Immunotherapy and non-small cell lung cancer: between lights and shadows

Since the early results obtained in advanced melanoma [1-4], immune-checkpoint inhibitors are progressively expanding their indications in solid tumor treatment, challenging the role of historical counterparts, such as chemotherapy and small molecules [5-10].

Lung cancer is the first tumor, among the so called "big-killers", where monoclonal antibodies directed against the PD-1/PD-L1 axis have proven efficacy when compared to standard treatment [5-7]. The introduction of these agents is hitting the headlines as a true revolution in thoracic oncology, a field where the biggest improvements in the last ten years have mainly concerned never- and light-smokers patients. However, these rays of light are still framed by some shadows, which are currently under clinical and preclinical investigation: are these new drugs for all-comers? If not, how can we select those patients, who will best benefit from this approach? Are these agents equally active regardless the line of therapy, marking the end of cytotoxic drugs era? Is the association of immunotherapy and other treatments a strategy to reach better results? How can we actually evaluate immunotherapy activity?

To date, the US Food and Drug Administration (FDA) approved two monoclonal antibodies against PD-1 (nivolumab [11, 12] and pembrolizumab [13]) for the treatment of locally advanced and advanced non-small cell lung cancer (NSCLC), who progress during or after platinum-based chemotherapy.

Nivolumab, a fully human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) directed against PD-1, was evaluated *versus* docetaxel in the second-line treatment of stage IIIB/IV squamous and non-squamous lung cancer patients in two phase 3 twin studies, Checkmate 017 and Checkmate 057 [5, 6]. In both studies nivolumab significantly increased median overall survival (mOS) by approximately 3 months along with the response rate, as compared to docetaxel. The main difference between the two trials, possibly reflecting the different pathogenesis of squamous and non-squamous NSCLC, relies on the biomarker role. Since both studies evaluated PD-L1 expression by immunohistochemistry (IHC) on tumor cells (pharm-Dx DAKO 28-8 clone), no differences in terms of survival, nor response rate (RR) or progression free survival (PFS) has been observed in PD-L1 positive or negative squamous cell lung cancer across all the pre-specified expression levels (1%, 5%, and 10%). By contrast, in non-squamous NSCLC, PD-L1 expression across all those expression levels was associated with higher OS and PFS.

Pembrolizumab, a humanized IgG4 mAb directed against PD-1, was

Correspondence to:
Paolo Bironzo, MD
Medical Oncology Unit
AOU S. Luigi Gonzaga,
Regione Gonzole 10,
10043 Orbassano (TO), Italy.
Phone: +39 011 9026334
E-mail: pbironzo@gmail.com
CANCER BREAKING NEWS 2016;4(2):3-6
DOI: 10.19156/cbn.2016.0011

approved by the FDA thanks to the positive results in terms of RR in previously treated advanced NSCLC patients, whose tumor cells express PD-L1 by IHC (pharmDx DAKO 22C3 clone) [14]. The drug was subsequently investigated in a randomized phase II/III trial in previously treated, advanced PD-L1 positive NSCLC patients, comparing two different schedules of pembrolizumab *versus* docetaxel [7]. Both pembrolizumab arms conferred a statistically significant OS advantage as compared to docetaxel, with no differences in PFS. However, in a subgroup analysis of patients with at least 50% of PD-L1 positive tumor cells, a PFS benefit, along with a greater OS, was described.

Similar results have been recently reported with an anti-PD-L1 mAb, atezolizumab, in a phase II randomised trial *versus* docetaxel, conducted in NSCLC patients previously treated with a platinum-based doublet [15]. Differently from the aforementioned trials, in this study PD-L1 was evaluated in both tumor cells and tumor-infiltrating immune cells (TI). The mOS was increased by 3 months in the experimental arm in positive patients only, while no differences between arms were present in PD-L1 and TI negative patients.

Checkpoint inhibitors demonstrated a manageable safety profiles, the main toxicities reported being asthenia, fatigue and decrease of appetite. These agents are characteristically associated with immune-related adverse events (e.g., rash, pruritus, diarrhea, hypothyroidism, hepatitis), which are consistent with their mechanism of action and can often be managed with protocol-specified guidelines (e.g., close patient follow-up and early administration of systemic corticosteroids and/or other immunosuppressive agents).

Criteria for response evaluation with immunostimulatory monoclonal antibodies (imAbs) are currently the matter of intense work and debate. The vast majority of trials in NSCLC evaluating anti-PD1/PD-L1 antibodies have traditionally used RECIST v1.0/v1.1 criteria. More recently, immune-related response criteria (irRC) have been proposed and validated in malignant melanoma to better assess the variety of responses that can be generated upon imAbs [16-18]. IrRC undoubtedly allow better taking into account the potential for an initial 'flare-up' or pseudo-progression at the tumour site, for the appearance of new non-target lesions as well as for the difference between kinetics of response observed between imAbs and cytotoxic therapy, but they are still insufficient to describe all response profiles or clinical benefits observed and further data are needed in this context. Also, alternative endpoints for clinical trials evaluating imAbs, such as disease control rate and tumour growth rate, could be probably implemented, especially considering the highly variable timing of response, ranging from 6 weeks to several months after treatment initiation, or even after treatment cessation [19-21].

Can we consider checkpoint inhibitors as the novel standard second-line agents in all NSCLC patients? As of today, the answer is no.

Available data show that only a part of non-squamous NSCLC patients, even if selected by PD-L1 expression, derives benefit from the treatment and, moreover, there are patients labeled as PD-L1 negative who do the same and this leads to the FDA approval of nivolumab in all previously treated non-squamous NSCLC patients, in order not to deny a potential active treatment to PD-L1 negative patients. Notably, one possible explanation

goes "beyond the biomarker": when looking at Checkmate057 prespecified subset analyses, the only large subgroup who don't seem to derive benefit from nivolumab over docetaxel is the never smoker population, underlining the potential link between immunogenicity and carcinogens exposition.
By contrast, pembrolizumab was approved, on the basis of early clinical data, for PD-L1 positive patients (as determined by the companion diagnostic assay).
All these controversial data, along with the observation that PD-L1 expression is highly variable and dynamic in cancer cells, make unrealistic, from a scientific point of view, that two similar molecules, hitting the same target in the same disease have such presumed different clinical activity and, thus, regulatory indication for lung adenocarcinoma. Moreover, this paradox makes the clinical scenario extremely confused, with the risk that patients found "negative" with the pembrolizumab PD-L1 assay would receive nivolumab due to its "wider" indication, having no clear demonstration of different efficacy of the two compounds.
A quite different landscape is that of squamous cell lung cancer, an historically "difficult" subset with a hard-to-treat although often more indolent disease. The diffuse benefit observed in all Checkmate017 patients, without any relationship with PD-L1 expression, strongly supports checkpoint inhibition as a valuable second-line approach.
Assuming that PD-L1 per se should not be considered as a "gold" biomarker, researchers are exploring other possible factors and pathways. Considering that the best results of immunotherapy have been reached in those cancers strongly related to chronic exposition to mutagens, such as melanoma and lung cancer, Rizvi and colleagues have elegantly described that those lung tumors who responded to pembrolizumab had a higher mutational tumor burden as compared with those which didn't respond [22], that is perfectly in line with similar data in mismatch-repair deficient colorectal cancer patients treated with pembrolizumab [23].
Other efforts in understanding such complex interactions are directed to the study of tumor microenvironment and its relationship with cancer cells. In the aforementioned POPLAR study the evaluation of PD-L1 expression by IHC (Ventana SP142 clone) in both tumor cells and tumor-infiltrating lymphocytes is another attempt to better select patients, who would benefit from the treatment. Moreover, an exploratory analysis conducted in this study suggests a potential role, in this setting, of T-effector-interferon-gamma-associated gene expression [15].
In conclusion, what was a simple decision in the second line setting of advanced NSCLC is now becoming more intriguing, if we consider these data on immunotherapy in squamous and non-squamous carcinoma, together with other available therapeutic options such as novel antiangiogenics. Certainly, as we are facing a new promising era in lung cancer treatment (and not only), a careful and deep study of the relationship between cancer and the immune system is mandatory, in order to thoroughly elucidate such connections along with all the possible involved factors, with the aim to fully exploit the potential of immunotherapy in this lethal disease.

Paolo Bironzo, Silvia Novello
Department of Oncology, University of Torino, Italy

Conflicts of Interest

P. Bironzo declares there are no conflicts of interest in relation to this article.

S. Novello: speakers bureau (Ely-Lilly, AstraZeneca, MSD, Boehringer Ingelheim, Roche).

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