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Targeted immunotherapy for non-small cell lung cancer

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Abstract

Targeted therapies that deliver the expected anti-tumor effects while mitigating the adverse effects are taking the cancer world by storm. The need for such therapies in non-small cell lung cancer (NSCLC), where systemic cytotoxic chemotherapies still remain the backbone of management, is felt more than ever before. Runway success of immunotherapies such as Ipilimumab for melanoma has brought excitement among oncologists. Immune-based treatments are in various stages of evaluation for NSCLC as well. Immunotherapies using strategies of antigen based or cell based vaccines, and blocking immune checkpoints are of substantial interest. Meaningful clinical responses are yet to be reaped from these new treatment modalities.

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Core tip: Lung cancer is the leading cause of cancer-death worldwide. Majority of these patients have non-small cell lung cancer (NSCLC). Traditional chemotherapy is limited by its high toxicity. Emerging data have

demonstrated promising outcome of immunotherapy in NSCLC. This review delineated the rationale and potential targets of cancer immunotherapy, with a summary of immunotherapeutic agents for treatment of NSCLC. Protein/peptide-based and cell-based vaccines, as well as immune checkpoint targeted agents such as Ipilimumab and PD-1 pathway inhibitors were discussed. In addition, we reviewed ongoing immunotherapy-based studies including several major phase II/III clinical trials, results of which will be available soon for incorporation into clinical practice.

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INTRODUCTION

Lung cancer remains the leading cause of death in the United States with about 160000 estimated deaths in 2013^[1]. Majority of these patients have non-small cell lung cancer (NSCLC). Over the past few decades, platinum based chemotherapy is the standard of care for advanced stages of NSCLC. These systemic therapies have significant toxicities and confer unacceptable morbidity. A decade ago, it was realized that advancement in treating NSCLC could not be reached with the use of cytotoxic agents alone^[2]. While entering the era of personalized medicine, focus of cancer therapy has been recently shifted to identifying and targeting certain driver mutations. This has been successful in certain solid tumors including NSCLC, wherein identifying the genetic mutation in epidermal growth factor receptor (EGFR) and fusion gene rearrangement in anaplastic lymphoma kinase has become the standard of care. Historically lung cancer was not seen as an “immunologic malignancy”. However recent success of Ipilimumab in melanoma^[3] and Sipuleucel-T in prostate cancer^[4] opened up a new realm

of cancer immunotherapy. Emerging data demonstrate promising outcome of immunotherapy in lung cancer. Herein we review the basics of cancer immunotherapy and development of immunotherapeutic agents for management of NSCLC.

We conducted a review of articles in the past 10 years, that harbored the terms “immunotherapies”, “non small cell lung cancer” in the Pubmed and Medline database as well as trials that are ongoing in clinicaltrials.gov.

BASIC IMMUNOLOGY PRINCIPLES AND ITS APPLICATION IN NSCLC

Immunity acts as a double edged sword when it comes to cancer. The cross talk between tumor and immunity is complex. Cancer immunoediting plays an important role in this context. Three phases of cancer immunoediting have been described: elimination, equilibrium and escape^[5].

In the initial phase of elimination, innate and adaptive immune systems work in concert to eradicate tumor cells, after which the survived cells enter a state of dormancy called the equilibrium phase. Under immune pressure, tumor cells may undergo phenotypic or genomic modification, resulting in the survival and proliferation of tumor variants that are capable of escaping immune attack. Important modulations of this immune escape include down-regulation of HLA class I, loss of tumor antigens, lack of death receptor signaling, insufficient costimulation, and negative regulation pathways including regulatory T cells, inhibitory cytokines and molecules involved in immune checkpoints.

The potential targets for immunotherapy can be tumor specific antigen or each component of the cross talk between the immune system and tumor. It has been proposed that targeting tumor specific antigen may be ideal in treating early stage cancers when the tumor cells are highly immunogenic; whereas targeting non antigen specific immune pathways may be optimal in managing advanced stage cancers. Advancement of our knowledge in cancer immunology has resulted in better cancer vaccine designs with hope to improve clinical outcomes^[6].

Previously lung cancer was not seen as immunogenic. However recent studies have shown the association of immune response with overall outcome, indicating a role of immunotherapy in lung cancer management. Histochemical analysis of lung tumors in retrospect, showed that increased infiltration of the stroma by CD4⁺/CD8⁺ cells was an independent favorable prognostic factor^[7]. In addition, it has been observed that in advanced NSCLC, favorable prognosis has been associated with higher number of macrophages and CD8 T in tumor nests as compared with surrounding stroma^[8]. In contrast, increased infiltration by Foxp3⁺ lineage Treg cells is associated with poor outcome. Furthermore depletion of Treg achieves prolonged survival in mouse models^[9,10]. Current development of NSCLC immunotherapy is mainly focused on tumor vaccines and blockade of immune checkpoint pathways.

CANCER VACCINES

A therapeutic cancer vaccine intends to treat an existing cancer by strengthening the body's natural defense against cancer. Broadly, cancer vaccines can be divided into protein/peptide based vaccines and cellular vaccines.

PROTEIN/PEPTIDE BASED VACCINES IN NSCLC

L-BLP25 vaccine

MUC1 is a transmembrane glycoprotein that is upregulated in many solid tumors including NSCLC. It is purported that aberrant up regulation of MUC1 in tumor cells favors tumor angiogenesis *via* activating Erk and Akt pathways^[11]. L-BLP25 is a peptide vaccine that targets the exposed core peptide of MUC1^[12].

The vaccine was studied in an open label, phase II randomized trial in 171 patients with stage III B/IV NSCLC with response or stable disease after first line therapy^[13]. The trial evaluated effect of L-BLP25 liposome vaccine on survival and toxicity in the above patients. Quality of life and immune related responses due to the vaccine were the secondary end points. Patients were prestratified by stage and randomly assigned to either L-BLP25 plus best supportive care (BSC) or BSC alone. Patients in the L-BLP25 arm received a single intravenous dose of cyclophosphamide 300 mg/m² followed by eight weekly subcutaneous immunizations with L-BLP25; and then every 6 wk, as this had been previously shown to boost immune response in certain other cancers^[14]. Though the study failed to achieve the primary end point of overall survival (OS); subgroup analysis of patients with stage III B disease showed strong positive trend towards 2 years survival. Update on these patients published later showed continued improved survival in patients on the L-BLP-25 arm^[15]. These results were achieved with minimal toxicity.

Based on the above results, a phase III trial, Stimulated Targeted Antigenic response to NSCLC (START, NCT00409188) was undertaken. One thousand two hundred and thirty-six patients with stable unresectable stage III disease were randomized to receive either intravenous cyclophosphamide followed by weekly BLP-25 *vs* placebo. The trial did not meet its primary end point of OS, however the subgroup that was pretreated with prior chemoradiation (either concurrent or sequential) had significant improvement in OS^[16]. They reported the vaccine to be well tolerated with some flu-like symptoms, but no significant immune associated adverse effects.

Other clinical trials of L-BLP25 include the multinational, double blinded, placebo controlled trial in Asian population, with unresectable stage III NSCLC who have been stable or responded to primary chemoradiation, L-BLP25 trial In Asian NSCLC Patients: Stimulating Immune Response^[17].

A phase II study of L-BLP-25 is looking in combination with bevacizumab in patients who have undergone

chemoradiation for stage III NSCLC is ongoing as well^[18].

Melanoma-associated antigen-A3 vaccine

Melanoma-associated antigen (MAGE) is a family of tumor specific antigens that is expressed on variety of tumor cells and specifically the MAGE-A3 is detected in about 35%-50% of NSCLC^[19,20]. It is also expressed on cells of other tumors such as melanoma, renal, bladder and liver cancer^[21]. MAGE-A3 is also expressed on normal testicular and placental. However with unique immune tolerance mechanisms these organs were able to escape immune attack. Hence MAGE-A3 is a unique tumor antigen and the vaccine against it should be well tolerated in theory^[22,23]. Presence of MAGE-A3 is independently associated with poor prognosis in NSCLC^[24].

MAGE-A3 vaccine is composed of recombinant fusion protein, in combination with immune-enhancing adjuvant. A phase II trial studying the efficacy and safety of the vaccine was performed in 182 patients with MAGE-A3 positive, resected stage I B/ II NSCLC. This was an international, double blinded, placebo controlled trial, where patients were randomized to receive either MAGE-A3 vaccine or placebo. The results were encouraging as the long term analysis showed a positive trend in OS, disease progression time and disease-free survival in those receiving the MAGE-A3. The vaccine was very well tolerated leading to good compliance^[25]. These encouraging results lead to the ongoing randomized trial in lung cancer, MAGE-3 as Adjuvant Non-Small Cell Lung Cancer Immunotherapy. It is a phase III trial looking at MAGE-A3 vaccine *vs* placebo used in adjuvant setting for patients with MAGE-A3 positive stage I B, II or IIIA resected NSCLC. Disease free survival is the primary end point and OS, lung cancer specific survival and adverse events (AE) amongst others are secondary end point. The results of the study are eagerly expected in early 2014^[26].

Epidermal growth factor vaccine

EGFR is a transmembrane receptor tyrosine kinase belonging to the Erb family of receptors and is activated by binding of its specific ligand epidermal growth factor (EGF), hypothesized to be responsible for pathways that regulates cell survival, cell death *via* controlling the extracellular growth factors^[27]. EGFR expression is altered in many cancer, including NSCLC. In NSCLC harboring mutated EGFR, use of EGFR tyrosine kinase inhibitors as first line therapy has been shown to improve survival and safety profile in a number of clinical trials and are approved for this indication^[28-30].

Recombinant human EGF vaccine is an antigen-based vaccine which prevents binding of the endogenous EGF to the receptors by stimulating production of anti-EGF antibodies that clear it from circulation.

A phase I clinical trial conducted in 43 patients with advanced NSCLC was randomized to receive either single or double dose EGF vaccination. Patients receiving double dose of vaccination had higher antibody titers,

were found to have a positive survival trend. Antibody titers and serum EGF levels appear to correlate with patient survival^[31]. Significant positive outcome between higher antibody response and increased survival was confirmed in a phase II trial by García *et al*^[32]. A phase III trial for safety and efficacy of EGF vaccine in inoperable advanced stage NSCLC is currently ongoing^[33].

WHOLE TUMOR CELL VACCINE

Belagenpumatucel vaccine

Transforming growth factor $\beta 2$ (TGF $\beta 2$) converts CD4⁺CD25⁻ naïve T cells to CD4⁺CD25⁺Treg cells by inducing transcription factor Foxp3^[34] which in turn mediate immunosuppression in NSCLC by blocking dendritic cells, natural killer cells and lymphokine activated killer cells. Higher levels of TGF $\beta 2$ are associated with worse outcomes in NSCLC^[35]. Belagenpumatucel is a non-viral gene based allogeneic vaccine that carries TGF $\beta 2$ antigen modification of tumor cells. It consists of 4 cell lines of NSCLC (2 adenocarcinoma, 1 squamous carcinoma and 1 large cell carcinoma)^[36] which downregulates TGF $\beta 2$ upon administration.

The vaccine was investigated in early as well as advanced NSCLC where patients were randomly assigned to receive a dose of either 1.25, 2.5 or 5×10^7 cells/injection. Patients with any prior therapy were able to participate in the trial. Antibodies reactive against the cell lines were evaluated using enzyme-linked immunosorbent assay. The vaccine was well tolerated with minimal side effects. Survival was significantly improved in cohorts who received higher doses of the vaccine ($\geq 2.5 \times 10^7$ cells/injection); however difference across dose cohorts for advanced NSCLC was only marginal. Estimated probabilities of surviving 1 and 2 years were 68% and 52% respectively for higher dose groups combined and 39% and 20% respectively for the low dose group. Patients in the advanced stage disease had a 15% response rate^[36]. A smaller phase II trial by the same group in 21 patients confirmed the safety and efficacy of the vaccine. They also suggested the possibility of using CTC (circulating tumor cells) as surrogate of OS^[37].

Encouraged by the above results, a phase III trial of belagenpumatucel is underway as maintenance therapy for patients with T3N2-III A, IIIB and IV NSCLC who did not progress after front line chemotherapy (STOP trial)^[38]. Findings were reported in September 2013 at the European Cancer Congress from the STOP trial. Of 532 patients enrolled, 42 had stage II A and 490 had stage IIIB/IV disease. Patients were randomized 1:1 to receive either the vaccine or placebo until disease progression or withdrawal. Though STOP did not meet its predefined primary end point in the entire population, it was noted that patients who were randomized to receive the vaccine within 12 wk of the end of their first line chemotherapy had better OS (20.7 mo) as compared to those with placebo (13.4 mo). In addition, pretreatment radiation showed improved median OS with treatment

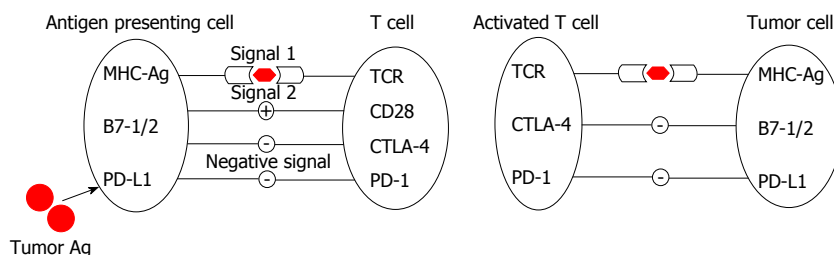


Figure 1 Interaction between T cells and antigen presenting cells or tumor cells. The quality and amplitude of T cells depends on the balance of the above co-stimulatory and inhibitory signals and ultimate orchestration of death of tumor cells. Agonists of costimulators or antagonist of inhibitors are the main topic of the study as described. MHC-Ag: Major histocompatibility complex antigen; TCR: T cell receptor; PD-1: Programmed death-1; PD-L1: Programmed death ligand 1; CTLA-4: Cytotoxic T lymphocyte antigen-4.

arm OS of 40.1 mo compared to 10.3 mo receiving placebo. The trial will be continued with focus on these specific subgroups^[39].

Immune checkpoints inhibitors

T cell receptors activate antigen specific cytotoxic T cells after recognition of the antigen peptide along with major histocompatibility complex. This activation usually requires costimulatory signal obtained *via* interaction of CD28 expressed on T cells with molecules expressed on antigen presenting cells (Figure 1). CD28 can also interact with inhibitory receptors on antigen presentation cells or tumor cells such as Cytotoxic T-Lymphocyte Antigen (CTLA)-4, PD-1, PD-L1 and B- and T-lymphocyte attenuator^[40], therefore inhibits T cell functions, a process called immune check point^[41,42]. Two promising strategies for immune check point modulation are currently being investigated in NSCLC.

CTLA-4 inhibitors

CTLA-4 inhibitors have been extensively studied and are thought to be responsible for initiating and maintaining peripheral tolerance as a part of physiological immune mechanism. Ipilimumab is a fully humanized mAb targeting the CTLA-4 inhibitory coreceptor, thus rescuing cytotoxic T cell activity and potentiating tumor death^[43]. It was approved for malignant melanoma^[3] and since then has been evaluated in various other malignancies.

A phase II study of Ipilimumab enrolled 204 patients with stage III B/IV NSCLC who had not received any prior chemotherapy^[44]. Patients were randomly assigned 1:1:1 to receive a concurrent Ipilimumab regimen (four doses of Ipilimumab plus paclitaxel and carboplatin followed by two doses of placebo plus paclitaxel and carboplatin), a phased Ipilimumab regimen (two doses of placebo plus paclitaxel and carboplatin followed by four doses of Ipilimumab plus paclitaxel and carboplatin), or a control regimen (up to six doses of placebo plus paclitaxel and carboplatin). In a previous study, lower dose of paclitaxel was found to be equally efficacious, with prospects of decreased toxicity when combined with Ipilimumab^[45]. Patients who tolerated the treatment well without evidence of progression then went on to receive either Ipilimumab or placebo for another 12 wk until disease progression or death. Clinical response patterns to Ipilimumab differs

from conventional cytotoxic therapies and hence a novel parameter, immune related response criteria (irRC) has been recently established to capture this phenomenon. Ipilimumab may cause regression of index lesions in the face of new lesions and initial progression followed by tumor stabilization or decrease in tumor burden. The irRC uses the total tumor burden obtained by adding measurable new lesions to index lesions in determining the tumor response. Changes in non-index or nonmeasurable lesions are discounted. Thresholds for immune-related complete response (CR, complete disappearance of all lesions), immune-related partial response (PR, decrease of total tumor burden from baseline by $\geq 50\%$), immune-related progressive disease (PD, increase of total tumor burden from nadir by $\geq 25\%$), and immune-related stable disease (all other settings including a slow steady decline in total tumor burden from baseline) were the same as for the CR, PR, PD, and stable disease^[44,46]. Here, immune related progression free survival (irPFS) which was defined as time from randomization to immune related progression or death was used as the primary end point.

Patients receiving phased Ipilimumab and carboplatin/paclitaxel showed improved irPFS as compared to carboplatin/paclitaxel alone, however no such benefit was seen in the group receiving concurrent Ipilimumab and carboplatin/paclitaxel. Also further subgroup analysis showed better outcome in patients with squamous histology. Hence the timing of Ipilimumab with cytotoxic chemotherapy seems to play an important role in the outcome.

Incidence of grade 3 or 4 AE was similar in all 3 arms. Though non hematologic AE related to carboplatin (alopecia, fatigue, nausea/vomiting, neuropathy) were similar across all arms, immune mediated adverse effects (rash, pruritis, diarrhea, colitis, transaminitis and pituitary dysfunction) showed a trend for increased incidence in Ipilimumab containing arms. These immune related side effects from Ipilimumab are thought to be secondary to CTLA4 inhibition. It is to be noted that though dose of Ipilimumab used in this trial was higher than that used in melanoma (10 mg/kg *vs* 3 mg/kg), the incidence of AE was comparable^[47].

A larger phase III trial of phased carboplatin/ paclitaxel and Ipilimumab in patients with stage IV NSCLC is underway^[48]. In addition, a safety and efficacy study of

Table 1 Ongoing clinical trials of programmed death-1 antibodies in non-small cell lung cancer

Therapy	Trial	Study population	Study design	Ref.
Nivolumab phase I safety study	NCT01454102 (checkmate 012)	Advanced NSCLC	Nivolumab as single agent <i>vs</i> combination with various chemotherapies	[55]
Nivolumab phase III study to determine OS	NCT01673867 (checkmate 057)	Previously treated (failed platinum based) advanced NSCLC	Nivolumab compared to docetaxel in previously treated patients	[56]
Nivolumab phase III study to look for tumor size and OS	NCT01642004 (checkmate 017)	Previously treated (failed platinum based) advanced NSCLC	Nivolumab compared to docetaxel in previously treated patients	[57]
Nivolumab phase III study assessing tumor size after treatment	NCT01721759 (checkmate 063)	Previously treated and failed 2 lines of chemotherapy	Assess response rate objectively (monitoring tumor size) in patients receiving Nivolumab	[58]
Nivolumab phase II study to determine Response	NCT01928576	Previously treated, advanced/recurrent NSCLC	Assess objective response with Nivolumab, preceded by epigenetic therapy (azacitidine IV or oral, entinostat) priming	[59]
MK-3475 (lambrolizumab) phase I dose limiting study followed by part B to assess safety and tolerability	NCT01928576	Any solid tumor, or advanced NSCLC	Patients with any solid tumor will receive lambrolizumab to assess dose; followed by part B where patients with advanced NSCLC will receive this therapy in combination with chemotherapy	[60]

NSCLC: Non-small cell lung cancer; OS: Overall survival.

Ipilimumab in stage IV NSCLC *vs* Pemetrexed in recurrent stage IV NSCLC who have not progressed after first line platinum based chemotherapy is also ongoing^[49]. A similar study of Ipilimumab and carboplatin/paclitaxel is also being conducted in Japan^[50].

Programmed death-1 pathway inhibitor

Programmed death-1 (PD-1) is another key receptor that can mediate immunosuppression by interacting with PD ligands 1 (PD-L1) and PD-L2. The anti-tumor activity of cytotoxic T cells can be enhanced by blocking this pathway^[51,52].

Anti PD-1 pathway agents gained momentum when a phase I dose escalation study of Nivolumab, a humanized IgG4 mAb, was performed in 39 patients with various cancers (melanoma, colorectal, prostate, NSCLC and renal cell). Among the 6 patients with NSCLC, all of whom had received multiple chemotherapies in the past, 1 patient achieved partial remission for over 14 mo, and the other 5 patients had stable disease post treatment^[53].

A larger phase I study then was conducted in patients with NSCLC, melanoma, castration resistant prostate cancer, colorectal cancer or renal cell cancer who largely had multiple lines of chemotherapy in the past. Nivolumab was administered Intravenous every 2 wk of 8 wk until CR, disease progression, unacceptable side effects or consent withdrawal. Of the 129 NSCLC patients, 17% had objective responses with best responses (24%) at the 3 mg/kg dose. The responses were rapid, durable and the unprecedented OS rate of 24% at 2 years was provocative and is termed "landmark OS". Major AEs were rash/pruritis (16%), colitis (12%) and specifically pneumonitis (6%). Drug related pneumonitis was severe in 3 patients resulting in 2 early deaths. Better management and monitoring strategies have been introduced since then to prevent such AE related deaths in future. This study opened the realm of possibility that multiple types of cancer could be responsive to immunotherapy if appropriate population is selected even if heavily pre-

treated^[41].

A follow up report on above trial was presented and confirmed the durable response and encouraging OS across all histological subtypes in NSCLC subgroup^[54]. Currently a number of studies are ongoing to test the efficacy of Nivolumab and another investigational PD-1 inhibitor, Lambrolizumab (Table 1).

Data on MK-3475 (Lambrolizumab) from phase I study of 38 patients with advanced NSCLC who had received atleast 2 prior therapies was presented at the 15th World conference on Lung cancer by Garon *et al*^[61]. Early responses were seen in 24% of patients even at 9 wk assessment in both squamous and non squamous subtypes. One patient had PR after a single dose. Median duration of response had not been reached and at the time of abstract presentation, 7 of 9 responding patients were continuing therapy. Median OS was 51 wk. Common AEs were fatigue, rash, pruritus and diarrhea. One case each of grade 2 pneumonitis and grade 3 pulmonary edema were reported, no fatalities occurred.

PD-L1 pathway inhibitor

As described above, PD-L1 is one of the 2 ligands for PD-1 receptor. Presence of PD-L1 has been associated with poor prognosis^[62].

A high affinity, fully humazined PD-L1 IgG4 monoclonal antibody, BMS-936559 was studied in phase I trial in patients with advanced cancers^[42]. Total of 207 patients, 75 of whom had advanced NSCLC, were given escalating dose of BMS-936559. Objective responses were seen in 5 of 49 patients who were evaluable; with both squamous and non-squamous histologies. Also 6 other patients with NSCLC had stable disease at 6 mo.

In all tumor types, it was encouraging to see both durable tumor regression and prolonged disease stabilization. Grade 3 or 4 AEs were seen in up to 9% of patients, however as compared to some other immune therapies, such as anti CTLA-4; these were milder. Again, the response with this agent was promising, and further

Table 2 Ongoing clinical trials of programmed death ligand 1 mAbs in non-small cell lung cancer

Therapy	Trial	Study population	Study design	Ref.
MPDL3280A	NCT01846416	Advanced NSCLC, tumor positive for PD-L1 on IHC	Assess safety, efficacy and objective response rates in patients with PD-L1 positive NSCLC	[64]
MPDL3280A	NCT01903993	Advanced NSCLC, failed platinum based chemo	MPDL-3280A <i>vs</i> Docetaxel after failure of platinum based therapy in patients with advanced NSCLC	[65]

NSCLC: Non-small cell lung cancer; PD-L1: Programmed death ligand 1; IHC: Immunohistochemistry.

studies are needed to outline the patient population and tumor type that would derive benefit from this therapy.

Another anti PD-L1 agent, MPDL-3280A, was studied in a phase I clinical trial, the results of which were exciting as it shows remarkable and durable outcomes in patients with either squamous cell carcinoma or adenocarcinoma. More pronounced effect was seen in smokers, who typically have a poor response to other immunotherapies. This suggests an association between smoking and PD-1/PD-L1 pathway. In this phase I study, 85 patients with advanced NSCLC were evaluated for safety and 53 for efficacy. They received monotherapy with MPDL-3280A every 3 wk and then assessed after a median duration of 48 wk. Objective response rate was 21%, with higher rate observed in patients whose tumor stains positive for PD-L1. The responses were sustained and dramatic response was seen in the smoking cohort. AEs were mild and limited to cough and diarrhea^[63]. Ongoing clinical trials using PD-L1 mAbs are summarized in Table 2.

CONCLUSION

Improved understanding of cancer and its interplay with immune system has now rendered more insight into NSCLC which is being looked at as a “immunogenic” cancer. The application of immunotherapy to NSCLC is being brought back in a big way. It is exciting to see that preclinical success of some of the immunotherapeutic agents is being reflected onto actual clinical success as seen with PD-1 and PD-L1 inhibitors. Data from some major phase II / III clinical trials will be available soon for incorporation into our clinical practice. There are still many unanswered questions regarding the precise timing of these therapies, targeted population, patient selection and appropriate bio-immuno markers to assess response. Ultimately, it would be a high point in medical science if these agents are able to confer survival benefit and improve quality of life of patients who otherwise struggle with the disease. The hope is to identify the best effective “immunotherapeutic targeted agent or combination” and change the treatment paradigm of NSCLC.

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