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RESEARCH ARTICLE

Immuno-Therapy in Lung Cancer - How Does Immuno-therapy for Lung Cancer Change Patients' Vision?

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Abstract

Survival rates of metastatic lung cancer including non-small cell lung cancer (NSCLC) and poor lung cell cancer (SCLC) are poor with a survival rate of less than 5%. The use of cell-oriented therapies has improved the overall survival of the median (OS) in a limited group of NSCLC patients whose tumors undergo certain genetic mutations. However in a large group of NSCLC and SCLC cell mutations are not available to lead to targeted targeted treatment. Recent positive results from new medical research and checkpoint inhibitors have proven against the common belief that lung cancer is not immune. In particular, checkpoint inhibitors targeting the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the proposed death-1 pathway (PD-1) have shown long-term clinical responses with controlled toxicity.

Several phase II and III clinical trials examining the combination of different chemotherapy schedules with immuno-therapy or immuno-therapy alone continue with lung cancer and significant results are expected in the near future. However, further research is needed to understand the appropriate combination of immuno-therapeutic agents with chemotherapy and radiation therapy for NSCLC and SCLC.

Keywords

Lung cancer, Immuno-therapy, Non-small cell lung cancer (NSCLC), Small cell lung cancer (SCLC), Checkpoint inhibitors

Introduction

Lung cancer is one of the leading causes of death in the world. Survival rates of metastatic lung cancer including non-small cell lung cancer (NSCLC) and poor lung cell cancer (SCLC) are poor with a survival rate of less than 5% [1]. The use of targeted therapeutic therapies, such as erlotinib and crizotinib, has improved the median survival of a group of NSCLC patients whose tumors contain specific genetic mutations [epidermal growth factor receptor (EGFR) that promote genetic modification: 15-18% frequency to non-elected NSCLC; Ana-plastic lymphoma kinase (ALK) trans-locations: 2-8% frequency in non-selective NSCLC] [2,3]. However in a large group of NSCLC and SCLC cell mutations are not available to lead to targeted targeted treatment.

Immuno-therapeutics can be defined as a broad class of therapies that are designed to suppress the destruction of tumor cells by the immune system. Various mechanisms have been developed to promote immune response to cancer, such as immuno-suppressive drugs, immuno-modulators, autologous cellular therapies, monoclonal antibodies targeted at checkpoint inhibitor signals on activated T cells and/or cancer cells. Historically, immuno-therapy has had limited success in lung cancer, leading to the widespread belief that lung cancer is not immune [4]. However, there are many ways in which lung cancer cells can block the immune system, including the production of protective cytokines, severe loss of histo-compatibility complex complex expression antigen and exposure to molecules that inhibit T cell function. Recent promising results have been reported with checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1) achieved with long-term clinical responses that were manageable and previously treated patients with lung cancer. This article will review the latest clinical trials of immuno-therapeutic agents in NSCLC and SCLC.

Immuno-Therapy in NSCLC- Vaccine Phase III

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NSCLC

The cancer vaccine is an antigen-specific immuno-therapy that activates the immune system to produce antigen-specific antibodies, CD4+ T helper cells and CD8+ cytotoxic T-lymphocytes against tumor-related antigens.

Different types of immunoadjuvants are used, including phospholipid, aluminum composition, viral vector, dendritic cells or liposome presentation. In this section we will review the various immunization strategies in the later stages of clinical growth. Two vaccines (MAGE-A3 and liposomal-BLP25) are in clinical development to treat treatable NSCLC. Others tested in phase III B-IV NSCLC (Table 1) [5-13].

MAGE-A3

It is an antigen that is directly related to various hardy plants, including NSCLC. It is a promising indicator of immuno-therapy because it is almost exclusively expressed in cancer cells. Studies show that 17-50% of NSCLC tumors express MAGE-A3 on their face and speech is associated with malignant prognosis [5,14]. MAGE-A3 antigen-specific immuno-therapeutic (ASCI) is made up of recombinant fusion protein (MAGE-A3 and protein D for Hemophilus influenza) combined with an adjuvant system that promotes immunity. In a double-blind, phase II study, 182 patients with MAGE-A3-positive rected stage IB/II NSCLC were randomly assigned to a vaccine or placebo at a ratio of 2: 1 (Table 1) [5,15]. Patients received five doses of MAGE-A3 ASCI or placebo once every three weeks followed by a maximum of eight combined doses administered once every three months. Long-term analysis showed a positive trend for MAGE-A3 treatment in this setting, with no significant but clinically related improvement in interval-free interval (DFI) [hazard ratio (HR) 0.75; 95% CI: 0.46-1.23; P = 0.254], disease-free survival (DFS) (HR 0.76; 95% CI: 0.48-1.21; P = 0.248), and OS (HR 0.81; 95% CI: 0.47-1.40; P = 0.454) favor Group MAGE-A3. The overall treatment was well tolerated, leading to higher compliance treatment. Based on MAGE-A3 immuno-therapy experience in advanced melanoma, genetic analysis of tumors has identified an autoimmune genetic signature that appears to be associated with a higher risk of recurrence. In fact, patients without this signature had a 5% risk of relapse [15]. This signature was included as a second term in phase III MAGRIT (MAGE-A3 as an adjuvant non-cell cell immuno-therapy) study [16]. The MAGRIT study examined

Table 1: Summary of completed NSCLC immuno-therapy trials.

Immuno-therapy	Target	Pt No.	Stage	Results
Stage I-III disease				
MAGE-A3	MAGE-A3	182	IB/II following complete resection	HR for DFS = 0.76 (95% CI: 0.48-1.21), HR for OS = 0.81 (95% CI: 0.47-1.40) with MAGE-A3 compared to SOC [5]
Stage III B-IV disease				
BLP-25	MUC1	171	IIIB/IV after 1st line chemotherapy	3 yr. OS 31% for BLP-25 and 17% for BSC (P = 0.035) Stage IIIB subset MS 30.6 months for BLP-25 *vs*. 13.3 months for BSC (HR = 0.548, 95% CI: 0.301-0.999) [6,7]
Belagenpimatucel-L	TGF-β2	75	II/IIIA/IIIB/IV after completion of therapy	Superior MS for high vaccine doses group *vs*. low vaccine doses group (P = 0.0069) [8]
EGF	Epidermal growth factor	80	IIIB/IV after first-line chemotherapy	MS 11.7 months with GAR and 3.6 months with PAR (P = 0.0002) [9]
TG4010	MUC1	148	IIIB/IV with 1st line chemotherapy	6-months PFS 43.2% for TG4010 *vs*. 35.1% for chemotherapy alone (P = 0.307) [10]
Ipilimumab	CTLA-4	204	IIIB/IV or recurrent disease in combination with first-line chemotherapy	Immune-related PFS 5.7 months for phased ipilimumab + chemotherapy *vs*. 4.6 months for placebo + chemotherapy (HR 0.72; P = 0.05) [11]
Nivolumab	PD-1	296 (122 NSCLC)	IV after completion of first-line chemotherapy	OR in 6 (33%) out of 18 with squamous cell histology; OR in 7 (12%) out of 56 with non-squamous histology [12]
BMS-936559	PD-L1	207 (75 NSCLC)	IV after completion of first-line chemotherapy	OR in 4 (11%) of 36 non-squamous histology; OR in 1 (8%) of 13 squamous histology [13]

BSC: Best Supportive Care; GAR: Good Antibody Response; HR: Hazard Ration; MS: Median Survival; NSCLC: Non-Small Cell Lung Cancer; OR: Overall Response; PAR: Poor Antibody Response; PFS: Progression-Free Survival; Pt: Patients; RR: Response Rate; SOC: Standard of Care

more than 13,000 patients with a retrospective stage of IB-IIIA NSCLC for immunohistochemical expression of the MAGE-A3 antigen. Finally, 2,270 patients were recruited in October 2011 [17]. Previous adjuvant chemotherapy was not an indication for discharge. Patients were randomly assigned 2:1 to the vaccine or placebo and treatment was given three times a week for five weeks followed by 12 weeks at eight doses [16]. DFS is a key conclusion and the expected confirmation of the estimated genetic signature value is a consistent component.

Liposomal BLP-25

MUC1 is a glycoprotein that binds to excess membranes and has glycosylation that reverses the negative modification of various plant types including NSCLC [18]. Liposomal BLP25 (L-BLP25, Stimuvax) is a liposomal vaccine that combines 25 amino acids from a number of immune mutations of the repetitive region of MUC1 combined with immuno adjuvant mono monophosphoryl lipid A in the liposomal delivery system [19]. The computer was screened in a phase II multi-center randomized clinical trial with 171 patients with a stable or responsive stage of IIB (38%) or IV (62%) of NSCLC after first-line chemotherapy or after chemo-radiation [6]. Patients were randomly assigned to L-BLP25 with the best supportive care (BSC) (n = 88) or BSC alone (n = 83) [6]. Patients randomly assigned to the vaccine arm received a low dose of cyclophosphamide (300 mg/m^2) followed three days later by the first eight weekly doses under the L-BLP25 skin. According to the investigator, patients can also receive nutritional vaccines once every six weeks from six weeks after the weekly vaccination and continue until the disease progresses. The main conclusion of the study was the OS. L-BLP25 was well tolerated, with most adverse events including mild symptoms such as fever and no increase in reported adverse events (L-BLP25 and BSC 26.1% vs. BSC 36.1%). Performance results raised a non-significant trend in OS developed in patients who received L-BLP25 (17.4 months vs. 13 BSC only, adjusted HR: 0.739; 95% CI: 0.509-1.073; P = 0.112). Post hoc analysis suggested that the benefit of L-BLP25 was limited to 65 patients with phase IIIB who underwent chemotherapy and radiation therapy (adjusted HR 0.524; 95% CI: 0.261-1.052; P = 0.069) with a tendency toward improvement. Two years of life (60% vs. 36.7% of BSC). However, it should be noted that this analysis was not the definitive conclusion of the study. The revised analysis recommended a continuous trend towards improved survival of vaccinated patients (OS 30.6 median vs. 13.3 months) and no serious long-term safety issues. Based on these findings, a large international phase III trial (Revitalization of Antigenic Targets in NSCLC) randomly assigned 1,513 patients with non-invasive phase IIIB NSCLC following direct chemo-radiation conversion to L-BLP25 by BSC or placebo and BSC [20]. This study, with the main end of the OS and the implementation of a phase II vaccine program, was completed in November 2011. The media release at the end of 2012 meant that the START test failed to meet its main OS development with L-BLP25 (25.6 vs. 22.3 months of placebo; P = 0.123), although the analysis of the second outcome previously described suggested that patients receiving simultaneous chemo-radiation may gain some benefit from vaccination (median OS chemo-radiation simultaneously followed by vaccine: 30.8 vs. 20.6 months. of simultaneous chemo-radiation following placebo; P = 0.016) [20]. In Asia, a small phase III INSPIRE study, with a design and number of patients such as START, began enrolling in December 2009 and is ongoing [21]. In the United States, a continuous study of phase II examined a combination of L-BLP25 and bevacizumab after phase III chemo-radiation NSCLC [22].

Enhanced NSCLC Vaccines

Belagenpumatucel-L

Transforming growth factor-beta (TGIF-β) is an active cytokines that activates normal and neoplastic cells to promote epithelial secretion and inhibit cell growth [23]. Elevated levels of TGF-β2 are known to be associated with immunity in cancer patients and in advanced NSCLC are associated with an aggressive phenotype and poor survival [24]. Belagenpumatucel-L is a complete cell allogeneic vaccine derived from irradiated NSCLC cell lines (two adenocarcinoma, one squamous, and one large cell), plasma-containing TGF-β2 anti sense trans-gene, which lowers TGF.-b2 [8]. The efficacy and safety of belagenpumatucel-L were investigated in 75 patients with phase II-IV NSCLC in a phase II study. Patients received one-third dose of belagenpumatucel-L (1.25 × 107, 2.5 × 107, or 5 × 107 cells/injection) administered as an intra-dermal injection once monthly or once monthly [8]. There were no significant differences in the adverse events noted between dose groups, and most of the adverse events were revealed by disease activity other than flu-like symptoms, which were noted in 16% of patients. A 15% response rate was reached in a subgroup of 61 patients with phase III B-IV (at all dose levels) and 59% of all registered patients were free from progression within four months. In a small cohort study patients with both cellular and humoral immune responses (n = 11) improved survival compared to those (n = 24) who were classified as immune response-negative: 32.5 months between 11.6 months (95%) CI: 5.6) -17.6; P = 0.011) [25]. In a subsequent phase II study that enrolled 20 patients with phase IV NSCLC, no partial or complete responses were noted. However, 14 of the 20 patients had a stable disease over four months and no new safety issues were noted [26]. Belagenpumatucel-L has also been investigated in a randomized trial of phase III STOP compared with placebo as a postoperative

treatment with double platinum chemical treatment of phase III-IV NSCLC [27]. The primary outcome was OS and the study completed enrollment of more than 500 patients during 2012. The results of this study are awaited.

EGF vaccine

The EGFR pathway is critical to the growth and development of NSCLC. High EGFR expression is common in NSCLC and EGFR mutation is associated with a response to EGFR tyrosine kinase inhibitors of the inner part of this receptor [28,29]. The EGF vaccine (CIMAvax EGF) was developed in Cuba and contains human regenerated EGF mixed with network protein found in Neisseria Meningitidis and immuno-adjuvant [30]. In a phase II study, 80 patients with phase III B-IV NSCLC previously treated with first-line plasma chemotherapy, were randomly assigned to 1:1 to receive EGF vaccine and BSC or BSC alone [9]. After cyclophosphamide treatment (200 mg/ m^2), patients in the vaccination group received the vaccine on days 1, 7, 14, 28 and monthly thereafter [9]. The tendency to increase survival was observed in all vaccinated patients compared with controls, and the difference was statistically significant (P = 0.0124) in the subgroup at < 60 years of age (an average OS of 11.5 months of vaccinated patients compared to 5.3 months of control). The vaccine was well tolerated, with less than 25% of patients experiencing adverse events and no grade 3 or 4 episodes were noted. The analysis of the subgroup indicates the predictable number of humoral immune reaction. Patients with anti-EGF antibody titers ≥ 1:4,000 and at least four times their pre-vaccinated doses have an average OS of 11.7 months compared to 3.6 months for those with no immune response.

Building on these results, a phase III international study completed the enrollment of 579 patients with advanced NSCLC who had stable or responsive disease after the start of platinum doublet chemotherapy [31]. Based on the evaluation analysis from a phase II study that suggests that younger patients may receive additional benefits from EGF vaccination, enrollment in phase III studies is limited to patients aged 20-65 years. Effective results from this study are expected in late 2013. This policy is currently licensed in Cuba for use in phase IIIB/IV NSCLC.

TG4010

TG4010 is a recombinant viral vector that combines the genetically modified Ankara virus that has been genetically modified to produce MUC1 and interleukin-2 (IL-2) [32]. IL-2 has been implicated in immuno-adjuvant because it is able to reverse the suppression of the MUC1 [33] cancer-associated T-cell response. In a phase II study, cisplatin/ gemcitabine chemotherapy first-line was randomly assigned with or without TG4010 to 148 untreated advanced NSCLC patients with tumors expressing MUC1 by immunohistochemistry [10]. The vaccine was given under the skin each week for 6 weeks and then every 3 weeks until the disease progressed to the main end of the six-month PFS with a target of 40% or more in the experimental group. The addition of TG4010 appears to enhance the effect of chemotherapy with a survival rate of no more than six months of 43% (95% CI: 33-54%) in TG4010 and a group of chemotherapy and 35% (95% CI: 26-45%) in the chemotherapy group only. The Median OS was not statistically different between the groups. Specific analysis of cellular immune response to MUC1 did not show significant differences between vaccinated and non-vaccinated patients. However, experimental analyzes have suggested that elevated levels of activated cells that kill the environment (anNK) may prevent the vaccine response. In fact, the median OS was 18 months in patients with normal levels of aNK cells, while it was 11.3 months in those with high levels of aNK cell (P = 0.02). The authors speculate that in addition to their role in tumor cell death, NK cells also inhibit an autoimmune immune response if present at very high levels. In January 2012, a phase IIB/III study of TG4010 was initiated, comparing dual chemical treatment of platinum with TG4010 and only chemotherapy with the primary end-stage OS phase III [34]. In the IIB section, the predictive role of aNK will be assessed based on the PFS terminal. Patients enrolled in this study will receive weekly subcutaneous injection or placebo within the first six weeks of chemotherapy followed by injections once every three weeks until the disease progresses [34].

Obstruction of the immune system

There are many experimental molecules that reduce the T-cell's immune response to antigen expressed by tumor cells [35]. Monoclonal antibodies interacting with two of these molecular mechanisms, PD-1 and CTLA-4, demonstrated activity in the enhanced NSCLC. Obstruction of the immune system is of great interest because some patients with advanced advanced tumors appear to receive unusually long-term benefits; this has been clearly demonstrated in metastatic melanoma, in which approximately 5-8% of patients will live for many years with stable or responsive disease after anti-CTLA-4 antibody treatment [36,37].

Anti-CTLA-4

Monoclonal antibodies against CTLA-4 are designed to block interactions between CTLA-4 and its ligands (CD80/ CD86) resulting in blockade of the CTLA-4 inhibitory signal and enhanced activation and proliferation of specific tumor T-cells, thus allowing an effective immune response against the tumor [38]. A comprehensive study of ipilimumab for advanced melanoma has led to controlled authorization demonstrating survival benefits in phase III clinical trials [36,37]. For lung cancer, a large blind phase II study assigned 204 patients with advanced NSCLC and randomized SCLC patients 1:1:1 in one arm: Three

standard carboplatin/paclitaxel chemotherapy and placebo, ipilimumab at a time. One (four doses of ipilimumab and paclitaxel and carboplatin followed by two doses of placebo and paclitaxel and carboplatin), or ipilimumab divided into doses (two doses of placebo plus paclitaxel and carboplatin followed by doses four of ipilimumab plus paclitaxel and carboplatin) [11]. Treatment was done by injection every 3 to 18 weeks. Patients with stable disease or tumor response after four cycles of chemotherapy continued receiving pilimumab or placebo injections every three months until the disease progressed. The dose of ipilimumab used in this study was higher than that allowed for melanoma (10 vs. 3 mg/kg).

NSCLC results are reported separately in the SCLC collection. The results of SCLC patients are reported in the SCLC section of this review paper. This study was new to the first reported phase II study to accept the immune-related PFS (irPFS) as its primary endpoint, defined as the time from random allocation to immunity-related progression or death. In fact, observations made in clinical trials of melanoma indicate differences in the pattern of responses in immuno-therapies compared with those in cytotoxic agents [39]. With the prevention of immune checkpoint, a number of patients initially showed progressive illness with the Traditional Solid Tumors Response Policy (RECIST) followed by delayed immuno-therapy response and in some cases long-term survival [40]. The second conclusions of the phase II study of ipilimumab in NSCLC included a modified World Health Organization response module, PFS, OS, and other immune-related response mechanisms. In the NSCLC, the study met its main objective of the enhanced irPFS of the divided pilimumab (HR: 0.72; P = 0.05) compared with controls, whereas interestingly this was not the case compared with the same ipilimumab (HR: 0.81; P = 0.13) and control. The reason why one dose of ipilimumab administration has caused significant statistical differences, while the other is unclear and annoying. Hypotheses suggest that a phased state regime allows for a significant short-term sequence of chemical antigen release before pilimumab treatment or the fact that simultaneous chemotherapy can reduce lymphocyte counts and thus reduce ipilimumab activity at a critical time. Separated ipilimimab, compliant ipilimumab, and control arms were associated with irPFS intervals of 5.7, 5.5 and 4.6 months, and an intermediate OS of 12.2, 9.7 and 8.3 months, respectively. Subset analysis of histology revealed improved squamous irPFS (HR: 0.55; 95% CI: 0.27-1.12) than adenocarcinoma histology (0.82) in divided pilimumab. The arm effects of ipilimumab at the same time were similar in different histologies. In terms of toxic profiles, in this study, grade 3-4 toxicity was higher at 15%, 20% and 6% in the categories divided into categories, simultaneously with the control group. Major side effects included diarrhea, colitis, transaminitis, and pituitary dysfunction, all of which were previously described as side effects of CTLA-4 inhibition [41]. Two medical-related deaths were reported. On the basis of phase II results, phase III trials are ongoing compared to a 1:1 phase pilimumab starting after two to six scheduled cycles of carboplatin-paclitaxel followed by pilimumab for care or the same schedule of chemotherapy and placebo treatment in patients. Stage IV or lung squamous cell carcinoma [42]. This large study is scheduled to complete the collection in September 2014 with a total of 920 patients and the first end of the OS.

Anti-PD-1 and anti-PD-L1

The proposed Death receptor 1 (PD-1) is a T-cell surface receptor that is a B7-CD28 component, expressed in T cells, B cells, natural killer cells (NK), activated monocytes and dendritic cells [43]. The role of PD-1 in normal human physiology is to regulate the body's immune system by acting as a site of immune inhibition expressed on the surface of T cells and other immune cells, including the tumor-infiltrating lymphocyte [44]. It has two lines: programmed death receptor ligands 1 (PD-L1/B7-H1) and 2 (PD-L2/B7-DC) [45]. Several agents of the PD-1 pathway are in clinical development, including nivolumab (BMS-936558, anti-PD1 human IgG4 fully), lambrolizumab (MK-3475, anti PD1 humanized IgG4), MEDI4736 (anti-PDL1), BMS-936559 (formerly MDX-1105, fully human anti-PDL1 IgG4) and MPDL-3280 (anti-PDL1). Promising preliminary data on NSCLC have been reported in various studies of phase I nivolumab, lambrolizumab and MPDL-3280.

Nivolumab was investigated in a large-scale study of phase I increase in patients with severe solid tumors. A total of 296 highly treated patients with advanced NSCLC, melanoma, renal cell carcinoma, prostate cancer, or advanced colorectal cancer were enrolled in the trial and received increased doses of nivolumab at 1, 3, 10 mg doses./kg. every two [12] weeks. Responses were tested after each 8-week treatment cycle using the Solid Tumors (RECIST) Response Testing Conditions, but research therapy may be continued in clinical stable patients in addition to the apparent disease progression until proven to be effective. Patients received up to 12 cycles of 8 weeks until the disease progressed or complete response. The toxins from nivolumab, which includes fatigue and diarrhea, are manageable, with grade 3 or 4 toxicity in 14% of patients. Notably, three patients in this initial study had fatal pneumonitis. Because of this problem, treatment regimens now include early use of immunosuppression and this appears to reduce toxicity.

Encouraging signs of success have been seen in renal cell carcinoma, melanoma, and most surprisingly, NSCLC, in which 16% of patients received a direct response and 33% were free of tumor progression within six [12] months. Responses were noted in 9 of the 48 patients

(18.8%) with squamous NSCLC and 11 of the 73 patients (15.1%) with non-squamous NSCLC, which elevated activity in both types of histologic sub-types [12]. Long-term data in 129 patients showed a total response rate of 17.2% (squamous 16.7%; nonsquamous 17.6%) with an average response time of 18.5 months [46]. Drug-related adverse events (of any grade) occurred in 71% of patients with NSCLC, with 3-4 drug-related adverse events reported in 14%. Drug-related pneumonitis occurred in 6% of patients; 2 percent of these were in stages 3-4, and two deaths from pneumonia occur in patients with NSCLC. The current proposed management algorithms in patients with suspected anti-PD-1 pneumonitis include drug withdrawal, immediate systemic steroid treatment, and consideration of antimicrobial drugs due to the challenges involved in differentiating drug-induced pneumonitis [47]. Grade 3-4 pneumonitis requires immediate discontinuation of the drug, timely steroid administration, and consideration of adjunctive immuno-suppressant treatment such as infliximab, mycophenolate mofetil, or cyclophosphamide [47]. In addition, patients may need long-term immunosuppression testing to avoid recurrence of the adverse event. Nivolumab has now entered phase III clinical trials as a single agent compared with second-line chemotherapy for single-dose NSCLC enhanced squamous and nonsquamous [48,49]. Exposure to PD-L1 by immunohistochemical analysis of tumor cells is a possible sign of an anti-PD-1 [12] response. Recent data on the use of PD-L1 expression deficit using these tests does not include the potential for benefit from immuno-modulators [50,51]. Lambrolizumab is a man-made antibody of monoclonal immunoglobulin G4 against PD1 that has shown early efficacy in phase I studies in solid tumors. Preliminary data from NSCLC patients showed that 17 patients received lambrolizumab at one of the three dose levels (1, 3, and 10 mg/kg). Lambrolizumab was generally well tolerated. Grade 2 pneumonitis responding to steroid treatment occurs in one patient, grade 1/2 pruritus was noted in 4 of 17 patients, and only one unconfirmed response was reported in a patient with NSCLC [52]. The anti-PD-L1 antibody, BMS-936559, was tested in a phase I trial of advanced tumors and progression of the disease after at least one treatment by injection every 1, 15, 29 days every six weeks. The study enrolled 207 patients, 75 of whom had NSCLC and 49 NSCLC patients were included in the performance appraisal. Among the 49 patients of NSCLC 5 patients (4 non-squamous and 1 squamous cell histology) had a purposeful response and 6 patients experienced disease recovery for at least 24 [13] weeks. Recently, the first results of another PD-L1 antibody, MPDL3280A, phase I trial were presented [51,53]. MPDL3280A is an immunoglobulin G4 antibody designed to eliminate its human-dependent cytotoxicity activity, thus avoiding the killing of tumor-targeted T cells. A cohort of 85 patients, who are part of a large, advanced advanced phase I study, were treated with intravenous drug therapy every three weeks for a period of 106 days (range, 1-450 days). Of the 85 patients of NSCLC, 55% were heavily treated with at least three previous therapies, and the majority were represented by current or former smokers (81%). The median duration of treatment was 48 weeks and the ORR was 21% of the total population and 23% of the NSCLC group. 17% of respondents were stable within 24 weeks. The 24-week PFS was 44% in squamous cell NSCLC and 46% in cells without NSCLC. No dose-limiting toxicity was identified in this study, and no grade 3 to 5 pneumonitis was reported or diarrhea. In patients treated with the study drug, an increase in PDL1 expression in immunohistochemistry was associated with an increased response. ORR was 46% in patients with IHC2 and IHC3 and 86% in patients with IHC3. Researchers analyzed whether smoking status was predicted for a different effect and found that former/current smokers had an ORR of 26% (n = 43) compared with 10% of non-smokers (n = 10) [51,53]. Currently a multi-arm phase I trial is continuing to test nivolumab in combination with cisplatin/gemcitabine, cisplatin/pemetrexed, carboplatin/paclitaxel, erlotinib (EGFR in patients with poor NSCLC mutations), or ipilimumab as mono-therapy for patients receiving treatment. -naïve class IIIB or IV NSCLC as a post-chemical nutritional therapy combined with bevacizumab [54].

Table 2: Summary of completed and ongoing immuno-therapy trials in small cell lung cancer.

Immuno-therapy	Target	Pt No.	Stage	Results
BEC2/BCG	GD3	III	Limited stage SCLC	OS 16.4 months with BSC and 14.3 months with BEC2/BCG; HR = 1.12; 95% CI: 0.91-1.371 [55]
Ipilimumab or placebo + paclitaxel/carboplatin	CTLA-4	II	Previously untreated extensive stage SCLC	Phased Ipilimumab improved irPFS *vs.* control (HR: 0.64; P = 0.03) [56]
Ipilimumab/carboplatin/etoposide	CTLA-4	II	Previously untreated extensive stage SCLC	Ongoing [57]
Carboplatin/etoposide +/– ipilimumab	CTLA-4	III	Previously untreated extensive stage SCLC	Ongoing [58]
Nivolumab +/– ipilimumab	PD1 and CTLA-4	II	Previously treated after first line extensive stage SCLC	Ongoing [59]

BSC: Best Supportive Care; HR: Hazard Ratio; OR: Overall Response

Immuno-therapy in SCLC

Few immuno-therapy trials were performed at SCLC (Table 2) [55-59]. The BEC2/BCG vaccine (Bacillus Calmette-Guerin) was extensively studied in SCLC over the past decade based on the fact that BEC2 is a monoclonal antibody that mimics GD3, a glycosphingolipid antigen that is highly expressed in SCLC but rarely in normal tissue [60]. When BSG was combined with GD3 three out of fourteen patients developed antibodies against GD3 [61]. BEC2/BCG showed promising results in the first clinical trial in SCLC by Grant, et al. [62], however, a large European trial by Giaccone, et al. [55] showed no statistically significant difference in the average OS in 515 patients with moderate SCLC (16.4 months with BSC and 14.3 months with BEC2/BCG; HR = 1.12; 95% CI: 0.91-1.371).

The combined Ipilimumab schedule (two cycles of chemotherapy and placebo followed by four cycles with ipilimumab) but not the ipilimumab schedule (four cycles of chemotherapy and ipilimumab followed by two cycles with placebo) improved irPFS against and control over the wider phase of the SCLC phase II team. Randomized double-blind randomized controlled trials associated with carboplatin / paclitaxel chemotherapy (HR: 0.64; P = 0.03) [56]. Ipilimumab combined with platinum-etoposide chemotherapy against platinum-etoposide alone is currently being evaluated in a phase III clinical trial in patients with a broad stage of SCLC in order to improve T-cell cell responses and increase OS [58]. Clinical trials of phase I/II of Nivolumab alone or combined with ipilimumab are currently concentrating in patients with solid tumors that include SCLC for a broader stage after the first line of chemotherapy [59]. There are many challenges to improving immunodeficiency treatment in SCLC, which includes a significant burden of disease and a lack of specific goal-based treatment. In addition, the response to immuno-therapy takes time. In extended SCLC infections patients have severe clinical deterioration with a rapidly developing disease that may not allow time to incorporate the proper immune response. Therefore, the timing and timing of immuno-therapy in relation to other therapies, in particular chemotherapy represents an important tool for facilitating disease control and improving immune response.

Radiation and immuno-therapy

The abscopal effect is mediated by the immune system where radiation provides the release of antigen that stimulates immune cells to cause tumor cell death outside the radiation site [63]. These impressive system responses have become increasingly evident among patients treated with a new generation of checkpoint inhibitors [64,65]. Therefore, there has been a growing interest in the strong immune effects of anti-CTLA-4, PD-1, and PDL-1 drugs to improve abscopal effects when used in combination with limited radiation, where the radiation can be used to give antigen. Reactivate and assist in initiating the immune response, which may improve the response rate in remote areas of non-radioactive disease. There are many ongoing trials examining the role of immuno-therapy in the treatment of lung cancer. Recent studies of novel agents, particularly checkpoint inhibitors, have shown the first promising results in achieving sensible and robust therapeutic responses that are toxic. To identify patient communities that can benefit the most from treatment with immuno-therapeutic agents and to determine the best duration of patient immuno-therapy treatment, at present, are the most important challenging questions that need to be answered. The combination of chemotherapy and/or radiation therapy with immuno-therapy and duration of treatment needs to be further investigated. Immuno-therapy trials after stereotactic ablative radiation therapy have recently revealed encouraging responses that will need to be re-evaluated in clinical trials. Finally a combination of two major groups of immuno-therapy, antigen-specific vaccines and immuno modulatory agents, may have synergistic effects in increasing the anti-tumor immune response.

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