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# Checkpoint Inhibitor Therapy in Gynecologic Clear Cell Carcinoma: A Narrative Review

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## Abstract

**Background:** Gynecologic clear cell carcinoma (CCC) represents a rare and biologically distinct subgroup of gynecologic malignancies arising predominantly from the ovary and endometrium, and less commonly from the cervix and vulva. Characterized by chemoresistance, a high rate of early recurrence, and a paucity of effective second-line therapies, CCC carries a disproportionately poor prognosis compared with other histologic subtypes. The emergence of immune checkpoint inhibitors (ICIs), particularly agents targeting the programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1) axis, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), has transformed the treatment landscape of multiple solid tumors. However, the immunologic microenvironment of CCC is uniquely complex, characterized by variable PD-L1 expression, moderate tumor mutational burden, a prominent inflammatory infiltrate, and a paradoxically immune-evasive phenotype driven by ARID1A co-mutation and HNF-1$\beta$ overexpression. This narrative review synthesizes the available clinical and translational evidence on the efficacy, biomarker landscape, and future directions of ICI therapy in gynecologic CCC. **Methods:** A comprehensive search of PubMed/MEDLINE, EMBASE, and the Cochrane Library was performed from January 2010 to January 2026, focusing on clinical trials, retrospective studies, and translational analyses reporting outcomes of ICIs in patients with CCC of gynecologic origin. **Results:** Emerging data from basket trials and histology-specific cohorts suggest modest but potentially clinically meaningful activity of ICIs in CCC, particularly in the recurrent setting and in tumors which harbor mismatch repair deficiency mutations or high tumor mutational burden. **Conclusion:** Combination strategies incorporating ICIs with VEGF inhibition, PARP inhibition, or targeted agents represent a rational and promising avenue. Standardization of biomarker testing and inclusion of CCC-specific cohorts in future trials are essential to advancing the field.

**Keywords**

Clear Cell Carcinoma, Immune Checkpoint Inhibitors, PD-L1, Gynecologic Oncology, Ovarian Neoplasms, Endometrial Neoplasms

## 1. Introduction

Gynecologic malignancies encompass a diverse spectrum of histologic entities, each with distinct molecular underpinnings, clinical behavior, and therapeutic vulnerabilities. Among these, clear cell carcinoma (CCC) occupies a particularly challenging clinical position. Ovarian CCC accounts for approximately 10% of all ovarian carcinomas, and the incidence ranges from 5% to 25% depending on geographic, ethnic, and racial factors, with the highest rates observed among Asian women [1]. Endometrial CCC represents approximately 1% - 3% of endometrial cancers in Western populations [2]. Despite its relative rarity, CCC is disproportionately represented among treatment failures, carrying a five-year survival rate below 40% in advanced-stage disease [3].

Standard platinum-taxane chemotherapy, the backbone of treatment for most gynecologic malignancies, yields objective response rates of only 11% - 50% in ovarian CCC, reflecting intrinsic chemoresistance [1]. The mechanisms underlying this resistance are multifactorial, encompassing decreased intracellular drug accumulation via upregulation of ATP-binding cassette (ABC) transporters (particularly ABCC3 and ABCF2), enhanced drug detoxification through the glutathione system, and increased nucleotide excision repair activity mediated by overexpression of ERCC1 and XPB [4]-[6]. Notably, CCC tumor cells demonstrate a significantly lower Ki-67 labeling index compared with serous adenocarcinoma, suggesting that low proliferative activity rather than a single dominant resistance pathway, may be the central driver of cisplatin insensitivity in this histotype [7]. As a consequence, meaningful second-line treatment options in recurrent disease remain limited, and improvements in overall survival have been elusive.

The immunotherapy revolution, catalyzed by the clinical development of ICIs targeting the PD-1/PD-L1 axis and CTLA-4, has fundamentally altered the therapeutic paradigm for multiple solid tumors. Pembrolizumab and nivolumab have achieved durable responses in malignancies previously considered refractory, particularly in those harboring mismatch repair deficiency (dMMR) or high tumor mutational burden (TMB-H). This has prompted exploration of ICI therapy across histologically rare and underrepresented tumor types, including gynecologic CCC [8].

Despite the clinical imperative, robust evidence for ICI activity in gynecologic CCC remains sparse. Most pivotal immunotherapy trials in gynecologic cancers have focused on high-grade serous ovarian carcinoma or endometrioid endometrial cancer, frequently excluding or under-enrolling patients with CCC [9]. This review aims to consolidate available evidence, characterize what is known about

the immune microenvironment of CCC, and outline rational combination strategies and future research priorities for ICI therapy in this understudied but clinically important entity.

## 2. Methods

This narrative review was conducted in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) framework to ensure methodological transparency [10]. A comprehensive literature search was performed in PubMed/MEDLINE, EMBASE, and the Cochrane Library from January 2010 to January 2026. Search terms included combinations of the following: "clear cell carcinoma", "ovarian cancer", "endometrial cancer", "gynecologic cancer", "immune checkpoint inhibitor", "pembrolizumab", "nivolumab", "atezolizumab", "durvalumab", "ipilimumab", "PD-1", "PD-L1", "CTLA-4", "immunotherapy", and "tumor microenvironment".

ClinicalTrials.gov was additionally searched for registered trials enrolling patients with gynecologic CCC. Reference lists of eligible publications were manually reviewed to capture additional relevant studies. Studies were included if they reported clinical outcomes, biomarker data, or translational analyses pertaining to ICI therapy in histologically confirmed gynecologic CCC among the study cohorts. Conference abstracts from major meetings (ASCO, ESMO, SGO, ESGO) published between 2018 and 2026 were also reviewed to incorporate emerging data. No formal statistical synthesis was performed given the heterogeneity of available data sources and the narrative nature of this review.

## 3. Results

This review includes sixteen single-armed, prospective, randomized and ongoing studies and trials that evaluated immune checkpoint inhibitors in gynecologic cancers with the inclusion of the clear cell subtype.

### 3.1. Molecular Biology and Immune Microenvironment of Clear Cell Carcinoma

#### 3.1.1. Molecular Landscape

Clear cell carcinoma of gynecologic origin shares several defining molecular features that distinguish it from other histologic subtypes. Loss-of-function mutations in ARID1A, a SWI/SNF chromatin remodeling gene, are present in 40% - 60% of ovarian CCC and up to 30% of endometrial CCC, representing one of the most frequent somatic alterations in this histotype [11]. ARID1A mutations carry significant immunologic implications: ARID1A-deficient tumors demonstrate impaired mismatch repair capacity, accumulation of DNA damage, and upregulation of PD-L1 expression via activation of the IFN-$\gamma$/JAK-STAT signaling pathway, thereby establishing a theoretical basis for ICI sensitivity [12].

Mutations in PIK3CA are observed in approximately 33% - 40% of ovarian CCC, with attendant activation of the PI3K/AKT/mTOR pathway driving prolif-

eration and survival [13]. HER2 amplification occurs in a small but targetable subset (~14% - 18%) of endometrial CCC [14]. PTEN loss, KRAS mutation, and TP53 alterations are relatively infrequent in ovarian CCC, further distinguishing it from high-grade serous carcinoma. Importantly, BRCA1/2 mutations are uncommon in CCC, limiting the utility of PARP inhibitors as single agents.

Mismatch repair deficiency (dMMR) and microsatellite instability-high (MSI-H) status, the most well-established predictors of ICI response across tumor types, occur in only 5% - 10% of ovarian CCCs but in up to 13% - 17% of endometrial CCCs [15]. While representing a minority of cases, dMMR/MSI-H CCC patients may theoretically derive meaningful benefit from pembrolizumab or other PD-1 inhibitors, analogous to their pan-tumor efficacy. Similarly, TMB-H (defined as ≥10 mutations per megabase) is observed in a subset of CCC tumors and has been associated with ICI response independent of MSI status.

#### 3.1.2. Tumor Immune Microenvironment

What makes ovarian CCC biologically distinct is not any single molecular aberration, but the manner in which its oncogenic drivers conspire to simultaneously fuel tumor growth and disable immune surveillance. Co-occurring mutations in ARID1A and PIK3CA sit at the apex of this immunosuppressive network, unleashing PI3K/AKT/mTOR and JAK/STAT3 signaling that collectively amplifies IL-6, upregulates VEGF, and stabilizes HIF-1*α*, a triad that locks the stroma into a hypoxic, angiogenic, and metabolically reprogrammed state [16]. ARID1A loss compounds immunosuppression through a separate arm: HDAC6 induction drives IL-10 secretion, skewing macrophages toward a pro-tumorigenic M2 phenotype [17]. Concomitant PTEN loss further cements the immune-evasive phenotype by inducing PD-L1, while PI3K/AKT hyperactivation simultaneously co-upregulates LAG-3, combination that enforces T-cell anergy, enhances regulatory T-cell (Treg) function, and blunts cytotoxic lymphocyte activity on multiple fronts. The physical tumor microenvironment (TME) adds an additional layer of immunosuppression: myofibroblastic cancer-associated fibroblasts sustain HIF-1*α* through PDGF signaling, iron-donating endometriosis-derived stromal cells fuel proliferation, and the resulting Treg- and tumor-associated macrophage (TAM)-rich milieu renders antigen-presenting function ineffective [18]. Paradoxically, this same molecular architecture, rich in targetable possibilities including PD-L1, LAG-3, VEGF, IL-6, and HDAC6, renders CCC a compelling, if challenging, candidate for rationally designed combination immunotherapy [19] [20].

### 3.2. Clinical Evidence for Checkpoint Inhibitors in Gynecologic Clear Cell Carcinomas

**Tables 1-3** summarize the clinical trials for ovarian, endometrial, and cervical cancers that include clear cell carcinoma subtypes.

#### 3.2.1. Disease Site: Ovarian Clear Cell Carcinoma

Clinical evidence for anti-PD-1/PD-L1 agents in OCCC derives from histology-

specific subset analyses of broader gynecologic oncology trials, dedicated single-arm Phase II studies, and emerging randomized data, several of which have prospectively stratified by CCC histology.

KEYNOTE-100 was a Phase II, open-label, multicenter study evaluating single-agent pembrolizumab 200 mg every three weeks in 376 patients with advanced recurrent ovarian cancer across two cohorts: cohort A (1 - 3 prior lines, platinum-free interval [PFI] 3 - 12 months) and cohort B (4 - 6 prior lines, PFI > 3 months), with PD-L1 expression by combined positive score (CPS) as the primary biomarker endpoint. In the clear cell carcinoma subgroup of 19 patients, the ORR was 15.8% (95% CI: 3.4 - 39.6), numerically the highest among all histologic subtypes and nearly double the overall cohort ORR of 8.0%, suggesting a trend toward preferential responsiveness of the CCC histotype to PD-1 blockade, though the small subgroup size precluded definitive conclusions [21].

NRG-GY003 (NCT02498600) was an open-label, randomized Phase II trial comparing nivolumab alone versus nivolumab plus ipilimumab induction followed by nivolumab maintenance in 100 patients with recurrent or persistent ovarian cancer of all histologic subtypes (except mucinous and carcinosarcoma), with a platinum-free interval under 12 months. Clear cell carcinoma represented 12% of the study population—six patients per arm and while the subgroup was underpowered for definitive conclusions, exploratory analysis revealed an approximately five-fold higher odds of response in CCC patients compared with other histologic subtypes. Patients with CCC also appeared to derive preferential benefit from the combination arm, with the forest plot demonstrating a PFS hazard ratio favoring nivolumab plus ipilimumab over nivolumab alone specifically in this subgroup (interaction P = 0.0498) [22].

NINJA (JapicCTI-153004) was a Phase III, multicenter, randomized, open-label trial comparing nivolumab 240 mg every two weeks against investigator-choice chemotherapy (gemcitabine or pegylated liposomal doxorubicin [PLD]) in 316 patients with platinum-resistant epithelial ovarian cancer, with CCC vs non-CCC histology as a prespecified stratification factor, making it one of the few large randomized trials to prospectively account for the CCC subtype. Clear cell carcinoma represented approximately 21% of the study population, with 34 patients in the nivolumab arm and 33 in the comparator arm, constituting the largest CCC cohort within any randomized ICI trial in ovarian cancer to date. While the trial was negative overall, nivolumab failing to improve OS (HR 1.0; 95% CI 0.8 - 1.3) or PFS (HR 1.5; 95% CI 1.2 - 1.9) versus chemotherapy, the CCC subgroup demonstrated a numerically favorable OS trend with nivolumab (HR 0.78; 95% CI 0.46 - 1.32), in contrast to the non-CCC serous carcinoma subgroup where the HR favored chemotherapy (HR 1.11; 95% CI 0.81 - 1.52). This CCC-specific OS signal is hypothesis-generating for future biomarker-stratified studies [23].

PEACOCC (NCT03425565) was a single-arm Phase II trial, the only study designed exclusively for clear cell gynecological cancer, evaluating pembrolizumab 200 mg every three weeks in 48 patients (85% ovarian CCC) with a median of

three prior lines of therapy across five United Kingdom centers. The trial met its primary endpoint with a 12-week PFS rate of 42% (95% CI: 28 - 57). Best ORR was 25%, median duration of response 13.1 months, median PFS 2.7 months, and median OS 14.8 months at a mature median follow-up of 46.9 months. The safety profile was favorable with no grade 4/5 treatment-related adverse events (TRAEs). Critically, 98% of evaluable patients had MMR-proficient tumors, establishing that pembrolizumab activity in clear cell gynecological cancer is independent of MSI-H status and driven by the distinct immunobiology of this histotype. There was no evidence of a difference in PFS or OS for patients with tumors that harbored MMR deficiency, ARID1A loss, aberrant expression of p53, or expressed PD-1, PD-L1 or a combination of PD-1/PD-L1 [24].

JAVELIN Ovarian 200 was an open-label, parallel-group, three-arm, randomised, Phase III trial, done at 149 hospitals and cancer treatment centres in 24 countries. 614 patients were enrolled across three arms; for platinum-resistant disease) and an Eastern Cooperative Oncology Group performance status of 0 or 1. Patients were randomly assigned (1:1:1) to avelumab (10 mg/kg intravenously every two weeks), avelumab plus PLD (40 mg/m$^2$ intravenously every four weeks), or PLD. Clear cell histology represented approximately 13% of patients (n = 73 across arms). In the subgroup forest plot, the HR for combination avelumab versus PLD was 0.79 (0.41 - 1.54) for PFS and 0.89 (0.38 - 2.06) for OS in the CCC subgroup—confidence intervals widely crossing 1.0, indicating no demonstrable benefit. The overall trial was negative, and clear cell carcinoma remains an unmet need where ICI combinations cannot currently be recommended based on this data alone [25].

MOCCA (Phase II RCT, n = 48) randomized recurrent OCCC patients 2:1 to durvalumab versus physician's choice chemotherapy—the first randomized ICI versus chemotherapy trial specifically designed for recurrent OCCC. Durvalumab failed to improve PFS (7.6 vs 14.0 weeks, HR 1.6, P = 0.92), OS (37.9 vs 40.6 weeks, HR-1.5; P = 0.85), or ORR (9.7% vs 18.8%; P = 0.83), with chemotherapy numerically outperforming immunotherapy across all endpoints. Notably, only 28.9% of tumors were PD-L1 CPS ≥1%. All tumors were MMR-proficient/MSS, and PIK3CA mutations were exploratorily associated with longer time to progression on durvalumab, while ERBB2 amplification predicted worse PFS. These results indicate that PD-L1 monotherapy has no role in unselected recurrent OCCC; future directions lie in combination strategies and biomarker-selected populations [26].

BrUOG 354 (Phase II RCT, n = 44; 82% ovarian CCC) compared nivolumab monotherapy versus nivolumab plus ipilimumab (N + I) in relapsed extra-renal CCC. N + I demonstrated superior activity over monotherapy with ORR 33% (including four complete responses (CRs)) versus 14.3%, and median PFS 5.6 versus 2.2 months, with median OS 24.6 versus 17 months. Notably, four patients (12%) achieved durable CR with N + I. Grade ≥ 3 TRAEs were higher with N + I (47% vs 21%) but no treatment-related deaths occurred [27].

MoST-CIRCUIT (Phase II, n = 28; 24 OCCC + four uterine CCC) evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every three weeks for four doses,

followed by nivolumab 480 mg every four weeks for 96 weeks in advanced gynecological CCC. Dual checkpoint blockade demonstrated an ORR of 50% (13% CR + 37% PR) across both subgroups, with median duration of response not reached and all responses ongoing at six months; 6-month PFS was 52%. TMB correlated with response (3.1 vs 1.15 mut/MB; p = 0.03), and responses were predominantly observed in ARID1A wild-type tumors. Grade 3/4 immune-related adverse events (irAEs) occurred in 25%, including one fatal myocarditis. Combined anti-CTLA-4/PD-1 blockade shows the highest ORR reported to date in gynecological CCC and warrants further randomized evaluation [28].

LARA (Phase II, single-arm, n = 27; 89% ovarian CCC;11% endometrium CCC) evaluated pembrolizumab 200 mg every three weeks plus lenvatinib 20 mg daily in recurrent clear cell gynecological cancer; notably, 63% of patients had received prior anti-angiogenic therapy and all tumors were MMR-proficient/MSS. The primary endpoint was met with an ORR of 40% at 24 weeks (95% CI 21 - 61), clinical benefit rate 84%, median PFS 6.4 months, and median OS 15.6 months—including a 47% ORR in the prior anti-angiogenic subgroup, suggesting lenvatinib may overcome VEGF-resistance through its broader multi-kinase inhibitory profile. Grade 3 - 4 TRAEs occurred in 52%, predominantly hypertension, with no treatment-related deaths. Responses occurred irrespective of PD-L1 CPS or TMB status, and findings are directionally consistent with the INOVA trial results [29].

NRG-GY016 (Phase II, single-arm, n = 14) evaluated pembrolizumab 200 mg every three weeks plus epacadostat (IDO1 inhibitor) 100 mg twice daily in recurrent OCCC. The combination yielded an ORR of 21% (three partial responses [PRs]), DCR 50%, median PFS 4.8 months, and median OS 18.9 months; however, the study closed prematurely after stage 1 due to insufficient drug supply, precluding definitive conclusions. The concurrent failure of epacadostat plus pembrolizumab in the ECHO-301/KEYNOTE-252 melanoma Phase III trial, alongside concerns regarding subtherapeutic IDO1 inhibition at the 100 mg twice-daily dose, further limits enthusiasm for this combination. IDO1 inhibition combined with PD-1 blockade is unlikely to be pursued further in this setting [30].

INOVA (Phase II, single-arm, n = 41; 37 evaluable) evaluated sintilimab (anti-PD-1) 200 mg plus bevacizumab 15 mg/kg every three weeks in relapsed or persistent ovarian CCC—the first prospective study evaluating an ICI plus anti-angiogenic combination exclusively in this histotype. The primary endpoint was met with an ORR of 40.5% (95% CI 24.8 - 57.9), comprising five complete responses (14%) and ten partial responses (27%). Median PFS was 6.9 months, and median OS was 28.2 months. Grade ≥ 3 TRAEs occurred in only 7% of patients with no treatment-related deaths, confirming a favorable toxicity profile and establishing this chemotherapy-free regimen as a promising option pending randomized validation [31].

#### 3.2.2. Disease Site: Endometrial Clear Cell Carcinoma

Endometrial CCC, though rarer than its serous or endometrioid counterparts, has been investigated as part of broader endometrial cancer ICI trials. Dedicated histotype-specific data remain sparse, and conclusions are largely extrapolated from

subgroup analyses and molecular phenotype-based evidence.

KEYNOTE-775 (randomised Phase III trial) enrolled all endometrial histologies except carcinosarcoma and sarcoma with clear cell carcinoma comprising 7.3% (n = 30) of the lenvatinib plus pembrolizumab arm. Although no histology-specific efficacy data are reported for clear cell carcinoma, the subgroup analysis favored lenvatinib plus pembrolizumab over chemotherapy across all histologic subtypes, including less-common aggressive histologies. As endometrial CCC is predominantly pMMR, the significant PFS (6.6 vs 3.8 months; HR 0.60; $p < 0.001$) and OS (17.4 vs 12.0 months; HR 0.68; $p < 0.001$) benefit demonstrated in the pMMR population represents the most clinically applicable evidence for this histology to date [32].

The NRG-GY018 Phase III trial randomized 816 patients with advanced/recurrent endometrial cancer to pembrolizumab plus carboplatin-paclitaxel versus placebo-chemotherapy, enrolling all histologic subtypes except carcinosarcoma. Clear cell carcinoma represented 6.3% of the overall population (37 patients), virtually all in the pMMR cohort (17 + 20 patients across arms), consistent with the predominantly pMMR phenotype of ECCC. The trial demonstrated significant PFS benefit in both dMMR (HR 0.30) and pMMR (HR 0.54) cohorts, with the authors explicitly noting benefit observed across less common histologic subtypes including clear cell—though no CCC-specific subgroup analysis was reported [33].

The RUBY trial was a Phase III randomized trial of dostarlimab plus carboplatin-paclitaxel versus placebo-chemotherapy in primary advanced or recurrent endometrial cancer (n = 494). Clear cell adenocarcinoma represented 3.3% - 3.6% of the overall population (8 - 9 patients per arm), making CCC-specific conclusions statistically untenable. The trial demonstrated significant PFS benefit overall (24-month PFS 36.1% vs 18.1%; HR 0.64) and a particularly striking benefit in the dMMR/MSI-H cohort (24-month PFS 61.4% vs 15.7%; HR 0.28). Crucially, a PFS benefit was also observed in the pMMR/MSS population (HR 0.76; 95% CI, 0.59 - 0.98), which is the predominant molecular phenotype of endometrial CCC, suggesting potential applicability to this histotype. Endometrial CCC patients were explicitly eligible under the inclusion criteria, but subgroup-level outcomes were not separately reported [34].

DUO-E was a Phase III trial randomizing 718 patients with advanced/recurrent endometrial cancer 1:1:1 to carboplatin-paclitaxel plus durvalumab followed by maintenance durvalumab ± olaparib versus chemotherapy alone. Clear cell adenocarcinoma represented only 1.7% - 3.3% of the overall population (4 - 8 patients per arm), rendering CCC-specific conclusions entirely untenable. The trial demonstrated significant ITT PFS benefit for both the durvalumab (HR 0.71) and durvalumab plus olaparib (HR 0.55) arms versus control, with benefit observed in the pMMR/MSS subgroup (HR 0.77 and 0.57 respectively)—directly relevant to the predominantly pMMR phenotype of endometrial CCC. Notably, the addition of olaparib appeared to confer incremental benefit specifically in the pMMR population (HR 0.76, durvalumab plus olaparib vs durvalumab alone), raising a hypothesis-generating question as to whether PARP inhibition may augment ICI ac-

tivity in pMMR clear cell tumors through synthetic lethality with ARID1A loss—a biologically plausible interaction given ARID1A's role in homologous recombination repair—warranting dedicated investigation [35].

DOVE is the largest ongoing Phase II RCT specifically designed for recurrent gynecologic CCC, randomizing 198 ICI-naive patients 1:1:1 to dostarlimab monotherapy, dostarlimab plus bevacizumab, or investigator's choice chemotherapy, with crossover to the combination arm permitted at progression. Uniquely, the trial enrolls all anatomical CCC subtypes including endometrial, cervical, vaginal, and vulvar CCC—directly addressing the critical evidence vacuum in non-ovarian subtypes—with comprehensive biomarker analyses including MMR, TMB, and ARID1A/PIK3CA profiling planned. Results are awaited as the potential practice-defining evidence for this histotype [36].

#### 3.2.3. Disease Site: Clear Cell Carcinoma of the Cervix

Dedicated ICI trial data for clear cell carcinoma of the cervix are virtually non-existent. The PEACOCC trial included only one cervical clear cell gynecological cancer patient (2%) among 48 enrolled, making any histotype-specific conclusions impossible [24]. Cervical CCC is a rare, predominantly non-HPV-driven tumor—associated with diethylstilbestrol (DES) exposure or arising de novo—with a distinct molecular biology from the squamous and adenocarcinoma subtypes for which ICI approvals exist [37]. Clear cell histology was not separately analyzed in any of the pivotal cervical cancer ICI trials, representing a critical evidence gap.

#### 3.2.4. Disease Site: Clear Cell Carcinoma of the Vulva

This is an exceedingly rare entity with essentially no ICI-specific data. The role of ICIs in vulvar cancer is mainly extrapolated from trials in cutaneous squamous cell and cervical cancers. Clear cell histology of the vulva was not represented in any published ICI basket trial with reportable outcomes, and management of this entity remains entirely empiric.

## 4. Discussion

The accumulating evidence positions immune checkpoint inhibition as a biologically rational and clinically meaningful therapeutic strategy in gynecologic CCC, albeit one that remains incompletely characterized across its anatomical subtypes. The overarching narrative emerging from the reviewed trials is one of consistent but heterogeneous ICI activity, where histotype-specific immunobiology, rather than conventional biomarkers such as PD-L1 expression or MMR status, appears to be the primary determinant of response.

The most compelling mechanistic basis for ICI sensitivity in CCC lies in its unique TME. The convergence of ARID1A loss, PIK3CA mutation, IL-6/STAT3 signaling, and VEGF upregulation creates a paradoxically immunogenic yet immune-evasive milieu that simultaneously provides multiple targetable nodes. ARID1A-deficient tumors demonstrate upregulation of PD-L1 via IFN-$\gamma$/JAK-STAT signaling and impaired mismatch repair capacity, theoretically sensitizing

them to PD-1 blockade independent of formal dMMR classification. This observation finds clinical validation in the PEACOCC trial, where robust ICI activity was demonstrated in a 98% MMR-proficient cohort, the single most important translational finding across all reviewed evidence, fundamentally challenging the paradigm that ICI benefit in gynecologic cancers is restricted to dMMR tumors [24].

Among the anti-PD-1/PD-L1 monotherapy data, a consistent directional signal emerges across KEYNOTE-100, NRG-GY003, NINJA, and PEACOCC:CCC appears to respond preferentially to PD-1 blockade compared with other epithelial ovarian cancer histotypes. However, monotherapy activity remains modest in unselected populations, with ORRs ranging from 14% to 25%, and the majority of patients experiencing early progression. The MOCCA trial's negative result with durvalumab monotherapy serves as an important cautionary counterpoint, highlighting that patient selection, prior therapy burden, and MMR status profoundly influence outcomes, and that PD-L1 expression alone is insufficient as a selection biomarker in CCC [26].

The combination immunotherapy data represent the most exciting and practice-informing frontier. The MoST-CIRCUIT trial, reporting the highest ORR yet observed in gynecologic CCC at 50% with nivolumab plus ipilimumab, and BrUOG-354 demonstrating superior outcomes for dual checkpoint blockade over monotherapy (ORR 33% vs 14%), collectively make a compelling case for CTLA-4 co-inhibition as a necessary component of effective ICI strategies in this histotype. The rationale is mechanistically sound: CTLA-4 blockade depletes intratumoral Tregs and enhances priming of naive T cells, complementing the effector T-cell reinvigoration achieved by PD-1 blockade, a dual mechanism particularly relevant in a TME characterized by Treg enrichment and impaired antigen presentation. The durable complete responses (12%) observed in BrUOG-354 with nivolumab plus ipilimumab are especially noteworthy and suggest a subset of patients capable of achieving long-term disease control [27] [28].

The ICI-antiangiogenic combination rationale is equally compelling given the central role of VEGF in CCC immunosuppression. The LARA trial (ORR 40%, pembrolizumab plus lenvatinib) and the INOVA trial (ORR 40.5%, sintilimab plus bevacizumab) provide convergent evidence from independent datasets that VEGF pathway co-inhibition meaningfully augments ICI activity, potentially by restoring dendritic cell maturation, normalizing tumor vasculature to improve T-cell trafficking, and reversing VEGF-mediated immunosuppression. The observation in LARA that responses occurred irrespective of prior anti-angiogenic therapy exposure suggests lenvatinib may overcome acquired VEGF-resistance through its broader multi-kinase inhibitory profile [29] [31].

For endometrial CCC specifically, the evidence base, while sparse, is directionally consistent. PEACOCC's MMR-proficient activity, RUBY's pMMR/MSS PFS benefit (HR 0.76), and KEYNOTE-775's favorable overall survival HR (0.68) in the endometrial CCC subgroup collectively support ICI-based strategies across molecular phenotypes. The predominantly pMMR phenotype of endometrial

CCC does not appear to preclude ICI benefit, an observation with immediate clinical relevance given the historically dismal second-line chemotherapy outcomes in this subtype.

The cervical and vulvar CCC subtypes represent a profound data vacuum. With only one cervical CCC patient enrolled in PEACOCC and no vulvar CCC representation in any published trial, management of these entities relies entirely on extrapolation from ovarian and endometrial CCC data, or from tissue-agnostic dMMR approvals in the minority of cases harboring MSI-H status.

The biomarker landscape remains unsatisfactory. PD-L1 expression has shown inconsistent predictive value across studies, ARID1A loss has not been validated as a clinical biomarker despite its mechanistic plausibility, and TMB-H occurs in only a minority of cases. The MoST-CIRCUIT finding of a TMB correlation with response and the MOCCA data implicating PIK3CA and ERBB2 as potential predictive markers represent early leads requiring prospective validation. Standardization of biomarker testing methodology, particularly given the known discordance between IHC-based and PCR-based MMR assessment in non-colorectal tumors—is an essential prerequisite for future progress.

Limitations of this analysis and the data cited come from the small sample sizes of clear cell cancers. Tables 1-3 summarize these key limitations for the different gynecologic disease sites that were included in the studies. Because of reliance on single-arm studies and abstract-level evidence for some trials, and missing histology-specific reporting in several pivotal studies, histology-specific outcomes from immune checkpoint inhibitor therapy must be viewed with caution.

**Table 1.** Immune checkpoint inhibitor trials in gynecologic clear cell carcinoma: disease site: ovarian carcinoma.

| Trial (reference) | Design | Agent(s) | CCC Population | Key Efficacy Outcomes | Key Limitations |
|---|---|---|---|---|---|
| **KEYNOTE-100 (21)** | Phase II single-arm | Pembrolizumab | OCCC n = 19 (subset) | ORR 15.8%; highest among histotypes | Small subgroup; no dedicated CCC arm |
| **NRG-GY003 (22)** | Phase II RCT | Nivolumab ± Ipilimumab | OCCC n = 12 (6/arm) | ~5 × higher odds of response vs other histotypes; PFS HR favored N + I in CCC | Underpowered subgroup |
| **NINJA (23)** | Phase III RCT | Nivolumab vs chemo | OCCC n = 67 (21%) | OS HR 0.78 for CCC (vs 1.11 non-CCC); overall trial negative | Negative overall; CCC subgroup not powered |
| **PEACOCC (24)** | Phase II single-arm | Pembrolizumab | CCGC n = 48 (85% ovarian, 13% endometrial, 2% cervical) | 12-wk PFS 42%; ORR 25%; mOS 14.8 months; 98% MMR-proficient | Single-arm; no randomized control |
| **MOCCA (26)** | Phase II RCT | Durvalumab vs chemo | rOCCC n = 48 | Negative: ORR 9.7% vs 18.8%; all MMR-proficient/MSS | Small sample; no histology review |
| **BrUOG-354 (27)** | Phase II RCT | Nivolumab vs Nivolumab + Ipilimumab | Extra-renal CCC n = 44 (82% ovarian) | ORR 33% vs 14.3%; mOS 24.6 vs 17 months; 4 CRs with N+I | Small sample; no chemotherapy control arm |
| **MoST-CIRCUIT (28)** | Phase II single-arm | Nivolumab + Ipilimumab | Gynecologic CCC n = 28 (24 OCCC + 4 uterine CCC) | ORR 50% (13% CR + 37% PR); 6-month PFS 52%; TMB correlated with response | Small sample; 1 fatal myocarditis |

**Continued**

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| **LARA (29)** | Phase II single-arm | Pembrolizumab + Lenvatinib | CCGC n = 27 (89% ovarian, 11% endometrium) | ORR 40%; mPFS 6.4 months; mOS 15.6 months; activity in prior anti-VEGF group | Single-arm; 52% grade 3 - 4 TRAEs |
| **INOVA (31)** | Phase II single-arm | Sintilimab + Bevacizumab | rOCCC n = 41 | ORR 40.5%; mPFS 6.9 months; mOS 28.2 months | Immature OS; single-arm |
| **NRG-GY016 (30)** | Phase II single-arm | Pembrolizumab + Epacadostat | rOCCC n = 14 | ORR 21%; mPFS 4.8 months; closed early | Premature closure; IDO1 strategy largely abandoned |
| **JAVELIN Ovarian 200 (25)** | Phase III RCT | Avelumab ± PLD vs PLD | OCCC n = 73 (13%) | PFS HR 0.79; OS HR 0.89 in CCC; overall trial negative | Negative trial; CCC subgroup underpowered |
| **DOVE (36)** | Phase II RCT (ongoing) | Dostarlimab vs Dostarlimab + Bevacizumab vs chemo | rGCCC n = 198 planned (ovarian, endometrial, cervical, vaginal, vulvar CCC; non-ovarian capped at 10%) | Primary endpoint: investigator-assessed PFS; results awaited | Ongoing; no efficacy data available; non-ovarian CCC enrolment capped at 10% |

**Table 2.** Immune checkpoint inhibitor trials in gynecologic clear cell carcinoma: disease site: endometrial carcinoma.

| Trial (reference) | Design | Agent(s) | CCC Population | Key Efficacy Outcomes | Key Limitations |
|---|---|---|---|---|---|
| **PEACOCC (24)** | Phase II single-arm | Pembrolizumab | CCGC n = 48 (85% ovarian, 13% endometrial, 2% cervical) | 12-wk PFS 42%; ORR 25%; mOS 14.8 months; 98% MMR-proficient | Single-arm; no randomized control |
| **MoST-CIRCUIT (28)** | Phase II single-arm | Nivolumab + Ipilimumab | Gynecologic CCC n = 28 (24 OCCC + 4 uterine CCC) | ORR 50% (13% CR + 37% PR); 6-month PFS 52%; TMB correlated with response | Small sample; 1 fatal myocarditis |
| **KEYNOTE-775 (32)** | Phase III RCT | Lenvatinib + Pembrolizumab vs chemo | ECCC n = 30 (7.3%); pMMR population | pMMR: PFS HR 0.60; OS HR 0.68; ECCC OS HR 0.33 | No separate ECCC efficacy reporting |
| **RUBY (34)** | Phase III RCT | Dostarlimab + carbo-paclitaxel vs placebo-chemo | ECCC n = 17 (~3.5%) | pMMR-MSS PFS HR 0.76; overall PFS HR 0.64 | No separate ECCC reporting; very small CCC subgroup |
| **NRG-GY018 (33)** | Phase III RCT | Pembrolizumab + carbo-paclitaxel vs placebo-chemo | ECCC n = 37 (6.3%); predominantly pMMR | pMMR PFS HR 0.54 (mPFS 13.1 vs 8.7 months); dMMR PFS HR 0.30; benefit noted across less common histotypes including CCC | No separate ECCC subgroup analysis; short median follow-up at primary analysis |
| **DUO-E (35)** | Phase III RCT | Durvalumab ± Olaparib + carbo-paclitaxel vs chemo | ECCC n = 19 (~3.3% across arms) | ITT PFS HR 0.71 (durvalumab) and 0.55 (durvalumab + olaparib); pMMR PFS HR 0.77 and 0.57; olaparib incremental benefit in pMMR subgroup | No separate CCC analysis; very small CCC subgroup; OS immature |
| **DOVE (36)** | Phase II RCT (ongoing) | Dostarlimab vs Dostarlimab + Bevacizumab vs chemo | rGCCC n = 198 planned (ovarian, endometrial, cervical, vaginal, vulvar CCC; non-ovarian capped at 10%) | Primary endpoint: investigator-assessed PFS; results awaited | Ongoing; no efficacy data available; non-ovarian CCC enrolment capped at 10% |

**Table 3.** Immune checkpoint inhibitor trials in gynecologic clear cell carcinoma: disease site: cervical and vulvar carcinoma.

| Trial (reference) | Design | Agent(s) | CCC Population | Key Efficacy Outcomes | Key Limitations |
|---|---|---|---|---|---|
| **PEACOCC (24)** | Phase II single-arm | Pembrolizumab | CCGC n = 48 (85% ovarian, 13% endometrial, 2% cervical) | 12-wk PFS 42%; ORR 25%; mOS 14.8 months; 98% MMR-proficient | Single-arm; no randomized control |
| **DOVE (36)** | Phase II RCT (ongoing) | Dostarlimab vs Dostarlimab + Bevacizumab vs chemo | rGCCC n = 198 planned (ovarian, endometrial, cervical, vaginal, vulvar CCC; non-ovarian capped at 10%) | Primary endpoint: investigator-assessed PFS; results awaited | Ongoing; no efficacy data available; non-ovarian CCC enrolment capped at 10% |
| **Cervical CCC (24)** | - | - | n = 1 (PEACOCC only) | No conclusions possible | Critical evidence vacuum |
| **Vulvar CCC** | - | - | n = 0 | No data | Critical evidence vacuum |

CCGC = clear cell gynecological cancer; OCCC = ovarian clear cell carcinoma; ECCC = endometrial clear cell carcinoma; rOCCC = recurrent ovarian CCC; N + I = nivolumab + ipilimumab; mOS = median overall survival; mPFS = median progression-free survival; TMB = tumor mutational burden; TRAEs = treatment-related adverse events.

## 5. Conclusion

Immune checkpoint inhibitor therapy holds genuine but incompletely realized promise in gynecologic clear cell carcinoma. Modest single-agent activity, enhanced by rationally designed combination strategies, supports the incorporation of ICIs into the therapeutic armamentarium for this chemoresistant malignancy. Biomarker-driven patient selection—particularly for dMMR/MSI-H and ARID1A-mutant tumors—and dedicated histotype-specific clinical trials are essential to translating biological rationale into meaningful clinical benefit. ARID1A-guided patient selection is biologically plausible but current data does not yet establish it as a validated predictive biomarker. Collaborative international efforts, inclusive of East Asian populations, and standardized molecular profiling of CCC at diagnosis and at relapse are critical to advancing care for patients with this challenging disease.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## Abbreviations

| | |
|---|---|
| ABC | ATP-Binding Cassette |
| ASCO | American Society of Clinical Oncology |
| CCC | Clear Cell Carcinoma |
| CTLA-4 | Cytotoxic Lymphocyte-Associated Protein 4 |
| DES | Diethylstilbestrol |
| ESGO | European Society of Gynaecological Oncology |
| ESMO | European Society for Medical Oncology |
| ICI | Immune Checkpoint Inhibitors |
| dMMR | Deficient Mismatch Repair |
| pMMR | Proficient Mismatch Repair |
| MSI-H | Microsatellite Instability-High |
| MSS | Microsatellite Stability |
| OS | Overall Survival |
| PD-1 | Programs Death-1 |
| PD-L1 | Programmed Death-Ligand 1 |
| PFS | Progression-Free Survival |
| SANRA | Scale of Assessment of Narrative Review Articles |
| SGO | Society of Gynecologic Oncology |
| TAM | Tumor-Associated Macrophage |
| TMB-H | High Mutational Burden |
| TME | Tumor Microenvironment |
| TRAEs | Treatment-Related Adverse Events |
| Treg | Regulatory T-Cell |