Implementation of immunotherapy in the treatment of advanced non-small cell lung cancer (NSCLC)

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Abstract: Mechanisms of tumor immune surveillance and immune escape have been recently elucidated and led to the development of a new therapeutic field in oncology, that of immunotherapy. Immunotherapy aims to reactivate the immune system against cancer. Neoplasias like non-small cell lung cancer (NSCLC) are of particular interest and clinical studies with immunotherapeutic agents have shown significant survival benefit. Several agents have gained corresponding regulatory approvals. In particular, nivolumab, pembrolizumab and atezolizumab have been approved for second-line treatment of NSCLC, pembrolizumab is the only immune checkpoint inhibitor that has been approved in the first-line treatment and durvalumab is approved in the locally advanced disease. In this review, we aim to present the implementation of immunotherapy in the treatment of advanced NSCLC. We will discuss not only the approved regimens but also the future perspectives, the serious adverse events such as hyperprogression and the possible predictive markers that will aid the selection of the patients that will benefit from immunotherapy.

Keywords: Lung cancer; immunotherapy; checkpoint inhibitor; anti-PD-L1; anti-PD-1

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Introduction

During the last few years, immunotherapy has revolutionized non-small cell lung cancer (NSCLC) treatment due to better understanding of the molecular basis of the interaction between the immune cells and the cancer (1). This revolution has led to the clinical development of several agents that reactivate the immune system against cancer. These agents have provided significant survival benefit in various settings of NSCLC disease course and have gained corresponding regulatory approvals (2).

In this review, we have focused on the development of immune checkpoint inhibitors in the treatment of NSCLC and challenges regarding molecular subtypes of the disease and the appropriate selection of patients as well as the future perspectives of this treatment modality.

Immune checkpoint inhibitors as monotherapy in the second-line of treatment

Clinical development of immune checkpoint inhibitors in NSCLCs begun in patients already treated for their metastatic disease (3,4). Currently, three immune checkpoint inhibitors have been approved by the FDA for second line treatment of NSCLC (nivolumab, pembrolizumab and atezolizumab) (5). Those agents have also received their authorization in the EU. Atezolizumab is immune checkpoint inhibitor targeting programmed cell

death-ligand 1 (PD-L1) and nivolumab, pembrolizumab are targeting programmed cell death-1 (PD-1).

Atezolizumab, a fully humanized anti-PD-L1 monoclonal antibody, has been approved on October 2016 for the treatment of patients with metastatic NSCLC that progressed during or after platinum-based chemotherapy (6,7).

Two clinical trials (POPLAR and OAK) led to this approval. More specific, POPLAR, a multicenter, open-label, phase 2 randomized controlled trial, assigned patients (1:1) to receive intravenous atezolizumab 1,200 mg or docetaxel 75 mg/m^2 once every 3 weeks (8). The findings of this study showed that atezolizumab improved overall survival (OS) [12.6 months for atezolizumab *vs.* 9.7 months for docetaxel: hazard ratio (HR), 0.73; P=0.04]. In that study—as is the case for all immunotherapy studies—survival was assessed in relation to the immunohistochemical expression of PD-L1 as estimated by the Vendana SP142 antibody. Indeed, the survival benefit shown with atezolizumab was statistically significant correlated with increased PD-L1 immunohistochemistry expression. This study proved also that the drug was not only effective in this population, but very well tolerated too, with only 11% of the patients in the atezolizumab group to experience grade 3/4 adverse events (AEs) *vs.* 39% in the docetaxel group.

OAK study, a multicenter, open-label, phase 3 randomized controlled trial, confirmed the results of the POPLAR study regarding the improvement of OS in patients receiving atezolizumab (9). Median OS was 13.8 months in the atezolizumab arm *vs.* 9.6 months for docetaxel (HR, 0.74; P=0.0003). In contrast to the POPLAR study though, no significant differences were seen in the survival benefit provided by the atezolizumab across subgroups with different PD-L1 expression. Patients in the high PD-L1 expression subgroup had benefit in OS (15.7 *vs.* 10.3 months for docetaxel: HR, 0.73; P=0.0102) but the same applied for patients in the PD-L1 low group (12.6 *vs.* 8.9 months for docetaxel: HR, 0.75). Moreover, the OS improvement was similar in patients with either squamous or non-squamous histology and atezolizumab was again better tolerated than docetaxel (grade 3/4 AEs 15% with atezolizumab *vs.* 43% with docetaxel).

Nivolumab, a human IgG4 anti-PD-1 monoclonal antibody, has been approved on March 2015 for the treatment of patients with metastatic squamous NSCLC that progressed during or after platinum-based chemotherapy and then on October 2015 its approval has been expanded to include also patients with non-squamous NSCLC (10-12).

Checkmate 017, an open-label, phase 3 randomized trial, assigned patients with advanced squamous NSCLC to receive nivolumab 3 mg/kg or docetaxel 75 mg/m^2 and evaluated the efficacy and the safety profile of nivolumab in this population (13,14). The median OS was 9.2 months with nivolumab *vs.* 6.0 months with docetaxel (HR, 0.59; P<0.001), the response rate was 20% with nivolumab *vs.* 9% with docetaxel (P=0.008) and the median progression-free survival (PFS) was 3.5 *vs.* 2.8 months respectively (HR, 0.62; P<0.001). Also, nivolumab was better tolerated than docetaxel (grade 3/4 AEs 7% with nivolumab *vs.* 55% with docetaxel). The survival benefit from nivolumab was independent of the PD-L1 expression.

In addition, Checkmate 057, an open-label, phase 3 randomized trial, recruited patients with non-squamous NSCLC and assigned them, also, to receive nivolumab or docetaxel (14,15). The results were comparative to those of Checkmate 017. The median OS (12.2 months with nivolumab *vs.* 9.4 months with docetaxel: HR, 0.73; P=0.002), the response rate (19% with nivolumab *vs.* 12% with docetaxel: P=0.02) and the safety profile (grade 3/4 AEs 10% with nivolumab *vs.* 54% with docetaxel) were better in the nivolumab group. Although median PFS was 2.3 months with nivolumab *vs.* 4.2 months with docetaxel, the rate of PFS at 1 year was higher with nivolumab (19% *vs.* 8% respectively).

Pembrolizumab, an IgG4-engineered humanized anti-PD-1 monoclonal antibody, has been approved on October 2015 for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 and who progress during or after platinum-based chemotherapy (16).

The first promising results for pembrolizumab, especially in patients with PD-L1 expression ≥50%, showed in the KEYNOTE-001 study (phase 1 trial) that explored the safety, tolerability and antitumor activity in advanced solid tumors. The trial, though, that established pembrolizumab as a new treatment option in the second-line treatment is KEYNOTE-010 (17).

KEYNOTE-010, an open-label, phase 2/3 randomized controlled trial, assigned patients with at least 1% PD-L1 expression to receive (1:1:1) pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg or docetaxel 75 mg/m^2. The median OS was 10.4 months with pembrolizumab 2 mg/kg, 12.7 months with pembrolizumab 10 mg/kg and 8.5 months with docetaxel but the median PFS was the same for the three subgroups. In patients with at least 50% PD-L1 expression, OS was significantly better with pembrolizumab 2 or 10 mg/kg than with docetaxel (14.9 *vs.* 17.3 *vs.*

8.2 months respectively: HR, 0.54; P=0.002) as was also the PFS (5.0 *vs.* 5.2 *vs.* 4.1 months, respectively). Moreover, pembrolizumab was better tolerated than docetaxel (grade 3/4 AEs 13% with 2 mg/kg *vs.* 16% with 10 mg/kg *vs.* 35% with docetaxel).

Immune checkpoint inhibitors in the first-line of treatment

In the first-line treatment the only immune checkpoint inhibitor that has been approved as monotherapy or combination therapy, is pembrolizumab.

Monotherapy

KEYNOTE-024, an open-label, phase 3 randomized trial assigned patients with previously untreated advanced NSCLC with PD-L1 expression at least 50% and no *EGFR* and *ALK* mutations, to receive either pembrolizumab or platinum-based chemotherapy (carboplatin plus pemetrexed, cisplatin plus pemetrexed, carboplatin plus gemcitabine, cisplatin plus gemcitabine or carboplatin plus paclitaxel) (18). It should be noted that the 50% cut-off for the first-line trial of pembrolizumab was chosen upon results from the phase I trial of the drug in pre-treated NSCLC patients, showing significantly better responses and survival benefit in this subgroup of patients (4). In addition, one should take into account that this is a preselected population accounting for approximately 20% of NSCLC patients (4,19).

The results of this trial have led to accelerated FDA approval of this immune checkpoint inhibitor. More specific, patients with at least 50% PD-L1 expression had greater median PFS (10.3 months with pembrolizumab *vs.* 6 months with chemotherapy: HR, 0.6; P=0.005), higher response rate (44.8% *vs.* 27.8%) and had also better tolerability with grade 3/4/5 AEs to be fewer than chemotherapy (26.6% *vs.* 53.3%).

Despite the success of pembrolizumab in the first-line setting raised the hopes for the efficacy of immunotherapy against the platinum-based chemotherapy that consisted the standard of care, these results were not confirmed in the analogous phase III clinical trial of nivolumab (20).

More specifically, in the CheckMate 026 trial, patients with a PD-L1 expression level 5% or more, were assigned to receive (1:1) nivolumab or platinum-based chemotherapy. Although nivolumab was better tolerated- with grade 3/4 AEs occurring in 18% of the patients with nivolumab *vs.* 51% with chemotherapy and OS was similar between groups (14.4 months with nivolumab *vs.* 13.2 months with chemotherapy), the median PFS was not longer in the nivolumab group (4.2 months with nivolumab *vs.* 5.9 months with chemotherapy). Similar results were also found in the subgroup of patients with a PD-L1 expression level >50%.

Combination therapy

Attempting to improve survival in NSCLC patients beyond the subgroup of highly expressing PD-L1 patients, KEYNOTE-021 studied the addition of pembrolizumab to standard platinum-based chemotherapy, in the first-line in all patients independent of their PD-L1 expression (21). In this randomized, open-label, phase 2 study, patients were assigned (1:1) to receive either 4 cycles of pembrolizumab plus carboplatin/pemetrexed followed by maintenance therapy with pemetrexed and pembrolizumab or 4 cycles of carboplatin/pemetrexed followed by pemetrexed maintenance only. The primary endpoint of this study was the percentage of patients who achieved objective response. Indeed, objective responses were significantly improved in the combinatorial chemotherapy and pembrolizumab (55% *vs.* 29%; P=0.0016). Median PFS was also longer for pembrolizumab plus chemotherapy (13.0 *vs.* 8.9 months) but no difference was seen in OS. These results, along with the manageable safety profile led to the FDA approval of pembrolizumab as first-line combination therapy with pemetrexed and carboplatin.

Immune checkpoint inhibitors in the locally advanced disease

KEYNOTE-021 and -024 studies proved that administration of immunotherapy in earlier lines of treatment could be efficacious in NSCLC (18,21). Under this perspective, durvalumab, a human IgG1 anti-PD-1 monoclonal antibody, has provided evidence that changed the therapeutic management of locally advanced patients and prolonged their survival which was extremely low with conventional chemotherapy (5-year survival 15%).

PACIFIC study, a randomized, double-blind, phase 3 trial has led to the FDA approval of durvalumab for the treatment of patients with locally-advanced, unresectable NSCLC whose disease has not progressed following platinum-based chemoradiation therapy (22).

Patients assigned (2:1) to receive either durvalumab (10 mg/Kg) or placebo every 2 weeks as consolidation

therapy after two or more cycles of platinum-based chemotherapy (with etoposide, vinblastine, vinorelbine, paclitaxel, docetaxel or pemetrexed) concurrently with definitive radiation therapy. The study drug was given for up to 12 months. Median PFS was 16.8 months with durvalumab *vs.* 5.6 months with placebo (HR, 0.52; P<0.001). A PFS benefit was observed in all subgroups and was independent of PD-L1 expression and smoking status. The median time to death or distant metastasis was 23.2 months with durvalumab *vs.* 14.6 months. Also, the objective response rate was significantly higher with durvalumab (28.4% *vs.* 16%; P<0.001). It must be noted that of the patients who had response to durvalumab, 72.8% remained in response at both 12 and 18 months as compared with the placebo group (56.1% and 46.8%, respectively). Finally, the drug was well tolerated with grade 3 AEs occurring in 29.9% of patients who received durvalumab *vs.* 26.1% with placebo.

Immunotherapy approaches in EGFR mutant patients

The most frequently detected actionable mutations in NSCLC are that of the *EGFR* gene (23). *EGFR* mutations appear in approximately 50% of Asians with NSCLC and in 10% of non-Asians (24,25). The development of EGFR tyrosine-kinase inhibitors has changed the natural history of this disease. These agents improved the response rates, the PFS and the OS of those patients in comparison to standard chemotherapy (26-29). However, as anticipated for targeted therapies resistance to these agents almost always occurs (30,31). Thus, novel therapeutic strategies need to be developed.

Preclinical studies, support the role of immunotherapy in *EGFR* mutant patients. *EGFR* mutations have been shown to activate the EGFR pathway leading to PD-L1 overexpression, suggesting that immunotherapy could be a promising therapeutic approach in these patients (32,33). However, the randomized clinical trials have casted doubt regarding the efficacy of immunotherapy in *EGFR* mutant patients.

Monotherapy

Subgroup analysis of several phase 3 trials that compared immunotherapy *vs.* docetaxel (CheckMate 057, KEYNOTE-001, OAK) (9,14,15) showed no difference in OS with immunotherapy in *EGFR* mutant patients in comparison to docetaxel.

Combination therapy

These results suggested that a different approach should be followed for this population and currently several combination therapies are under investigation. As part of a phase 1 study, nivolumab combined with erlotinib in *EGFR* mutant patients (34). The overall response rate (ORR) was 19%, PFS at 24 weeks was 51% and OS at 18 months was 64%. Grade 3 toxicities appeared in 19% of the patients with the majority being dermatological. As part of TATTON study, osimertinib combined with durvalumab has been tested in pretreated or chemo naïve NSCLC patients and showed encouraging responses (35). However, interstitial lung disease (ILD) was developed in 38% of these patients with the osimertinib-durvalumab combination, leading to premature termination of the study. Combination of gefitinib plus durvalumab is being investigated and demonstrated encouraging activity (36). However, safety concerns were also raised in this study, since the percentage of AEs was approximately 80%, with liver enzyme elevation grade 3/4 being the most common [alanine transaminase (ALT) elevation, 60–70%/aspartate transaminase (AST), 40–50%] and were managed by dose interruption and corticosteroid. Another combination though, namely atezolizumab plus erlotinib, was better tolerated and only 39% of the patients developed treatment related grade 3/4 AEs including ALT elevation, pyrexia and rash, while no ILD was reported (37).

Predictive biomarkers

Immunotherapy has changed the therapeutic management of patients with NSCLC and improved OS and clinical responses. Unfortunately, the percentage of those who respond remains low (~20%) and the need of discovering predictive factors that will identify the subgroup of patients who derive the greater benefit is essential (38).

The analysis of the immunohistochemical expression of PD-L1 as a predictive biomarker has a strong biological rational (39). PD-L1 expression has already been used in clinical trials with contradictory results. However, it should be noted that pembrolizumab has been approved in the first-line setting as monotherapy in patients with at least 50% PD-L1 expression as determined by the companion diagnostic kit of Vendana (40,41). The discrepancy noted between PD-L1

expression and response to immunotherapy in several clinical trials could be attributed in several factors (42). This could be explained by the fact that every company uses different diagnostic tests with different antibodies for PD-L1. Some tests evaluate the percentage of tumor cells stained and others not only tumor cells stained but also tumor-infiltrating cells. Also, the cutoff points for a positive result or scoring system differ among diagnostic tests creating this way a confusion. Moreover, PD-L1 is a dynamic marker and when a specimen is used for PD-L1 expression might be an archive specimen and not reflect the current situation. For that reason, the Blueprint Initiative tries to harmonize the various PD-L1 assays and standardize testing so that no more than one testing is required to receive the appropriate drug (43). However, only 15–45% of patients with PD-L1 expression response to anti-PD-1/PD-L1 treatment and on the other hand, response can occur in PD-L1 negative patients. Moreover, it was found a correlation between high expression of PD-L1 and the presence of *EGFR* mutations in surgically resected NSCLC which also found to be an independent negative prognostic factor for this disease (44,45).

IFN-γ expression signatures could also be a potential predictive marker. The immune response against cancer by activated T lymphocytes elicits IFN-γ. The latter induces the expression of its transcriptional targets within the cells and these signatures of expression of IFN-γ associated genes were correlated with better response to durvalumab and atezolizumab (46). Further research though is needed to prospectively validate these results.

Tumor mutation burden has, also, been associated with response to immunotherapy (47-49). In fact, tumors with more mutations tend to have greater response to immunotherapy and that can be explained by the increased number of neo-antigens on the surface of the tumor cells which can trigger immune response. This theory can also explain the association of smoking status with the response to anti-PD-1/PD-L1 treatment. It is shown in several studies that former or current smokers response better to nivolumab or pembrolizumab (50,51). The latter could be attributed to the higher expression of PD-L1 found in smokers (52), suggesting that this immunosuppressive mechanism predominates NSCLCs among smokers.

Future perspectives

In the era of targeted therapy and personalized medicine, immunotherapy has shift the treatment paradigm of NSCLC. Although immune checkpoint inhibitors have already proven their efficacy as monotherapy or in combinatorial approaches, further research is required to determine other regimens or combinations that will improve efficacy and tolerability such as anti-CTLA-4 with anti-PD-L1 or antiangiogenic agents with immunotherapy (53). It is noticed, in particular, that antiangiogenic agents could increase lymphocyte infiltration into the tumor increasing the efficacy of immunotherapy. Finally, in an era that health management costs have skyrocketed, it is essential to find predictive markers for favorable clinical response which will help us to identify the patients who will benefit from immunotherapy, instead of administering the drug to unselected populations aiming at responses to a minority of them. This later approach may have also further detrimental effects. Recently, a percentage of patients treated with immunotherapy are presented with an accelerated disease progression. This phenomenon has been characterized as hyperprogression and is associated with older age and worse OS. This is confirmed by observations in the clinical studies conducted in unselected populations of NSCLC patients showing that chemotherapy outperforms current immunotherapy approaches in terms of progression rate early after initiation of study treatment. Further characterization of the population of hyperprogressors is warranted and may provide insights into the more efficacious administration of immunotherapy. In conclusion, immunotherapy has undoubtedly provided an exciting new therapeutic opportunity in NSCLC, however its use raises some concerns and caution must be taken especially in older people (54).

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Footnote

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