SAKK 16/18: Immune-modulatory radiotherapy to enhance the effects of neo-adjuvant PD-L1 blockade after neo-adjuvant chemotherapy in patients with resectable stage III (N2) non-small cell lung cancer (NSCLC). A multicenter phase II trial

Project

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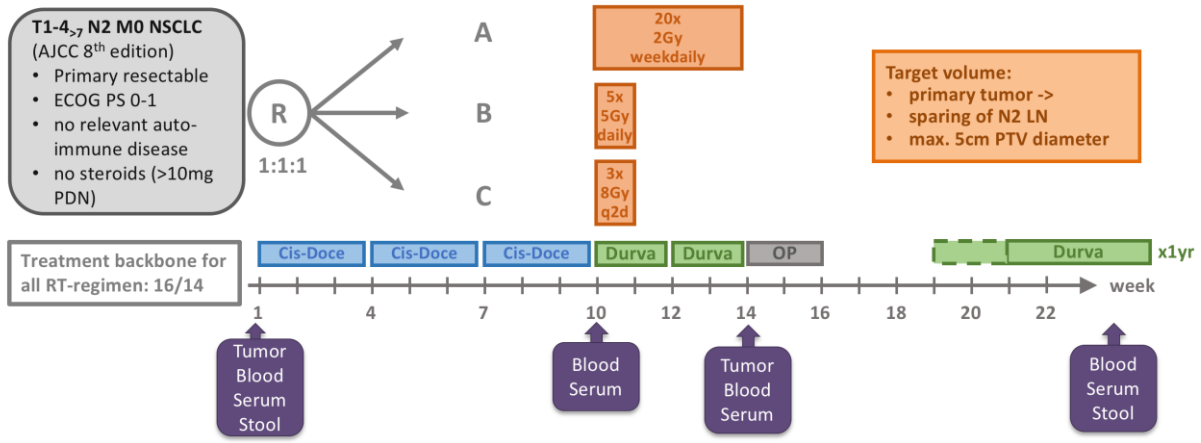
The research project described here is the translational part of the clinical study SAKK 16/18, sponsored by the Swiss Group for Clinical Cancer Research (SAKK). The study investigates the role of immune-modulatory radiotherapy in combination with the anti-PD-L1 inhibitor durvalumab in the neoadjuvant setting in patients with locally advanced-stage non-small cell lung cancer (NSCLC stage IIIA (N2)). Through various studies, the SAKK has made relevant contributions to the establishment of standard therapies in this disease setting over the last decades. The SAKK 16/14 study has achieved a significant improvement of these results by adding perioperative immunotherapy with the anti-PD-L1 inhibitor durvalumab. The SAKK 16/18 study was initiated a few months ago, based on these results, and will include 90 patients.



Our current trial is so far among the first trials worldwide investigating the therapeutic efficacy of PD-L1 inhibition combined with immune-modulatory radiotherapy in a neoadjuvant setting. In addition to enabling the testing of the trial hypothesis regarding the improvement of the cure rate, the neoadjuvant use of the anti-PD-L1 antibody durvalumab combined with immune-modulatory radiotherapy allows for extensive translational research by dissecting immunological changes within the tumor microenvironment before and after treatment. We here aim for a deeper understanding of the *in vivo* mechanisms in NSCLC patients treated with durvalumab in combination with immune-modulatory radiotherapy, in order to better characterize the possible immunomodulating property of irradiation and to investigate possible resistance mechanisms.

This trial is unique and highly innovative: immune checkpoint inhibitors combined with immune-modulatory radiotherapy have so far been investigated only in preclinical, and early and small clinical studies in the metastatic disease setting, in which surgical resection of the tumor plays no role and tumor tissue is rare. Furthermore, the available tissue does not necessarily reflect the composition of the tumor microenvironment at the time point of immune checkpoint inhibition, as tumor biopsies are usually performed only once, at the time of diagnosis of the metastatic disease. Taking advantage of these unique tumor resections, we will apply high-throughput RNA sequencing, quantitative gene expression analysis, and multidimensional immune profiling of single cells, using mass cytometry and multi-color immunohistochemistry, to comprehensively analyze the cancer immunome, i.e. the highly complex and diverse network of cancer-infiltrating immune cell subsets, following immune checkpoint inhibition. We surmise that a holistic picture of the complex dynamics of the tumor-immune interactions upon treatment is required 1) to unravel the underlying molecular as well as immunological mechanisms of immune checkpoint inhibition in combination with immune-modulatory radiotherapy, and 2) to provide an accurate immunological definition of changes in the tumor microenvironment. This knowledge is clearly needed to optimally implement these new agents in the armamentarium of oncological therapies. The results of our project should help in the designing of new clinical trials with immune checkpoint inhibitors and immune-modulatory radiotherapy for the benefit of our patients.