suppressor cells. Such features are associated with poor priming and expansion of effective cytotoxic T-cell responses and with rapid restoration of immune tolerance, even when checkpoint pathways are blocked. Moreover, most clinical experience with ICIs has been in heavily pretreated, recurrent disease, where immune exhaustion and treatment-induced clonal evolution further reduce the likelihood of durable benefit. Together, these factors help explain why, to date, immunotherapy has yielded only incremental efficacy in advanced ovarian cancer.

8.2 Lack of reliable patient selection biomarkers

A central barrier to optimizing immunotherapy in advanced ovarian cancer is the absence of robust, clinically validated biomarkers that can reliably identify patients likely to benefit. While markers such as PD-L1 expression, tumor mutational burden, homologous recombination deficiency, and tumor-infiltrating lymphocytes are being actively investigated, their predictive value in ovarian cancer is inconsistent and often modest (Na et al., 2024). For example, although PD-L1 positivity and higher $CD8^+$ T-cell infiltration correlate with improved prognosis, these features have not translated into reproducible enrichment of ICI responders in large trials, and many PD-L1–positive tumors still fail to respond. Similarly, high tumor mutational burden and microsatellite instability, strong predictors of ICI benefit in other cancers, are rare in ovarian cancer, limiting their practical utility.

Recent efforts employing multi-omics approaches underscore both the promise and current limitations of biomarker-guided immunotherapy. Comprehensive reviews highlight homologous repair deficiency, PD-L1, chemokine signatures, and TIL density as key candidate biomarkers for advanced ovarian cancer, but emphasize that assay heterogeneity, dynamic biomarker changes, and intratumoral spatial variation impede standardization and validation (Na et al., 2024). Novel composite signatures, such as protein-based immune risk scores derived from integrated proteomic and transcriptomic profiling, have shown superior prognostic performance and may better stratify patients into immunotherapy-responsive versus resistant subgroups (Chen et al., 2024b). However, these models remain exploratory, often lack external validation, and are not yet ready for routine clinical use. As a result, most immunotherapy trials still enroll largely unselected populations, diluting observable benefit and slowing progress toward precision strategies.

8.3 Complex resistance mechanisms and limited evidence base

The mechanisms of primary and acquired resistance to immunotherapy in ovarian cancer are multifactorial and only partially understood. Reviews of immune resistance highlight tumor heterogeneity, low immunogenicity, defective antigen presentation, and a profoundly immunosuppressive tumor microenvironment as major contributors. Ovarian tumors often exhibit low neoantigen load, downregulation of MHC class I, and upregulation of alternative inhibitory checkpoints and metabolic suppressive pathways, all of which blunt T-cell activation despite PD-1/PD-L1 or CTLA-4 blockade. Within the microenvironment, regulatory T cells, M2 macrophages, and myeloid-derived suppressor cells secrete cytokines such as IL-10, TGF-β, and VEGF that further dampen effector function and sustain tolerance. Recent spatial-genomic data also implicate tumor-derived factors such as IL-4 in reprogramming macrophages toward tumor-supportive phenotypes and driving resistance to checkpoint inhibition (Rausch et al., 2025).

At the same time, the clinical evidence base for overcoming resistance remains limited, with most data derived from small, heterogeneous early-phase studies and retrospective analyses. Combination approaches integrating ICIs with chemotherapy, anti-angiogenic agents, PARP inhibitors, radiotherapy, vaccines, or adoptive cell therapies are being actively explored, but results to date are mixed and often show only incremental improvements in progression-free survival, accompanied by added toxicity (Kefas and Flynn, 2024). Many trials lack embedded, hypothesis-driven translational programs capable of systematically dissecting resistance pathways and validating candidate biomarkers, leading to fragmented and sometimes conflicting findings (Ghisoni et al., 2024). Consequently, while a broad conceptual framework of immune resistance in ovarian cancer has emerged, high-quality prospective data linking specific molecular or microenvironmental features to defined resistance mechanisms and tailored therapeutic strategies are still scarce. Addressing this gap will require large, integrated, and biomarker-rich clinical trials that can couple mechanistic insight with clinically meaningful endpoints.