

Cancer Treatment in the Checkpoint Inhibitor Era

Ghazaleh Shoja E Razavi*

Department of Clinical Development- Oncology and Respiratory, Global Allied Pharmaceutical, 160 Vista Oak Dr. Longwood, FL 32779, USA

*Corresponding author: Ghazaleh Shoja E Razavi, Department of Clinical Development- Oncology and Respiratory, Global Allied Pharmaceutical, 160 Vista Oak Dr. Longwood, FL 32779, USA, Tel: 1+ 416-520-8835; E-mail: ghazal966@gmail.com

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Editorial

Cross talk between antigen presenting cells, effector T cells and immune regulatory cells through co-stimulatory and inhibitory signals orchestrates the anti-tumor immune response that eventuates in either the effective tumor directed immune activity leading to the tumor removal or an immune suppressed tumor microenvironment leading to the tumor progression and metastasis. The co-stimulatory signals have been shown to be mediated by CD28 and members of the tumor necrosis factor receptor (TNFR) family, such as CD40, OX-40, 4-1BB, CD30, and CD27, while the regulatory signals are generally mediated through cytotoxic T lymphocyte activator-4 (CTLA-4) and programmed death -1 (PD-1) receptors that share structural homology with the CD28 co-stimulatory class and also bind to the B7 family members. Despite the observed similarities in their structure and receptors, CTLA-4 and PD-1 show the main regulatory role and considered as checkpoints. Targeting these co-stimulatory or inhibitory receptors with either stimulating or blocking antibodies may lead to the enhanced immune response within tumor microenvironment and clinical benefits.

Successful treatment of tumors with primary resistance to conventional chemotherapy and radiation, such as melanoma in advanced and metastatic setting with CTLA-4 and PD-1 targeted monoclonal antibodies and the encouraging results of checkpoint inhibitors in the treatment of non-small cell lung cancer and renal cell carcinoma have led to more than 2000 ongoing clinical studies addressing safety and efficacy of these classes of monoclonal antibodies in a wide range of solid tumors and hematologic malignancies either alone or combined with other therapeutic options from conventional chemotherapy and radiation to other members of the checkpoint inhibitor family, small molecule kinase inhibitors and even cancer vaccines. These combination treatment modalities may demonstrate synergic anti-tumor effect beyond their specific therapeutic effects. One of the proposed mechanisms for this synergic effect is the increased load of tumor associated antigens within tumor microenvironment that results from accumulation of the dead tumor cells in response to the treatment [1]. The conventional chemotherapy may also change the population of the immune cells within tumor stroma in favor of effector T cells rather than regulatory T cells (T reg) and myeloid derived suppressor cells (MDSCs) that have been recognized as the main immune suppressive cells within tumor microenvironment [2]. Moreover, the small molecule kinase inhibitors may influence the activation, survival and apoptosis of the effector T cells in a different way compared to the MDSCs and T regs. Hence, selected kinase inhibitors may change the immune microenvironment by increasing the immune stimulating populations rather than the number of the immune suppressive cells [3].

Unlike conventional treatment and small molecule targeted therapies in which the therapeutic response may present shortly after

the treatment, the maximum therapeutic effects of these immune checkpoint inhibitors are yet to be determined in long term follow up of those patients receiving them. A recent update on the phase I clinical study in metastatic melanoma patients receiving PD-1 inhibitor nivolumab by Hodi et al. has shown the five-year overall survival of 34% that is considered a significant survival benefit in this group of patients [4]. Similarly, long term follow-up of melanoma patients receiving CTLA-4 directed monoclonal antibody ipilimumab alone or combined with other immunotherapies in a phase III clinical trial has shown the two-year overall survival rate of 20% while 45% of the patients who survived up to 2 years were still alive at 3 years [5]. This long term survival benefit, observed in patients treated with checkpoint inhibitors may suggest that the therapeutic effects of this class of drugs is not limited to those observed in short term clinical studies. The anti-tumor immune response that is activated within tumor microenvironment through checkpoint inhibitors, may re-establish the tumor-immune response equilibrium and keep the tumor in a stable, non-progressive status. Moreover, this long term overall survival may suggest the possibility of successful reintroduction of the previously administered lines of the treatment, later in the course of the disease in selected groups of the patients. Taken together, successful introduction of checkpoint inhibitors into cancer treatment may be considered as a new era in cancer treatment. Growing knowledge on tumor induced activation of the immune system and recognizing the effector and regulatory T cells and their interaction within tumor microenvironment suggests the immunotherapy as a potent treatment option, capable of inducing long term anti-tumor immune response. Checkpoint inhibitors play a major role to keep this immune response active and tumor-oriented. Synergic effects are expected while combining checkpoint inhibitors with other available anti-tumor modalities. However, the optimal clinical setting, selection of the best available treatment combination, as well as the duration of the treatment and questions that needs to be answered through further studies.

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