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Clinical development of CTLA-4 targeted immunotherapy of cancer

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To enhance anti-tumour immune response by targeting some receptors expressed on T-lymphocytes that are involved in the mechanism of tolerance, it's an interesting and innovative approach for the treatment of cancer. Among these new immunotherapies there are monoclonal antibodies which block the cytotoxic T lymphocyte- associated antigen-4 (CTLA-4). CTLA-4 is a key negative regulator of T cell activation and antibodies anti-CTLA4 potentiate the T-cell response against tumour.

Two studies using ipilimumab, an anti-CTLA-4 monoclonal antibody, demonstrated improvements in overall survival in the treatment of advanced melanoma. These studies utilized two different schedules of treatment in different patient categories (first and second line of treatment). However, the results were quite similar despite of different dosage used and the combination with dacarbazine in the first line treatment. Anti-CTLA-4 antibody therapy represents the start of a new era in the treatment of advanced melanoma but we are on the steep slope of the learning curve toward the optimization of their utilization either a single agents or in combination.

Over the last few years, through numerous clinical trials and real-world experience, we have accumulated a large amount of evidence regarding the potential for long-term survival with anti-CTLA-4 agents in various types of malignancy. The results of these studies have also highlighted a number of recurring observations with immuno-oncology agents, including their potential for clinical application across a broad patient population and for both conventional and unconventional response patterns. Furthermore, given the numerous immune checkpoints that exist and the multiple mechanisms used by tumours to escape the immune system, targeting distinct checkpoint pathways using combination approaches is an attractive therapeutic strategy with the potential to further enhance the antitumour immune response. Of course combination could also mean sequential rather than concomitant treatment. Currently, data on sequential therapy in cancer patients are limited.

The next challenge for cancer therapy will be to optimize the treatment of patients on the basis of their individual genetic signature or immunoprofiling. This may involve using new agents in combination, either sequentially or concomitantly, and/or together with traditional anti-cancer modalities such as chemotherapy, radiation or surgery.