Editorial

A phase I study of MEDI4736, NNT-PD-L1 antibody in patients with advanced solid tumors

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Abstract: A review and critical consideration of immunotherapeutical concepts in non-small cell lung cancer (NSCLC) is given. Nivolumab represents a promising option in various malignancies with more results exceeding treatment of metastatic malignant melanoma eagerly awaited.

Keywords: Immunotherapy; lung cancer; nivolumab

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Our concept on the emergence and persistence of tumor cells multiplying in an uncontrolled way to become a threatening accumulation of malignant cells visible upon various detection methods has changed quite considerably during the last two decades. Whereas tumors have been primarily thought of as an accumulation of malignant cells proliferating due to molecularly relevant signals to invade vessels and thus spread to distant organs bringing to them malignancy-associated destructive potential, we have recently recognized that tumor cell growth, multiplication and spread is under the influence of the surrounding stroma (1). Tumor cells and the surrounding stroma cells are in close interaction by their *vice versa* influence upon their behaviour by the help of a series of messengers including cytokines, stroma-cell derived products and growth factors for so divergent cellular compounds as endothelial cells, fibroblasts, osteoclasts or immunocompetent cells (1). It is the latter aspect which has generated considerable hope following the discovery and description (2-5) followed by proof of the clinical efficacy of immune checkpoint inhibitors in cancer (6,7). With CTLA4 being the first such immune checkpoint inhibitor and having proved its potential to modulate the disease course in patient with metastatic malignant melanoma (6) and perhaps also in those with non-small lung cancer of squamous cell histology by the anti-CTLA-4 antibody ipililumab (8), the search continued for further compounds targeting tumour-mediated immunosuppression. A major step forward was achieved by the discovery of the induction of T-cell suppression via PD-1 activated by the tumor-cell associated ligand PD-L1 (9). This discovery started the clinical development of antibodies directed against PD-1 or PD-L1 for the use in humans with cancer. The anti-PD-1 antibody nivolumab proved to be effective in patients with malignant melanoma both as monotherapy (10) as well as in combination with ipililumab (11) proving clinically the correctness of the assumption generated by preclinical data.

In the midst of these developments, the study on MEDI4736, an anti-PD-L1 antibody was presented by Lutzky and co-workers at the Annual Meeting of American Society of Clinical Oncology (12). The authors reported on the effect of the human anti-PD-L-1 antibody which prevents binding to PD-1 and CD-80. Within this phase I trial, MEDI4736 was administered i.v. every 2 or 3 weeks in a 3+3 dose escalation in 26 patients with various malignancies. Treatment-related adverse events occurred in 34% of all patients, but—similarly to studies on nivolumab—with a remarkably limited toxicity of grades 1 to 2. Side effects consisted mainly of diarrhoea, fatigue, rash and vomiting. It is noteworthy that particularly autoimmune

phenomena were not induced by the antibody which is in contrast to reports on the toxicity of ipililumab (6). MEDI4736 proved to be clinically effective by inducing four partial remissions and five additional minor responses. These occurred not only in melanoma, but even more so in patients with non-small cell lung cancer (NSCLC) further igniting interest in the use of immune checkpoint inhibitors in this disease with phase III trials on nivolumab in NSCLC are under way and awaited with great interest. Moreover, disease control rate was obtained in almost half of the patients with a durable decrease in tumor size. Thus, the current report corroborates and expands previous observations on the clinical importance of PD-1 and PD-L1 and the therapeutic efficacy of their inhibition. Thus, interventions aiming at a modulation in immune regulation resulting in an increase in T-cell activity by reducing tumor-cell-induced immunosuppression seem more and more to constitute a viable and important concept the results of which will be reported in the very near future and are eagerly awaited. Compounds targeting PD-1 including Nivolumab and Pembrolizumab as well as PD-L1 including MEDI4736, BMS-936559 and MPDL3280A have presented with impressive efficacy and are thus under development in phase I to III studies which will be presented to us in the not too distant future. Thus, the present abstract on the clinical efficacy of MEDI4736 is one more part of the fascinating puzzle successfully linking the immune system to the clinical control of malignant processes.

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