Review Article

The revolution of lung cancer treatment: from vaccines, to immune checkpoint inhibitors, to chimeric antigen receptor T therapy

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Abstract: Lung carcinoma is one of malignant tumors to human health worldwide. The two main types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). In recent years, despite the great progress in the treatment of lung cancer, the survival rate of lung cancer patients is still not satisfactory. Nowadays, the revolution of lung cancer managements is changing the situation. Here, we review recent advances in vaccines, immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T (CAR-T) cell immunotherapy in the field of lung cancer. ICIs proved to have promising efficacy and safety compared with chemotherapy. Preclinical data on CAR-T are still insufficient, and several phase I trials are being conducted. We have attempted to provide an overview of the most recent progress and a prediction on prospective advancements.

Keywords: Lung cancer; immunotherapy; vaccine; immune checkpoint inhibitor (ICI); chimeric antigen receptor T (CAR-T)

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Background

Lung cancer is the leading cause of cancer death among men and the second leading cause of cancer death among women worldwide (1,2). For several years, surgery, chemotherapy (including neoadjuvant chemotherapy), radiotherapy and targeted therapy have been widely used clinically (3). Nevertheless, the overall survival (OS) rate of lung cancer still remains unacceptable (4). Whereas, with the leap and bounce of lung cancer immunotherapy, we predict that the scientific turning point is coming. So it is fair to conclude that treatment with immune checkpoint inhibitors (ICIs) and chimeric antigen receptor T (CAR-T) cell immunotherapy will become the backbone of lung cancer therapy in the near future (5,6).

In the review, we categorized the progress in pulmonary carcinoma therapy into three parts, including the closely completion of vaccines, the galloping of ICIs and the initial exploration of CAR-T therapies. (I) Clinical results of vaccines are far from impressive, in that most of the related works have been done about one decade ago. In most cases, even no significant difference of the efficacy between vaccines and chemotherapy was observed, however, the toxicities and side effects of vaccines can be neglected. In addition, in order to treat precancerosis or prevent relapsed tumor, taking vaccines is a perfect choice. (II) With respect to ICIs, their efficacy has convinced numerous scientists to conduct more profound researches. Ipilimumab [anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)], a generation 1 inhibitor, was early approved by the US Food and Drug Administration (FDA) in 2011. Currently, the generation 1 inhibitors are under study in combination with generation 2 inhibitors or CAR-T therapies. Generation 2 inhibitors, the anti-programmed death 1 (PD1) agents, proved to have approximately a 20% object response rate (ORR). All anti-PD1 inhibitors, including nivolumab and pembrolizumab have all been approved by FDA in 2015 and

Table 1 Cancer vaccination approaches investigated in NSCLC

Vaccines	Target	Indication	Key results
Belagenpumatucel-L	TGF-β2	First-line CTx ± radiotherapy pretreated, stage IIIA–IV NSCLC (phase III, n=532)	Improved survival
Racotumomab-alum	NeuGcGM3	First-line CTx pretreated, stage IIIB–IV NSCLC (phase II/III, n=176)	Improved MST
TG4010	MUC1/IL-2	No previous treatment pretreated, stage IIIB–IV NSCLC (phase IIB , n=148)	TG4010 enhances the effect of chemotherapy
Cyclophosphamide	MUC1	Chemo-radiotherapy pretreated, stage IIIA–IIIB NSCLC (phase III, n=1239)	No significant but improved OS
L-BLP25	MUC1	First-line CTx pretreated, stage IIIB–IV NSCLC (phase IIB , n=171)	No significant but improved ST *vs*. placebo
Tecemotide	MUC1	Chemo-radiotherapy pretreated, stage III NSCLC (phase I/II, n=172)	No improved OS
recMAGE-A3 + AS15	MAGEA3	Surgery pretreated, stage IB–IIIa NSCLC (phase III, n=2272)	No increased DFS
EGF	EGF	First-line CTx pretreated, stage IIIB–IV NSCLC (phase II, n=74)	Increased survival in patients younger than 60 years

NSCLC, non-small cell lung cancer; TGF-β2, transforming growth factor-beta 2; NeuGcGM3, n-glycolylneuraminic acid; MUC1, mucin 1; IL-2, interleukin-2; MAGEA3, melanoma antigen family A 3; EGF, epidermal growth factor; MST, median survival time; OS, overall survival; ST, survival time; DFS, disease-free survival.

2014 respectively. Furthermore, scientists are attempting to find out whether generation 2 inhibitors can be used as first-line therapy (7). Trials on generation 3 inhibitors, the anti-programmed cell death-1 ligand-1 (PDL1) drugs, are still ongoing. Besides, the selection of biomarker and immune related adverse events are now the advanced research hotspots. (III) Breakthroughs in CAR-T therapy on hematologic malignancies have been achieved about half a decade ago, albeit, studies on solid tumors have just been initiated. To date, all published trials on lung cancer only include four preclinical studies and one phase I study. Based on data obtained from www.clinicaltrials.gov (up to January 2017), nine phase I or phase I/II studies are currently on the way. The initial clinical outcomes manifest that CAR-T therapy has a more robust antitumor effect than ICIs and vaccines, and the perfect example is that epidermal growth factor receptor (EGFR)-CAR T therapy benefit patients who could not respond to EGFR tyrosine kinase inhibitors. So what is the future of lung cancer therapy? Vaccines, ICIs and CAR-T therapies provide an instructive answer.

Thus far, multiple reviews have summarized the efficacy of vaccines in treatment of lung cancer (8,9). Likewise, outcomes and toxicities of lung cancer related ICIs have also been reviewed (10-12). However, there are no reviews with regard to CAR-T therapy on lung cancer.

In this review, we attempt to have a retrospective assessment of the freshly minted therapies, where the lung cancer therapy has been evolving from antitumor vaccines and ICIs to CAR-T therapies.

Vaccines

Compared with CAR-T therapy and ICIs based therapy, vaccines seem to develop less rapidly. In recent years, there is no remarkable breakthrough. Antitumor vaccines are designed to trigger a robust T cell response, rather than affecting the mechanism of immunosuppression. Different with CAR-T or ICIs therapy, the mechanism of vaccine is far from complex. These vaccines elicit antitumor responses against tumor related antigens. It directly stimulates the patient's own immunological surveillance. Thus, antitumor vaccines have been applied more successfully in the case of less immunosuppression. As is illustrated in *Table 1*, vaccines alone usually have a mild antitumor activity. Compared with chemotherapy, even, statistically significant differences of OS or progression-free survival (PFS) cannot be seen (13), while, dual-target or multi-target vaccines can have a comparatively robust antitumor effect. Moreover, when treating precancerosis, or preventing relapsed tumor, injecting vaccines is a perfect selection. Another advantage

of vaccines over other therapies is the slight toxic. More related discussion and data can be seen in the detailed meta-analysis (8).

In the future, two main trends will lead the development of antitumor vaccines. The first one is more researches on dual-target or multi-target vaccines. A typical example is BI-1361849 vaccine, which include six targets in all. Latest vaccines, such as MUC1-granulocyte-macrophage colony stimulating factor (GM-CSF) vaccine and MUC1-VEGFR2-GM-CSF vaccine, are also targeted multiple antigens. The second trend is that more studies will be focused on the combination between vaccines and other immunotherapies, because features of vaccine, ICIs and CAR-T are different. At present, preclinical studies on vaccines combining with anti-PD1 agents are emerging, while only a small amount of clinical trials were published. With respect to combinations between vaccines and CAR-T therapy, a few scientists are making efforts preliminarily. Below, we discussed different kinds of vaccines and combination of vaccines.

EGFR belongs to the receptor tyrosine kinases (RTKs) family. It is expressed in 40% to 80% of non-small-cell lung carcinoma (NSCLC) cases. Epidermal growth factor (EGF), EGFR's major ligand, can activate EGFR. Recombinant human EGF conjugated to a carrier protein (CIMAvax EGF) vaccines, developed by Cuban scientists, can raise antibodies targeting EGF and hence reduce the concentrations of EGF in the blood (14). Recently, a randomized phase III study was conducted in treatment with advanced NSCLC. Among 405 patients with stage IIIB/IV NSCLC, long-term vaccination turned out to be safe, in that most of adverse events were grade 1 or grade 2. A longer median survival time (MST) of 10.83 months was observed compared with the control arm (10.8 *vs.* 8.9 months). A higher MST of 14.66 months was reported when treated patients with high EGF concentration (15). Another research assessed the efficacy of the CIMAvax EGF vaccines in treatment of NSCLC patients. The 2-year OS rate and PFS rate was 20.7% and 30.5% respectively, and a median OS of 13 months was noted (16). A phase I/II trial (NCT02955290) is currently recruiting patients, studying the best dose and side effects of CIMAvax EGF vaccine combined with nivolumab in treating patients with stage IIIB–IV NSCLC.

MUC1-GM-CSF vaccine is a newly developed dual-target vaccine for lung cancer. MUC1, overexpressed aberrantly in lung tumors, can be a potential target in the use of lung cancer immunotherapy (17). GM-CSF, which worked as an adjuvant, is able to stimulate hematopoietic progenitors' proliferating, differentiating and maturing (18,19). Therefore, its existence often marks the infiltration and metastasis of tumor cells. In a preclinical study, researchers tested the DNA vaccine based on MUC1-GM-CSF fusion gene in a mouse model, and compared with MUC-1 vaccine, GM-CSF vaccine and empty vector. As a result, significant decline of tumor weight and tumor growth rates in the group treated with MUC1-GM-CSF vaccine was observed (20). Vascular endothelial growth factor receptor 2 (VEGFR-2) belongs to the VEGF-family, expressed in newly born endotheliocytes of vessels. Another similar preclinical a study, was conducted in 2016, to evaluate the synergistic efficacy of MUC1-VEGFR2-GM-CSF DNA vaccines in comparison with MUC1 or VEGFR2 alone and MUC1-VEGFR2 vaccines in tumor-bearing mouse model. The enhanced inhibition of tumor growth and significant weight loss of tumor was showed in MUC1-VEGFR2-GM-CSF DNA vaccines treatment group (21). In conclusion, the synergistic antitumor efficacy of MUC1-VEGFR2-GM-CSF vaccines is robust.

BI-1361849, also named as CV9202, is a therapeutic self-adjuvanting mRNA vaccine. It targets six NSCLC-associated antigens (NY-ESO-1, MAGEC1, MAGEC2, 5 T4, survivin and MUC1). In a phase Ib trial, 26 patients with stage IV NSCLC were recruited to test RNActive cancer vaccine BI-1361849 combined with local radiotherapy. One confirmed partial remission was seen in a patient on maintenance pemetrexed. In conclusion, BI-1361849 can be safe in combination with local radiotherapy and maintenance pemetrexed treatment (22).

To date, quantities of studies concerning combinations of vaccines and other therapies are ongoing (23). Firstly, vaccines complement ICIs based therapies. Vaccines are able to induce the activation of T cells, while ICIs agents are likely to maintain the activity of T cells. A few preclinical studies have proved its efficacy in mice by now (24-28). And combinations of vaccines and ICIs based therapies had been proved to enhance OS and PFS in the treatment of lung cancer (8). Secondly, vaccine-chemotherapy combinations are also effective. Due to the robust killing efficacy of chemotherapeutics, it improved the microenvironment of tumor and spares much more time for vaccines to activate T cell responses. So many studies tended to examine vaccine-chemotherapy combinations (29-32). Thirdly, vaccines can enhance the antitumor effect of CAR-T cells (33). Relative studies on other cancers such as myeloma are currently on the way (34,35). Nevertheless, data related to lung cancer are now absent. Therefore, we hypothesize that large amount of

studies will be started as the CAR therapy matures.

ICIs based therapy

ICIs based therapy, which is a vital part of immunotherapy, is revolutionizing the treatment of lung cancer. Astoundingly, *Science* magazine declared the immunotherapy as the breakthrough of 2013 owing to the prosperity of ICIs based therapy (36). So far, a few anti-PD drugs have been approved in many countries and regions, including US, Europe, Japan and so on (37).

In contrast with the other immunotherapies, the mechanism of immune checkpoint blockade is unique. Through blocking vital regulation of immune system, ICIs activate the T cells and augment their population, and T cells subsequently infiltrate and wipe out the tumor cells. As a result, the immune checkpoint blockade based agents have at least three features. Firstly, ICIs do not directly activate the immune system to attack tumor cells, but to eradicate the immune checkpoint blockade. So, ICIs are not specific for the type of cancer. And the immune response is universal, which independents of patients' history of cancer or personal tumor-specific antigens. Secondly, unlike CAR-T therapy where the expression of target really occurs, the ongoing T cell response after injections of ICIs, rather than PD1 expressions, is the key factor. Thirdly, this treatment leads to durable responses, whose effect can remain even over a decade (38).

A consensus review published had a sound grip of the field of ICIs, and the writer Axel Hoos categorized the development of ICIs based therapies into three generations (39). Generation 1 consists of ipilimumab (anti-CTLA-4) and sipuleucel-T, which were approved by FDA on the basis of several randomized phase III clinical trials. Nevertheless, the failure of sipuleucel-T's mass production prevented it from becoming a commercial success. In recent three years, the generation 2, which includes PD1, has been progressing by leaps and bounds. Surprisingly, the PD1 based therapy, already approved by FDA, has been widely applied in routine clinical practice. It can be said without exaggeration that anti-PD1 therapy has been rapidly established as a widely used second-line treatment for lung cancer. Compared with chemotherapy, a stronger efficacy and less toxicity were noted based on the reported data. Combining anti-PD1 agents with chemotherapy also been proved to result in better ORR and OS rates. In 2016, multiple studies attempted to find out whether ICIs are more appropriate to be used in first-line therapy than platinum-doublet chemotherapy. Notably, the third generation, which contains atezolizumab (Tecentriq) and durvalumab (MEDI4736) that are both agents blocking PDL1, has aroused large quantities of scientists' interest. The PDL1 molecule is essential for tumor-mediated immune evasion. Though anti-PDL1 therapy is still in the state of phase I/II trials, high chances are that it will be approved for the treatment of lung cancer. On account of data reported so far, we can safely arrive at the conclusion that the generation 3 can be the most competitive. Latest breakthroughs include relation between mutations and resistance to PD-1 blockade (40), a new way to handle the anti-PD drug-resistance (41), the reason why response rates vary in patients (42).

CTLA-4, also named CD152, is a protein receptor, which is expressed in activated T cells and regulatory T cells (Tregs). It plays an important role in regulating immune responses as an immune checkpoint. Ipilimumab is a human IgG1 anti-CTLA-4 monoclonal antibody. Likewise, tremelimumab is a fully human monoclonal antibody against CTLA-4. About one semi-decade ago, randomized phase III trials of ipilimumab and tremelimumab are successful (39). As a consequence, in 2011, ipilimumab was approved by FDA in treatment of metastatic melanoma (43). Now, researcher has focused on the synergistic effects of ipilimumab or tremelimumab in combination with other methods (such as PD1/PDL1 inhibitors). Moreover, the combination therapy proves to have better therapeutic effects than monotherapy (44,45).

PD1 inhibitors

PD1, termed as CD259, is another immune checkpoint receptor expressed in T cells, blocking T cell activity in parenchyma. It has two ligands, including PDL1 and PDL2 (B7-H1 or CD273), located on the surface of antigen presenting cells and tumors. PD1/PDL1 had been proved to inhibit activating of T cells. Though related tests and studies are currently absent, PD1/PDL2 seems to induce the similar effects (7). Compared with CTLA-4, an advantage of PD1 is its expression in other immune related cells, including B cells and NK cells, hence resulting in an enhanced stimulation of antibody production. Due to its features, quantities of studies endeavored to explore on the efficacy and safety of PD1 inhibitors such as nivolumab and pembrolizumab. Thus far, based on established data, an approximate ORR of 20% associated with PD1 monotherapy was reported. Higher ORR and lower

toxicities of PD1 inhibitors have aroused the interest of numerous scientists.

Nivolumab (Opdivo) is a human IgG4 anti-PD1 monoclonal antibody, which can activate host immune system. FDA approved it in March 2015 for the treatment of metastatic squamous NSCLC based on the promising results of the CheckMate 017 (CM017) clinical trial (46). Excitingly, it was the first approved immunotherapy of squamous cell lung cancer (47). In 2015, multiple studies tended to evaluate the efficacy and safety of nivolumab, and find that nivolumab-based therapy produced durable responses and great survival rates in patients with NSCLC (48). In a phase I trial, median OS in patients with heavily pretreated NSCLC was 9.9 months at the 3 mg/kg dose (49). The result of other phase I study manifested that the ORR was 18% (95% CI, 11–29), under the condition that patients were injected at doses of 0.1–10 mg/kg once every 2 weeks (50). In 2016, a phase I/II trial (NCT01928394) showed that 98 patients with small-cell lung cancer (SCLC) was treated with nivolumab 3 mg/kg, and the median follow-up for patients was 198.5 days (51).

In comparison with other therapies, it seems fair to reach the conclusion that nivolumab is much more efficient based on a bunch of established researches. First of all, in contrast to chemotherapy, nivolumab was associated with significantly better OS, ORR and PFS in a randomized, open-label, international, phase III study (52). CheckMate 026 (NCT02041533) is examining nivolumab versus standard platinum-based doublet chemotherapy (PT-DC) in patients with stage IV or recurrent PD1-expression NSCLC who never received previous chemotherapy. Another trial, CheckMate 227 (NCT02477826) was initiated in order to investigate nivolumab and nivolumab combined with ipilimumab versus standard PT-DC with or without nivolumab. Secondly, the relationship between tumor PD1 expression and efficacy of agents are sufficient in a phase I, multi-cohort, Checkmate 012 trial (53). Thirdly, comparisons concerning the efficacy of nivolumab in treatment of SCLC versus NSCLC are now absent, and relevant studies are ongoing.

Nivolumab, coming of age, has been gradually applied. Thereby, the safety-related reports are numerous. A 2016 study reported two cases of NSCLC showing pseudoprogression during the nivolumab treatment (54). According to multiple reports, nivolumab can also potentially induce immune thrombocytopenia (55), psoriasis and psoriatic arthritis (56) or severe akathisia symptoms (57) in a patient with advanced lung cancer, acute demyelinating polyneuropathy in a patient with metastatic NSCLC (58), immune related pancreatitis in a patient with recurrent lung adenocarcinoma (LAD) (59), "disease flare" in a patient with stage IIB LAD (60), organizing pneumonitis in a patient with lung sarcomatoid carcinoma (61), relapse of morphea in a patient with LAD (62). More details of infusion-related adverse events (IRAEs) are discussed below.

Pembrolizumab (MK-3475 or Keytruda) is a humanized antibody against PD1 receptor. On the basis of the available data, some aspects of pembrolizumab are striking. First, with respect to the efficacy of pembrolizumab, a pivotal 2015 phase I study assigned 495 advanced NSCLC patients treated with pembrolizumab at a dose of either 2 or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks (63). Among all the patients, the ORR was 19.4%, while the median duration of response was 12.5 months. In 2016, multiple phase Ib or phase II studies manifested that pembrolizumab significantly prolongs OS for patients with PD1-positive advanced NSCLC (64-71). Second, with regard to the proper dose, a phase Ib trial characterized the relationship between different doses of pembrolizumab, indicating that no significant exposure dependency on efficacy or safety was identified across doses of 2 to 10 mg/kg (72). Third, a latest phase III study compared pembrolizumab-based therapy with standard PT-DC, with a result of better PFS and OS than chemotherapy (73). To put it in a nutshell, pembrolizumab is a mature agent. Impressively, on October 2, 2015, FDA granted accelerated approval for pembrolizumab (74).

PDL1 inhibitors

Atezolizumab (MPDL3280A) is a humanized monoclonal antibody of IgG1 isotype against PDL1. It is the first anti-PDL1 agent approved by the FDA for NSCLC, by virtue of the enhanced OS in a phase III trial (75). Another randomised, open-label, phase III trial (NCT02008227) tested the efficacy of atezolizumab in patients with squamous or NSCLC, suggesting that atezolizumab was associated with better OS in comparison with docetaxel (76). Analogously, a phase III trial comparing atezolizumab with chemotherapy proved that atezolizumab was applicable for the treatment of NSCLC (77), and atezolizumab plus chemotherapy in chemotherapy-naive patients with advanced NSCLC has robust efficacy (78). Clinical data obtained from three up-to-date trials concerning atezolizumab illustrate the broad potential of treatment on

extensive stage small cell lung cancer (ES-SCLC) (79-81). With respect to the safety of atezolizumab, adverse events were less common in patients, compared with docetaxel (82). Interestingly, a phase II study pointed out the positive relation between the rate of PDL1 expression and OS (83).

Durvalumab (MEDI4736) is a fully human IgG1 antibody that is invented to inhibit PDL1, similar to atezolizumab. Compared with atezolizumab, nivolumab and pembrolizumab, the development and study of durvalumab is still being carrying on, in that almost all the clinical trials are in phase I. In other words, 2016 witnessed the preliminary advancement of durvalumab. In a recent phase I/II study, ORR was 25% when treating patients with advanced NSCLC (84). A phase I, open-label study aimed to examine the safety and antitumor activity of durvalumab in treatment of US patients with advanced NSCLC, and find that durvalumab was a safe and robust agent which was even effective in PDL1-negative patients (85). The safety of durvalumab also reported in the study (NCT01693562) showed that 50% of patients were confronted with durvalumab-related adverse events (86). Results of another phase II clinical study manifested a 5-year OS of 37% when treated in stage 3 NSCLC.

In the future, more efforts will be made from the following aspects. (I) Besides the known inhibitors, brand new immune checkpoint blockades will be explored, and the emerging inhibitors such as lymphocyte-activation gene 3 (LAG3) and T cell immunoglobulin- and mucin-domain-containing molecule 3 (TIM3) inhibitors will be thoroughly under study. (II) Optimum doses of anti-CDLA4 agents and anti-PD1 agents will be one of the key topics in the field of ICIs. (III) Investigations into ICIs-CAR therapy are now almost absent. Very few researches examine it in mouse model, and in the field of lung cancer, there is no related work regardless of its robust efficacy. Hence, more and more investigators will get involved in combining ICIs with CAR therapies.

LAG3, a new target, is a member of the immunoglobulin superfamily (IgSF), which has large quantities of impacts on T cell function (87). A preclinical trial managed to report that, in the experimental lung metastasis mouse models, MVA-BN-HER2 and/or anti-PD1 and anti-LAG3 dual checkpoint inhibition significantly reduced the size of tumor (88).

TIM3 is a transmembrane protein, which is T helper 1 (Th1) specific regulator of macrophage responses. Though researches about TIM3 are preliminary, the great potential in this field has generated a large amount of interest. A review titled "Immunotherapy: PD1 says goodbye, TIM3 says hello" published seems to predict the promising future of this therapy as its title manifests (89). Recently, preclinical trials revealed that TIM3 upregulation was observed in the tumor microenvironment in two fully immunocompetent mouse models of NSCLC (90). Currently, a phase I/II trial (NCT02608268) is on the way, testing anti-TIM3 monoclonal antibody along with PD1 inhibitor in patients with advanced solid malignancies, including NSCLC. Likewise, a phase I trial (NCT02817633) of TSR-022, an anti-TIM3 monoclonal antibody, is recruiting patients with NSCLC.

In recent 3 years, combination ICIs therapy, as a hot spot of this field, has been investigated by large quantities of studies. With the assistance of combination immunotherapies, durable responses have been obtained and OS and PFS of patients were significantly prolonged. In particular, success of nivolumab plus ipilimumab combination immunotherapy led to the approval by FDA owing to CheckMate 067 trial results (91). Whereas, some studies reported that combining anti-PD1 agents with anti-CTLA-4 agents or EGFR-tyrosine kinase inhibitors (TKIs) may not have significantly better results than anti-PD1 monotherapy. Recently, according to an important study published by *Nature Medicine*, Moynihan *et al.* combined four kinds of agents: anti-PD1 drugs, an antigen-targeting antibody, a recombinant IL-2 and a robust vaccine, and synergetic antitumor efficacy was observed (92). Additional data, another influential research published by *Nature Medicine* reported that focal adhesion kinase (FAK) inhibitors (VS-4718) plus checkpoint immunotherapy was much more efficient than monotherapy (93). In the near future, high chances are that combination immunotherapy will be used as the first-line therapy by virtue of its great clinical benefit.

Encouraging results of anti-PD1/PDL1 plus chemotherapy were reported, and toxicity was acceptable. (I) With respect to nivolumab (anti-PD1) plus chemotherapy, a phase I, multi-cohort study was aim to test nivolumab monotherapy versus combination therapy. A better ORR, PFS and OS were observed than PT-DC alone. And the grade 3/4 IRAE rate of 45% was seen (n=56) (94). Likewise, a phase Ib study reported a median PFS of 6.28, 9.63 months, not reached, and 3.15 months was observed among 4 arms (n=6 respectively). Higher chances of skin toxicities and hepatic toxicities were reported than chemotherapy or nivolumab alone, albeit, IRAEs were all mild (95). (II) Concerning atezolizumab (anti-PDL1) plus chemotherapy, multiple studies have been initiated, including IMpower130 (NCT02367781) (96), IMpower131 (NCT02367794) (97),

IMpower132 (NCT02657434) (98) and IMpower133 (NCT02763579) (81).

Recently, an influential study reported that anti-PD1 drugs plus systemic chemotherapy (SC) can enhance antitumor efficacy in glioblastoma (GBM) (99). This trend may lead the future study in the field of lung cancer immunotherapy.

Data related to the efficacy of combination ICIs therapies are sufficient, especially nivolumab (anti-PD1) plus ipilimumab (anti-CTLA-4). The characteristics of nivolumab and ipilimumab account for the popularity of this combination immunotherapy. Based on established studies, anti-CTLA-4 agents will push T cells into tumors. As a result, the population of T cells will be enlarged, thereafter inducing PDL1-expression in the microenvironment. Hence, if anti-PD1 or anti-PDL1 agents are simultaneously used, more promising results will be possible (38). Also, on the basis of large quantities of data, CTLA-4 inhibitors, including ipilimumab, usually deliver relative poor response rates but low toxicities. On the other hand, nivolumab, a PD1 inhibitor, is able to have high response rates in most occasions. Thereby, combination immunotherapy works fairly well. Researches indicated nivolumab plus ipilimumab therapy in the first-line setting generated antitumor activities with higher response rate compared with nivolumab monotherapy (51,100). It made patients have better ORR in treatment of lung cancer, and the rate of IRAE is normal (101). Another example is durvalumab (anti-PDL1) plus tremelimumab (anti-CTLA-4), but related studies are comparatively fewer (102).

Besides anti-PD1/PDL1 plus chemotherapy and anti-PD1/PDL1 plus anti-CTLA-4, durvalumab (anti-PDL1) plus OX40 (NCT02221960), nivolumab (anti-PD1) plus lirilumab (NCT01714739), nivolumab (anti-PD1) and ipilimumab (anti-CTLA-4) plus radiotherapy (NCT02046733) cisplatin and etoposide plus thoracic radiotherapy followed by nivolumab or placebo (NCT02768558) are ongoing (103,104).

Notably, anti-PD agents plus CAR-T therapies has also aroused interest of investigators. In a preclinical study, investigators found that CAR-T cells secreted anti-PD-L1 antibodies more effectively, regressing renal cell carcinoma (105). It is fair to predict that more highly promising achievements will be made in the near future.

CAR-T cell immunotherapy therapy

With the ultimate goal of enhancing antitumor responses which is mediated by immune system, the adoptive cell therapy (ACT) was born, containing tumor-infiltrating lymphocyte (TIL) therapy (106), γδ T cell therapy (107), natural killer (NK) cell-based therapy (108), cytokine-induced killer (CIK) cell-based therapy (109) and CAR-T therapy. Originated from TIL immunotherapy, CAR is composed of three parts, including an extracellular antigen-target domain, a transmembrane domain and an intracellular signaling domain. The extracellular domain, in the simplest form, consists of a single-chain variable fragment (scFv), which is derived from the variable heavy and variable light chains of an antibody and used to target the tumor-associated antigen (TAA). The transmembrane domain anchors the CAR to the cell membrane. And the intracellular domain is composed of signaling domains that is essential for activation of T cells.

To date, CARs have developed to the third generation. The initial generation of CAR is composed of a single intracellular CD3ζ chain. The comparatively simple structure results in the anergy of T cells, because CD3ζ chain merely delivers activation signal 1 to T cells, thereby having a low overall expansion and antitumor ability (110-112). Further advancements of the CAR, known as the second generation, have included the addition of a co-stimulatory signaling chain on the basis of a CD3ζ domain. Thus, the receptor provides both a signal 1 and signal 2 to induce the activation of T cells. The latest co-stimulatory chains that is being studied includes CD28 (111,113,114), 4-1BB (115,116), OX40 (117), CD27 (118), ICOS (119) and so on. The co-stimulatory domains vary in their attributes, such as the ability to confer cytokine secretion, cytotoxicity and proliferation. The third generation of CAR includes a CD3ζ domain and two co-stimulating domains, endowing CAR with enhanced activity, persistence and great antitumor efficacy. February 06, 2017 was a "big day", witnessing the approval of the first off-the-shelf CAR product UCART123 by FDA. Recently, major breakthroughs are emerging. An important study had an in-depth study on exhausted T cells in cancer, making CAR-T therapy more promising (120). Scientists found that S-2-hydroxyglutarate regulated $CD8^+$ T-lymphocyte fate, providing a new strategy to improve persistence of CAR-T cells (121). A study engineered T cells with dual-receptor and made CAR-T cells to recognize targets more precisely (122). Another study used double synNotch receptors in one T cell, allowing flexible user-customized extracellular cues (123).

There are several advantages of CAR. (I) In comparison with T cell receptor (TCR), CARs can avoid being

Table 2 The ongoing trials of CAR-T therapy for lung cancer

Clinical trials	Type of lung cancer	Phase	CAR-T antigens	Institution
NCT02349724	Lung cancer	Phase 1	CEA	Southwest Hospital, China
NCT01869166	NSCLC	Phase 1/2	EGFR	Chinese PLA General Hospital, China
NCT02876978	LSCC	Phase 1	GPC3	Carsgen Therapeutics Ltd. , China
NCT02713984	Lung cancer	Phase 1/2	HER2	Southwest Hospital, China
NCT01935843	NSCLC	Phase 1/2	HER2	Chinese PLA General Hospital, China
NCT00889954	Lung cancer	Phase 1	HER2	Baylor College of Medicine, USA
NCT01583686	Lung cancer	Phase 1/2	Mesothelin	National Cancer Institute (NCI), USA
NCT02587689	NSCLC	Phase 1/2	MUC1	PersonGen BioTherapeutics Co, Ltd, Suzhou, China
NCT02706392	NSCLC	Phase 1	ROR1	Fred Hutchinson Cancer Research Center, USA

CAR-T, chimeric antigen receptor T; NSCLC, non-small cell lung cancer; LSCC, lung squamous cell carcinoma; CEA, carcinoembryonic antigen; EGFR, epidermal growth factor receptor; GPC3, glypican-3; HER2, human epidermal growth factor receptor 2; MUC1, mucin 1; ROR1, receptor tyrosine kinase-like orphan receptor.

constrained by major histocompatibility complex (MHC) specificity according to a fundamental 1990 research (124). As a result, CARs are likely to be applied to a wider range of patients than TCRs (125). (II) In CAR-T cells, a receptor was combined with T cell populations, allowing CAR-T cells to target at almost all the tumors. (III) Proteins, glycoproteins and glycolipids can be used as potential targets. (IV) CAR-T cells have a robust overall antitumor ability and greater persistence compared with normal T cells (126). However, there is no denying that the structure of CAR has a limitation that the intracellular antigens cannot be targeted, such as the MAGE family and NY-ESO1 (127). When it comes to the safety of this therapy, CAR T cells are likely to elicit potential toxicities, such as cytokine release syndrome (CRS), neurological toxicity, on-target/off-tumor recognition, anaphylaxis, insertional oncogenesis, graft versus host disease and off-target antigen recognition (128,129). And lots of studies have been initiated in order to manage the toxicity, including pharmacological immunosuppression, suicide genes, elimination genes and targeted activation (130-132).

Conspicuous clinical success observed in CAR-T based therapy has generated the growing interest (133) in the field of haematological malignancies, especially B-cell acute lymphoblastic leukemia (B-ALL) (134,135), chronic lymphocytic leukaemia (CLL) (136,137), multiple myeloma (MM) (138) and non-Hodgkin lymphoma (NHL) (139). Nevertheless, the majority of the studies concerning solid tumors are at the preclinical state or early phase clinical trials (140), indicating that CAR-T cell therapy for solid tumors will be progressing by leaps and bounds in the near future. In addition to lung tumor, multiple studies are concentrating on the treatment of prostate cancer (141-143), pancreatic cancer (144,145), mesothelioma (146), glioma (147), neuroblastoma (148), melanoma (149), sarcoma (150), GBM (151-155) and a growing list of other malignancies. Simultaneously, the researchers focused on solid tumors may be confronted with more challenges, and there are at least three main rationales for this puzzle. Firstly, the micro-environment of solid tumors may be significantly more immunosuppressive than B-ALL. Secondly, high chances are that the so-called 'on-target, off-tumor' toxicity may have negative effects on the antigen selection, because the immunotherapeutic target can also be expressed in normal tissues. Hence, it is more difficult to find an effective potential target, requiring the previous study of new antigens and the development of preclinical models (156). Thirdly, due to higher antigen heterogeneity in solid tumors, the selection of antigen becomes less possible (112).

At present, researches of lung cancer CAR-T therapy are still in the initial stage. Investigators focused on finding new potential targets and conducting clinical trials based on previous preclinical studies. Thus far, all published researches in the field of lung cancer only include four preclinical studies and one phase I study. Furthermore, there are nine ongoing trials, most of which are phase I trials. In *Table 2*, the ongoing phase I/II trials related to CAR-T therapy were summarized. The information in this table came from www.clinicaltrials.gov (up to January 2017).

Simultaneously, new potential targets also exist. Targets including Tspan8, MUC1, CD151, CD146, LRP1 are promising (157), and encouraging results of these targets have been observed in other cancers, especially MUC1 (158-160). Scientists including Posey *et al.* recently provided insights and proved it (160). It is fair to predict that, in the near future, more investigators will get involved in testing the new targets.

EGFR is a transmembrane glycoprotein, which is also referred to as human epidermal receptor 1 (HER1). EGFR plays an important role in cell proliferation, survival, metastasis and tumor-induced vascularization (161). EGFR is expressed in normal epithelial cells and a lot of epithelial tissue deprived malignancies. Besides lung cancer, EGFR-CAR T therapy was applied to other kinds of cancers such as GBM (151). Compared with normal tissues, EGFR tends to be a promising therapeutic target because of the significant elevation of low-affinity and high-affinity of binding sites in lung tumors.

In 2013, a preclinical study firstly tested EGFR-CAR T cells in the A549 advanced lung cancer model. Consequently, EGFR-CAR T cells eliminate almost all tumor cells compared with other groups. Also, weights of lung significantly decreased in the group of EGFR-CAR T compared with all other groups (162). This study provided a basis for clinical trials of EGFR-CAR T. When it comes to the safety of EGFR-CAR T, no obvious fluctuating of cytokines and few adverse events were observed in mice (162). Thereafter, a 2016 phase I clinical trial (NCT01869166) proved the safety and feasibility of CAR-modified T cells for the immunotherapy of patients with EGFR-expressing advanced relapsed or refractory NSCLC. In their study, 6 women and 5 men with advanced relapsed or refractory NSCLC took part in, and the EGFR expression was over 50%. The EGFR-CAR T cells were produced from peripheral blood, with the result that a median of 29.28% of T cells from patients expressed the CAR. In other words, the specific toxicity of EGFR-CAR T cells from patients was able to act against EGFR-positive tumor cells. The certain toxicity of the EGFR-CAR T cells was observed after incubation with the EGFR-positive cells, HeLa and MCF7 Plus the infusions of EGFR-CAR T cells were well tolerated, indicating unserious cytotoxicity. Among 11 patients, a partial response of 2 patients was observed, while 5 stable diseases was reported, which range from two to eight months. Interestingly, the patients, where EGFR-TKIs were not effective, were able to benefit from the EGFR-CAR T therapy (163). This trial is the first clinical CAR study about lung cancer, and further studies on EGFR-CAR T cells are required.

Human EGF receptor 2 (HER2) is overexpressed in multiple malignancies, including breast cancer, lung cancer, ovary cancer, prostate cancer, brain cancer, colon cancer and ovarian cancer (156). In 2015, a phase I/II trial evaluated the efficacy of HER2-CAR T cells, where 19 patients with recurrent/refractory HER2-expressed sarcoma were recruited in. The median OS was 10.3 months, and the cells have great persistence without obvious toxicities (164). At present, an ongoing preclinical study is attempting to evaluate the efficacy of HER2-CAR T cells *in vitro* experiments in an established lung cancer model (165). Currently, a phase I/II study (NCT02713984) tested the efficacy of HER2-CAR T cells to confirm the ability of CAR T cells to eliminate HER2 positive cancer cells, including lung cancer cells. Another phase I/II research (NCT01935843) is currently recruiting participants with NSCLC in order to determine the safety and feasibility of HER2-CAR T cells.

Glypican-3 (GPC3) is affiliated to the family of heparin sulfate proteoglycans (HSPG), which are dependent on the cell surface by a glycosylphosphatidylinositol anchor. It has important effects on cellular growth, differentiation, and migration (166,167). GPC3 is over-expressed in many kinds of tumor cells, including lung tumor, and it is deficient in normal tissues. In addition to lung cancer, researches on CAR-T-GPC3 therapy for hepatocellular carcinoma are also under way (168-170).

In 2016, a preclinical study found that the antitumor affected generation 3 GPC3-CAR T cells in an established lung squamous cell carcinoma (LSCC) model. They firstly explored by immunohistochemistry (IHC) that GPC3 was expressed in LAD (3.33% positive) cases and LSCC cases (63.33% positive). However, GPC3 was not expressed in normal lung tissues. In the assay of a cytokine release, GPC3-CAR T cells released a strikingly increased amount of IFN-γ, IL-2, TNF-α, IL-4 and IL-10, indicating a strong activation of T cells. The results of cytotoxicity assay proved that GPC3-CAR T cells were capable of eradicate GPC3-positive cells. In LSCC models, GPC3-CAR T cells could eradicate almost all the growth of GPC3-positive cells. To put it in a nutshell, high chances are that GPC3-CAR T cells based therapy can be a promising therapeutic agent for the treatment of patients with LSCC (171). A phase I clinical trial (NCT02876978) is currently recruiting LSCC participants in order to examine the tolerance of GPC3-CAR T cells and the survival of the GPC3-CAR T cells *in vivo*.

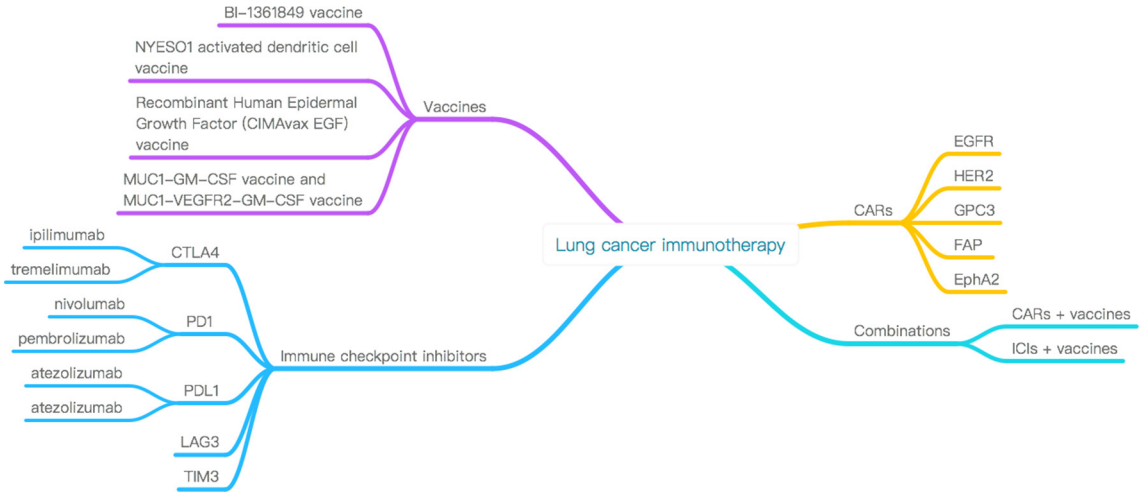

Figure 1 The summary of immunotherapy for lung cancer in the review.

Fibroblast activation protein-α (FAP) is a type 2 dipeptidyl peptidase, expressed in cancer-associated fibroblasts (CAFs) in most of the solid tumors, including lung tumors (172,173). In a preclinical study, researchers genetically modified a generation 2 CAR, which is specific for murine-FAP (mFAP) and human-FAP (hFAP). In lung cancer models, the cytotoxicity of mhFAP-CAR T cells against mFAP and hFAP was significant, compared with the non-transduced T cells. The trial manifested that mhFAP-CAR T cells could perfectly recognize and eradicate both hFAP-expressing and mFAP-expressing cells. In addition, mhFAP-CAR T cells had antitumor activity in both a loco-regional tumor model and a systemic tumor model. An application of FAP-CAR T cells tends to be a promising and feasible therapy (174).

Ephrin type-A receptor 2 (EphA2), composed of a mono-kinase domain and an ectocytic domain, is overexpressed in primary lung tumor cells. It belongs to the largest family of RTKs (175,176). In a preclinical trial, using A549 lung cancer models, EphA2-CAR T cells recognized and eradicated EphA2-expressed targets, and EphA2-CAR T cells enable bystander T cells to eradicate EphA2-expressed tumor cells. The potent antitumor efficacy of EphA2-CAR T cells was observed in mice, inducing a significant survival advantage (177). A combination of EphA2-CAR T cells plus FAP-CAR T cells was tested in another preclinical study of lung tumor. A median expression rate of 36.6% was reported in EphA2-CAR T cells. As a result, EphA2-expressed targets were recognized and eradicated by EphA2-CAR T cells, whereas the EphA2-negative cells stay uninjured. The combination of EphA2-CAR T cells plus FAP-CAR T cells had a better antitumor activity, and the difference between it and other therapies was significant. Thus, EphA2-CAR T combining with FAP-CAR T cells significantly enhanced overall antitumor activity (174).

With respect to CAR-T therapy, promising therapeutic targets are available, such as Tspan8, MUC1, CD151, CD146, LRP1, which are overexpressed in lung tumor cells. More preclinical studies will be initiated in mouse models in order to examine their efficacy. In particular, MUC-1 will be a promising target based on an influential research (160). In addition, results of nine ongoing phase I/II trials may be encouraging. Combining CAR-T therapy with vaccines, ICIs will be promising, and scientists have proved it in a similar way (92). This field is still young, but a lot of potential for progress and clinical improvements exists.

Summary

The immunotherapy for lung cancer in the review is summarized in *Figure 1*. The field of lung cancer therapy is undergoing revolutionary changes. New antitumor vaccines can prolong OS and PFS, and it is useful when treating precancerous lesion or preventing relapse tumor. Anti-PD1 agents may have roughly a 20% ORR, associated with significantly better OS and PFS than chemotherapy. Emerging ICIs, including PDL1, LAG3 and TIM3, will generate prolonged OS and PFS, though, more in-depth studies are required. Combinations between PD1/PDL1 inhibitors, CTLA-4 inhibitors and chemotherapies are

under study, and the optimum dose remains unknown. Patients who haven't been pretreated with chemotherapy are likely to benefit more from ICIs. Preclinical studies on CAR-T in treatment lung cancer have produced preliminary achievements, including HER2-CAR T cells, GPC3-CAR T cells, FAP-CAR T cells and EphA2-CAR T cells therapies. Multiple phase I/II studies are continuing. In the future, scientist in the world will move ahead on the road of immunotherapy for lung cancer to bring more hope.

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Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/biotarget.2017.05.02). MJ serves as Editor-in-Chief of *Biotarget*. The other author has no conflicts of interest to declare.

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