# The prognostic role of immune infiltrate in metastatic ovarian carcinoma and its implication for immunotherapy

Despite advances in diagnostics and modern oncological treatment, high-grade serous ovarian carcinoma (HGSOC) remains the leading cause of mortality among gynecologic malignancies. Both tumor genomics and the level of anti-tumor immunity influence HGSOC prognosis. High levels of immunosuppression within the tumor microenvironment (TME) promote tumor growth, facilitate metastatic spread, and contribute to an overall poor prognosis. Compared to immunologically active tumors, ovarian carcinoma, including HGSOC, exhibits a limited response to immunotherapy, largely attributed to its low tumor mutational burden and active immunosuppression, despite baseline infiltration of CD8+ T cells. Therefore, a deeper understanding of the immune system's role and the biological processes leading to antitumor immunity exhaustion is essential for the development of novel therapeutic strategies for this highly aggressive oncological disease.

This dissertation demonstrates that immune composition in both primary and metastatic tumor sites significantly impacts the prognosis of HGSOC patients. Particularly, M2-like tumor-associated macrophages constitute a myeloid immune population responsible for the active immunosuppression within metastatic HGSOC. Although antitumor immunity develops primarily in secondary lymphoid organs, the presence of intratumoral tertiary lymphoid structures (TLS) supports the differentiation of effector T and B lymphocytes. A higher TLS density in TME correlates not only with improved prognosis but also with an enhanced response to immunotherapy. However, mature TLS form in only a limited number of HGSOC cases, which may contribute to the limited efficacy of immunotherapy in this malignancy. Preclinical findings suggest that neoadjuvant chemotherapy in HGSOC positively modulates immune infiltration and promotes TLS formation and maturation. Therefore, optimizing the administration schedules of conventional chemotherapy may enhance the response to immunotherapeutic treatment. Despite recent therapeutic advances, there remains a significant need for the development of alternative targeted therapies and immunotherapies in HGSOC. In line with this, autologous dendritic cell-based therapy (DCVAC) has been tested in advanced clinical trials in patients with epithelial ovarian carcinoma (EOC) (NCT02107937; NCT02107950). DCVAC has been demonstrated to be safe and significantly prolong the time to relapse in EOC patients. Based on additional immune profiling of patients randomized in the above-mentioned clinical trials, DCVAC provides a statistically significant clinical benefit to patients with immunologically cold tumors. These responses were accompanied by improved effector functions in patients with lower levels of circulating and intratumoral immunosuppression, thus facilitating the activation of a DCVAC-mediated clinically relevant antitumor immune response.

This dissertation expands our understanding of the dynamics of antitumor immunity in both primary and metastatic HGSOC lesions in the context of current oncological treatment standards and contributes to the development of novel approaches for personalized cancer therapy.

**Keywords:** ovarian carcinoma, antitumor immunity, immunotherapy, tertiary lymphoid structures, neoadjuvant chemotherapy, immune checkpoint inhibitors