PD-1/PD-L1 trials showed no significant PFS benefit and, by extension, no convincing OS advantage in the overall or PD-L1-positive populations, highlighting a disconnect between mechanistic rationale and realized clinical benefit (Vida et al., 2025). Broad reviews of ICI experience in ovarian cancer similarly conclude that, while some regimens achieve encouraging disease control and prolonged remission in small subsets of patients, robust and consistent OS improvements across trial populations remain elusive (Ghisoni et al., 2024). This pattern reflects both the immunologically "cold" nature of many ovarian tumors and the dominance of competing resistance mechanisms that blunt durable immune control.

Nevertheless, specific combination strategies and immunophenotypically enriched cohorts show signals of meaningful survival benefit that inform ongoing development. Maintenance triplets integrating anti-angiogenic therapy, PARP inhibition, and PD-L1 blockade have prolonged PFS compared with bevacizumab-based standards in selected biomarker-defined groups, suggesting a path toward incremental survival improvement when immune therapy is used as part of rationally designed, biology-driven regimens (Bogani et al., 2025). Moreover, innovative multi-immunotherapy approaches, such as the phase II regimen of pembrolizumab plus bevacizumab and metronomic cyclophosphamide, have reported a median PFS of 10.2 months and a 47.5% objective response rate in heavily pretreated recurrent ovarian cancer, with a subset achieving disease control beyond one year, hinting at the possibility of durable clinical benefit in carefully selected patients (Rosario et al., 2024). Overall, current evidence supports a nuanced view: survival gains from immunotherapy in advanced ovarian cancer are modest and context-dependent at present, but rational combinations and precision immunophenotyping are beginning to delineate scenarios in which clinically meaningful benefit can be achieved.

7 Safety and Adverse Reactions

7.1 Types and manifestations of immune-related adverse events

Immune checkpoint inhibitors (ICIs) trigger a characteristic spectrum of immune-related adverse events (irAEs) that differ fundamentally from cytotoxic chemotherapy toxicities. The most frequently involved organs are skin (rash, pruritus), gastrointestinal tract (diarrhea, colitis), endocrine glands (thyroiditis, hypophysitis, adrenal insufficiency), lung (pneumonitis), liver (hepatitis), and musculoskeletal system (arthritis, myositis), whereas neurologic, cardiac, renal, hematologic, and ophthalmologic irAEs are less common but potentially life-threatening. Incidence and pattern vary by drug class: CTLA-4 blockade is more strongly associated with high-grade gastrointestinal and dermatologic toxicity, while PD-1/PD-L1 inhibitors more often produce thyroid dysfunction, pneumonitis, and rheumatologic manifestations (Casagrande et al., 2024). Overall, most irAEs are grade 1-2, but grade 3-4 events occur in a relevant minority, and treatment-related mortality is reported in up to ~2% of patients, depending on agent and regimen.

Gynecologic oncology cohorts illustrate these patterns in the ovarian cancer population. In a retrospective series of 61 patients with gynecologic malignancies (including ovarian cancer) treated with ICIs, 32.8% developed at least one irAE; hypothyroidism was the most common event, followed by hepatitis and colitis, and nearly half of irAEs were grade 3-4, though they were generally manageable with standard interventions. Median time to irAE onset was about 24 weeks, underscoring the delayed and sometimes prolonged course of toxicity compared with chemotherapy (Shehaj et al., 2024). Across tumor types, cutaneous, gastrointestinal, and endocrine toxicities frequently appear early, whereas some neurologic, cardiac, and rheumatologic irAEs may present late and with nonspecific symptoms, complicating diagnosis (Casagrande et al., 2024). These observations highlight the need for sustained vigilance throughout the entire course of immunotherapy, including maintenance and combination phases commonly used in advanced ovarian cancer.

7.2 Safety risks in combination immunotherapy strategies

As combination strategies gain prominence in advanced ovarian cancer, safety profiles become more complex. Dual checkpoint blockade (e.g., PD-1 plus CTLA-4 inhibition) typically increases both the incidence and severity of irAEs compared with monotherapy, with higher rates of high-grade colitis, hepatitis, dermatitis, and endocrinopathies reported across solid tumors (Casagrande et al., 2024). In addition, combining ICIs with agents such as PARP inhibitors, anti-angiogenic drugs, or chemotherapy, common in ovarian cancer regimens, may