Science and biology drives the immune system to cure lung cancer patients: a revolution but not without challenges

Ther Adv Med Oncol

2018, Vol. 10: 1–4

DOI: 10.1177/1758835918763723

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Keywords: anti-PD-1/PD-L1, biomarkers, combinations, immunotherapy, lung cancer

Received: 6 December 2017; accepted in revised form: 15 February 2018

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Introduction

In 2002, the immune checkpoint programmed death ligand-1 (PD-L1), also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1), was for the first time described as a mechanism of immune escape for tumor cells.[1,2] Injection with an anti-PD-1 monoclonal antibody, subsequently developed by Bristol-Myers Squibb as nivolumab, inhibited the hematogenous dissemination of various tumor cells in mice models.[1] Now in 2017, several drugs that release the constraints of immune checkpoints offer unique therapeutic opportunities in several type of tumor. Immunotherapy has redefined standard-of-care treatment of non-small cell lung cancer (NSCLC) patients in the first- and second-line setting. There is also enthusiasm about its potential in small-cell lung cancer.[3,4] In this Special Collection for *Therapeutic Advances in Medical Oncology*, entitled 'Immunotherapy for Lung Cancer: Progress, Opportunities and Challenges', many prestigious investigators will express their opinion and describe their own experience on the progress of immunotherapy for lung cancer patients, including the benefits and the challenges that this novel therapeutic approach has posed in our daily clinical practice.

NSCLC patients who receive nivolumab as second-line therapy have a 28% lower risk of death in comparison with those receiving standard chemotherapy.[5–7] Another anti-PD-1 monoclonal antibody, pembrolizumab, prolongs overall survival of previously treated metastatic NSCLC patients but only if at least 1% of tumor cells express PD-L1.[8] In two clinical trials, the anti-PD-L1 antibody atezolizumab benefited the survival of previously treated NSCLC patients compared with docetaxel, independent of PD-L1 status.[9,10] The safety and antitumor activity of the anti-PD-L1 inhibitor avelumab has been reported in patients with progressive or platinum-resistant metastatic or recurrent NSCLC, irrespective of PD-L1 expression.[11] Finally the anti-PD-L1 inhibitor durvalumab achieved durable responses in heavily-pretreated PD-L1-positive metastatic NSCLC patients.[12] Nivolumab, pembrolizumab and atezolizumab are approved for the management of previously treated patients with advanced NSCLC, with pembrolizumab being restricted to tumors expressing PD-L1.

Single-agent pembrolizumab provides a clear progression-free survival and overall survival benefit for previously-untreated NSCLC patients with PD-L1 expression on at least 50% of tumor cells.[13] In the CheckMate-026 study, nivolumab was not able to demonstrate similar clinical benefit in the first-line setting for NSCLC patients with PD-L1 expression on at least 5% of tumor cells, when compared with platinum-based chemotherapy.[14] Single anti-PD-L1 monotherapies with atezolizumab or avelumab are currently being evaluated for the first-line treatment of PD-L1-positive NSCLC patients, in the phase III clinical trials IMpower 110 [Clinical Trials.gov identifier: NCT02409342] and JAVELIN Lung 100 [ClinicalTrials.gov identifier: NCT02576574], respectively. Clinical activity was seen with durvalumab as first-line therapy in NSCLC patients with more than 25% PD-L1 positive tumor cells,[15] data that are further being evaluated in the ongoing PEARL phase III clinical trial.[16]

Very importantly, adjuvant durvalumab after chemoradiotherapy prolonged progression-free survival compared with placebo for patients with locally advanced unresectable NSCLC.[17] The results of the PACIFIC study undeniably point to implementing immunotherapy after chemoradiotherapy in patients with stage III NSCLC.[17,18] Doubts may be raised on the efficacy of immune checkpoint blockade as adjuvant therapy for resectable NSCLC. For instance, in breast cancer, neoadjuvant immunotherapy eradicated distant metastases more efficiently than adjuvant immunotherapy.[19] This may be due to the fact that lymph node dissection reduces the antitumor activity of the immune system.[20,21]

The most important challenge for lung cancer immunotherapy is that these treatments have demonstrated efficacy in a minority of patients. Until now, the identification of biomarkers that can help us to select patients for cancer immunotherapy has been a very difficult process. Immunohistochemistry assays that evaluate the proportion of tumor cells expressing PD-L1 are the ones that have been prospectively evaluated in clinical trials and are most commonly used in daily clinical practice. However, there are concerns regarding how a test using a fixed percentage of PD-L1-positive tumor cells can determine the appropriate patients for treatment. No single biomarker can discriminate responders from nonresponders in PD-1/PD-L1 blockade therapy, and this point will be extensively discussed in the current Special Collection of *Therapeutics Advances in Medical Oncology*.

PD-L1 expression is induced by interferon gamma (IFN-γ), or by oncogenic signaling pathways.[22,23] Smoking status and high tumor-mutation burden have been associated with clinical efficacy of immune checkpoint blockade in lung cancer.[24] In contrast, response rates to immune checkpoint blockade of only 3–4% have been reported for lung cancer patients who are never or light smokers, or their tumor is driven by epidermal growth factor receptor (*EGFR*) mutations or echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) rearrangements.[25] The association of tumor-mutation burden with response to immune checkpoint blockade is higher when clonality or neoantigen heterogeneity is simultaneously assessed.[26] Tumor-mutation burden can be assessed in the blood, and recently a blood-tumor mutation burden of more than 16 was retrospectively found to be predictive of outcome to atezolizumab.[27] Currently, the blood-tumor mutation burden has been incorporated as a noninvasive companion diagnostic assay of response to first-line atezolizumab in advanced NSCLC patients in the randomized phase III Blood First Assay Screening Trial (BFAST). The recent finding that both the tumor genome and the features of the microenvironment evolve in response to anti-PD-1/PD-L1 therapy has added to the complexity of the mechanisms of action of immune checkpoint blockade. Mutational contraction, defined as a decrease of the initial high frequency of tumor clonal and single nucleotide variations after therapy with nivolumab, is observed in good responders.[28] In contrast, a high frequency of novel single nucleotide variations during nivolumab therapy (mutational persistence) was observed in nonresponders to PD-1 blockade. Therefore, more than a clinical assessment of response, a molecular phenotype of response (tumor genomic contraction/persistence) at an early time point of treatment could more adequately represent the underlying biological changes and predict the outcome to immune checkpoint blockade.[28]

Another point that will be highlighted in the Special Collection is combinational immunotherapy strategies. Apart from the inhibitory receptors PD-1 and PD-L1, there are several other T-cell activating or inhibitory receptors that control immune responses and immune tolerance. The combination of anti-PD-1 and anti-cytotoxic T-lymphocyte associated antigen-4 (CTLA-4) antibodies has been approved for melanoma patients and is being clinically tested in other type of tumors, including lung cancer.[29] The safety and promising efficacy of the anti-CD137 (or anti-41BB) monoclonal antibody utolimumab combined with pembrolizumab was recently demonstrated.[30,31] Several clinical trials combining immune checkpoint inhibitors, chemotherapy and targeted therapies are underway.[32] Finally, immune checkpoint blockade alone and even more in combinatorial therapeutic approaches have generated a new type of adverse events, the immune-related adverse events (IrAEs). IrAEs can be potentially fatal and require early identification and management,[33–36] and the optimal management of IrAEs will also be discussed in the collection.

The Special Collection is composed of original research studies, reviews and editorials that highlight advances in the field of lung cancer

immunotherapy but also decipher critical points, such as: 'Why do only some patients respond to anti-PD-1/PD-L1 therapies?', 'Which can be the best biomarkers to discriminate responders from nonresponders?', 'Which are the best partners to be combined with anti-PD-1/PD-L1 antibodies for lung cancer patients'? We hope that this collection will be of great interest to researchers in a diverse range of fields.

Funding

Work in Dr. Rosell´s laboratory is partially supported by a grant from La Caixa Foundation, by a European Grant (ELBA No 765492) and an Instituto de Salud Carlos III grant (RESPONSE, PIE16/00011).

Conflict of interest statement

The authors declare that there is no conflict of interest.

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