Review Article

Immunotherapy and new frontiers in the treatment of lung cancer

Paola Fuso[1], Leonardo Petracca Ciavarella[2], Mariantonietta Di Salvatore[3]

[1]Department of Woman and Child Health, [2]Department of Thoracic Surgery, [3]Department of Medical Oncology, Catholic University of the Sacred Heart, "Policlinico A. Gemelli—IRCCS" Foundation, Rome, Italy

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Correspondence to: Paola Fuso. Department of Woman and Child Health, Catholic University of the Sacred Heart, L.go F. Vito 1, 00168 Rome, Italy. Email: paolafuso82@gmail.com.

Abstract: Lung cancer is the malignancy with a high mortality rate. Despite considerable progresses in targeted therapy, advanced lung cancer patients have not experienced a substantial improvement of survival. In the last few years, immune checkpoint inhibitors (ICIs) have represented as promising therapeutic agents in non-small cell lung cancer (NSCLC). In numerous randomized studies, PD-1/PD-L1 inhibitors have allowed to obtain significant improvements in overall survival (OS) with response rates much higher and more durable than single-agent docetaxel in patients with pretreated, advanced NSCLC. Therefore, PD-1 inhibitors such as nivolumab and pembrolizumab were rapidly approved by the United States Food and Drug Administration (FDA) for both squamous and non-squamous lung cancer in the second-line setting. These encouraging results have led to change the current therapeutic paradigm of metastatic NSCLC also for first-line treatment, adding a new standard option for patients with PD-L1-positive tumors. Pembrolizumab, was approved by FDA in October 2016 for treatment-naïve advanced NSCLC patients with tumor high PD-L1 expression and tumor proportion score (TPS) ≥50%. Combining immunotherapy with novel immunomodulatory agents, chemotherapy or radiation therapy are currently being evaluated to achieving higher response rates and improving OS rate. The correct combination and order of therapy is under investigation. In this review, we discuss the clinical results and safety data for the treatment-naïve and pretreated settings in both early and advanced NSCLC. An update of the future perspectives will also be discussed.

Keywords: Lung cancer; immune-checkpoint inhibitors; PD-1; PD-L1

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Introduction

Lung cancer is the leading cause of cancer death worldwide (1). The prognosis of patients with advanced non-small cell lung cancer (NSCLC) is very poor with 5-years survival rates reported as less than 5%. Platinum-based chemotherapy (CT) is the standard first-line therapy in metastatic NSCLC patients without sensitizing mutations and gene re-arrangements such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) or ROS-1 re-arrangements, having showed an improvement in survival, symptom control and quality of life when compared with best supportive care (2,3). Moreover, despite mortality has improved with targeted drugs for driver mutations, few patients harbor these mutations and resistance to targeted treatment frequently occurs (4-11). In second-line setting, docetaxel and erlotinib (12) have been the standard of care (SOC) for patients with NSCLC and wildtype molecular status, and also pemetrexed, but for non-squamous NSCLC only. Recently, the combination

of docetaxel with new antiangiogenic agents, such as nintedanib or ramucirumab, showed higher efficacy compared with single agent docetaxel, though associated with a greater toxicity (13-15).

Over the last few decades, the improved understanding of tumor biology showed that there is a strong interaction between immune system and cancer progression. NSCLC is a considerably heterogeneous disease with a large mutational load encoding numerous potential neo-antigens and can evade immune surveillance by different immunosuppressive mechanisms, including "immune check points" which are receptors expressed on T cells regulating the immune response (16,17). T cells express cytotoxic T lymphocyte-associated protein 4 (CTLA-4) on their surface which, in the "priming phase" in lymphatic tissue, regulates the amplification of T cell activation, down-modulates T helper cell activity and enhances regulatory T cell (Treg) immunosuppressive activity (18). PD-1 receptor is one of the most important inhibitory receptors of the "effector phase", which is expressed by T activated cells, B cells, monocytes, and natural killer cells and binds to two specific ligands, programmed death-ligand PD-L1 and PD-L2. Such ligands are usually found in tumor cells and antigen-presenting cells and the interaction with their receptor leads to the inhibition of cytotoxic T lymphocyte proliferation as well as to the apoptosis of infiltrative T cells and the increase of Treg cells in the tumor microenvironment (16,19). Moreover, the tumor microenvironment promotes the secretion of pro-inflammatory molecules leading to overexpression of PD-L1 in tumor cells, thus facilitating immune suppression. Tumor cells, on the other hand, produce down-regulation of the major histocompatibility complex (MHC)-I and antigen expression and increase PD-L1 expression in tissue. As a result, solid tumors attain an immunological response insufficient to eliminate cancer cells, which is the reason why enhancing the function and quantity of cytotoxic T cells may be of clinical benefit (16,20,21). PD-L1 has been found to be overexpressed in different types of tumors including NSCLC.

To overcome these immune suppression mechanisms and restore antitumor immunity, clinical research has focused on targeting these immune checkpoints using monoclonal antibodies like ipilimumab and tremelimumab (anti-CTLA-4), pembrolizumab and nivolumab (anti-PD-1) and atezolizumab, avelumab and durvalumab (anti-PD-L1).

This update provides to review the rapidly expanding role of immunotherapy for advanced NSCLC using immune checkpoint inhibitors (ICIs).

ICIs for first-line treatment

Nivolumab

Nivolumab an anti-PD-1 IgG4 monoclonal antibody is not approved by the Food and Drug Administration (FDA) for use in the first-line setting for NSCLC.

Two phase III trials have evaluated this drug as first line in advanced NSCLC. The CheckMate 026 trial (22) randomized 541 patients with advanced, untreated, PD-L1-positive NSCLC (at least 1% of tumor cells with PD-L1 staining) in a 1:1 ratio to nivolumab (3 mg/kg IV every 2 weeks) or standard first-line, histology-based, platinum-doublet chemotherapy. Neither PFS, the primary endpoint of the study, nor OS were prolonged with nivolumab (HR for disease progression or death in patients with >5% tumor PD-L1 staining 1.15, 95% CI: 0.91–1.45; HR for death 1.02, 95% CI: 0.80–1.30). The reasons for the negative results of CheckMate 026 are not clear. This may be possibly due to patient selection as a cut-off of ≥5% PD-L1. Expression was utilized compared to a ≥50% cut-off which was explored in the positive Keynote-024 trial. One hypothesis is that nivolumab is less active that pembrolizumab. This would be in contrast with results of previous phase II and III trials that showed equivalent overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) in unselected patient. Another reason could be that the characteristics of patients were different: there was a higher rate of non-smoker in CheckMate 026 compared to the Keynote study-024, and non-smokers may exhibit a lower response rate to ICI, possibly because of a lower mutational load. Moreover, patients with brain metastasis were allowed in the CheckMate 026 while they had to be pretreated in the Keynote study. The CheckMate 227 (23) is a multi-part trial randomizing patient with advanced, untreated NSCLC to histology-based, platinum-doublet chemotherapy; nivolumab plus ipilimumab; or either nivolumab monotherapy (for PD-L1 ≥1%) or nivolumab plus chemotherapy (for PD-L1 <1%). Results from part 1 of this study comparing nivolumab plus ipilimumab to chemotherapy in patients with known tumor mutational burden (TMB) have been reported. Of 679 evaluable patients, 299 (44%) had tumors with high TMB, defined as >10 mutations per megabase. PFS in patients with high TMB (co-primary endpoint) was longer with nivolumab plus ipilimumab than chemotherapy, irrespective of tumor PD-L1 expression level, with median PFS (mPFS)/1-year PFS rate of 7.2 months/43% *vs.* 5.4 months/13%, and HR

for disease progression or death 0.58 (97.5% CI: 0.41–0.81). ORR in the high TMB population was 45.3% with nivolumab plus ipilimumab and 26.9% with chemotherapy. OS analysis is not mature.

Nivolumab in association with CT

The association of Nivolumab and platinum-based CT in first line treatment of advanced NSCLC has been tested only in a phase I trial [multi cohort Checkmate-012 trial (24,25)]: 55 patients were assigned to receive nivolumab plus cisplatin-gemcitabine, nivolumab plus cisplatin-pemetrexed, nivolumab (10 mg/kg) plus carboplatin-paclitaxel or nivolumab (5 mg/kg) plus carboplatin-paclitaxel. No selection on the PD-L1 expression was made at the inclusion. The primary objective was to assess safety and tolerability. A high rate of adverse events was observed as 45% of patient experienced grade 3–4 toxicities, mainly pneumonitis (7%), fatigue (5%) and acute renal failure (5%). In terms of efficacy, ORR were 33% (cisplatin-gemcitabine), 47% (cisplatin-pemetrexed), 47% (carbo-paclitaxel with nivo 10), 43% (carbo-paclitaxel with nivo 5 mg/kg). This small study suggested that the combining chemotherapy with immunotherapy may be feasible and improve response rates.

Pembrolizumab

Pembrolizumab is highly selective humanized IgG4 monoclonal, antibody directed against PD-1, approved by the FDA in October 2016 for previously untreated metastatic NSCLC patients whose tumors have high PD-L1 expression, tumor proportion score (TPS) ≥50%.

Keynote 024 is phase III, multicenter, open-label, 1:1 randomized trial comparing fixed dose pembrolizumab 200 mg every 3 weeks to the investigator's choice of five different platinum-based chemotherapy regimens in patients, treatment-naïve, with both squamous and non-squamous stage IV NSCLC and PD-L1 expression on ≥50% of tumor cells. Treatment with pembrolizumab and platinum-based chemotherapy continued for a total of 35 cycles (~2 years) and 4–6 cycles, respectively, or until the patient had radiologic disease progression or unacceptable toxicity. Pemetrexed maintenance was allowed for patients with non-squamous histology. Crossover from chemotherapy to pembrolizumab was allowed if progression disease (PD) occurred. The primary end point was PFS. Patients were stratified to ECOG status, histology, and race, with PFS as a primary endpoint. Secondary endpoints include OS, ORR, and safety. mPFS was longer for pembrolizumab *vs.* chemotherapy (10.3 *vs.* 6.0 months) and disease progression or death was significantly better for pembrolizumab (HR 0.50, 95% CI: 0.37–0.68; P<0.001). Median OS (mOS) has yet to be reached; however, the six-month OS for pembrolizumab *vs.* chemotherapy was 80.2 and 72.4%, respectively (HR 0.60, 95% CI: 0.41–0.89; P=0.005). The response rate was 44.8% with pembrolizumab *vs.* 27.8% with chemotherapy. These results are consistent with the preliminary data from the Keynote 001 trial, where the ORR was 50% in the untreated PD-L1 ≥50% population (26). The median duration of response was not reached with pembrolizumab *vs.* 6.3 months with chemotherapy. Treatment-related adverse events (AEs) of any grade were 73.4% with pembrolizumab *vs.* 90.0% with chemotherapy, and grade 3–5 AEs were 26.6% with pembrolizumab *vs.* 53.3% with chemotherapy: the main adverse event with Pembrolizumab were diarrhea (14.3%), nausea, fatigue, pyrexia and loss of appetite; the main adverse events with chemotherapy were anemia (44%), nausea (43.3%), fatigue (28.7%), loss of appetite (26%), neutropenia (22.7%) and vomiting (20%). Although pembrolizumab had higher rates of immune-AEs (29.2% *vs.* 4.7%) most were grade 1–2 events and did not lead to any deaths; only 9.7% of patients reported grade 3–4 AEs (mainly pneumonitis, skin reaction and colitis) (27). In contrast to CheckMate 026, KEYNOTE-024 met its primary endpoint and has established a new SOC in the first-line setting for advanced NSCLC with >50% PD-L1 expression.

Pembrolizumab in association with CT

Keynote 021 is a multi-cohort Phase 1/2 randomized trial investigating the safety, tolerability, and efficacy of pembrolizumab in combination with platinum doublets, targeted therapy, and ipilimumab in pre-treated, advanced, non-squamous NSCLC. The data, recently published from the randomized phase 2 cohort G, compared pembrolizumab (200 mg IV every 3 weeks, up to 2 years) in addition to chemotherapy (carboplatin AUC5 + 500 mg/mq IV every 3 weeks, for four cycle) followed by pemetrexed maintenance with chemotherapy alone in 123 patients with chemo-naïve stage IIIb–IV EGFR/ALK-WT non-squamous NSCLC. Patients were stratified according to their PD-L1 TPS <1% *vs.* ≥1%. Crossover from the chemotherapy group to the pembrolizumab group was permitted in the event of PD. The primary endpoint was ORR. Pembrolizumab combined with chemotherapy has

a superior ORR *vs.* chemotherapy alone (55% *vs.* 29%, 95% CI: 9–42%; P=0.0016). Subgroup analysis of PD-L1 stratification <1% *vs.* ≥1% showed similar ORR for the pembrolizumab group (57% *vs.* 54%, respectively) while the chemotherapy alone group showed a difference in ORR (13% *vs.* 38%, respectively). Further stratification of PD-L1 to 1–49% and ≥50% had an ORR of 26% and 80%, respectively, for the pembrolizumab with chemotherapy group, *vs.* 39% and 35%, respectively, for the chemotherapy alone group. Pembrolizumab with chemotherapy was able to achieve a superior mPFS *vs.* chemotherapy alone (13.0 *vs.* 8.9 months, HR 0.53, 95% CI: 0.31–0.91; P=0.0102). mOS has not yet been met, and the 12-month OS has been 75% for those with pembrolizumab and chemotherapy *vs.* 72% for chemotherapy alone. The main adverse event with combination therapy were fatigue (64%), nausea (58%), anemia (32%), rash (27%) and vomiting (27%); the main adverse events with chemotherapy were anemia (53%), nausea (44%) and fatigue (40%). Grade 3–5 AEs were similar between groups (39% in the pembrolizumab plus chemotherapy group *vs.* 26% in the chemotherapy alone group), with similar treatment discontinuation rates (10% for the pembrolizumab arm compared to 13% for the chemotherapy only arm) and treatment-related deaths (one death in the pembrolizumab group secondary to sepsis, and two deaths in the chemotherapy alone group due to sepsis and pancytopenia) (28).

Atezolizumab

Atezolizumab (MPDL3280A) is an anti-PD-L1 IgG1 antagonist designed to antagonize antibody-dependent, cell-mediated cytotoxicity (ADCC) of activated T cells that may express PD-L1. It was approved on October 18, 2016 by the FDA for the treatment of patients with PD-L1 positive NSCLC whose cancer had progressed during or after first line standard treatments.

Atezolizumab in association with CT

Although not FDA approved in the first-line setting, preliminary reports from recent phase III studies have suggested benefit when atezolizumab is added to standard first-line, platinum-doublet chemotherapy for advanced NSCLC. The IMpower 150 trial (29) randomized patients with PD-L1-unselected, advanced, non-squamous NSCLC to chemotherapy (carboplatin and paclitaxel every 3 weeks) combined with either atezolizumab [1,200 mg IV every 3 weeks (arm A)], atezolizumab plus bevacizumab [15 mg/kg IV every 3 weeks (arm B)], or bevacizumab (arm C). Crossover on progression was not allowed. Co-primary endpoints of PFS and OS (arm B *vs.* arm C) were met, favoring the addition of atezolizumab and bevacizumab rather than bevacizumab alone to chemotherapy (HR for disease progression or death 0.62, 95% CI: 0.52–0.74). Notably, this PFS benefit was also observed in the 14% of enrolled patients who had EGFR- or ALK-positive NSCLC, all of whom had received at least one line of targeted therapy (HR 0.59, 95% CI: 0.37–0.94 for arms B *vs.* C, respectively). Details concerning OS have not been released.

The IMpower 131 trial (30) compare efficacy of chemotherapy (carboplatin and nab-paclitaxel) alone or combined with atezolizumab (1,200 mg IV every 3 weeks) in advanced squamous NSCLC patients unselected for PD-L1 status. Preliminary data showed improvement in PFS with the addition of atezolizumab.

Durvalumab

Durvalumab is another anti-PD-L1 IgG1 antibody designed to prevent ADCC. When administered as a single agent at 10 mg/mg every 2 weeks, durvalumab shows encouraging antitumor activity with a manageable safety profile, particularly as front-line therapy and in high PD-L1 expression patients.

In a phase I/II study by Antonia *et al.* (31) durvalumab (10 mg/kg every 2 weeks) showed an ORR of 27% in 59 treatment-naïve NSCLC patients. Histology did not show to influence ORR. The most common drug-related AEs were fatigue (15%), diarrhoea (12%) and decreased appetite (10%). In the expansion cohort, durvalumab demonstrated a global ORR of 17.5% for the overall population, with 27.1% in first-line setting, 18.8% in second-line and 13.0% in third or later lines. Thus, in summary, durvalumab is also being assessed as maintenance therapy after platinum-based chemotherapy.

Another phase II trial [SAPHIR02 Lung trial (32)] compare pemetrexed or durvalumab in non-squamous and durvalumab in squamous patients administered according to the identified molecular anomaly *vs.* the same treatments administered without considering the tumor genome analysis. Primary end point is PFS in the targeted drug arm compared with standard maintenance arm, and secondary endpoints include PFS with durvalumab compared with the standard maintenance arm; data are awaited.

Durvalumab in association with CT

The Canadian Cancer Trials Group Phase1B Study (IND. 226) (33) is evaluating the combination of platinum-based chemotherapy plus durvalumab with or without tremelimumab as front-line therapy in metastatic NSCLC patients, not selected for PD-L1 status. The primary endpoint was the safety and tolerability of durvalumab with or without tremelimumab in combination with each of four standard platinum-doublet regimens: nab-paclitaxel (with carboplatin) or gemcitabine, pemetrexed, etoposide (each with cisplatin). To date, have been reported only data from the cisplatin/pemetrexed cohort in non-squamous patients: durvalumab 15 mg/kg every 3 weeks and tremelimumab 1 mg/kg (multiple doses every 6 weeks) or 3 mg/kg (3 doses every 6 weeks). A maintenance with pemetrexed plus durvalumab was planned after completion of pemetrexed/cisplatin. An ORR of 53% was experienced among the 17 patients evaluable for response. The majority of AEs related to durvalumab or tremelimumab were less than or equal to grade 2, the most frequent including fatigue (46%), nausea/vomiting (25%), anorexia (21%) and diarrhoea (13%). Severe adverse events (SAEs) were observed in two patients (8%), one febrile neutropenia and lung infection/pneumonitis, being considered dose-limiting toxicity. Juergens *et al.* (33) concluded that this combination is safe in advanced NSCLC, regardless of PD-L1 expression and additional studies are planned.

ICIs for second and third-line treatment

Nivolumab

Nivolumab is FDA approved for the treatment of patients with advanced squamous NSCLC and non-squamous NSCLC who experience progression of disease on or after standard platinum-based chemotherapy (regardless of tumor PD-L1 protein expression).

Squamous NSCLC

Nivolumab has shown to be superior than docetaxel as second line therapy in the phase III CheckMate 017 trial (34). The study enrolled 272 patients with advanced, squamous NSCLC progressed during or after first line therapy with platinum-based doublet chemotherapy: patients were randomly assigned to nivolumab (3 mg/kg intravenously every 2 weeks) or docetaxel (75 mg/m^2 intravenously every 3 weeks). ORR was higher with nivolumab (20% *vs.* 9%), as was the duration of response (25.2 *vs.* 8 months). The mPFS was 3.5 months with nivolumab *vs.* 2.8 months with docetaxel (HR: 0.62; 95% CI: 047–0.81). Nivolumab showed a statistically significant improvement in OS *vs.* docetaxel (9.2 months, 95% CI: 7.3–13.3 months *vs.* 6.0 months, 95% CI: 5.1–7.3 months). PD-L1 expression did not shown correlation with any endpoint. Nivolumab was better tolerate with less frequent percentage of severe (grade 3 or higher) adverse events compared with docetaxel (7% *vs.* 54%). Any-grade pneumonitis was seen in 5% of patients treated with nivolumab (1% had grade 3 or higher pneumonitis).

Non-squamous NSCLC

In the phase III CheckMate 057 trial (35), 582 patients with advanced, progressive non-squamous NSCLC were randomly assigned to nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m^2 every 3 weeks). Nivolumab showed a statistically significant improvement in OS, the primary endpoint (mOS, 12.2 *vs.* 9.4 months). Ten percent of patients receiving nivolumab experimented severe (grade 3 to 4) treatment-related adverse effects, compared with 54% of those treated with docetaxel. Any-grade pneumonitis was reported in 1% of patients treated with nivolumab, with another 1% with any-grade interstitial lung disease; there were no reports of pneumonitis or interstitial lung disease among patients receiving docetaxel. Any degree of tumor PD-L1 expression (≥1% of tumor cells staining positive) was appreciated in 55% of evaluable samples and was associated with improved survival with nivolumab (PD-L1 1%, HR 0.59, P=0.06; PD-L1 5%, HR 0.43, P=0.0004; and PD-L1 10%, HR 0.4, P=0.0002). Interestingly, opposite to squamous population, PD-L1 negative, non-squamous NSCLC patients did not benefit from immunotherapy over chemotherapy (<1% PD-L1 OS HR 0.9, 95% CI: 0.66–1.24; <5% PD-L1 OS HR 1.01, 95% CI: 0.76–1.33; <10% PD-L1 OS HR 1.00, 95% CI: 0.76–1.31). Due to non-inferiority in term of efficacy and the better profile of toxicity, Nivolumab appear a desirable option over docetaxel. Taking into account these considerations, nivolumab was approved by the FDA as second line therapy for metastatic NSCLC with progression on or after standard therapy, regardless PD-L1 status.

Pembrolizumab

Pembrolizumab was approved by the FDA in October 2016, as second line therapy, for metastatic NSCLC patients with tumor PD-L1 expression and TPS ≥1% progressing on or

after platinum-based chemotherapy.

KEYNOTE-010 study was an open-label, multicenter, phase II/III trial which enrolled over one thousand patients with pretreated advanced NSCLC with tumor PD-L1 expression ≥1%. Patients were 1:1:1 randomly assigned to receive pembrolizumab 2 mg/kg (arm A) or 10 mg/kg (arm B) or docetaxel 75 mg/mq (arm C), every 3 weeks. Treatment was continued for 24 months or until PD or discontinuation caused by toxicity. Patients, with PS of 0 or 1, had no active brain metastasis or chronic immune disease. Primary endpoints were OS and PFS. In the overall population, mOS was 10.4 months for patients in arm A, 12.7 months in arm B and 8.5 months for patients enrolled in the control arm. OS were prolonged with pembrolizumab *vs.* docetaxel (P=0.0008 for pembrolizumab 2 mg/kg HR 0.71, 95% CI: 0.58–0.88 and P<0.0001 for pembrolizumab 10 mg/kg HR 0.61, 95% CI: 0.49–0.75). Patients with tumors PD-L1 expression ≥50% had significantly longer OS with pembrolizumab 2 mg/kg *vs.* docetaxel (median 14.9 *vs.* 8.2 months; P=0.0002, HR 0.54, 95% CI: 0.38–0.77) and with pembrolizumab 10 mg/kg *vs.* docetaxel (median 17.3 *vs.* 8.2 months; P<0.0001 HR 0.50, 95% CI: 0.36–0.70). In the overall population, only in patients with a PD-L1 TPS ≥50% of tumor cells, PFS was significantly longer for arm A (median 5.0 *vs.* 4.1 months; P<0.0001, HR 0.59, 95% CI: 0.44–0.78) and arm B (median 5.2 *vs.* 4.1 months; P<0.0001, HR 0.59, 95% CI: 0.45–0.78) compared to docetaxel. ORR was significantly higher for patients treated with pembrolizumab compared with docetaxel, both in the overall population (P=0.005 and 0.002 for arm A and B, respectively) and in the PD-L1 TPS ≥50% subgroup (P<0.0001 for each arm). Treatment with pembrolizumab was overall well tolerated. AEs were registered in 65% of all patients treated with pembrolizumab and 81.2% with docetaxel. AEs of grade 3–5 had a higher incidence in the docetaxel arm (35%) *vs.* pembrolizumab 2 mg/kg (13%) and 10 mg/kg (16%). Immune-related AEs were described in 19.5% of all patients treated with pembrolizumab and the most relevant were hypothyroidism. At the 2016 ASCO Annual Meeting were presented a post hoc analysis, that assessed the efficacy of pembrolizumab in patients with PD-L1 TPS of 1–49% enrolled in KEYNOTE-010. About 60% of enrolled patients had a TPS of 1–49%: in this population, pembrolizumab provided a significant prolonged survival when compared with docetaxel. mOS was 9.4 (arm A), 10.8 (arm B) and 8.6 months with docetaxel (arm C). Furthermore, pembrolizumab improved OS also in non-responding patients and this benefit seemed to be restricted to patients who remained on study for at least 18 weeks (36,37). No difference was reported in terms of PFS and ORR across all treatment arms, whereas median duration of response was longer for patients treated with pembrolizumab over docetaxel. Overall, pembrolizumab showed better efficacy and toxicity profile than docetaxel in PD-L1 ≥1% NSCLC for second-line treatment or more, and a greater efficacy in PD-L1 ≥50% NSCLC.

Atezolizumab

Atezolizumab monotherapy (1,200 mg IV every 3 weeks) was compared with standard salvage chemotherapy with docetaxel in the OAK study (38), a phase III trial enrolling 1,225 patients with PD-L1-unselected advanced NSCLC that had been treated with one or more platinum-based combination therapies. Patients were randomized by histology (squamous *vs.* non-squamous), prior chemotherapy regimens and PD-L1 expression. Patients treated with atezolizumab benefitted regardless PD-L1 status and histology. Atezolizumab prolonged OS in the first 850 patients enrolled, compared with docetaxel regardless of PD-L1 expression (mOS, 13.8 *vs.* 9.6 months; HR 0.73, 95% CI: 0.62–0.87) and in the 55 % of patients having tumors with ≥1% PD-L1 staining (mOS, 15.7 *vs.* 10.3 months; HR 0.74, 95% CI: 0.58–0.93). PFS did not statistically differ with atezolizumab compared with docetaxel (2.8 *vs.* 4 months; HR 0.95, 95% CI: 0.82–1.10). ORRs for atezolizumab and docetaxel were 14 and 13%, respectively. Atezolizumab was better tolerate with 15% of severe (grade 3 to 4) treatment-related adverse effects compared with 43% with docetaxel. Any-grade pneumonitis was reported in 1% of patients receiving atezolizumab, with severe pneumonitis (grade 3 to 4) in 0.7%. In the subgroup of patients with ≥50% of tumor cells or ≥10% of tumor area with immune cells staining for PD-L1, mOS was 20.5 *vs.* 8.9 months (HR 0.41, 95% CI: 0.27–0.64) in the atezolizumab arm compared to docetaxel. ORR was 31% *vs.* 11%, respectively. OS was prolonged with atezolizumab *vs.* docetaxel regardless of NSCLC histology (mOS, 15.6 *vs.* 11.2 months in non-squamous NSCLC; HR 0.73, 95% CI: 0.60–0.89; mOS, 8.9 *vs.* 7.1 months in squamous NSCLC; HR 0.73, 95% CI: 0.54–0.98).

Durvalumab

The phase II, open-label, single-arm ATLANTIC study (39,40), included three cohorts exposed to durvalumab at

10 mg/kg every 2 weeks: cohort 1 was EGFR-mutated or ALK-rearranged NSCLC patients with ≥25% PD-L1, and cohorts 2 and 3 were EGFR/ALK wild-type or unknown stage IIIB/IV NSCLC patients, with PD-L1 high (≥25% tumor cells; cohort 2) or PD-L1 high (≥90% tumor cells; cohort 3). Durvalumab was active with durable responses in this heavily pre-treated population.

S1400A Lung-Map (41) is an ongoing phase II trial (NCT02766335). This 'umbrella' trial included all screened patients not eligible for a biomarker-driven sub study in the second-line setting, with stage IV squamous NSCLC (refractory to prior systemic treatment regimens, including one platinum based), comparing durvalumab with docetaxel. The primary end point is ORR. Preliminary results were recently presented by Papadimitrakopoulou *et al.* A total of 68 patients had received durvalumab and 30 had received docetaxel as second-line treatment. The ORR was 16.2% (95% CI:7.4–24.9%) in the durvalumab arm, with 14.3% in patients with high PD-L1 expression (≥25%) and 6.9% in patients with low/negative PD-L1 (<25%). OS was 10.7 months (95% CI: 9.2–14.3) and 11.6 months (95% CI: 7.7–13.1), respectively. In the docetaxel group, the ORR was 6.7% (95% CI: 0–15.6%), with a 6-month PFS rate of 13.3% and mOS of 7.7 months (95% CI: 6.6–10.5). Durvalumab showed a manageable toxicity profile: most AEs were low grade with 34% of patients having a G3/4 treatment-related AEs, leading to discontinuation in 9%.

ICIs for adjuvant and neoadjuvant treatment in NSCLC

Pembrolizumab is being assessed in PD-L1 positive NSCLC in adjuvant setting to improve the cure rate of NSCLC in early stage. PEARLS trial (Pembrolizumab *vs.* Placebo for Patients with Early Stage NSCLC After Resection and Completion of Standard Adjuvant Therapy) is a 1:1 randomized, placebo-controlled, phase III study evaluating pembrolizumab after surgery and adjuvant chemotherapy. Primary endpoint is disease-free survival and it is currently underway (42). In the perioperative setting there is SAKK 16/14 trial, a phase II, multicenter, single-arm study, that compare durvalumab with standard adjuvant therapy in resectable NSCLC regardless of PD-L1 expression and histology. The primary endpoint is event-free survival at one year; the secondary endpoints include OS, ORR, complete resection, recurrence pattern, down-staging and toxicity (43).

Nivolumab is being evaluated in NSCLC in the neoadjuvant setting while after surgical resection, standard adjuvant therapy is planned: primary endpoint is safety and exploratory endpoints are tumor markers and pathologic response. To note that, in a squamous tumor that had a brisk T cell response, two of the three patients demonstrated major response and one complete response (44).

Conclusions

Immune-checkpoint inhibitors have revolutionized the treatment of lung cancer. Immunotherapy has become an interesting field of investigation in NSCLC therapy, as a result of the success of emerging multiple antibody inhibitors of PD-1/PD-L1 in clinical trials. This therapeutic approach has shown efficacy as first- second- and even third-line treatment in patients with NSCLC. The future for checkpoint blockade immunotherapy as monotherapy and in combination with novel agents or radiotherapy or standard chemotherapy appears bright in lung cancer. However, there are many unanswered questions concerning the proper use of these new agents including the best sequence, the identification of biomarkers in those patients with durable remission and the correct duration of therapy, what lead to acquired resistance. In the next years, it is likely that significant advancement will be made in addressing many of these questions.

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Footnote

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