

The recent years have witnessed at least two tremendous steps forward in the war against lung cancer: the identification of oncogene-addiction as a key to precisely target an extremely featured population of patients and the ‘renaissance’ of immunotherapy, which, after years of none or moderate clinical advances, has significantly revolutioned the way to unblock and trigger the innate immune response. Both innovations allow clinicians to offer to patients affected by such disease a life-expectancy which nowadays in many cases differs from what the very same doctors have experienced and they have been used to discuss with patients and families no longer than 5-10 years ago.

Why that happens this way and now? On one hand, brilliant and brave investigators significantly contributed to science by characterizing human and cancer genomes, tracking those bio-molecular pathways which have been demonstrated to dysregulate normal cells’ homeostasis and to drive tumor transformation and proliferation; concurrently, a series of smart scientists focused upon what did happen around tumor cells and how the surrounding microenvironment interplay with such pathological process with the final result to not reject that.

In this regard, the discovery of the interaction between PD1 and PD-L1 at the immune-checkpoint as the key-block inducing immune cancer tolerance, indicated to develop monoclonal antibodies specifically engineered to disrupt this binding, thus allowing immune reaction cascade to start and face the tumor. From the clinical standpoint, these antibodies have demonstrated to work in a series of tumors and settings where previously no major advances were reported in the latest 15 years, such as non-small-cell lung cancer, with a particular regard to squamous histology.

A critical finding of this way to unravel the tumor immune escape was that the benefit of these drugs did not significantly impact upon traditional intermediate end-points (such as progression-free-survival, response rate), while the overall survival was significantly improved, with a characteristic long-term effect. In addition, the unique biomarker able to maximize the benefit of antibodies targeting PD1/PD-L1 was PD-L1 overexpression, although it did not entirely allow to identify all potentially sensitive patients (i.e. a series of negative patients did respond to immunotherapy as well). As expected, translational and basic research with innovative technologies has arrived to help to solve this crucial issue, by suggesting a potential role of other key-players in activating immune response, such as the mutational and neoantigen load, which both represent today a new research frontier with fascinating implications.

All these reasons leave to clinical and translational research a series of major challenge for the forthcoming years, such as the optimization of PD-L1 as a selection factor, the identification of additional biomarkers beyond PD-L1 (mutational and neoantigen load), the development of more reliable preclinical model able to specifically derive hypotheses for clinical research for drugs targeting the tumor-host microenvironment, and the development of clinical trials plans with methodological tools specifically tailored to how immunotherapy impact upon the patients’ prognosis.

With this intent, I am sincerely honoured to serve as a Co-Editor of this special issue, whereas international experts and opinion leaders in lung cancer research who are dedicating their career to clinical and translational research have been asked to report their personal views and perspectives on a series of given topic according to their skilled expertise. What clearly emerges for readers is a model of team-work, where the collaboration as a network of different professionals (such as basic and translational scientists, pathologists, immunologists, clinicians, methodologists) may pave the way to further improve clinical opportunities for lung cancer patients in the very near future.



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