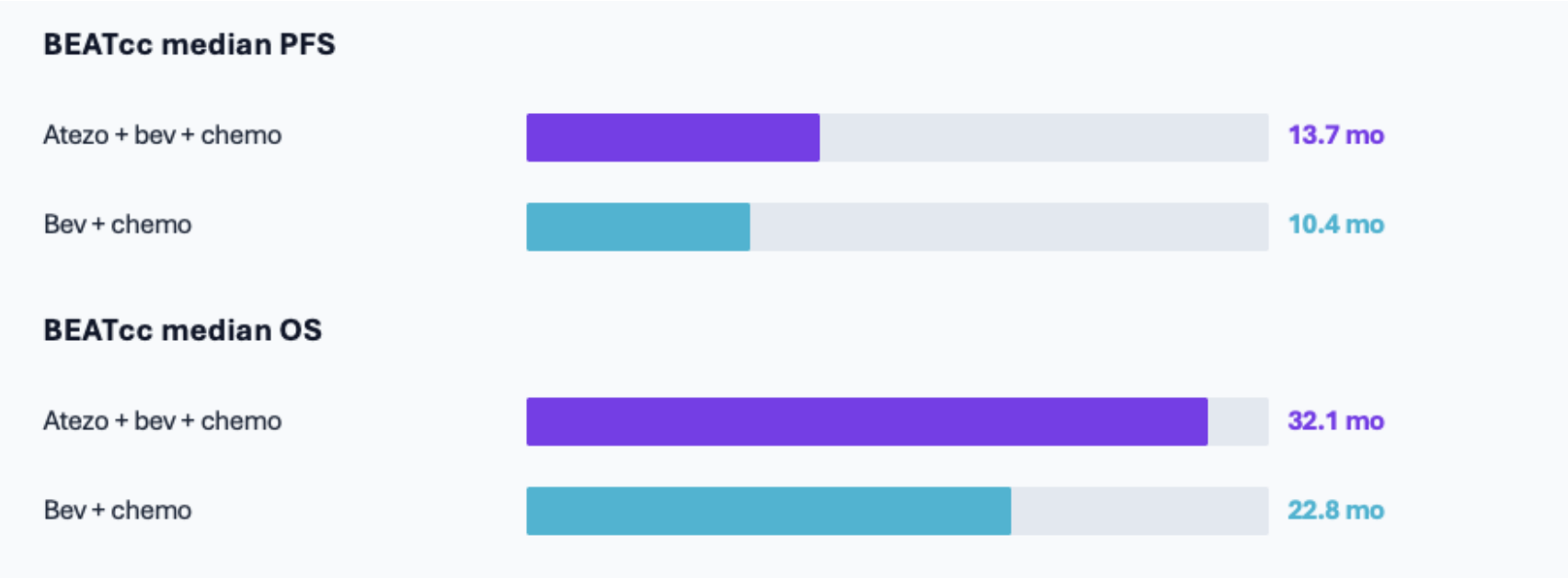
Cervical cancer:

Immunotherapy for first-line metastatic/recurrent disease

BEATcc tested adding PD-L1 blockade to a bevacizumab-containing chemotherapy backbone.

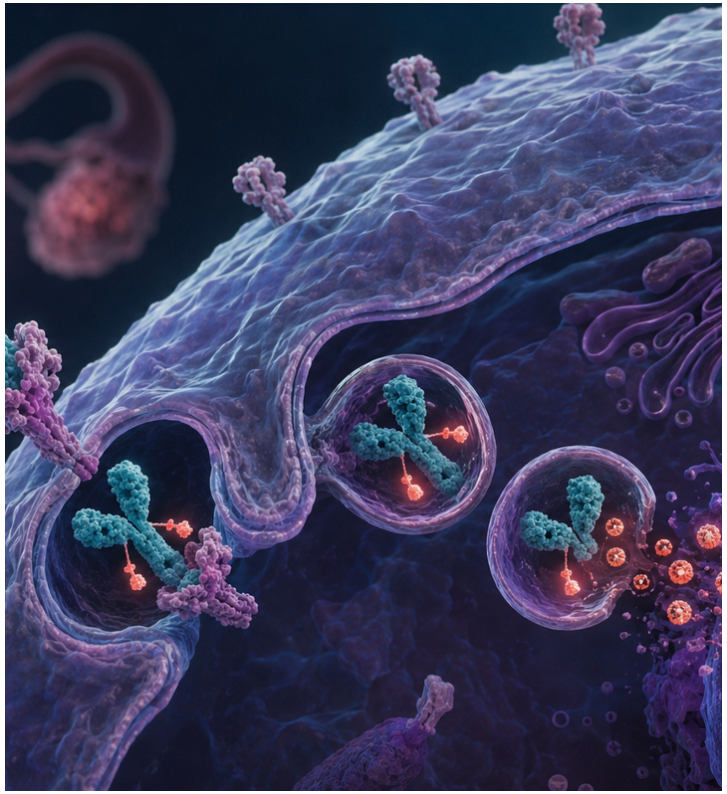
Metastatic / persistent / recurrent cervical cancer • Phase III

Atezolizumab + bevacizumab + chemotherapy improved PFS and OS versus bevacizumab + chemotherapy.



Cervical cancer: ADCs have a proven survival role after chemotherapy

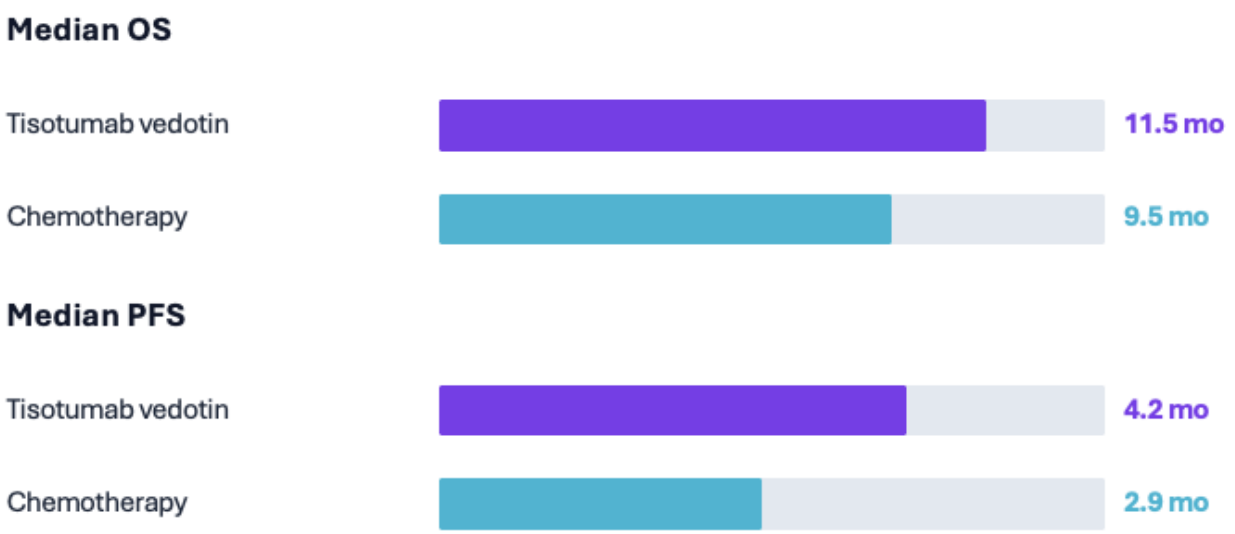
innovaTV 301 converted tisotumab vedotin from accelerated to traditional FDA approval.



innovaTV 301 / ENGOT-cx12 / GOG-3057

2L/3L recurrent or metastatic cervical cancer • Phase III • N=502

Tisotumab vedotin improved OS, PFS, and ORR vs investigator's choice chemotherapy after progression on or after chemotherapy.



ORR 17.8% vs 5.2% • OS HR 0.70

Cervical cancer watchlist: where the next delta may come from

Prioritize trials that either intensify curative therapy or solve post-IO resistance.

COMPASSION-16 / Cadonilimab

PD-1/CTLA-4 bispecific + chemo ± bev • Phase III

Reported PFS/OS benefit in advanced/recurrent/metastatic cervical cancer; NMPA approval in China for first-line advanced disease.

Sacituzumab tirumotecan (MK-2870)

TROP2 ADC • Phase III programs

Ongoing studies in recurrent/metastatic cervical cancer after standard therapies, including platinum and immunotherapy exposure.

GRWD5769 + cemiplimab

ERAP1 inhibition + PD-1 • Early phase

Aims to increase tumor antigen presentation and overcome immune invisibility; early multi-tumor data include cervical cancer patients.

Patient-selection lens: progression after IO, measurable disease for response endpoint, fresh tissue for antigen expression, and ability to tolerate ocular / neuropathy / immune toxicities.

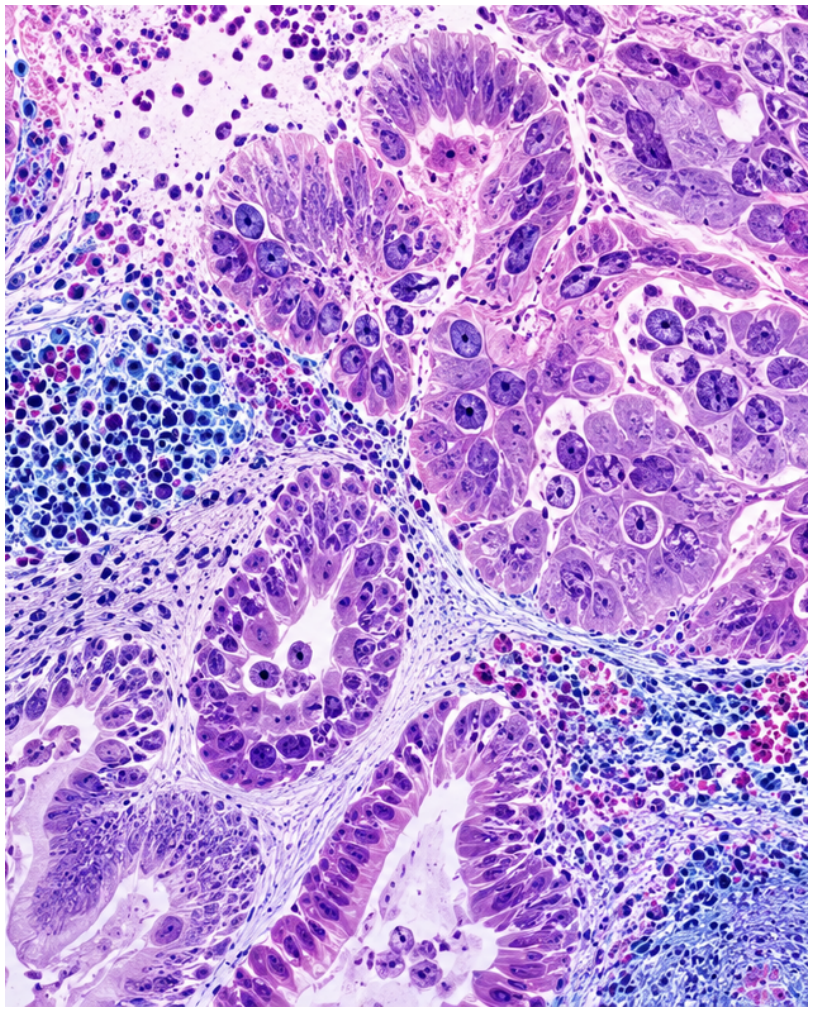
Sources: ASCO 2025 abstracts; ClinicalTrials.gov; NMPA/cadonilimab reports; The Guardian 2026 ASCO coverage for GRWD5769 early data.

Endometrial cancer: the frontline standard is now biology-aware

MMR/MSI status predicts the magnitude of immunotherapy benefit, but all-comer approvals changed practice.

MMRd/MSI-H	Large benefit from immune checkpoint + chemo; durable control is the goal.
pMMR/MSS	Benefit is more modest but clinically meaningful; maintenance strategy and toxicity matter.
p53-abnormal / serous	Add HER2 testing; trastuzumab and T-DXd are important considerations.
POLE-mutated	Excellent prognosis in early-stage disease; avoid overtreatment when guideline-supported.

The clinic shift: every recurrent/advanced endometrial patient should have a biomarker result before the first systemic therapy decision when feasible.



Sources: ESMO endometrial guideline; FDA approvals for pembrolizumab, dostarlimab, durvalumab; molecular classification literature.

Endometrial cancer: two phase III trials re-set first-line therapy

Both NRG-GY018/KEYNOTE-868 and RUBY support checkpoint blockade with carboplatin/paclitaxel followed by maintenance.

NRG-GY018 / KEYNOTE-868

Primary advanced or recurrent EC • Phase III

Pembrolizumab + carboplatin/paclitaxel → pembrolizumab reduced progression/death by 70% in dMMR and 40% in pMMR tumors vs chemo alone.

RUBY Part 1

Primary advanced or recurrent EC • Phase III

Dostarlimab + carboplatin/paclitaxel → dostarlimab improved PFS, and demonstrated overall survival benefit in the overall population.

NRG-GY018 hazard ratios

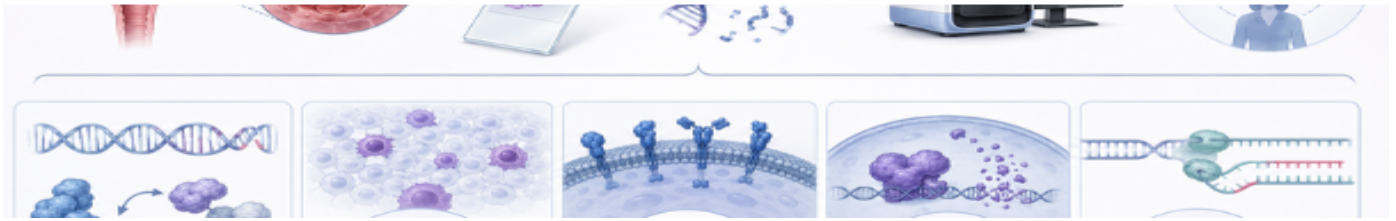
RUBY overall survival

Median OS 44.6 vs 28.2 months
HR 0.69

Sources: FDA Jun/Aug 2024 approvals; Powell et al. 2024 RUBY OS; NRG-GY018/KEYNOTE-868 FDA summary.

Endometrial frontline IO: how to choose among approved options

Pembrolizumab + CP → pembro	FDA-approved all-comers; NRG-GY018 showed large dMMR and meaningful pMMR PFS benefit. stage III-IV, **except carcinosarcomas**
Dostarlimab + CP → dostarlimab	FDA-approved all-comers as of Aug 2024; RUBY showed OS benefit in overall population, stage III-IV
Durvalumab + CP → durvalumab	FDA-approved for **dMMR** primary advanced/recurrent EC; DUO-E showed strong dMMR PFS benefit.
Clinical choice	Consider MMR, comorbid autoimmune disease, steroid dependence, prior IO, maintenance duration, payer/formulary, and patient preference .



Endometrial cancer after platinum: pMMR disease still needs active combinations

KEYNOTE-775 established pembrolizumab + lenvatinib for previously treated advanced pMMR/non–MSI-H disease.

WHY IT MATTERS

IO monotherapy has lower activity in pMMR/MSS endometrial cancer.

VEGFR/multikinase inhibition can remodel tumor vasculature and immune contexture.

Toxicity—not response—is often the determinant of durable benefit.

Common management issues: hypertension, diarrhea, fatigue, hypothyroidism, proteinuria, palmar-plantar toxicity, and immune-related AEs.

Median OS: all-comer population

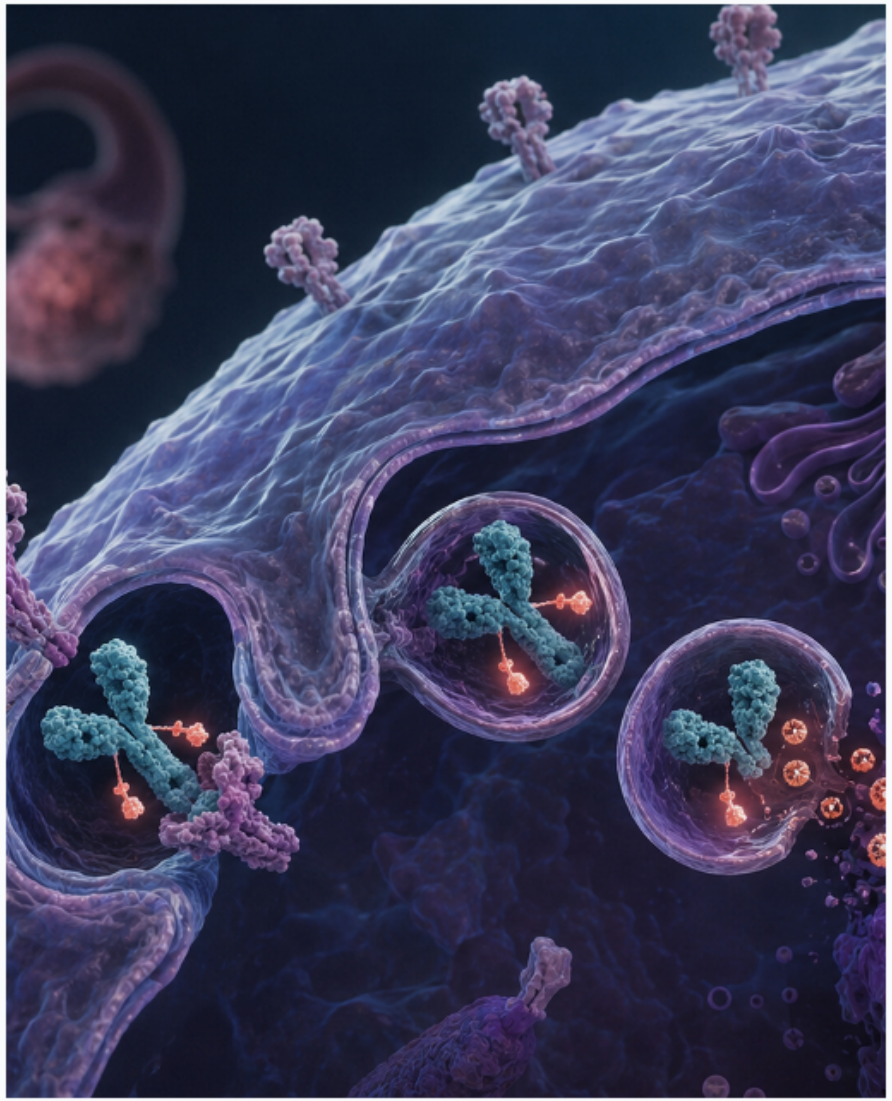
Median PFS: all-comer population

KEYNOTE-775 final analysis confirmed sustained OS/PFS benefit versus physician's-choice chemotherapy.

Sources: Makker et al., JCO 2023 final prespecified analysis; KEYNOTE-775/Study 309 HCP label summaries.

Endometrial cancer: HER2 and ADCs are expanding the targetable space

Especially relevant for serous/p53-abnormal disease and post-platinum / post-IO settings.



Trastuzumab + CP	Randomized phase II evidence supports adding trastuzumab in HER2+ uterine serous carcinoma.
T-DXd	Tumor-agnostic FDA accelerated approval for HER2 IHC3+ solid tumors after prior systemic therapy and no satisfactory alternatives.
DESTINY-PanTumor02	Endometrial cohort ORR ~57.5%; higher responses in centrally confirmed HER2 IHC3+ tumors.
TROP2 ADCs	Sacituzumab govitecan and datopotamab deruxtecan have phase II activity; sac-TMT phase III data are emerging.

Do not miss HER2 testing in serous/p53-abnormal EC: it can determine both immediate therapy and the most rational clinical trial.

Sources: Fader et al., Clin Cancer Res 2020; FDA Apr 5, 2024 T-DXd solid tumor approval; DESTINY-PanTumor02 JCO 2024 and 2026 gynecologic cohort analysis.

NCCN Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2026
Endometrial Carcinoma

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA[a]

Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy[c]**
Preferred • Cisplatin plus RT followed by Carboplatin/Paclitaxel[1,2]	**Preferred** • Carboplatin/Paclitaxel + Pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,d,e,3,4] • Carboplatin/Paclitaxel + Dostarlimab-gxly (for stage III–IV tumors) (category 1)[d,f,5] • Carboplatin/Paclitaxel + Durvalumab (for stage III–IV dMMR tumors only) (category 1)[d,g,6] • Carboplatin/Paclitaxel + Trastuzumab (for stage III–IV HER2-positive uterine serous carcinoma or carcinosarcoma)[d,h,7] • Carboplatin/Paclitaxel + Bevacizumab (for stage III–IV tumors)[d,8,9] • Carboplatin/Paclitaxel[10] **Other Recommended** • Carboplatin/Paclitaxel/Durvalumab + Durvalumab/Olaparib (for stage III–IV pMMR tumors) (category 2B)[d,11]

NCCN Guidelines

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA[a]

RECURRENT DISEASE[i,j]
First-Line Therapy for Recurrent Disease[c,k]
Preferred • Carboplatin/Paclitaxel + Pembrolizumab (except for carcinosarcoma) (category 1)[d,e,l,3] • Carboplatin/Paclitaxel + Dostarlimab-gxly (category 1)[d,l,5] • Carboplatin/Paclitaxel + Durvalumab (for dMMR only) (category 1)[d,l,6] • Carboplatin/Paclitaxel + Trastuzumab (for HER2-positive uterine serous carcinoma or carcinosarcoma)[d,h,7] • Carboplatin/Paclitaxel (category 1 for carcinosarcoma)[m,10] **Other Recommended** • Carboplatin/Docetaxel[n] • Carboplatin/Paclitaxel + Bevacizumab[d,8,9] **Useful in Certain Circumstances** • MMR-proficient (pMMR) tumors ▸ Carboplatin/Paclitaxel/Durvalumab + Durvalumab/Olaparib (category 2B)[d,11] • Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant ▸ pMMR tumors ◊ Lenvatinib + Pembrolizumab (category 1)[e,12,13] ▸ TMB-high (TMB-H) tumors[o] ◊ Pembrolizumab[e,14] ▸ MSI-H/dMMR tumors[p] ◊ Pembrolizumab[e,15] ◊ Dostarlimab-gxly[16]

2026 endometrial watchlist: TROP2 ADCs may define the post-IO era

The most recent phase III signal is sacituzumab tirumotecan in platinum- and IO-exposed disease.

TroFuse-005 / ENGOT-en23 / GOG-3095 / MK-2870-005

Advanced/recurrent EC or carcinosarcoma after platinum + PD-1/PD-L1 • Phase III • N=776

Merck reported statistically significant and clinically meaningful improvements in both OS and PFS versus physician's choice chemotherapy in May 2026; magnitude pending full presentation/publication.

TroFuse-033 / GOG-3119 / ENGOT-en29

pMMR maintenance after 1L therapy • Phase III

Sac-TMT + pembrolizumab versus pembrolizumab alone tests whether an ADC can deepen maintenance benefit in pMMR disease.

DESTINY-Endometrial01

HER2-expressing pMMR primary advanced/recurrent EC • Phase III

T-DXd combinations with rilvegostomig or pembrolizumab versus platinum chemo + pembrolizumab; recruiting in 2026.

Clinical discipline: until full data and approvals are available, use these as trial-enrollment prompts and not routine off-label substitution.

Sources: Merck May 18, 2026 TroFuse-005 release; Reuters May 18, 2026; ClinicalTrials.gov NCT06132958, NCT06952504, NCT06989112.

Toxicity management is what lets novel therapeutics move the needle

Success depends on anticipation, early recognition, and keeping patients on effective therapy safely.

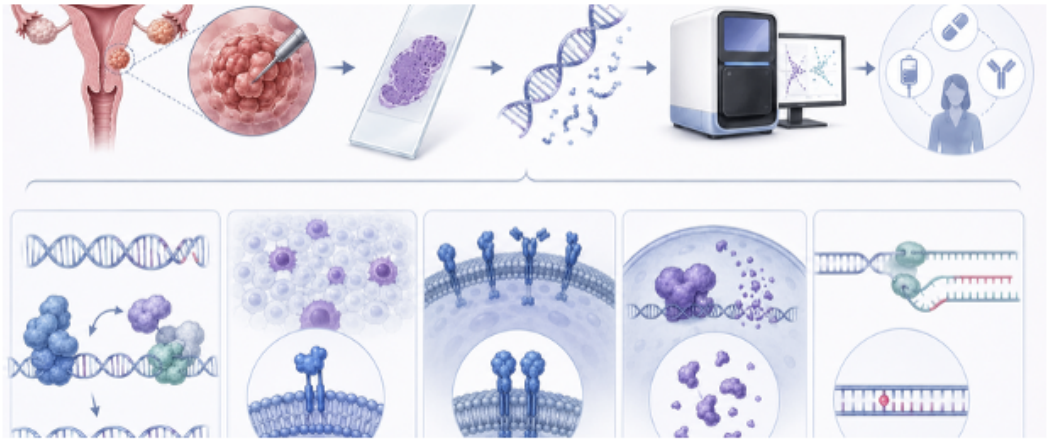
PD-1/PD-L1	Colitis, hepatitis, pneumonitis, endocrinopathies, nephritis; educate patients to report symptoms early, not at next cycle.
Bevacizumab	Hypertension, proteinuria, bleeding, thrombosis, impaired wound healing, fistula/perforation risk after pelvic RT.
Tisotumab vedotin	Ocular toxicity, epistaxis/bleeding, neuropathy; eye-care workflow, prophylactic drops/cold packs, and exam schedule matter.
HER2 ADCs / T-DXd	Interstitial lung disease/pneumonitis risk; low threshold to hold drug and evaluate dyspnea/cough/CT changes.
Lenvatinib	Hypertension, diarrhea, fatigue, weight loss, hypothyroidism, proteinuria; proactive dose optimization preserves duration.

Pearl: build toxicity checklists into ordersets; treatment discontinuation from preventable toxicity is a failed implementation, not just a drug issue.

Sources: FDA drug labels; trial safety reports from KEYNOTE-A18/826, innovaTV 301, RUBY, NRG-GY018, KEYNOTE-775, DESTINY-PanTumor02.

Clinical trial matching: a fast screen every physician can use

A 3-minute schema can capture most novel-therapeutic opportunities before the patient leaves clinic.

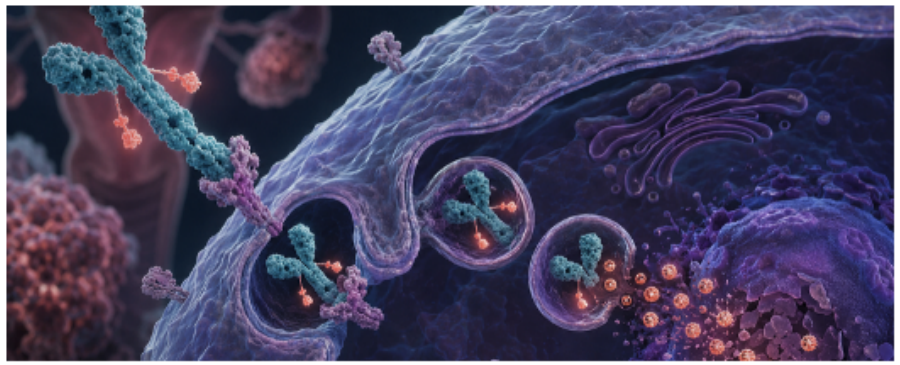


Tumor-board ask

“What is the next rational mechanism if this line fails?”

That question should drive tissue, testing, imaging, and referral timing.

1. Disease state	Curative-intent LACC vs primary advanced vs recurrent/metastatic vs post-platinum/post-IO.
2. Exposure history	Prior platinum, bevacizumab, checkpoint blockade, RT/brachytherapy, HER2 therapy, ADC exposure.
3. Biomarker map	MMR/MSI, PD-L1 CPS, p53/POLE, HER2, ER/PR, TMB/NTRK, target antigen if trial-specific.
4. Trial fit	Measurable disease, organ function, autoimmune disease, neuropathy/ocular/pulmonary constraints, washout windows.



Sources: ClinicalTrials.gov and major phase III trial eligibility structures.

How to “move the needle” in practice

The highest-yield work is building a system that gets the right drug to the right patient earlier.

1	**Reflex testing**	MMR/MSI, p53/POLE context, HER2 where indicated, PD-L1 CPS in cervical, plus trial-specific targets.
2	**Line-of-therapy map**	Document prior IO, platinum-free interval, bevacizumab exposure, RT/brachytherapy, and residual toxicities.
3	**Toxicity workflows**	Eye-care protocol for TV; hypertension pathway for lenvatinib/bev; ILD pathway for T-DXd.
4	**Trial-first mindset**	If a patient is likely to progress on current therapy, screen now—not at radiographic progression.
5	**Shared decision**	Translate HR/PFS/OS into patient-centered tradeoffs: visits, maintenance duration, adverse events, goals.

Deliverable for any practice: a one-page GYN systemic therapy + trial routing pathway updated quarterly.

Implementation synthesis from current approvals and trial evidence; verify against local pathways and NCCN/ESMO updates.

Key takeaways

- ★ Cervical cancer: pembrolizumab has moved into CRT and first-line metastatic treatment; tisotumab vedotin is a proven post-platinum ADC.
- ★ Endometrial cancer: immune checkpoint + carboplatin/paclitaxel is now the dominant first-line paradigm, with regimen choice shaped by MMR and logistics.
- ★ ADCs are not future theory: tissue factor and HER2 are already actionable;
- ★ TROP2 is the major watchpoint.
- ★ The “needle” moves when biomarker reflex testing, toxicity workflows, and trial screening happen before progression.

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