extracellular matrix rich in cytokines, chemokines, growth factors, and metabolites (Chen et al., 2024a). Tumor-infiltrating lymphocytes (TILs), particularly $CD8^+$ cytotoxic T cells and $CD4^+$ helper T cells, are key mediators of antitumor immunity, and their presence in primary tumors or ascites correlates with improved survival, underscoring the inherent immunogenicity of epithelial ovarian cancer. Innate effectors, including natural killer (NK) cells and dendritic cells, can directly lyse tumor cells or orchestrate T-cell priming, while B cells contribute through antibody production and antigen presentation. However, chronic antigen exposure, persistent inflammation, and hypoxia progressively remodel this initially protective milieu into a protumor niche that supports immune evasion, metastatic spread, and therapy resistance (Garlisi et al., 2024).

A defining feature of advanced ovarian cancer TIME is the dominance of immunosuppressive networks that blunt effector cell function. Regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and M2-polarized tumor-associated macrophages accumulate in tumors and ascites, where they secrete IL-10, TGF-β and other mediators, downregulate antigen presentation, and inhibit cytotoxic T and NK cell activity. High densities of these suppressive cells associate with poor prognosis and reduced responsiveness to checkpoint blockade. In parallel, abnormal angiogenesis, increased interstitial fluid pressure, and extensive fibrosis impede immune-cell trafficking and reduce drug penetration, further limiting the efficacy of systemic therapies (Garlisi et al., 2024). These intertwined cellular and structural barriers help explain why single-agent immune checkpoint inhibitors have shown modest response rates in unselected ovarian cancer populations, and they provide a strong rationale for combinatorial strategies that simultaneously recondition the TIME and enhance antitumor immunity.

3.2 Immune checkpoint pathways: PD-1/PD-L1 and CTLA-4

The programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis is a central inhibitory pathway exploited by ovarian tumors to escape immune surveillance. PD-1 is an inhibitory receptor expressed on activated $CD4^+$ and $CD8^+$ T cells, B cells, and some innate lymphoid cells; its ligands PD-L1 and PD-L2 are upregulated on tumor cells, tumor-associated macrophages, dendritic cells, and other stromal elements within the TIME. Engagement of PD-1 by PD-L1 recruits phosphatases that dephosphorylate proximal T-cell receptor (TCR) signaling molecules, attenuating PI3K/AKT and RAS/ERK pathways, thereby inducing T-cell exhaustion, reducing cytokine secretion, and promoting apoptosis of effector cells (Lin et al., 2024). In ovarian cancer, PD-L1 expression is frequently observed on immune cells and, to a lesser extent, tumor cells, and can be induced by inflammatory cytokines such as IFN-γ, linking adaptive immune resistance to local immune activation (Garlisi et al., 2024). Antibodies targeting PD-1 or PD-L1 restore effector function and have revolutionized the treatment of several solid tumors, but in ovarian cancer their activity has generally been limited by the strongly suppressive microenvironment and low baseline T-cell infiltration (Chen et al., 2024a).

CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) represents a complementary checkpoint that regulates earlier stages of T-cell activation, primarily within lymphoid organs. CTLA-4 is expressed on activated conventional T cells and constitutively on Tregs, where it competes with the costimulatory receptor CD28 for binding to CD80/CD86 on antigen-presenting cells (APCs) with much higher affinity, thereby dampening the second signal required for full T-cell activation. CTLA-4 engagement transduces inhibitory signals and promotes trans-endocytosis of CD80/CD86 from APCs, globally reducing their ability to costimulate naïve and memory T cells and enhancing Treg-mediated suppression. In ovarian cancer, CTLA-4 contributes to defective priming and expansion of tumor-reactive T cells and to the maintenance of an expanded intratumoral Treg compartment. Dual blockade of PD-1/PD-L1 and CTLA-4 can synergistically reinvigorate exhausted effector cells and deplete or functionally inhibit Tregs, but at the cost of increased immune-related toxicities, and clinical trials in ovarian cancer have so far produced modest and heterogeneous benefits, underscoring the need for rational combinations and biomarkers to identify likely responders (Figure 1) (Chen et al., 2024a; Garlisi et al., 2024).

3.3 Cancer vaccines and cell-based immunotherapies

Beyond checkpoint blockade, several active and adoptive immunotherapy strategies are being developed to exploit the immunogenicity of ovarian cancer. Cancer vaccines aim to prime or boost tumor-specific T-cell responses by presenting tumor-associated antigens (TAAs) or neoantigens in an immunostimulatory context, often