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Immunotherapy of pancreatic cancer—weal and woe

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We appreciated reading the commentary "Pancreatic ductal adenocarcinoma—a new hope?" of Irving and Lobo (1) on our recent paper in the *British Journal of Cancer* (2). Indeed, pancreatic ductal adenocarcinoma (PDAC) is one of the deadliest cancers in the world. At present, only multimodal treatment including surgical resection can prolong survival of patients with this disease (3). Therefore, new therapeutic approaches against PDAC are urgently needed. One new option is to apply immunotherapy for these patients. Immunotherapy possesses a bright spectrum of approaches: (I) passive immunotherapy includes a treatment of patients with monoclonal antibodies (specific immunotherapy) or checkpoint inhibitors (non-specific immunotherapy); (II) cancer vaccines and cellular therapy belong to the active immunotherapy as well as interferon treatment (non-specific immunotherapy).

For R0/R1 resected PDAC patients a non-specific immunotherapy with interferon α (IFN) in combination with chemoradiotherapy (5-fluorourocil and beam radiation) was applied adjuvantly in a randomized phase III CapRI trial (4). However, the IFN addition to chemoradiation did not prolong survival in these patients. Therefore, the non-specific stimulation with IFN cannot be suggested for the adjuvant therapy of PDAC patients. However, since some patients from the CapRI trial showed a very good survival in arms, the experimental as well as the control arm, we made an attempt to identify possible immunological predictive and prognostic biomarkers for the CapRI cohort. Our preliminary data demonstrated that some immunological parameters (i.e., immune cells, functionality of the cells, cytokines and other) could indeed serve as potential biomarkers (2). We agree with Irving and Lobo that further evaluation of these parameters should include a multifactorial analysis to make a fundament for deeper investigation of these markers in future prospective clinical trials.

It remains an important task to identify a subgroup of patients who could profit from IFN-therapy. It would be ideal, if a simple blood test could help to identify such responders at the beginning of the therapy. By this non-responders could avoid IFN-medication including its side effects.

Nowadays, it becomes clear that the immunosuppressive environment established by a tumor play a decisive role in the development of cancer and the response to therapy. Especially in PDAC, quickly established immunosuppression can be found on cellular, molecular and mediator level and immune activation could be decelerated by immunosuppressive mechanisms (5). We believe that new approaches including inhibition of immune checkpoint molecules (i.e., CTLA-4, PD-1, PD-L1 and others) and inhibition of suppressive cellular compartments (i.e., MDSC, Treg) are promising treatments for PDAC. Additionally, it should be recognized that immune stimulating agents including IFN can not only be limited to their immunosuppressive effects. Thus, both additional stimulation of the immune system and the interference with tumor induced suppression should be considered in order to improve PDAC anti-tumor responses.

Thus, new therapies combining activation of immune system (like IFN) and inhibition of immunosuppression should be investigated in future. Consequently, the exploration of immunological biomarkers in cancer therapy remains an important field of clinical research. It may

allow the identification of patients who will profit from personalized medication and provide new impulse for establishing new combinatory treatments. Future concepts for PDAC immunotherapy need to be designed, but further understanding of the complexity of the immune network as well as the interaction of the immune system and PDAC are required.

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