mesothelin, MUC16 (CA-125), and folate receptor-α. Preclinical models and early clinical experience indicate that CAR-T cells can mediate potent cytotoxicity and durable tumor control, but their efficacy in solid tumors is constrained by antigen heterogeneity, limited trafficking and persistence, and inhibitory signals from the TIME (Garlisi et al., 2024). To address these barriers, next-generation CAR-T constructs are being engineered to resist PD-1/PD-L1–mediated suppression, secrete checkpoint-blocking antibodies or cytokines, or co-target multiple antigens, and are increasingly combined with checkpoint inhibitors, anti-angiogenic agents, or chemotherapy (Gitto et al., 2024). Together, cancer vaccines and ACT exemplify how immunotherapy can be tailored to the specific antigenic and immune context of ovarian cancer, providing a mechanistic foundation for their integration into comprehensive, multimodal treatment strategies.

4 Application Strategies of Immunotherapy

4.1 Current use of immune checkpoint inhibitors as monotherapy

Immune checkpoint inhibitors (ICIs) targeting PD-1, PD-L1, and CTLA-4 have been extensively investigated as single agents in advanced and recurrent ovarian cancer, largely in phase I–III trials involving heavily pretreated populations. Overall response rates with monotherapy nivolumab, pembrolizumab, avelumab, atezolizumab, durvalumab, or ipilimumab have generally been modest, typically in the 8%-15% range, with few complete responses and no clear overall survival advantage over historical controls. Several phase III trials testing PD-1/PD-L1 inhibitors as frontline or maintenance monotherapy failed to demonstrate significant benefit, and to date, no ICI monotherapy has been approved as standard of care in ovarian cancer (Bogani et al., 2025). These disappointing outcomes contrast sharply with the transformative impact of ICIs in melanoma, lung cancer, and other solid tumors, underscoring disease-specific barriers such as a highly immunosuppressive tumor microenvironment and relatively low tumor mutational burden.

Despite limited efficacy at the population level, monotherapy studies have provided important mechanistic and translational insights that shape current application strategies. Clinical data confirm that a subset of patients, often characterized by higher PD-L1 expression, inflamed immune phenotypes, or mismatch repair deficiency, can achieve durable benefit, suggesting that more refined biomarker-driven selection may rescue the therapeutic potential of single-agent ICIs in defined niches (Ghisoni et al., 2024; Na et al., 2024). Additionally, early trials have clarified toxicity profiles, revealing largely manageable immune-related adverse events but also occasional severe colitis, pneumonitis, endocrinopathies, and rare hyper-progressive disease, which must be carefully monitored when ICIs are deployed alone or in combination. These experiences have shifted the field away from broad, unselected monotherapy use toward rationally designed regimens that embed ICIs within multimodal strategies and individualized treatment algorithms.

4.2 Combination immunotherapy with chemotherapy, targeted therapy, and radiotherapy

Given the modest activity of ICI monotherapy, a major focus has been on combinations that can recondition the tumor microenvironment and enhance antitumor immunity. Chemotherapy can increase tumor antigen release, upregulate MHC expression, and transiently deplete regulatory T cells, providing a biologic rationale for pairing platinum-taxane regimens with PD-1/PD-L1 blockade in both frontline and recurrent settings. Early signal-seeking trials suggested improved response rates with chemo-immunotherapy compared with historical chemotherapy controls, but large randomized studies have yielded heterogeneous and often disappointing results, with no consistent overall survival benefit and increased hematologic and immune-related toxicities (Bogani et al., 2025). These findings indicate that simple additive regimens may be insufficient and that timing, sequencing, and patient selection are critical to unlock synergy.

Combination strategies with targeted agents, particularly anti-angiogenic drugs and PARP inhibitors, have shown more promising activity and are now central to the evolving therapeutic landscape. Anti-VEGF therapy can normalize aberrant vasculature, improve immune-cell trafficking, and reduce myeloid-derived suppressor cell recruitment, potentially sensitizing tumors to ICIs; accordingly, regimens such as bevacizumab plus PD-1/PD-L1 inhibitors have achieved higher response rates and prolonged progression-free survival in subsets of patients, albeit with more hypertension, proteinuria, and immune toxicity. Similarly, PARP inhibitors induce DNA damage