Chapter 5

Immunotherapy in Advanced Lung Cancer Treatment

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Abstract

Despite the improvement in overall survival (OS) by platinum-based chemotherapy (NSCLC Meta-Analyses Collaborative Group, 2008), prognosis remains unsatisfactory for patients with advanced non-small cell lung cancer (NSCLC). We discuss in this chapter the new era of advanced lung cancer systemic therapy represented by immunotherapy. First of all I presented one of the modalities of immunological diagnostics based on new technology. The mechanism of action of the immunoagents is shortly described. In the in most part of the chapter, the main immunotherapeutic agents used in lung cancer immunotherapy are analyzed: vaccines, cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitors, and checkpoint inhibitors. In the end of the chapter, the combination between immunotherapeutic agents is discussed.

Keywords: lung cancer, systemic treatment, immunotherapy

1. Immunotherapeutic diagnosis

In order to have a therapy, it is known that we must first have a correct diagnosis. In this respect, we present an evolved oncology diagnostic system (http://www.carismolecularintelligence.com/i-o/). First of all, immunotherapy options should be sought through the development of complex immunoregulatory pathways. One of the systems that can be used in immunological diagnosis is Caris Molecular Intelligence. This system provides oncologists with reliable molecular information to make decisions about the use of immunotherapy. The tests are validated for testing PD-L1, MSI, and tumor mutation load (TML). Programmable cell death-ligand 1 (PD-L1) is one of the most important control immune proteins that mediates tumor-induced suppression by T-cell downregulation. Expression of PD-L1 may indicate a more likely response to immunotherapy. Of course, a perfect marker to predict the response

to PD-L1 inhibitor therapy has not been validated for the moment, but with these tests, we have an important orientation (Cochrane Collaboration Guidelines).

Microsatellite instability (MSI) is caused by the failure of the mismatch repair (MMR) system. MSI-High correlates with the increase in neoantigenic burden, which is more likely to respond favorably to immunotherapy.

Tumor mutation load (TML) measures the total number of non-sinusoidal somatic mutations identified on the megabase of the genome coding region. High TML supports neoantigens and responds favorably to immunotherapy.

2. Immuno-oncological agents: action mechanism

The immune system is capable of recognizing and destroying tumor cells as well as pathogens. However, one of the hallmarks of cancer is its ability to avoid the immune system [1].

There are a lot of complex interactions between the cells presenting the antigen, the lymphocytes, and the tumor cells. The most studied is the cell membrane T-cell receptor binding, called programmed cell death 1 (PD-1), and its ligands 1 or 2 (PD-L1 or PD-L2) expressed by some tumor cells. This interaction results in inactivation of T lymphocytes in an effort to avoid the immune response against tumor cells [2, 3]. Inhibition of this pathway is the target of inhibitors of immune control points. There are two types of agents: anti-PD-1 and anti-PD-L1 monoclonal antibodies.

Among these, anti-PD-1 agents that bind the lymphocyte receptor and block both PD-L1 and PD-L2 bindings are considered to be more toxic than anti-PD-L1 due to their broad spectrum of clinical activity. However, this has not been confirmed by recent clinical trials [4, 5]. Pembrolizumab and nivolumab, two monoclonal antibodies against PD-1, as well as avelumab monoclonal IgG1 anti-PD-L1 antibodies, atezolizumab and MEDI4736, showed consistent antitumor activity against NSCLC [6].

3. Lung cancer immunotherapy

Despite an improvement in overall survival (OS) by platinum-based chemotherapy (NSCLC Meta-analyses Collaborative Group, 2008), prognosis remains unsatisfactory for patients with advanced NSCLC, with a median survival of 8–12 months [7, 8].

In 2006, there was a plateau for chemotherapy in a study that none of the four chemotherapy regimens compared offered a significant advantage over the others in the treatment of advanced non-small cell lung cancer [8].

The development in molecular characterization of NSCLC, especially in histological subtypes of adenocarcinoma, has allowed the identification of key genetic aberrations in NSCLC, which can be addressed with molecular targeted therapy. Genetic aberrations in EGFR, ALK, ROS1, RET, BRAF, and NTRK have a predictive value for susceptibility to receptor tyrosine

kinase inhibitors [9–11]. Despite the success of molecular diagnostics, acquired resistance and disease progression are inevitable [9–11].

Treatment options for patients with small-cell lung cancer (SCLC) where the disease progressed after platinum-based chemotherapy are even more limited.

Immunotherapy in cancer has been described as any therapy that interacts with immunity. Immunotherapy in cancer can be classified into passive and active types. Passive immunotherapy has been described as administration of an active agent produced or generated outside the patient's body. Theoretically, such an approach does not depend on the host's own immune system to have an effect. Examples of passive immunotherapy include the use of monoclonal antibodies, such as trastuzumab [12, 13], and adoptive cell therapy, such as tumor-infiltrating lymphocytes (CAR-T cell) [14]. This new approach of therapy has and specific toxicity: cytokine release syndrome, neurologic toxicity, "on target/off tumor" recognition, and anaphylax [15].

Active immunotherapy involves stimulating or determining the host's immune system to recognize a tumor as a foreign. Examples of active immunotherapy include vaccination against cancer with tumor antigens and an adjuvant enhancement of immune cell function with cytokines, as well as targeting of immune control regulators with immune control inhibitor control.

Inhibitors targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death 1 (PD-1)/programmed cell death-ligand 1 (PD-L1) are used in NSCLC and SCLC.

Studies that examine the efficacy of cytokines such as interferon alpha and interleukin-2 (IL-2) in lung cancer patients were negative and will not be discussed [16].

3.1. Vaccines against cancer

Therapeutically acting vaccines in cancer are designed to eliminate cancer cells by increasing their own immune responses. This type of vaccine contrasts with prophylactic vaccines, which are usually administered to healthy people. Cancer vaccines can be classified into several major types, such as cellular vaccines, peptide vaccines, and genetic vaccines [17].

Vaccines against cancer, despite despite setbacks attempt to harness the patient's immune system to fight tumor cells and show a promise in clinical trials.

Cellular vaccines may be either autologous or allogeneic. Autologous tumor cell vaccines are developed by isolating tumor cells from an individual (patient), creating a vaccine that is administered back to the same patient, usually in combination with an adjuvant that stimulates the immune system. These vaccines have been among the first types of cancer vaccines tested and have the advantage of provoking an immune response to a wide range of tumors. Antigens expressed by the patient's own tumor result in tumor destruction. Although similar to autologous vaccines, allogeneic vaccines are obtained by administering tumor cells to a patient, creating a vaccine that is then administered to another patient with the same type of cancer [18].

Unlike cellular vaccines that are made directly from patient tumors, peptide vaccines are often synthesized in vitro to mimic tumor-associated proteins in order to elicit an immune response against tumor cells expressing that protein [19].

Genetic vaccines are composed of DNA molecules or synthetic RNAs encoding tumor-associated proteins and are administered either alone or packaged in a nonpathogenic virus. The genetic material is taken up by the recipient cells, translated into proteins encoded, processed, and presented to the immune system to elicit the immune response against tumor-associated proteins [20].

DNA vaccination has suddenly become a favored strategy for inducing immunity. The molecular precision offered by gene-based vaccines, together with the facility to include additional genes to direct and amplify immunity, has always been attractive. However, the apparent failure to translate operational success in preclinical models to the clinic, for reasons that are now rather obvious, reduced initial enthusiasm. Recently, novel delivery systems, especially electroporation, have overcome this translational block. Here, we assess the development, current performance, and potential of DNA vaccines for the treatment of cancer.

Early studies on Calmette-Guerin adjuvant Calmette-Guerin adjuvant and neoadjuvant bacillus vaccine therapy were negative [21, 22].

In the modern age, multiple-stage, locally advanced, and advanced NSCLC vaccine studies have been conducted. The recombinant protein-associated anti-melanoma-antigen-associated antigen (MAGE)-A3 vaccine has been extensively studied in adjuvant therapy after complete resection. A randomized phase II trial showed that for patients with stage IB–II, MAGE-A3 in NSCLC, who did not receive any adjuvant chemotherapy, there was a tendency toward survival gain. And, survival without signs of disease was positively influenced by the MAGE-A3 vaccine compared to placebo after a median follow-up to 70 months (HR, 0.75; 95% CI, 0.46–1.23; p = 0.254) [23].

However, clinical benefit was not found in the randomized, double-blind, placebo-controlled phase III (MAGRIT) study in fully resected NSCLC IB–IIIA MAGE-A3, with or without adjuvant chemotherapy. Subsequently, for the total population in this study, median disease-free survival was 60.5 months for the MAGE-A3 vaccine group and 57.9 months for the placebo group (HR, 1.02; 95% CI, 0.89–1.18; p = 0.74). In the subgroup that performed adjuvant chemotherapy, median disease-free survival was 58.0 months in the vaccine group and 56.9 months in the placebo group (HR, 0.97; 95% CI, 0.80–1.18; p = 0.76) [24].

Tecemotide (L-BLP25) is a peptide vaccine based on a 25 amino acid sequence of mucin-1 (MUC1), which has shown promising activity in locally advanced NSCLC in a phase II study [25].

Subsequently, the result led to the initiation of two randomized trials. One was a complete phase III trial, START, in which the placebo tecemotide was compared for patients with stage III NSCLC without disease progression after chemoradiation therapy [26].

The second study, INSPIRE, was a randomized phase II study of Asian patients that did not have convincing results after the Asian phase [27].

Analysis of the START study showed that there was no significant difference in median overall survival between the tecemotide arm and placebo arms (25.6 months vs. 22.3 months; HR adjusted, 0.88; 95% CI, 0.75–1.03; p = 0.123). However, following a prespecified subgroup

analysis, median overall survival was different between the vaccine arm and the placebo arm for patients receiving concomitant chemoradiation therapy (30.8 months vs. 20.6 months; HR, 0.78; 95% CI, 0.64–0.95; p = 0.016) compared with patients receiving sequential chemoradiation therapy (19.4 months vs. 24.6 months; HR, 1.12; 95% CI, 0.87–1.44; p = 0.38) [28].

In the advanced stage of the disease, the TG4010, another vaccine targeting MUC1, used a viral vector to express both MUC1 and IL-2 (a T-cell stimulus). The results were promising.

In a phase IIb study (TIME) results (part of the randomized, double-blind, placebo-controlled, phase IIb/III study), showed that in the overall population, disease-free survival was 5.9 months for the TG4010 group and 5.1 months for placebo (HR, 0.74; 95% CI, 0.55–0.98; p = 0.019) [29].

Belagenpumatucel-L is an allogeneic tumor cell tumor vaccine derived from four cell lines of NSCLC with different histologies, also express an antisense transgene for transforming beta2 growth factor that reduces the regulation of its immunosuppressive transformation. The results of a phase II study suggested clinical efficacy in patients with advanced NSCLC, and a randomized phase III (STOP) study was initiated. Patients with stage III/IV NSCLC in whom the disease did not progress after platinum-based chemotherapy received either belagenpumatucel-L or placebo [30]. There was no significant difference in overall survival between the two arms (20.3 months vs. 17.8 months; HR, 0.94; p = 0.594); there was also no difference in progression-free survival (PFS) (4.3 months vs. 4.0 months; HR, 0.99; p = 0.947) [30].

The epidermal growth factor receptor (EGFR) is an important signaling pathway in NSCLC, and a vaccine has been developed against its related EGF ligand, using recombinant human EGF coupled to a carrier protein. In a randomized phase II trial, patients with stage IIIB/IV NSCLC were randomly assigned to receive the best supportive treatment or EGF vaccines after first-line chemotherapy [31]. In the global population, there was a trend toward improved overall survival and a significant survival advantage for patients who had a good antibody response to the EGF [31].

A subsequent phase III study included patients with stage IIIB/IV NSCLC who were randomly assigned to the first line of chemotherapy to make the vaccine or the best supportive care. In the safety population, overall survival was 10.83 months for the vaccine arm and 8.86 months for the control arm [32]. For patients who received at least four doses of vaccine, overall survival differed significantly between the vaccine group and the supportive treatment group (12.43 months vs. 9.43 months; HR, 0.77; p = 0.036). In addition, overall survival was longer (14.66 months) for patients vaccinated with high concentrations of EGF at the baseline [32].

3.2. CTLA-4 inhibitors

Ipilimumab in combination with chemotherapy has been studied in patients with advanced NSCLC who have not received the previous treatment. In this phase II triple-arm study, patients were randomly assigned to chemotherapy (carboplatin plus paclitaxel), sequential chemotherapy with ipilimumab, or chemotherapy with concomitant ipilimumab. The primary endpoint of the study was overall survival and progression-free survival, which was 4.6 months for the chemotherapy arm, 5.7 months for the sequential ipilimumab chemo arm

(HR, 0.72; p = 0.05), and 5.5 months for the ipilimumab arm concomitantly with chemotherapy (HR, 0.81; p = 0.13) [33]. Progression-free survival was better in NSCLC patients with squamous histology than patients with nonsquamous NSCLC. To confirm these results, a larger phase III trial (NCT02279732) was initiated for patients with squamous cell NSCLC.

Conclusion of the study was that phased ipilimumab plus paclitaxel and carboplatin improved irPFS and PFS, which supports additional investigation of ipilimumab in NSCLC [33].

In the Govindan study ipilimumab added to chemotherapy (carboplatin plus paclitaxel) did not improve the survival of patients with advanced NSCLC [34].

3.3. PD-1 and PD-L1 inhibitors

PD-1 inhibitors include agents such as nivolumab and pembrolizumab. Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that disrupts PD-1-mediated signaling, thus releasing T cells from their inhibitory interaction with PD-L1 and PD-L2. Pembrolizumab is a monoclonal antibody, the humanized IgG4/kappa isotype, which also blocks the binding of PD-L1 and PD-L2 to PD-1 on T cells, resulting in activation of tumor-specific cytotoxic T cells. Cytotoxicity is complement-dependent (CDC) (Alsaab) [35].

Action may be important because cytotoxicity can cause an exhaustion of activated T cells and infiltrating lymphocytes into tumors. PD-1 is expressed on effector T cells and other immune cells [36].

Checkmate 026 did not show a benefit in PFS for nivolumab versus chemotherapy. The authors reveal the fact that nivolumab monotherapy did not result in longer progression-free survival than platinum-based chemotherapy as first-line treatment for stage IV or recurrent NSCLC in a broad population of patients with a PD-L1 expression level of 5% or more. Overall survival with single-agent nivolumab was similar to overall survival with platinum-doublet chemotherapy. Nivolumab had a favorable safety profile as compared with chemotherapy, and no new safety signals were observed [37].

The new data from the phase 1b CA209-003 study were presented at the American Association for Cancer Research annual meeting: "The longest follow-up to date on patients treated with nivolumab for advanced non-small cell lung cancer (NSCLC) shows a 16% 5-year overall survival (OS) rate, according to new results presented here at the American Association for Cancer Research annual meeting." Suzanne Topalian, from Johns Hopkins University, and a coinvestigator (April 03, 2017): "the 5-year overall survival really quadrupled the survival that we would otherwise expect if these same patients had received chemotherapy" (April 03, 2017) (https://www.medscape.com/viewarticle/878148).

Nivolumab provides a long-term clinical benefit and a favorable tolerability profile compared to docetaxel in previously treated patients with advanced NSCLC [38]. FDA approved of nivolumab for second-line treatment of patients with advanced NSCLC.

In a single-arm phase II study (CheckMate 063) with nivolumab for patients with squamous cell NSCLC who were treated with third-line therapy and beyond, the partial response rate

was 14.5, and 26% of patients had a stable disease [4]. Overall survival was 8.2 months, and 1-year survival was about 41%. Noteworthy, the study population was very refractory to treatment, with 65% of patients treated with at least three previous systemic therapy lines. In addition, 61% of patients had disease progression as the best response to the latest therapy [39].

In another phase II trial (CheckMate 153), 824 patients with advanced NSCLC were treated for 1 year with nivolumab. The partial response and stable disease rates were 12 and 44%, respectively. The answers were independent of the PD-L1 expression [40].

The second-line treatment with nivolumab was superior to docetaxel in two subsequent phase III randomized phases in advanced NSCLC patients receiving double-blind platinum chemotherapy.

In a study of 272 patients with squamous NSCLC (CheckMate 017), median overall survival and 1-year survival were better for nivolumab than for docetaxel. The risk for death was 0.59 with nivolumab ($p < 0.001$) [6].

In the study (CheckMate 057), which included patients with advanced nonsquamous NSCLC histology, nivolumab in line 2 was also associated with better overall survival and survival over 1 year, also better than docetaxel (HR, 0.73) [41]. In subset analysis of subset biomarker values, PD-L1 expression ≥1, ≥5, and ≥10% corresponded to an improvement in PFS with a HR of 0.70, 0.54, and 0.52, respectively, and in OS with a HR of 0.58, 0.43, and 0.40. In contrast, in tumors with a low PD <1, <5, and <10% PD-L1 expression, HR for PFS was 1.19, 1.31, and 1.24, respectively, and for OS was 0.87, 0.96, and 0.96 [41].

The safety and efficacy of single-agent nivolumab in first-line treatment of patients with advanced NSCLC have been reported in CheckMate 012 adverse events occurred in 71% of patients, the most common being fatigue (29%), rash (19%), nausea (14%), diarrhea (12%), pruritus (12%), and arthralgia (10%). The overall confirmed response was 23%, and progression-free survival and overall survival were 3.6 months and 19.4 months. The nonprogression-free survival rate of 24 weeks was 41%. The survival rate at 1 year was 73% [42].

Recently, in a phase III study, first-line nivolumab compared to a platinum-based chemotherapy for tumors with a PD-L1 expression of 5% or greater (CheckMate 026) showed progression-free survival greater for the chemotherapy arm, but overall survival was better for the nivolumab arm [43]. The objective response rate was lower for the nivolumab arm. In conclusion, nivolumab monotherapy did not result in longer progression-free survival than platinum-based chemotherapy as first-line treatment for stage IV or recurrent NSCLC. In this study the PD-L1 expression level was 5% or more [43].

3.4. Activity in SCLC

SCLC is most often an extended stage disease at the time of diagnosis. Although the first line of platinum-based chemotherapy has activity, the disease progresses inevitably, and response rates in the second-line treatment are low and are not sustainable. The activity and safety of nivolumab

with or without ipilimumab in previously treated SCLCs were evaluated in CheckMate 032. The objective response rate was 10% with nivolumab 3 mg/kg alone, 23% with 1 mg/kg of nivolumab in combination with 3 mg/kg of ipilimumab, and 19% with 3 mg/kg of nivolumab in combination with 1 mg/kg of ipilimumab. PD-L1 expression was not associated with responses [44].

Patients with small-cell lung cancer (SCLC) and a high tumor mutation burden had an important increase in survival (near doubling in response rate and 1-year overall survival) with ipilimumab combined with nivolumab versus nivolumab alone.

The efficacy and safety of pembrolizumab at two different doses in previously untreated patients, advanced NSCLC, were reported in the Keynote-001 study. The objective response rate was 19.4%, and the median response time was 12.5 months. The progression-free survival was 3.7 months, and overall survival was 12.0 months [45]. The objective response rate was 18% in those treated previously and 24.8% of untreated patients. The objective response rate was 45.2%, and no time to progression was 6.3 months. The objective response rate was similar regardless of dose, schedule, and histology subtype. The response rate was higher among smokers than nonsmokers. Treatment-related adverse events of any grade occurred in 70.9% of patients, 9.5% having a grade 3 or higher adverse event [45].

Pembrolizumab was evaluated in a phase II/III study of patients previously treated with advanced NSCLC (Keynote-010). A total of 1034 patients were randomized to receive either 2 mg/kg dose or 10 mg/kg of pembrolizumab or 75 mg/m^2 of docetaxel every 3 weeks [46]. All patients had at least 1% tumor cells that were positive for PD-L1. Overall survival was improved with both doses of pembrolizumab compared to docetaxel. Among patients with at least 50% of the tumor cells expressing PD-L1, overall survival rates were 14.9 and 17.3 months with pembrolizumab at doses of 2 mg/kg and 10 mg/kg, respectively, compared to 8.2 months with docetaxel. Any degree of treatment-related adverse events occurred in 63% of pembrolizumab 2 mg/kg and 66% of patients receiving 10 mg/kg. The treatment-related toxicity was higher (81%) in the docetaxel arm.

Grade 3–5 treatment-related adverse events were less common in pembrolizumab-treated patients (2 mg/kg (13%), 10 mg/kg (16%)) versus docetaxel (35%) [46].

The Keynote-024 phase 3 clinical trial was the basis for pembrolizumab approval as a first-line treatment for patients with a diagnosis of metastatic NSCLC for whom PD-L1 expression is in 50% or more of tumor cells. Keynote-024 is a randomized, open-label phase 3 study evaluating pembrolizumab monotherapy at a fixed dose of 200 mg compared to the platinum-based chemotherapy standard for the treatment of patients with metastatic NSCLC with both squamous and unscrupulous histologies.

In phase III trial for first-line therapy of patients with advanced NSCLC (Keynote-024), with a PD-L1 tumor expression of 50% or greater, patients were randomly assigned to pembrolizumab- or platinum-based chemotherapy doublets, and progression-free survival was significantly better for pembrolizumab (HR, 0.50, 95% CI, 0.37–0.68; $p < 0.001$) median 10.4 months [47].

Overall survival was 0.60 (95% CI, 0.41–0.89; $p = 0.005$). The estimated percentage of patients in life at 12 months with pembrolizumab was 70%. In addition, the response rate was higher for pembrolizumab than for chemotherapy. Adverse events associated with pembrolizumab

therapy were fewer than chemotherapy. The results are innovative because this is the first to demonstrate the superiority of anti-PD-1 therapy to platinum [47].

3.5. Activity in SCLC

Preliminary data from a multicohort phase Ib study on pembrolizumab with previously treated PD-L1-positive subjects include a 25% objective response rate and a 31% disease control rate [48].

3.6. PD-L1 inhibitors

3.6.1. Avelumab and atezolizumab

PD-L1 inhibitors also inhibit PD-1/PD-L1 interactions. PD-L1 inhibitors include atezolizumab, durvalumab, and avelumab. Atezolizumab and durvalumab are human IgG1 anti-PD-L1 antibodies with mutations in their Fc domains to eliminate both antibody-dependent cell-mediated cytotoxicity (ADCC) activity and complement-dependent cytotoxicity (CDC) activity. Avelumab is a fully human IgG1 anti-PD-L1 monoclonal antibody and, unlike another PD-1/PD-L1 inhibitor, has been shown to retain ADCC and CDC activity in preclinical studies [49].

In a single-arm phase II study (IMpower 110 study), the objective response rate for atezolizumab was 16%, regardless of PD-L1 expression in immune cells, and 28% in patients with 5% or more high expression PD-L1 [50]. Atezolizumab (MDPL3280A) clearly is an added value in the treatment of advanced-stage pretreated NSCLC. Its interest in contrast with other immune checkpoint inhibitors relies on its efficacy, even in low or no PD-L1 expression subgroups. Considering that the efficacy of anti-PD-1 such as pembrolizumab or nivolumab is overall higher in PD-L1-positive patients, atezolizumab might be preferable in PD-L1-negative patients. It will be necessary to consider other variant methods of PD-L1 testing used for each therapy to further explore this hypothesis [51].

In a randomized phase II (Poplar) study in patients receiving platinum-based chemotherapy, atezolizumab was associated with a higher overall survival (HR, 0.73; CI 95%, 0.53–0.99; $p = 0.04$) [52]. In another phase II trial (BIRCH), advanced NSCLC patients who were selected for PD-L1 expression received atezolizumab as first-line or as a subsequent therapy. Response rates ranged from 17 to 27% [53], and median overall survival was 14 months for patients receiving atezolizumab as the first line of therapy. Overall survival has not yet been achieved for patients receiving atezolizumab as a subsequent therapy [53]. In the OAK study, a phase III trial of previously treated NSCLC patients randomly assigned to atezolizumab or docetaxel, the overall survival was significantly better for atezolizumab (13.8 months vs. 9.6 months; HR, 0.73; 95% CI, 0.62–0.87; $p = 0.0003$) [54]. The OAK study led to the FDA approval of atezolizumab for second-line therapy of advanced NSCLC [54].

3.6.2. Durvalumab

In a phase I/II study with durvalumab in 2009 in the first-line treatment in NSCLC patients irrespective of PD-L1 status, the overall response rate was 27 and 29% for PD-L1-positive tumors (defined as ≥25% of tumor cells expressing PD-L1) and 11% in PD-L1-negative tumors [55]. In a phase II trial of patients with advanced NSCLC who received at least two previous systemic therapy lines, the activity was extremely encouraging. The objective response rate

and survival rate at 1 year increased according to the PD-L1 expression: 7.5% (PD-L1 expression less than 25%), 16.4% (more than 25% expression), and 30.9% (greater than 90% expression). The corresponding 1-year survival rates were 34.5, 47.7, and 50.8% [56].

The study PACIFIC was presented to the ESMO Congress 2017 and was a randomized, double-blind, international, phase 3 study comparing durvalumab as consolidation therapy with placebo in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after platinum-based chemoradiotherapy. Median progression-free survival as assessed by means of blinded independent central review was 16.8 months (95% confidence interval [CI], 13.0–18.1) with durvalumab versus 5.6 months (95% CI, 4.6–7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42–0.65; two-sided $p < 0.001$). Authors consider that this study will change the clinical practice [57].

3.7. Combinations of immunotherapy agents

CTLA-4 and PD-1/PD-L1 are combination. CTLA-4 inhibitors are also studied in conjunction with PD-1 and PD-L1 inhibitors. Results of preclinical studies indicate that this combination can work synergistically to produce improved antitumor activity [58].

Nivolumab was combined with ipilimumab for first-stage NSCLC in setting up in a phase I (CheckMate 12) study. The results included objective response rates ranging from 13 to 39%.

In NSCLC, the first-line nivolumab plus ipilimumab had a tolerable safety profile and showed an encouraging clinical activity characterized by a high response rate and durable response. In our study, the results of this study are the first suggestion of improved benefit compared with anti-PD-1 monotherapy in patients with NSCLC, supporting further evaluation of this combination in a phase 3 study [59].

Durvalumab was combined with the tremelimumab CTLA-4 inhibitor in a phase Ib study of patients with advanced NSCLC. Although many adverse events occurred during the study dose phase, the antitumor activity (23% objective response rate) was evident regardless of the PD-L1 status in the evaluable patients in the dose study—the expansion phase of the study [60].

In a phase III randomized study, the frontline durvalumab, either in combination with tremelimumab or as a single agent, did not improve progression-free survival (PFS) in patients with stage IV metastatic non-small cell lung cancer (NSCLC) compared with standard platinum-based chemotherapy [61].

4. Conclusions

Immunotherapy has become one of the most important therapeutic tools in advanced lung cancer. Existing studies have revealed a response rate of between 13 and 39%. It is also important that this therapy, unlike TKI-targeted therapy, also responds to smokers who make up most of the lung cancer patients.

Another important benefit from immunotherapy in advanced lung cancer is that squamous non-small cell lung cancer also responds to this therapy. Some promising results are and in treatment of small-cell lung cancer.

From existing studies, it is trembling that immunotherapy can improve survival compared to chemotherapy in a selected patient population, both in the first line and in the second line.

There is not yet a valid predictive marker that can be used to choose patients who will respond to immunotherapy. Currently, the only marker used is PD-1 expression that does not have a good validity. For the moment, there are not criteria to select patients for treatment with PD-1 or PD-L1 inhibitor because data to compare these two pathways is lacking. Better results were however obtained with a percent of PD-L1more then 50%. More study are needed to define the best combination of immunotherapy with chemotherapy or radiotherapy.

Vaccine therapy is promising but needs additional evaluation. Vaccine in combination with other therapeutic modalities especially checkpoint inhibitors is possible to have some benefits and must be studied.

Many guidelines are developed to treat side effects of immunotherapy. Despite a correct supportive therapy, some side effects are life-threatening. But generally, the quality of life of patients treated with immunotherapy is improved.

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