We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 5

Immunotherapy in Advanced Lung Cancer Treatment

Alexandru C. Grigorescu

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77005

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.

Author details

Alexandru C. Grigorescu

Address all correspondence to: alexgrigorescu2004@yahoo.com

Department of Medical Oncolog, Institute of Oncology Bucharest, Romania

References

[1] Hanahan D, Weinberg RA. Hallmarks of cancer: The next generation. Cell. 2011; **144**(5):646-674

[2] Pilotto S, Kinspergher S, Peretti U, et al. Immune checkpoint inhibitors for non-small-cell lung cancer: Does that represent a 'new frontier'? Anti-Cancer Agents in Medicinal Chemistry. 2015;**15**(3):307-313

[3] De Mello RA, Pousa I, Pereira D. Nivolumab for advanced squamous cell lung cancer: What are the next steps? The Lancet Oncology. 2015;**16**(3):234-235

[4] Rizvi NA, Mazières J, Planchard D, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): A phase 2, single-arm trial. The Lancet Oncology. 2015;**16**(3):257-265

[5] Brahmer JR, Drake CG, Wollner I, et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: Safety, clinical activity, pharmacodynamics, and immunologic correlates. Journal of Clinical Oncology. 2010;**28**(19):3167-3175

[6] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. The New England Journal of Medicine. 2015; **373**(2):123-135

[7] Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. The New England Journal of Medicine. 2002;**346**(2):92-98

[8] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DHN. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. New England Journal of Medicine. 2006;**355**(24):2542-2550

[9] Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA, Fukuoka M. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. The New England Journal of Medicine. 2009;**361**(10): 947-957. DOI: 10.1056/NEJMoa0810699. Epub 2009 Aug 19

[10] Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, Doebele RC, Le LP, Zheng Z, Tan W, Stephenson P, Shreeve SM, Tye LM, Christensen JG, Wilner KD, Clark JW, Iafrate AJ. Crizotinib in ROS1-rearranged non-small-cell lung cancer. New England Journal of Medicine. 2014;**371**(21):1963-1971. DOI: 11.1056/NEJMoa1406766. Epub 2014 Sep 27

[11] Planchard D, Besse B, Groen HJM, Souquet PJ, Quoix E, Baik CS, Barlesi F, Kim TM, Mazieres J, Novello S, Rigas JR, Upalawanna A, D'Amelio AM Jr, Zhang P, Mookerjee B, Johnson BE. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: An open-label, multicentre phase 2 trial. Lancet Oncology. 2016;**17**(7):984-993. DOI: 10.1016/S1470-2045(16)30146-2. Epub 2016 Jun 6

[12] Chan BA, Hughes BGM. Targeted therapy for non-small cell lung cancer: Current standards and the promise of the future. Translational Lung Cancer Research. 2015;**4**(1):36-54

[13] Mazières J, Barlesi F, Filleron T, Besse B, Monnet I, Beau-Faller M, Peters S, Dansin E, Früh M, Pless M, et al. Lung cancer patients with *HER2* mutations treated with chemotherapy and *HER2*-targeted drugs: Results from the European EUHER2 cohort. Annals of Oncology. 2016;**27**(2):281-286. DOI: 10.1093/annonc/mdv573

[14] Johnson LA, Heemskerk B, Powell DJ Jr, Cohen CJ, Morgan RA, Dudley ME, Robbins PF, Rosenberg SA. Gene transfer of tumor-reactive TCR confers both high avidity and tumor reactivity to nonreactive peripheral blood mononuclear cells and tumor-infiltrating lymphocytes. Journal of Immunology. 2006;**177**(9):6548-6559. DOI: 10.4049/jimmunol. 177.9.6548

[15] Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ. Toxicity and management in CAR T-cell therapy. Molecular Therapy—Oncolytics. 2016;**3**:16011

[16] Testera WJ, Kim KM, Krigel RL, Bonomi PD, Glick JH, Asbury RF, Kirkwood JM, Blumg RH, Schillerb JH. A randomized Phase II study of interleukin-2 with and without beta-interferon for patients with advanced non-small cell lung cancer. Lung Cancer. 1999; **25**(3):199-206

[17] Cuppens K, Vansteenkiste J. Vaccination therapy for non-small-cell lung cancer. Current Opinion in Oncology. 2014;**26**(2):165-170

[18] de Gruijl TD, Van den Eertwegh AJM, Pinedo HM, Scheper RJ. Whole-cell cancer vaccination: From autologous to allogeneic tumor- and dendritic cell-based vaccines. Cancer Immunology, Immunotherapy. 2008;**57**:1569

[19] Rosenberg SA, Yang JC, Schwartzentruber DJ, Hwu P, Marincola FM, Topalian SL, Restifo NP, Dudley ME, Schwarz SL, Spiess PJ, Parkhurst MR, Kawakami Y, Seipp CA, Einhorn JH. Immunologic and therapeutic evaluation of a synthetic peptide vaccine for the treatment of patients with metastatic melanoma. Nature Medicine. 1998;**4**:321-327. DOI: 10.1038/nm0398-321

[20] Rice J, Ottensmeier CH, Stevenson FK. DNA vaccines: Precision tools for activating effective immunity against cancer. Nature Reviews Cancer. 2008;**8**:108-120. DOI: 10.1038/nrc2326

[21] Giaccone G, Debruyne C, Felip E, Chapman PB, Grant SC, Millward M. Phase III study of adjuvant vaccination with Bec2/Bacille Calmette-Guerin in responding patients with limited-disease small-cell lung cancer (European Organisation for Research and Treatment of Cancer 08971-08971B; Silva Study). Journal of Clinical Oncology. 2005;**23**(28):6854-6864. DOI: 10.1200/JCO.2005.17.186

[22] Al-Moundhri M, O'Brien M, Souberbielle BE. Immunotherapy in lung cancer. British Journal of Cancer. 1998;**78**:282-288. DOI: 10.1038/bjc.1998.486

[23] Vansteenkiste JF, Cho BC, Vanakesa T, De Pas T, Zielinski M, Kim MS, Jassem J, Yoshimura M, Dahabreh J, Nakayama H, Havel L, Kondo H, Mitsudomi T, Zarogoulidis K, Gladkov OA, Udud K, Tada H, Hoffman H, Bugge A, Taylor P, Gonzalez EE, Liao ML, He J, Pujol JL, Louahed J, Debois M, Brichard V, Debruyne C, Therasse P, Altorki N. Efficacy of the MAGE-A3 cancer immunotherapeutic as adjuvant therapy in patients with resected MAGE-A3-positive non-small-cell lung cancer (MAGRIT): A randomised, double-blind, placebo-controlled, phase 3 trial. The Lancet Oncology. 2016;**17**(6):822-835. DOI: 10.1016/S1470-2045(16)00099-1

[24] Tyagi P, Mirakhur B. MAGRIT: The largest-ever phase III lung Cancer trial aims to establish a novel tumor-specific approach to therapy. Clinical Lung Cancer. 2009;**10**(5):371-374

[25] Nokihara H, Katakami N, Hida T, Imamura F, Sakai H, Atagi S. Phase I/II study of tecemotide cancer immunotherapy for Japanese patients with unresectable stage III non-small cell lung cancer (NSCLC). Journal of Clinical Oncology. 2015;**33**(15_suppl):3036-3036

[26] Butts C, Socinski MA, Mitchell PL, Thatcher N, Havel L, Krzakowski M, Nawrocki S, Ciuleanu TE, Bosquée L, Trigo JM, Spira A, Tremblay L, Nyman J, Ramlau R, Wickart-Johansson G, Ellis P, Gladkov O, Pereira JR, Eberhardt WE, Helwig C, Schröder A, Shepherd FA, START trial team. Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): A randomised, double-blind, phase 3 trial. The Lancet. 2014;**15**(1):59-68

[27] Wu Y-L, Park K, Soo RA, Sun Y, Tyroller K, Wages D, Ely G, Yang JC-H, Mok T. INSPIRE: A phase III study of the BLP25 liposome vaccine (L-BLP25) in Asian patients with unresectable stage III non-small cell lung cancer. BMC Cancer. 2011;**11**:430. DOI: 10.1186/1471-2407-11-430

[28] Mitchell P, Thatcher N, Socinski MA, Wasilewska-Tesluk E, Horwood K, Szczesna A, Martín C, Ragulin Y, Zukin M, Helwig C, Falk M, Butts C, Shepherd FA. Tecemotide in unresectable stage III non-small-cell lung cancer in the phase III START study: Updated overall survival and biomarker analyses. Annals of Oncology. 2015;**26**(6):1134-1142. DOI: 10.1093/annonc/mdv104. Epub 2015 Feb 26

[29] Quoix E, Lena H, Losonczy G, Forget F, Chouaid C, Papai Z, Gervais R, Ottensmeier C, Szczesna A, Kazarnowicz A, Beck JT, Westeel V, Felip E, Debieuvre D, Madroszyk A, Adam J, Lacoste G, Tavernaro A, Bastien B, Halluard C, Palanché T, Limacher JM. TG4010 immunotherapy and first-line chemotherapy for advanced non-small-cell lung cancer (TIME): Results from the phase 2b part of a randomised, double-blind, placebo-controlled, phase 2b/3 trial. The Lancet Oncology. 2016;**17**(2):212-223. DOI: 10.1016/S1470-2045(15)00483-0. Epub 2015 Dec 23

[30] Giaccone G, Bazhenova LA, Nemunaitis J, Tan M, Juhász E, Ramlau R, van den Heuvel MM, Lal R, Kloecker GH, Eaton KD, Chu Q, Dunlop DJ, Jain M, Garon EB, Davis CS, Carrier E, Moses SC, Shawler DL, Fakhrai H. A phase III study of belagenpumatucel-L, an allogeneic tumour cell vaccine, as maintenance therapy for non-small cell lung cancer. European Journal of Cancer. 2015;**51**(16):2321-2329. DOI: 10.1016/j.ejca.2015.07.035. Epub 2015 Aug 14

[31] García B, Neninger E, de la Torre A, Leonard I, Martínez R, Viada C, González G, Mazorra Z, Lage A, Crombet T. Effective inhibition of the epidermal growth factor/epidermal growth factor receptor binding by anti-epidermal growth factor antibodies is related to better survival in advanced non-small-cell lung cancer patients treated with the epidermal growth factor cancer vaccine. Clinical Cancer Research. 2008;**14**(3):840-846. DOI: 10.1158/1078-0432.CCR-07-1050

[32] Rodriguez PC, Popa X, Martínez O, Mendoza S, Santiesteban E, Crespo T, Amador RM, Fleytas R, Acosta SC, Otero Y, Romero GN, de la Torre A, Cala M, Arzuaga L, Vello L, Reyes D, Futiel N, Sabates T, Catala M, Flores YI, Garcia B, Viada C, Lorenzo-Luaces P, Marrero MA, Alonso L, Parra J, Aguilera N, Pomares Y, Sierra P, Rodríguez G, Mazorra Z, Lage A, Crombet T, Neninger E, A phase III clinical trial of the epidermal growth factor vaccine CIMAvax-EGF as switch maintenance therapy in advanced non-small cell lung

cancer patients. Clinical Cancer Research. 2016;**22**(15):3782-3790. DOI: 10.1158/1078-0432.CCR-15-0855. Epub 2016 Feb 29

[33] Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Neal J, Lu H, Cuillerot JM, Reck M. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: Results from a randomized, double-blind, multicenter phase II study. Journal of Clinical Oncology. 2012;**30**(17):2046-2054. DOI: 10.1200/JCO.2011.38.4032. Epub 2012 Apr 30

[34] Govindan R, Szczesna A, Ahn MJ, Schneider CP, Gonzalez Mella PF, Barlesi F, Han B, Ganea DE, Von Pawel J, Vladimirov V, Fadeeva N, Lee KH, Kurata T, Zhang L, Tamura T, Postmus PE, Jassem J, O'Byrne K, Kopit J, Li M, Tschaika M, Reck M. Phase III trial of Ipilimumab combined with paclitaxel and carboplatin in advanced squamous non-small-cell lung cancer. Journal of Clinical Oncology. 2017;**35**(30):3449-3457. DOI: 10.1200/JCO.2016.71.7629. Epub 2017 Aug 30

[35] Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, Iyer AK. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: Mechanism, combinations, and clinical outcome. Frontiers in Pharmacology. 2017;**8**:561. DOI: 10.3389/fphar.2017.00561

[36] Chen J, Feng Y, Lu L, Wang H, Dai L, Li Y, Zhang P. Interferon-γ-induced PD-L1 surface expression on human oral squamous carcinoma via PKD2 signal pathway. Immunobiology. 2012;**217**(4):385-393. DOI: 10.1016/j.imbio.2011.10.016. Epub 2011 Nov 3

[37] Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu T-E, Badin F, Ready N, Jeroen T, Hiltermann N, Nair S, Juergens R, Peters S, Minenza E, Wrangle JM, Rodriguez-Abreu D, Borghaei H, Blumenschein GR Jr, Villaruz LC, Havel L, Krejci J, Jaime JC, Chang H, Geese WJ, Bhagavatheeswaran P, Chen AC, Socinski MA, for the CheckMate 026 Investigators. First-line Nivolumab in stage IV or recurrent non–small-cell lung Cancer. The New England Journal of Medicine. 2017;**376**:2415-2426. DOI: 10.1056/NEJMoa1613493

[38] Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, More S. Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: Two-year outcomes from two randomized, open-label, phase III trials (CheckMate 017 and CheckMate 057). Journal of Clinical Oncology. 2017;**35**(35):3924-3933. DOI: 10.1200/JCO.2017.74.3062

[39] http://www.esmo.org/Conferences/Past-Conferences/ELCC-2016-Lung-Cancer/News-Press-Releases/Updates-from-CheckMate-063-and-017-Trials-Confirm-Nivolumab-Efficacy-in-Patients-with-Advanced-Platinum-Refractory-Squamous-NSCLC

[40] Spigel D, Schwartzberg L, Waterhouse D, Chandler J, Hussein M, Jotte R, Stepanski E, Mccleod M, Page R, Sen R, Mcdonald J, Bennett K, Korytowsky B, Aanur N, Reynolds C. P3.02c-026 is nivolumab safe and effective in elderly and PS2 patients with non-small cell lung cancer (NSCLC)? Results of checkmate 153. Journal of Thoracic Oncology. 2017;**12**(1, Supplement):S1287-S1288

[41] Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, Chow LQ, Vokes EE, Felip E, Holgado E, Barlesi F, Kohlhäufl M, Arrieta O, Burgio MA, Fayette J, Lena H, Poddubskaya E, Gerber DE, Gettinger SN, Rudin CM, Rizvi N, Crinò L, Blumenschein GR Jr, Antonia SJ, Dorange C, Harbison CT, Finckenstein FG, Brahmer JR. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. The New England Journal of Medicine. 2015, 2015;**373**:1627-1639. DOI: 10.1056/NEJMoa1507643

[42] Antonia SJ, Gettinger SN, Goldman J, Brahmer J, Borghaei H, Chow LQ, Ready NE, Gerber DE, Juergens R, Shepherd F, Laurie SA, Young T, Geese WJ, Agrawal S, Li X, Hellmann MD. ORAL01.03: CheckMate 012: Safety and efficacy of first-line Nivolumab and Ipilimumab in advanced NSCLC. Journal of Thoracic Oncology;**11**(11, Supplement):S250-S251

[43] Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu T-E, Badin F, Ready N, Hiltermann TJN, Nair S, Juergens R, Peters S, Minenza E, Wrangle JM, Rodriguez-Abreu D, Borghaei H, Blumenschein GR Jr, Villaruz LC, Havel L, Krejci J, Jaime JC, Chang H, Geese WJ, Bhagavatheeswaran P, Chen AC, Socinski MA, for the CheckMate 026 Investigators. First-line Nivolumab in stage IV or recurrent non-small-cell lung Cancer. The New England Journal of Medicine. 2017;**376**:2415-2426. DOI: 10.1056/NEJMoa1613493

[44] Antonia SJ, Lopez-Martin JA, Bendell JC, Ott PA, Taylor MH, Eder JP. Checkmate 032: Nivolumab (N) alone or in combination with ipilimumab (I) for the treatment of recurrent small cell lung cancer (SCLC). Journal of Clinical Oncology. 2016;**34**(15_suppl):100-100

[45] Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, Carcereny E, Ahn M-J, Felip E, Lee J-S, Hellmann MD, Hamid O, Goldman JW, Soria J-C, Dolled-Filhart M, Rutledge RZ, Zhang J, Lunceford JK, Rangwala R, Lubiniecki GM, Charlotte Roach BS, Emancipator K, Gandhi L, for the KEYNOTE-001 Investigators. Pembrolizumab for the treatment of non–small-cell lung cancer. The New England Journal of Medicine. 2015, 10.1056/NEJMoa1501824;**372**:2018-2028

[46] Herbst RS, Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, Molina J, Kim J-H, Arvis CD, Ahn M-J, Majem M, Fidler MJ, Gilberto de Castro MG Jr, Lubiniecki GM, Shentu Y, Im E, Dolled-Filhart M, Garon EB. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial. The Lancet. 2016;**387**(10027):1540-1550

[47] Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR, for the KEYNOTE-024 Investigators. Pembrolizumab versus chemotherapy for PD-L1–positive non-small-cell lung cancer. The New England Journal of Medicine. 2016;**375**:1823-1833. DOI: 10.1056/NEJMoa1606774

[48] Ott PA, Elez E, Hiret S, Kim DW, Morosky A, Saraf S, Piperdi B, Mehnert JM. Pembrolizumab in patients with extensive-stage small-cell lung cancer: Results from the phase Ib KEYNOTE-028 study. Journal of Clinical Oncology. 2017;**35**(34):3823-3829. DOI: 10.1200/JCO.2017.72.5069. Epub 2017 Aug 16

[49] Boyerinas B, Jochems C, Fantini M, Heery CR, Gulley JL, Tsang KY, Schlom J. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody Avelumab (MSB0010718C) on human tumor cells. Cancer Immunology Research. 2015;**3**(10):1148-1157. DOI: 10.1158/2326-6066.CIR-15-0059. Epub 2015 May 26

[50] Herbst RS, de Marinis F, Jassem J, Spigel DR, Shankar G, Mocci S, Sandler A, Lopez-Chavez A, Li S, Giaccone G. Phase III clinical trials of atezolizumab compared with standard chemotherapy in PD-L1–selected chemotherapy-naïve patients with advanced NSCLC. Annals of Oncology. 2015;**26**(suppl_9):ix105-ix106

[51] Jean F, Tomasini P, Barlesi F. Atezolizumab: Feasible second-line therapy for patients with non-small cell lung cancer? A review of efficacy, safety and place in therapy. Therapeutic Advances in Medical Oncology. 2017;**9**(12):769-779

[52] Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Artal-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A, Rittmeyer A. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial. The Lancet. 2016;**387**(10030):1837-1846

[53] Besse B, Johnson M, Janne PA, Garassino M, Eberhardt WEE, Besse B, Johnson M, Janne PA, Garassino M, Eberhardt WEE, Peters S, Toh CK, Kurata T, Kowanetz ZLM, Mocci S, Sandler A, Rizvi NA. Phase II, single-arm trial (BIRCH) of atezolizumab as first-line or subsequent therapy for locally advanced or metastatic PD-L1-selected non-small cell lung cancer (NSCLC). European Journal of Cancer. **51, 3**(Supplement 3):S717-S718

[54] Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, Gadgeel SM, Hida T, Kowalski DM, Dols MC, Cortinovis DL, Leach J, Polikoff J, Barrios C, Kabbinavar F, Frontera OA, De Marinis F, Turna H, Lee JS, Ballinger M, Kowanetz M, He P, Chen DS, Sandler A, Gandara DR, OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): A phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;**389**(10066):255-265. DOI: 10.1016/S0140-6736(16)32517-X. Epub 2016 Dec 13

[55] Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, Narwal R, Steele K, Gu Y, Karakunnel JJ, Rizvi NA. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: A multicentre, phase 1b study. The Lancet Oncology. 2016;**17**(3):299-308. DOI: 10.1016/S1470-2045(15)00544-6. Epub 2016 Feb 6

[56] Garassino M, Vansteenkiste J, Kim J-H, Léna H, Mazières J, Powderly J, Dennis P, Huang Y, Wadsworth C, Rizvi N. PL04a.03: Durvalumab in ≥3rd-line locally advanced or metastatic, EGFR/ALK wild-type NSCLC: Results from the phase 2 ATLANTIC study. Journal of Thoracic Oncology. 2017;**12**(1, Supplement):S10-S11

[57] Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, Yokoi T, Chiappori A, Lee KH, de Wit M, Cho BC, Bourhaba M, Quantin X, Tokito T, Mekhail T, Planchard D, Kim Y-C, Karapetis CS, Hiret S, Ostoros G, Kubota K, Gray JE, Paz-Ares L, de Castro Carpeño J, Wadsworth C, Melillo G, Jiang H, Huang Y, Dennis PA, Özgüroğlu M, for the

PACIFIC Investigators. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. The New England Journal of Medicine. 2017;**377**:1919-1929. DOI: 10.1056/NEJMoa1709937

[58] Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proceedings of the National Academy of Sciences of the United States of America. 2010;**107**(9):4275-4280

[59] Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, Ready NE, Gerber DE, Chow LQ, Juergens RA, Shepherd FA, Laurie SA, Geese WJ, Agrawal S, Young TC, Li X, Antonia SJ. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study. Lancet Oncology. 2017;**18**(1):31-41. DOI: 10.1016/S1470-2045(16)30624-6. Epub 2016 Dec 5

[60] Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, Narwal R, Steele K, Gu Y, Karakunnel JJ, Rizvi NA. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: A multicentre, phase 1b study. The Lancet Oncology. 2016;**17**(3):299-308. DOI: 10.1016/S1470-2045(15)00544-6. Epub 2016 Feb 6

[61] http://www.onclive.com/web-exclusives/frontline-durvalumabtremelimumab-falls-short-in-phase-iii-nsclc-trial. 2017