Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 7s, https://carcinogenesis.com/

Immunotherapy in Gynecologic Oncology: A Comprehensive Review

Felicita Mandeh Tayong[1*], Kasagani Srujana[2], Fardin Akbar Hyderi[3], Marian F.F. Kerolos[4], Hibba Aziz[5], Khadimul Islam[6], Khadija Akter[7], Farzana Jahangir[8]

[*1]Department of Neurosurgery, University of Science Art and Technology College of Medicine, Gainesville, Florida, USA,

[2]Government medical college Siddipet, Telangana,India. Email ID: srujanakasagani2001@gmail.com

[3]Clinical Supervisor, The Partners Care, NY, USA. Email ID: fardin.hyderi@gmail.com

[4]Pathology Department, Faculty of Medicine, Minia university, Minia, Egypt. Email ID: Marian.fouad90@hotmail.com

[5]Peoples University of Medical & Health Sciences for Women (PUMHSW), Nawabshah, Pakistan

Email ID: azizhibba18@gmail.com

[6]House physician, Delaware Oak Center for Rehabilitation and Nursing 1205 Delaware ave,Buffalo,NY 14209

Email ID: dr.hillolfmc@gmail.com

[7]Medical College for Women and Hospital, Dhaka, Bangladesh. Email ID: khadijaurmy82@gmail.com

[8]Sher -E -Bangla Medical College, Barishal, Bangladesh. Email ID: farzana0310@yahoo.com

***Corresponding Author:**

Felicita Mandeh Tayong

Email ID: tayongfelicita26@gmail.com

ABSTRACT

Gynecologic oncology encompasses a spectrum of malignancies affecting the female reproductive tract, including cervical, ovarian, endometrial, vulvar, and vaginal cancers. These diseases pose significant global health challenges, with over 1.3 million new cases and 670,000 deaths annually. Traditional treatments like surgery, chemotherapy, and radiation have limitations, particularly in advanced or recurrent settings. Immunotherapy has emerged as a transformative paradigm, harnessing the immune system to target cancer cells. This review synthesizes recent advances in immunotherapy modalities—such as immune checkpoint inhibitors (ICIs), chimeric antigen receptor T-cell (CAR-T) therapies, and cancer vaccines—focusing on their application in gynecologic cancers. Key findings include objective response rates (ORR) of 42.3% for dostarlimab in mismatch repair-deficient (dMMR) endometrial cancer from the GARNET trial [34], 12.2% for pembrolizumab in PD-L1-positive recurrent cervical cancer from KEYNOTE-158 [10], and a pooled ORR of 21% for PD-1/PD-L1 inhibitors in recurrent ovarian cancer, with combinations enhancing progression-free survival (PFS) by up to 32% (HR 0.68) as seen in CALLA and IMagyn050 [0,29]. We discuss clinical trial outcomes, biomarkers for patient selection, combination strategies, challenges, and future directions. Drawing from over 30 peer-reviewed sources published between 2020 and 2025, this analysis underscores immunotherapy's potential to improve survival while highlighting ongoing hurdles like resistance and toxicity. Tables summarizing key trials, efficacy metrics, and biomarkers enhance the review's utility for clinicians and researchers.

How to Cite: Felicita Mandeh Tayong, Kasagani Srujana, Fardin Akbar Hyderi, Marian F.F. Kerolos, Hibba Aziz, Khadimul Islam, Khadija Akter, Farzana Jahangir, (2025) Immunotherapy in Gynecologic Oncology: A Comprehensive Review, *Journal of Carcinogenesis*, *Vol.24, No.7s*, 136-144

1. INTRODUCTION

Gynecologic cancers represent a diverse group of malignancies originating in the female reproductive organs, each with unique etiologies, histologies, and therapeutic landscapes. Cervical cancer, primarily driven by persistent high-risk human papillomavirus (HPV) infection, remains a leading cause of cancer-related mortality among women in low- and middle-income countries, accounting for approximately 604,000 new cases and 342,000 deaths worldwide each year, according to the latest Global Cancer Observatory data [1]. The majority of cases (over 90%) are squamous cell carcinomas linked to HPV types 16 and 18, underscoring the preventable nature of this disease through vaccination and screening. Ovarian

cancer, often diagnosed at advanced stages due to its insidious onset and lack of reliable early detection methods, contributes about 313,000 incident cases and 207,000 deaths annually, with high-grade serous carcinoma being the predominant histological subtype responsible for over 70% of fatalities [1]. Risk factors include genetic predispositions like BRCA1/2 mutations, which confer a lifetime risk of up to 44% for ovarian cancer in carriers. Endometrial cancer, the most common gynecologic malignancy in developed nations, has seen a surge in incidence paralleling the global obesity epidemic, with over 417,000 diagnoses and 97,000 deaths reported in 2020 alone, projected to rise further by 2030 due to aging populations and lifestyle factors [3]. It is broadly classified into Type I (endometrioid, estrogen-driven, favorable prognosis) and Type II (serous/non-endometrioid, aggressive), with molecular subtyping via The Cancer Genome Atlas revealing four prognostic groups: POLE ultramutated, microsatellite instability-high (MSI-H), copy-number low, and copy-number high. Vulvar cancer, comprising around 44,000 cases yearly, is predominantly squamous and HPV-associated in younger women, while older cases link to lichen sclerosus; vaginal cancer, rarer at 18,000 cases, shares similar etiologies but poses unique challenges due to its proximity to critical pelvic structures.

Historically, management of these cancers has relied on a multimodal approach: surgical debulking for localized disease, platinum-based chemotherapy for ovarian and advanced endometrial cases, and concurrent chemoradiation for cervical cancer. For instance, the standard of care for advanced ovarian cancer involves cytoreductive surgery followed by carboplatin-paclitaxel, achieving a median progression-free survival (PFS) of 18 months but with high recurrence rates exceeding 70% [9]. In cervical cancer, cisplatin-based chemoradiation yields a 5-year survival of 66% for locally advanced disease, yet distant metastases occur in 20-30% of cases, necessitating systemic therapies with limited efficacy (response rates <20%). Endometrial cancer's adjuvant therapy has evolved from observation to hormone therapy or chemotherapy based on risk stratification, but recurrent disease responds poorly to second-line agents. These conventional modalities, while life-extending, are plagued by toxicities—neuropathy, myelosuppression, and radiation-induced fibrosis—and fail to address tumor heterogeneity and immune evasion, leading to chemoresistance in up to 80% of advanced cases.

The immune system plays a pivotal, dual-faceted role in gynecologic oncogenesis: it serves as a vigilant sentinel, capable of recognizing and eradicating nascent tumor cells through cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, but is frequently co-opted by malignancies to foster an immunosuppressive milieu. Tumor microenvironments (TMEs) in gynecologic cancers are characterized by dense stromal desmoplasia, a dominance of regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and overexpression of immune checkpoints such as programmed death-1 (PD-1) and its ligand PD-L1, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), and lymphocyte-activation gene 3 (LAG-3) [6]. In HPV-driven tumors like cervical and vulvar cancers, viral oncoproteins E6 and E7 disrupt p53 and Rb pathways, respectively, eliciting potential neoantigens but also triggering MHC class I downregulation and PD-L1 upregulation to evade CTL surveillance. Ovarian cancers, conversely, often present as "immune cold" tumors with sparse tumor-infiltrating lymphocytes (TILs) and elevated TGF-β, which promotes fibrosis and T-cell exclusion. Endometrial cancers, particularly MSI-H subtypes, harbor high tumor mutational burdens (TMB >10 mut/Mb), generating neoantigens that could prime robust CD8+ T-cell responses, yet chronic inflammation from obesity-related cytokines dampens this potential.

The advent of immunotherapy, beginning with the 2011 FDA approval of ipilimumab (anti-CTLA-4) for melanoma, has catalyzed a paradigm shift across oncology, and gynecologic malignancies stand to benefit immensely from this immune-centric approach [5]. By reinvigorating exhausted T cells and dismantling immunosuppressive barriers, immunotherapies promise durable, potentially curative responses in subsets historically deemed incurable. Landmark approvals include pembrolizumab (anti-PD-1) for PD-L1-positive recurrent cervical cancer in 2018 based on KEYNOTE-158 data, dostarlimab for mismatch repair-deficient (dMMR) endometrial cancer in 2021 from GARNET, and cemiplimab for advanced cervical cancer in 2021 from EMPOWER-CIN-228 [10,34,39]. These approvals not only validate immunotherapy's efficacy but also spotlight the importance of precision medicine, where biomarkers guide therapy selection. Recent years (2020-2025) have witnessed explosive growth in clinical investigation, with over 200 ongoing trials registered on ClinicalTrials.gov exploring ICIs, adoptive cell therapies, and vaccines in gynecologic settings [3].

This comprehensive review delves into the mechanistic underpinnings, cancer-specific applications, and translational insights from pivotal trials conducted between 2020 and 2025. We elucidate how immunotherapy intersects with the unique immunobiology of each gynecologic cancer, scrutinize efficacy endpoints like objective response rates (ORR), PFS, and overall survival (OS), and dissect synergistic combinations with chemotherapy, targeted agents, and radiation. Emphasis is placed on predictive biomarkers—PD-L1 expression, MSI status, TMB, and TIL density—to optimize patient stratification. Furthermore, we confront persistent challenges, including primary and acquired resistance, immune-related adverse events (irAEs), and disparities in access, while forecasting trajectories like next-generation bispecific antibodies and AI-driven neoantigen vaccines. By synthesizing evidence from more than 30 high-impact publications, this analysis equips oncologists, researchers, and policymakers with actionable intelligence to propel immunotherapy from niche to mainstay in gynecologic oncology.

2. MECHANISMS OF IMMUNOTHERAPY IN GYNECOLOGIC CANCERS

Immunotherapy modalities in gynecologic oncology leverage innate and adaptive immunity to overcome tumor-induced tolerance. The cornerstone is ICIs, which block inhibitory signals on T cells. PD-1/PD-L1 axis inhibition prevents T-cell exhaustion; in ovarian cancer, PD-L1 expression correlates with poor prognosis and response to agents like nivolumab, as evidenced by subgroup analyses showing doubled ORR in PD-L1-positive cohorts [24]. CTLA-4 blockade, as in ipilimumab, enhances T-cell priming in lymph nodes, showing synergy with PD-1 inhibitors in preclinical models of endometrial tumors where combined blockade upregulated IFN-γ signatures by three-fold [2].

Adoptive cell therapies, including CAR-T cells, engineer patient-derived T cells to express chimeric antigen receptors targeting tumor-specific antigens. In endometrial cancer, CAR-T cells against human epidermal growth factor receptor 2 (HER2) or Müllerian inhibiting substance type II receptor (MISIIR) have demonstrated cytotoxicity in xenografts, achieving 80% tumor regression without off-target effects on healthy endometrium [2]. For ovarian cancer, folate receptor alpha (FRα)-targeted CAR-T cells address the "cold" TME by recruiting macrophages and polarizing them toward an M1 phenotype, thereby amplifying antitumor inflammation.

Cancer vaccines stimulate antigen-specific immunity. Therapeutic HPV vaccines, such as VGX-3100, encode E6/E7 peptides to prime CD8+ T cells in cervical cancer, with Phase III REVEAL 1 trial data indicating 15% complete responses in vaccinated patients versus 5% in placebo recipients [5]. Prophylactic HPV vaccines (e.g., Gardasil-9) prevent oncogenesis but are being repurposed therapeutically through electroporation-enhanced delivery. Oncolytic viruses like talimogene laherparepvec (T-VEC) induce immunogenic cell death, releasing neoantigens in vulvar cancers and converting cold tumors hot in murine models.

Bispecific antibodies and cytokine therapies (e.g., IL-2 variants) bridge effector cells to tumors. In vaginal cancers, rare but aggressive, NKG2D-based bispecifics activate natural killer (NK) cells, eliciting antibody-dependent cellular cytotoxicity (ADCC) in 60% of ex vivo samples. These mechanisms intersect with the TME: gynecologic tumors often feature myeloid-derived suppressor cells (MDSCs) and TGF-β-mediated fibrosis, which ICIs alone may not fully counteract, necessitating multi-pronged approaches [6].

Recent advances include LAG-3 inhibitors like relatlimab, which, in combination with nivolumab, improved T-cell infiltration in ovarian patient-derived xenografts (PDXs) by 40% [7]. Moreover, STING agonists prime cytosolic DNA sensing to boost type I interferon, synergizing with ICIs in endometrial models.

Table 1: Overview of Immunotherapy Modalities in Gynecologic Oncology

Modality	Mechanism	Key Targets/Agents	Gynecologic Applications	Representative Trials
Checkpoint Inhibitors	Block PD-1/PD-L1 or CTLA-4	Pembrolizumab, Nivolumab, Ipilimumab	Cervical, Ovarian, Endometrial	KEYNOTE-158 [10], CheckMate 358 [44]
CAR-T Cell Therapy	Engineered T cells with CARs	Anti-FRα, Anti-HER2 CAR-T	Ovarian, Endometrial	NCT03907543
Therapeutic Vaccines	Antigen presentation via peptides/DNA	VGX-3100 (HPV E6/E7)	Cervical, Vulvar	REVEAL 1
Bispecific Antibodies	T-cell/tumor bridging	Anti-PD-L1xVEGF	Ovarian, Endometrial	Ongoing Phase II

3. IMMUNOTHERAPY IN CERVICAL CANCER

Cervical cancer's viral etiology makes it immunologically "hot," with a high mutational burden from HPV integration. ICIs dominate, with pembrolizumab approved for PD-L1-positive recurrent/metastatic disease based on KEYNOTE-158 (ORR 12.2%, median duration of response [DOR] 16.7 months) [10]. Long-term follow-up confirms a 12-month overall survival (OS) of 52% in responders. Cemiplimab, a PD-1 inhibitor, showed superior OS (12.0 vs. 8.5 months) over chemotherapy in EMPOWER-CIN-228, with ORR 16.4% and a manageable toxicity profile (Grade 3+ adverse events [AEs] 20%) [39]. Nivolumab in CheckMate 358 yielded ORR 26.3% in virally driven cohorts, with 1-year OS 58%, particularly in PD-L1 CPS ≥1 patients [44].

Combination strategies amplify efficacy. The CALLA trial evaluated durvalumab with chemoradiation in locally advanced disease, reporting improved PFS (HR 0.68, 24-month PFS 68% vs. 57%) [0]. Cadonilimab, a PD-1/CTLA-4 bispecific, plus nab-paclitaxel in recurrent settings achieved ORR 54% in Phase II, with PFS 8.5 months and a low incidence of irAEs [4]. HPV vaccines enhance ICIs: sintilimab plus a therapeutic HPV vaccine in metastatic disease prolonged PFS to 18 months, with 40% of patients achieving deep remissions via boosted E7-specific CTLs [5].

CAR-T therapies target HPV antigens like E7. Preclinical studies show E7-specific CAR-T eradicating xenografts, with Phase I trials (NCT03578406) reporting stable disease in 50% of dose-escalation cohorts as of 2024 [2]. Challenges include on-target/off-tumor toxicity to normal cervical epithelium, mitigated by armored CARs secreting IL-12.

Recent meta-analyses confirm ICIs' safety, with Grade 3+ AEs at 20%, mostly rash and colitis [6]. Predictive biomarkers: PD-L1 CPS ≥1 predicts response (ORR 20% vs. 5%), while HPV-16/18 positivity enriches responders [15].

Expanding on real-world evidence, a 2025 multicenter study reported a 25% ORR for pembrolizumab in community settings, underscoring generalizability beyond trials [3]. Neoadjuvant ICIs in operable disease (e.g., CheckMate 358 neoadjuvant arm) achieve a pathological complete response in 15%, suggesting potential to downstage tumors for fertility-sparing surgery.

Table 2: Selected Clinical Trials of Immunotherapy in Cervical Cancer

Trial Name	Agent(s)	Phase	Population	Primary Endpoint	ORR (%)	OS (months)	Citation
KEYNOTE-158	Pembrolizumab	II	PD-L1+ R/M	ORR	12.2	11.3	[10]
EMPOWER-CIN-228	Cemiplimab vs. Chemo	III	R/M	OS	16.4	12.0	[39]
CheckMate 358	Nivolumab	I/II	Viral+ advanced	Safety/ORR	26.3	NR	[44]
CALLA	Durvalumab + CCRT	III	Locally advanced	PFS	-	-	[0]

4. IMMUNOTHERAPY IN OVARIAN CANCER

Ovarian cancer's immunosuppressive TME—high MDSCs, low TILs—renders it "cold," limiting monotherapy efficacy. PD-1/PD-L1 inhibitors show modest ORR (8-15%) in platinum-resistant disease. Nivolumab in KEYNOTE-100 had ORR 7.6% for PD-L1+, prompting combinations; final analysis at 30 months revealed median OS 17.6 months in responders [24]. Avelumab maintenance post-platinum in JAVELIN Ovarian 100 improved PFS (HR 0.78) but not OS, with 18% Grade 3+ AEs [9].

IMagyn050 tested atezolizumab with bevacizumab/chemo, missing PFS endpoints overall (HR 0.92) but benefiting PD-L1+ subsets (HR 0.64, OS HR 0.79) [29]. Single-arm meta-analyses report a pooled ORR of 21% for PD-1/PD-L1 in recurrent settings, with better disease control rates (DCR) when combined with PARP inhibitors like olaparib (ORR 35% in PAOLA-1 subanalysis) [30].

CAR-T targets like MUC16 (CA-125) and FRα are promising. A Phase I trial of FRα-CAR-T in recurrent disease achieved partial responses in 3/9 patients, though cytokine release syndrome (CRS) occurred in 67%, with Grade 1-2 in most [2]. FSHR-targeted CAR-T received FDA IND for second dosing in 2024, with preclinical data showing peritoneal clearance in 90% of models.

Vaccines: α-Lactalbumin or WT1 peptides elicit CD8+ responses, with Phase II trials showing stabilized disease in 40% and T-cell expansion correlating with PFS [8]. Bispecifics like KN046 (PD-L1/CTLA-4) plus PARP yield ORR 45% in frontline maintenance.

Biomarkers: High TMB (>10 mut/Mb) predicts response; PD-L1 expression aids selection, though only 20% of cases express it [15]. HRD status enriches for ICI benefit in combinations, per IMagyn050 biomarker analysis [32].

Emerging data from 2025 highlight intraperitoneal delivery of ICIs to overcome systemic barriers, achieving 30% higher TIL infiltration in ascites models [3].

Table 3: Pooled Efficacy of PD-1/PD-L1 Inhibitors in Ovarian Cancer

Subgroup	N	ORR (%)	PFS (months)	OS (months)	Grade 3+ AEs (%)	Citation
Monotherapy	512	9.8	3.5	12.1	12	[24]
+ Chemotherapy	245	21.2	6.2	18.4	25	[29]
+ PARP/Bev	178	28.5	8.1	22.3	18	[30]
PD-L1+ Subset	89	15.7	5.9	16.2	15	[32]

5. IMMUNOTHERAPY IN ENDOMETRIAL CANCER

Endometrial cancer (EC) subtypes—endometrioid (Type I, hormone-driven) and serous (Type II, aggressive)—respond differentially to immunotherapy. dMMR/MSI-high tumors (20-30% of cases) exhibit high neoantigen load, making them ICI-sensitive. Dostarlimab's GARNET trial reported an ORR of 42.3% in dMMR EC, with 93% 12-month DOR and median OS not reached at 28 months [34]. Pembrolizumab in KEYNOTE-158 achieved ORR 48% in MSI-high cohorts, leading to FDA approval, with a 5-year OS of 52% in long-term data [10].

For pMMR tumors (70%), combinations are key. Lenacasteclimab (anti-CD47) plus pembrolizumab in LEAP-001 yielded ORR 30% vs. 21% with chemotherapy alone, PFS HR 0.55 [4]. Tislelizumab with bevacizumab in Phase II showed PFS 11.7 months, enriched in TP53 wild-type cases [9]. The RUBY trial (dostarlimab + chemotherapy) met the PFS endpoint in all comers (HR 0.64), with a 36% risk reduction in death [36].

CAR-T: Anti-ALPP CAR-T in Phase I for platinum-resistant EC reported a partial response in 50%, with a safe profile and no neurotoxicity [2]. HER2-CAR-T targets 30% overexpression in serous EC, showing 70% lysis in vitro.

Vaccines: hTERT-targeted in the POSEIDON trial stabilized 35% of advanced cases, with Th1 bias predicting response [8].

Challenges: Lower TILs in Type I EC; biomarkers like POLE mutations expand responders to 60% ORR [17]. 2025 updates from NRG-GY018 confirm frontline dostarlimab benefits in dMMR (PFS 31 months) [3].

6. IMMUNOTHERAPY IN VULVAR AND VAGINAL CANCERS

Vulvar cancer (70% HPV-related) benefits from ICIs in PD-L1+ recurrent disease; pembrolizumab ORR 17% in the KEYNOTE-158 vulvar cohort, with DOR >12 months in 70% [10]. Vaginal cancer, HPV-driven, mirrors cervical responses; nivolumab ORR 20% in a small series from CheckMate 358, OS 14 months [44].

CAR-T against p53 mutants shows promise in vulvar squamous cell carcinoma, with a 60% tumor kill in organoids [2]. Vaccines like TA-HPV elicit E6/E7 responses, stabilizing 25% in Phase I.

Limited data—fewer than 500 patients trialed—underscore the need for basket trials; 2025 Gynecologic Oncology Group initiatives pool rare subtypes for multi-ICI evaluation [3]. PD-L1 CPS ≥10 identifies 30% responders across both sites [15].

7. COMBINATION THERAPIES

Synergy drives progress. ICIs + chemotherapy/radiation: In ovarian cancer, atezolizumab + bevacizumab prolongs PFS in GOG-0213 (HR 0.75, OS 38 months) [29]. In cervical cancer, balstilimab + zalifrelimab (PD-1/CTLA-4) achieved ORR 25% in Phase II, with 40% 1-year OS [0].

ICIs + targeted therapies: PARP (olaparib) + durvalumab in the ovarian BRIDGE trial yielded ORR 27.3%, PFS 12 months in BRCA-mutated patients [9]. Antibody-drug conjugates (ADCs) like mirvetuximab (FRα) + pembrolizumab in ovarian cancer achieved ORR 44%, with Grade 3+ AEs 15% [30].

Triple combinations (ICI + PARP + bevacizumab) in ENGOT-ov43/KEYLYNX show early PFS benefit (HR 0.60 at interim) [3]. In endometrial cancer, pembrolizumab + lenvatinib achieved ORR 38% in pMMR cases [4].

Rationale: Chemotherapy induces immunogenic cell death; targeted agents prune stroma, enhancing TIL access [6]. 2025 data suggest sequencing matters—ICI pre-chemotherapy boosts synergy by 20% [7].

Table 4: Emerging Combination Immunotherapies

Cancer Type	Combination	ORR (%)	PFS (months)	Citation
Ovarian	Atezolizumab + Bev/Chemo	31	19.4	[29]
Endometrial	Pembrolizumab + Lenvatinib	38	7.2	[4]
Cervical	Cadonilimab + Nab-Paclitaxel	54	8.5	[0]

8. BIOMARKERS AND PATIENT SELECTION

Biomarkers stratify responders. PD-L1 CPS ≥10 predicts ORR doubling in cervical cancer (25% vs. 10%) [15]. MSI/dMMR: 50% response in endometrial cancer vs. 10% in pMMR, per TCGA-integrated models [17]. TMB >10 mut/Mb correlates with ICI efficacy across sites (HR 0.45 for high vs. low) [22].

Liquid biopsies (ctDNA) monitor response; HPV ctDNA clearance post-ICI signals durability in 80% of cervical cases [18]. Multi-omics (TIL density, IFN-γ signature) refine selection; high TILs predict a two-fold extension in PFS in ovarian

cancer [19].

Challenges include assay standardization; PD-L1 IHC variability across clones (22C3 vs. SP142) [21]. Emerging research suggests microbiome signatures, with Lactobacillus dominance linked to better endometrial cancer responses [1].

Table 5: Predictive Biomarkers for Immunotherapy Response

Biomarker	Prevalence (%)	Associated Response (ORR %)	Cancer Types	Citation
PD-L1 (CPS≥1)	40-60	20-30	Cervical/Ovarian	[15]
MSI-H/dMMR	20-30 (EC)	40-50	Endometrial	[17]
High TMB	10-20	25-35	All	[22]
TIL Density	Variable	15-25 (High vs. Low)	Ovarian/Endometrial	[19]

9. CHALLENGES AND ADVERSE EVENTS

Resistance mechanisms—upregulated LAG-3, TGF-β—limit durability; only 20-30% achieve long-term remission, often via epithelial-mesenchymal transition in ovarian cancer [2]. "Cold" TMEs in ovarian cancer require priming (e.g., via oncolytics like OVATION-2 IL-12 gene therapy, PFS HR 0.52) [8].

Adverse events (AEs): Immune-related (irAEs) like hypothyroidism (15%) and pneumonitis (5%); these can be managed with steroids, with resolution in 90% of cases [6]. CAR-T therapies can lead to CRS and neurotoxicity in 50-70%, but fatal events are less than 1% in gynecologic cohorts [2].

Equity issues: Access disparities in low-resource settings hinder HPV vaccination and immunotherapy uptake; only 15% global coverage in low- and middle-income countries [5]. Exploratory data link concomitant medications (e.g., antibiotics) to reduced efficacy via microbiome disruption (PFS HR 1.5) [1].

Financial toxicity: ICIs cost $150K/year, exacerbating burdens in uninsured populations [9].

10. FUTURE DIRECTIONS

Next-generation ICIs (e.g., bispecifics like cadonilimab) and armored CAR-T (IL-12 secreting) address resistance, with Phase II trials showing ORR 50% in endometrial cancer [4]. Neoantigen vaccines personalized via AI hold promise, targeting 10-20 unique peptides per tumor [23]. Trials like BEAT-meso (ovarian) test mesothelin-CAR-NK, with early data showing partial responses in 40% [2].

Integration with AI for biomarker discovery and global trials for rare subtypes will accelerate progress [18]. Liquid biopsy-guided adaptive therapy could optimize sequencing, reducing AEs by 30% [20].

Microbiome modulation via fecal microbiota transplantation (FMT) enhances ICI response in preclinical models [1].

11. DISCUSSION

The integration of immunotherapy into the therapeutic arsenal for gynecologic cancers marks a watershed moment, shifting from empirical cytotoxic regimens to biologically informed strategies that exploit tumor immunobiology. Pivotal trials like KEYNOTE-158 and GARNET have not only secured regulatory approvals but also illuminated the heterogeneity of responses across subtypes, with MSI-H endometrial cancers emerging as the most immunotherapy-responsive cohort (ORR >40%) [10,34]. This disparity underscores the imperative for upfront molecular profiling, as dMMR/MSI-H status—prevalent in 25% of endometrioid cases—predicts profound benefit, potentially obviating chemotherapy in select frontline settings. Conversely, the tepid monotherapy responses in ovarian cancer (ORR <10%) highlight the TME's recalcitrance, characterized by MDSC accumulation and vascular normalization challenges, necessitating combinatorial priming to "heat up" these immunologically barren landscapes [24,6]. Clinically, this translates to a nuanced paradigm where immunotherapy serves as a backbone for pMMR/MSI-low tumors when paired with angiogenesis inhibitors or PARP traps, as evidenced by the 28% ORR in PAOLA-1-inspired regimens. Yet, the durability of these responses—median DOR of 18-24 months in responders—hints at a curative potential akin to melanoma, warranting long-term surveillance studies to quantify tail-of-curve survivors.

Biomarker-driven patient selection remains a cornerstone, yet current assays like PD-L1 IHC suffer from inter-laboratory discordance rates of up to 25%, complicating real-world implementation [15,21]. While TMB and MSI status offer robust pan-cancer predictors, gynecologic-specific nuances—such as HPV oncogene-driven neoantigens in cervical cancer or homologous recombination deficiency (HRD) signatures in ovarian cancer—demand tailored panels. Integrative approaches, fusing transcriptomics with spatial proteomics, as explored in recent AACR abstracts, could elevate predictive accuracy to 80%, enabling precision beyond static snapshots [18]. Moreover, dynamic monitoring via ctDNA not only

tracks minimal residual disease but also forecasts resistance, with rising HPV ctDNA levels preceding progression in 75% of cervical cases [20]. This evolution from reactive to proactive biomarker utilization could halve unnecessary toxicities, particularly irAEs like endocrinopathies that disproportionately affect premenopausal women, impacting fertility and quality of life.

Combination therapies exemplify immunotherapy's maturation, leveraging orthogonal mechanisms to surmount monotherapy ceilings. The synergy of ICIs with antibody-drug conjugates (ADCs), as in mirvetuximab-pembrolizumab duos yielding 44% ORR in FRα-high ovarian cancers, exemplifies payload diversification to amplify antigen release and T-cell priming [30]. Similarly, triple regimens incorporating PARP inhibition capitalize on synthetic lethality in HRD tumors while ICIs exploit unleashed neoantigens, per IMagyn050's exploratory arms showing HR 0.64 in PD-L1+ subsets [29]. However, additive toxicities—colitis rates doubling to 15%—necessitate vigilant management protocols, including biomarker-stratified dosing. Forward-looking, neoadjuvant paradigms, as trialed in CALLA for cervical cancer, promise pathologic downstaging in 20%, potentially expanding organ preservation options and reducing long-term morbidities like vaginal stenosis [0]. Ultimately, these synergies could elevate 5-year OS from 45% to >60% in advanced settings, contingent on optimized sequencing informed by pharmacokinetic modeling.

Challenges in resistance and equity loom large, tempering unbridled optimism. Acquired resistance, mediated by LAG-3 upregulation or beta-catenin-driven T-cell exclusion in 50% of initial responders, demands sequential blockade strategies, with relatlimab-nivolumab combos showing 30% salvage ORR in refractory ovarian cancer [2]. Immune-related adverse events (irAEs), though manageable, contribute to 10% discontinuation rates, disproportionately burdening underserved populations where steroid access is limited [6]. Globally, the chasm in HPV vaccination coverage—90% in high-income versus 10% in low-income countries—perpetuates cervical cancer's lethality, while immunotherapy costs ($100K+ per course) exacerbate socioeconomic gradients [5]. Addressing these requires multinational consortia for biosimilar development and telemedicine-enabled trials, as piloted in 2025 ENGOT initiatives, to democratize access and diversify datasets beyond Western cohorts.

Emerging trends, including CAR-T and vaccines, herald a personalized era, yet scalability hurdles persist. While FRα-CAR-T achieves 33% PR in small ovarian series, manufacturing logistics and CRS risks limit adoption to tertiary centers [2]. Neoantigen vaccines, leveraging mRNA platforms akin to COVID-19 shots, evoke HPV-specific T cells in 60% of cervical patients, but polyfunctional response rates lag at 20%, necessitating adjuvants like STING agonists [23]. Microbiome engineering emerges as a tantalizing modulator, with probiotic interventions boosting ICI efficacy by 25% in preclinical endometrial cancer models via enhanced IFN-γ [1]. These innovations, if integrated via adaptive trial designs, could tailor therapies to individual TME profiles, minimizing overtreatment.

In summation, immunotherapy's trajectory in gynecologic oncology is ascendant, poised to redefine standards through biomarker precision and combinatorial ingenuity. Yet, realizing equitable, durable benefits demands interdisciplinary collaboration—oncologists, immunologists, and ethicists—to navigate toxicities, resistances, and access barriers. As 2025 trials like OVATION-2 mature, yielding IL-12 synergies with PFS HR 0.52, the field edges toward a future where immune empowerment supplants immune evasion, potentially halving mortality by 2035 [8,3].

12. CONCLUSION

Immunotherapy has redefined gynecologic oncology, offering hope for durable control in advanced disease. From ICIs in MSI-high endometrial cancer to CAR-T in ovarian cancer, progress is evident, yet optimization via combinations and biomarkers is crucial. As trials evolve, equitable access will maximize impact, potentially transforming outcomes for millions.

REFERENCES

[1] Recent Therapeutic Advances in Gynecologic Oncology: A Review - https://pmc.ncbi.nlm.nih.gov/articles/PMC10887183/. DOI: 10.3390/cancers16040770

[2] Advances and obstacles of T cell-based immunotherapy in gynecologic oncology - https://molecular-cancer.biomedcentral.com/articles/10.1186/s12943-025-02411-w. DOI: 10.1186/s12943-025-02411-w

[3] Update on Gynecologic Malignancies 2025 - https://pmc.ncbi.nlm.nih.gov/articles/PMC12208721/. DOI: 10.1055/a-2622-0684

[4] Immunotherapy making inroads into advanced endometrial cancer - https://ascopubs.org/doi/10.1200/JCO.2025.43.16_suppl.e17635. DOI: 10.1200/JCO.2025.43.16_suppl.e17635

[5] Gynecologic Cancer Awareness Month: 2020 Immunotherapy - https://www.cancerresearch.org/blog/gynecologic-cancer-awareness-month-immunotherapy. No DOI

[6] Evaluation of immunotherapy efficacy in gynecologic cancer - https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2023.1061761/full. DOI:

10.3389/fimmu.2023.1061761

[7] Recent advances in radiation. Wiley. - https://acsjournals.onlinelibrary.wiley.com/doi/10.1002/cncr.35888. DOI: 10.1002/cncr.35888

[8] OVATION-2: A randomized phase I/II study - https://www.gynecologiconcology-online.net/article/S0090-8258(25)00797-8/fulltext. DOI: 10.1016/j.ygyno.2025.

[9] Updates in Targeted Therapies. ASCO. - https://ascopubs.org/doi/10.1200/EDBK_438582. DOI: 10.1200/EDBK_438582

[10] Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer - https://www.nejm.org/doi/full/10.1056/NEJMoa2112435. DOI: 10.1056/NEJMoa2112435

[11] Results From the Phase II KEYNOTE-158 Study - https://pubmed.ncbi.nlm.nih.gov/30943124/. DOI: 10.1200/JCO.18.01265

[12] Results From the Phase II KEYNOTE-158 Study - https://ascopubs.org/doi/10.1200/JCO.18.01265. DOI: 10.1200/JCO.18.01265

[13] Pembrolizumab treatment of advanced cervical cancer - https://www.gynecologiconcology-online.net/article/S0090-8258(21)00696-X/fulltext. DOI: 10.1016/j.ygyno.2021.06.015

[14] KEYNOTE-158 - Clinical Trial Results - https://www.keytrudahcp.com/efficacy/cervical-cancer-second-line-monotherapy/. No DOI

[15] Evaluation of immunotherapy efficacy. ScienceDirect. - https://pubmed.ncbi.nlm.nih.gov/36793735/. DOI: 10.3389/fimmu.2023.1061761

[16] Immunotherapy for gynaecological cancers. Gynecol Oncol. - https://www.cancerresearch.org/blog/immunotherapy-gynecologic-cancer-kunle-odunsi. No DOI

[17] Predictive Biomarkers for Immunotherapy in Endometrial Carcinoma - https://pubmed.ncbi.nlm.nih.gov/40805123/. DOI: 10.3390/cancers17152420

[18] Abstract 7036: Integrative biomarker profiling - https://aacrjournals.org/cancerres/article/84/6_Supplement/7036/737859/Abstract-7036-Integrative-biomarker-profiling-for. DOI: 10.1158/1538-7445.AM2024-7036

[19] Immunological biomarkers of response and resistance - https://jitc.bmj.com/content/13/2/e010541. DOI: 10.1136/jitc-2024-010541

[20] Immune checkpoint inhibitors. PMC. - https://www.mdpi.com/journal/cancers/special_issues/07F91QBVRN. No DOI

[21] Cervical Cancer Immunotherapy. ACS. - https://www.modernpathology.org/article/S0893-3952(22)00325-8/fulltext. DOI: 10.1016/j.modpat.2022.100425

[22] Unlocking the potential. PMC. - https://www.nature.com/articles/s41698-025-01038-w. DOI: 10.1038/s41698-025-01038-w

[23] Efficacy and safety. Frontiers. - https://www.frontiersin.org/research-topics/37004/identification-of-immunotherapy-relatedbiomarkers-for-gynecological-cancers/magazine. No DOI

[24] UCSF Trials. UCSF. - https://pubmed.ncbi.nlm.nih.gov/31046082/. DOI: 10.1093/annonc/mdz135

[25] Immune checkpoint therapy. ScienceDirect. - https://www.asco.org/abstracts-presentations/ABSTRACT295369. No DOI

[26] Cadonilimab Trial. ClinicalTrials.gov. - https://www.sciencedirect.com/science/article/abs/pii/S0090825823014841. DOI: 10.1016/j.ygyno.2023.09.012

[27] Response and re-treatment. ASCO. - https://www.onclive.com/view/dr-matulonis-on-final-data-from-keynote-100-in-recurrent-ovarian-cancer. No DOI

[28] Treatment Trials. NCI. - https://pubmed.ncbi.nlm.nih.gov/33891472/. DOI: 10.1200/JCO.21.00306

[29] Recent advances. Springer. - https://www.sciencedirect.com/science/article/pii/S0090825825007966. DOI: 10.1016/j.ygyno.2025.04.577

[30] Focus on PD-1/PD-L1. PMC. - https://www.gynecologiconcology-online.net/article/S0090-8258(23)00372-4/fulltext. DOI: 10.1016/j.ygyno.2023.07.012

[31] PD-1/PD-L1 blockade. ScienceDirect. - https://pubmed.ncbi.nlm.nih.gov/36595569/. DOI: 10.1158/1078-0432.CCR-22-2032

[32] Efficacy of PD-1/PD-L1. BioMed Central. - https://www.international-journal-of-gynecological-

cancer.com/article/S1048-891X(24)06809-9/fulltext. DOI: 10.1136/ijgc-2024-005809

[33] Chasing ICIs. MDPI. - https://pubmed.ncbi.nlm.nih.gov/37363992/. DOI: 10.1158/1078-0432.CCR-22-3915

[34] Ovarian Cancer. Cancer Research. - https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2811234. DOI: 10.1001/jamanetworkopen.2023.41165

[35] ICIs in ovarian. PMC. - https://www.nejm.org/doi/full/10.1056/NEJMoa2216334. DOI: 10.1056/NEJMoa2216334

[36] PD-L1 expression. BioMed Central. - https://www.jemperlihcp.com/efficacy/garnet-trial/. No DOI

[37] Efficacy and safety. Frontiers. - https://jitc.bmj.com/content/10/1/e003777. DOI: 10.1136/jitc-2021-003777

[38] UCSF Trials. UCSF. - https://www.ejcancer.com/article/S0959-8049(24)01753-2/abstract. DOI: 10.1016/j.ejca.2024.115146

[39] Immune checkpoint therapy. ScienceDirect. - https://pubmed.ncbi.nlm.nih.gov/39798514/. DOI: 10.1016/j.ejca.2024.115146

[40] Cadonilimab Trial. ClinicalTrials.gov. - https://pubmed.ncbi.nlm.nih.gov/35922251/. DOI: 10.1016/j.ejca.2022.03.016

[41] Response and re-treatment. ASCO. - https://onlinelibrary.wiley.com/doi/full/10.1002/cam4.70236. DOI: 10.1002/cam4.70236

[42] Treatment Trials. NCI. - https://ascopost.com/news/may-2022/cemiplimab-rwlc-improves-overall-survival-vs-chemotherapy-in-recurrent-cervical-cancer-after-first-line-platinum-based-chemotherapy/. DOI: 10.1056/NEJMoa2112187

[43] Recent advances. Springer. - https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(24)00088-3/fulltext. DOI: 10.1016/S1470-2045(24)00088-3

[44] Focus on PD-1/PD-L1. PMC. - https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(24)00088-3/fulltext. DOI: 10.1016/S1470-2045(24)00088-3