

Immunotherapy for lung cancer

This issue of *Translational Lung Cancer Research (TLCR)* focuses on advances in lung cancer immunotherapy. Lung cancer has traditionally been considered to be an immune resistant disease. However, great advances have been made in recent years in the field of immunotherapy for solid tumors (1) and today there are several approved drugs available which modulate the immune response (1).

A large number of studies have demonstrated how T-cell exhaustion is central in the clinical evolution of chronic viral infections such as HIV, as well as cancer (2-4). Patients with chronic viral infections or cancer often display weak T-cell reactivity, a state of 'exhaustion' characterized by poor effector cytotoxic activity, impaired cytokine production and sustained expression of multiple inhibitory receptors, such as programmed cell death-1 (PD-1) (5-9). Functional restoration of CD8⁺T cells by PD-1 blockade has already been verified in several human tumors, including lung cancer (10-12). Anti PD-1/PD-L1 antibodies interrupt check point inhibition produced by the PD-1 receptor binding to its ligand PD-L1. The response rate in non-small cell lung cancer (NSCLC) treated with anti PD-1 antibodies is approximately 20% (11-16).

A great effort has been made to identify predictive factors that can help select those patients most likely to benefit from these therapies. Immunohistochemistry (IHC) analysis of PD-L1 on tumor cells or infiltrating lymphocytes is currently being performed with mixed results. Nivolumab has been recently approved for treatment of squamous lung cancer irrespective of PD-L1 status (16). In the case of non-squamous lung cancer, nivolumab seems to be more active in cases that are PD-L1 positive by IHC than in negative patients. Patients with PD-L1 expression level $\geq 10\%$ in tumor biopsies had median overall survival (OS) of 19.4 months when treated with nivolumab versus 9.9 months for lower levels of expression ($P=0.0002$) (14). Also, FDA approval of pembrolizumab for metastatic NSCLC is restricted to PD-L1 positive patients based on results demonstrating 41% tumor shrinkage in patients, with duration between 2.1 and 9.1 months (12).

The important role of neoantigens as predictors of anti PD-1/PD-L1 antibodies activity has also been described: higher nonsynonymous mutation burden was found in tumors responding to pembrolizumab using whole-exome sequencing analysis. Efficacy also correlated with molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations, suggesting that anti-PD-1 therapy enhances neoantigen-specific T cell reactivity (17).

Primary resistance to anti PD-1 antibodies is a common feature. Interaction with the tumor microenvironment, secretion of TGF- β and other immunosuppressive factors, and tumor heterogeneity are involved in this phenomenon (18,19). TGF- β plays an important role as an immunosuppressive molecule throughout tumor evolution, and research is ongoing to try to inhibit TGF- β to improve the efficacy of anti PD-1 antibodies. Immunotherapy is able to debulk tumors but also exerts selective pressure, leading to the development of therapy resistance. Resistant cells usually have cancer stem cells properties and activate other metabolic pathways that could be treated with selective drugs (20).

Another possible means of overcoming resistance is the combination of anti PD-1 antibodies with targeted drugs against driver molecular alterations such as mutations in EGFR or ALK translocations. The strengths and weaknesses of targeted agents and immunotherapy suggest that these two approaches might be complementary and that combinatory therapy could be synergistic (21-23).

The clinical data obtained with immune checkpoint inhibitors blocking PD-1 provide the ideal context for reflection on the future perspectives of immunotherapeutic agents. The activity of these drugs differs from that of conventional therapies such as targeted drugs or chemotherapy, raising questions about the best endpoints for clinical trial design, statistical methodology and context (24).

In this special issue expert authors in the field review current clinical results obtained with checkpoint inhibitors in NSCLC, the molecular pathways involved in response and resistance to these drugs, and the most relevant clinical strategies for future development of immunotherapy in lung cancer.

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María González-Cao, MD, PhD. *Translational Cancer Research Unit, Instituto Oncológico Dr. Rosell, Quirón Dexeus University Hospital, Barcelona 08028, Spain. (Email: mgonzalezcao@oncorosell.com.)*

María González-Cao, MD, PhD

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