exacerbate overlapping toxicities (myelosuppression, diarrhea, fatigue, hepatic injury) and make it challenging to distinguish immune-mediated events from drug-specific adverse effects. These overlapping patterns can delay correct diagnosis and appropriate immunosuppressive treatment if clinicians attribute symptoms solely to cytotoxic or targeted agents.

Meta-analytic data across multiple tumor indications show that adding ICIs to chemotherapy increases the risk of all-grade adverse events (relative risk~1.11) and serious (grade ≥3) events (relative risk~1.16), particularly high-grade diarrhea, dyspnea, fatigue, rash, and elevated liver enzymes, although treatment-related mortality is not substantially increased compared with chemotherapy alone (Rached et al., 2024). In gynecologic malignancies, a single-center analysis found that the duration of ICI exposure, rather than use of combination regimens per se, was the main predictor of irAE occurrence, suggesting a cumulative immune-stimulatory burden (Shehaj et al., 2024). For ovarian cancer specifically, systematic reviews note that ICI-based combinations can improve efficacy but at the cost of a "worse safety profile," reinforcing the need to balance modest survival gains against heightened toxicity when designing and selecting combination strategies.

7.3 Monitoring and management strategies

Effective management of irAEs in advanced ovarian cancer relies on early recognition, standardized grading, and prompt initiation of immunosuppression when appropriate. Major oncology societies, including ASCO and SITC, recommend organ-specific algorithms built on common principles: continue ICI with close observation for most grade 1 toxicities (except select neurologic, hematologic, and cardiac events), hold treatment for grade 2 events with consideration of low- to moderate-dose corticosteroids, and suspend ICIs with initiation of high-dose systemic steroids (prednisone or methylprednisolone 1-2 mg/kg/day) for grade 3 toxicities. Grade 4 events usually mandate permanent discontinuation, except for endocrine irAEs that can be controlled with hormone replacement. Steroid tapers should extend over at least 4-6 weeks to minimize relapse; steroid-refractory cases should prompt the use of additional immunosuppressants such as infliximab, mycophenolate mofetil, or other agents, depending on the affected organ.

Given the broad organ spectrum and often subtle onset of irAEs, structured monitoring programs are critical for patients receiving immunotherapy as part of comprehensive treatment for ovarian cancer. Consensus guidelines emphasize baseline assessment (history of autoimmunity, organ function tests, endocrine panels), regular interval monitoring of blood counts, liver enzymes, renal function, thyroid tests, and glucose, as well as low thresholds for imaging and subspecialty referral when new symptoms arise. Multidisciplinary toxicity teams involving oncologists, endocrinologists, gastroenterologists, pulmonologists, cardiologists, and rheumatologists are recommended to optimize diagnosis and management, particularly for rare or overlapping syndromes such as myositis-myocarditis-myasthenia gravis complexes. Patient education about early warning symptoms (diarrhea, dyspnea, palpitations, visual changes, severe fatigue) and clear pathways for rapid evaluation can reduce the risk of severe or fatal outcomes while allowing continuation of efficacious immunotherapy whenever safely possible.

8 Problems and Challenges

8.1 Limited overall response to immunotherapy

Despite a compelling biological rationale, the clinical response rate to immune checkpoint inhibitors in ovarian cancer remains low, especially with PD-1/PD-L1 monotherapy. Across early- and late-phase trials, objective response rates typically range around 8%-15% in unselected advanced or platinum-resistant populations, with no consistent survival advantage compared with standard therapies. A recent synthesis of 20 ICI trials in advanced ovarian cancer reported no improvement in overall survival and only modest gains in response when ICIs were added to chemotherapy, anti-angiogenic agents, or PARP inhibitors, emphasizing that immunotherapy has not yet altered the standard of care in this disease. These disappointing results contrast sharply with the transformative impact of ICIs in melanoma and lung cancer, underscoring intrinsic disease-specific barriers.

The "cold tumor" phenotype of many ovarian cancers contributes substantially to these limited responses. Ovarian tumors frequently display low tumor mutational burden, sparse tumor-infiltrating lymphocytes, and an immunosuppressive microenvironment dominated by regulatory T cells, M2 macrophages, and myeloid-derived