Immunotherapy revisited

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Immunotherapy has revolutionized cancer treatment during the last few years. Impressive long-term survival rates (beyond 5 years) even in deadly diseases such as metastatic lung cancer or malignant melanoma were achieved by checkpoint inhibitor (CPI) therapy.

For melanoma patients a 5-year overall survival (OS) rate of 52% was reported upon administration of dual CPI therapy with ipilimumab plus nivolumab [4]. Despite promising outcomes in this setting, it is evident that a considerable number of patients do not benefit from this approach and novel immunoncological concepts beyond established/approved programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibition are needed.

Fortunately, intensive research discovered and suggested promising immunomodulatory T-cell or immune–microenvironment directed targets. In their article Dr. Zila, Prof. Hoeller and Prof. Paulitschke provide an overview about the most relevant strategies to overcome primary or acquired resistance to PD-1/CTLA-4 CPI in melanoma patients. They comprehensively summarize preclinical and clinical data on the efficacy of both novel CPI (including T-cell immunoglobulin and mucin-domain containing-3 [TIM-3], Lymphocyte-activation gene 3 [LAG-3] or T cell immunoreceptor with Ig and ITIM domains [TIGIT]) and activators of costimulatory pathways such as OX-40 or glucocorticoid-induced tumor necrosis factor receptor (GITR). In addition, Zila et al. address the challenges we faced modulating

the immune microenvironment by IDO inhibitors and discuss recent developments on intratumoral immunotherapy by STING agonists [1].

Immunotherapy, however, does not only comprise T-cell and immune microenvironment targeted agents, but also adoptive T cell therapy utilizing engineered chimeric antigen receptors (CAR). Positive clinical trials in heavily pretreated patients suffering from B-cell malignancies led to the approval of CAR-T cell therapy both in the US and in Europe. Long-term data from the ZUMA-1 study, for instance, showed durable responses and a median overall survival (OS) of 25.2 months with single infusion axicabtagene-ciloleucel in patients suffering from refractory large B-cell lymphomas [5].

Unfortunately, the success of CAR-T cell therapy in hematological malignancies could not be replicated in solid tumors so far. In their manuscript Drs. Umut, Gottschlich, Endres and Prof. Kobold outline the current developments and limitations of CAR-T cell therapy in solid tumors [2]. Most notably, the authors state that there are three predominant hurdles for CAR-T cell therapy in solid tumors (i.e., trafficking of T-cells into the tumor tissue, tumor cell recognition and the hostile tumor microenvironment).

Irrespective of the distinct immunotherapy administered, identification of a predictive biomarker for patient selection is highly desirable. Although PD-L1 expression on tumor or immune cells is considered as a biomarker for CPI response, the predictive value is limited. Since PD-L1-negative patients eventually respond to CPI therapy as well, multiple antibody clones are utilized and cut-off values vary between the different studies, the employment of PDL-1 as a biomarker is far from optimal [6]. Thus, alternative biomarkers such as tumor mutational burden or mismatch repair deficiency have been developed. A novel exciting approach as a potential biomarker for immunotherapy

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response might be the profiling of the deoxyribonucleic acid (DNA) methylation pattern. In his article Prof. Heller describes the molecular rationale and the potential role of epigenetic factors as a biomarker in this setting. In addition, he critically reviews the current clinical data supporting this approach [3].

Overall, this series of articles provides an update about the recent developments in the immuno-oncological field and addresses the most relevant unresolved questions. We want to thank the experts for their valuable contribution.

Conflict of interest T. Füreder declares the following. Honoraria: MSD, MerckDarmstadt; Amgen, Roche, BMS; Böhringer Ingelheim; Pfizer.

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