

Monoclonal antibody therapy in Non-Small Cell Lung Cancer

Hong Li¹, Guru Sharan Sah², Yusheng Li^{3*}, Avinash Chandra³

¹Master, Affiliated Hospital of Zhengzhou University Cancer Hospital, Henan Tumor Hospital, Zhengzhou, Henan, China

²Department of Medical Oncology, National Cancer Hospital P. Ltd., Lalitpur, Nepal

³Department of neurology, The first affiliated hospital of Zhengzhou university, Zhengzhou, Henan 450052, China
Email: xyt979299@163.com

Abstract: Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer related death worldwide. Till date, surgery is the treatment of first choice for lung cancer. But most of the cases diagnosed in clinics are inoperable, so chemotherapy and/or radiotherapy are the next option for those cases. Because these treatment modalities have adverse effects and are sometimes lethal to patients, new effective strategies with minimal side effects are urgently needed. Monoclonal antibody (Mab) therapy has recently gained attractions as an adjuvant treatment of patients with NSCLC. Multiple Mabs have been proposed and tested for potential therapeutic benefit against NSCLC with fewer side effects as compared to conventional chemotherapy and radiotherapy. In this article, focus on Mabs for treatment of patients with NSCLC, with emphasis on evidence based outcome in order to create a knowledge base that is well grounded in clinical reality. We summarize the current experience on the use of these agents for the treatment of NSCLC. Finally, we also highlight the critical questions and challenge in the clinical applicability of the existing Mab therapy and its future implications. We believe that Mab agents alone or with other forms of treatment can be recognized as next modality of lung cancer treatment despite waiting for results of ongoing phase II/III clinical trials.

[Hong Li, Guru Sharan Sah, Yusheng Li, Avinash Chandra. **Monoclonal antibody therapy in Non-Small Cell Lung Cancer.** *Life Sci J* 2013; 10(3): 16-24]. (ISSN: 1097-8135). <http://www.lifesciencesite.com>. 4

Keywords: NSCLC, Monoclonal Antibody, Efficacy, Side Effects

INTRODUCTION

Lung cancer is the most commonly diagnosed cancer as well as the leading cause of cancer death. According to GLOBOCAN 2008 FAST STATS, Lung cancer accounts for 12.7% (1.6 million) of the total cases and 18.2% (1.4 million) of the deaths in 2008. In males, the highest lung cancer incidence rates are in Eastern and Southern Europe, North America and Eastern Asia, while rates are low in sub-Saharan Africa. In females, the highest lung cancer incidences are seen in North America, Northern Europe, and Australia/New Zealand. In Chinese male population lung cancer accounts for 21.7% (0.35 million) of the total cases of cancer and the mortality rate is 24.9% (0.3 million) and in female population the incidence rate is 14.3% (0.17 million) and the mortality rate is 20.2% (0.14 million) (1). Lung cancer is categorized into two major subtypes depending on their histological feature, non-small cell (NSCLC) and small cell (SCLC). NSCLC constitutes 85% and SCLC 15% of total cases of lung cancer (2). Both subtypes show distinct biological behavior and genetic alterations. Mode of treatment is also different between these two types. Thus far, screening for lung cancer has not proven to be effective since no modality has been shown to decrease mortality. Most patients with both SCLC and NSCLC present with symptoms of either

locally advanced or metastatic disease, and only about 25% of patients with NSCLC have early-stage, resectable disease. For patients with stage I or II NSCLC, surgical resection is the treatment of choice and among these groups of patients; long-term survival is 60–80% or 40–50% of patients, respectively (3; 4). For patients with stage III, locally advanced NSCLC or limited-stage SCLC, aggressive chemotherapy plus radiotherapy can offer a cure in 25% of patients with a 3 year survival period of 34% (5). Stage IV, or metastatic, NSCLC and extensive-stage SCLC is incurable in which chemotherapy can prolong survival and palliate symptoms. However use of these therapeutic strategies has lots of unwanted side effects and drawback. Chances of missing micro metastasis and recurrence are common problems observed in operated patients, while chemotherapy, radiotherapy or concomitant chemo-radiotherapy for inoperable cases may not prevent recurrences.

Recent advances in our understanding of the molecular biology in lung cancer have driven to novel therapeutic strategies targeting relevant pathways that regulate the proliferation and/or progression of lung cancer. Several of these molecularly targeted therapies such as monoclonal antibody (Mab) therapy alone or in combination with conventional chemotherapy and/or radiotherapy has now demonstrated significant clinical benefits in

subsets of patients with lung cancer, leading to increased overall survival (OS) rate, prolongation of progression free survival (PFS) with expenses of few or no drug related adverse effect (AE)s. Bevacizumab, cetuximab, Ipilimumab etc are among the wide range of MABs with large number of data suggesting improved survival in treating NSCLC patients. Bevacizumab is the first such agent to show promising clinical effect in NSCLC (6). The drug is recently approved for use in NSCLC patients (7). Following that different MAB are developed, some of which have been approved for clinical use in different tumors, some are undergoing clinical trials and a lot are in the process of investigations.

This review basically focuses on the clinical successes and the excitement generated from the MABs. The earliest clinically developed MAB for treating NSCLC until the recently discovered MAB agents will be summarized, along with their efficacy, safety will also be discussed.

MONOCLONAL ANTIBODY THERAPY OF LUNG CANCER

MAB recently received prompt attention for treatment of different cancers, including NSCLC for its potential to induce an inflammatory response against a tumor. They act through activation of the antibody dependent cytotoxicity (ADCC) pathway and complement system, which ultimately leads to different biological processes such as chemotaxis for phagocytic cells and production of the membrane attack complex. Furthermore ADCC, mediated by monocytes, macrophages, NK cells and neutrophils, is an important mechanism by which MABs kill tumor cells (8, 9, 10). MAB are also said to inhibit tumor cell proliferation and survival by blocking ligand binding or growth factor receptor dimerization, thereby inhibiting downstream signaling (11). Conjugation of MAB therapy with radionuclides or toxins, offers more therapeutic approaches (12, 13; 14). Besides that, the combination of antibodies with chemotherapy enhances the activity of chemotherapy (15). The first generation of therapeutic MABs were of mouse origin and with the progressive developments in recombinant DNA and cloning techniques led to discovery of Humanized MAB (16, 17).

Ipilimumab

Ipilimumab is a MAB, designed to target cytotoxic T-lymphocyte antigen 4 (CTLA-4), which inhibits T-cell activation; the blockage of CTLA-4 leads to an increased immune response against tumor cells. The rationale of Ipilimumab as a targeted therapy is based on the notion that blocking CTLA-4 may produce an increased immune response against tumor cells (18). In addition to that, some studies have suggested that combining chemotherapy with

CTLA-4 antibody would promote tumor immunogenicity along with sensitization of tumor cells to lymphocyte killing (19, 20). Thus clinical trials using Ipilimumab as MAB therapy in melanoma, had shown significant results and have been approved by the FDA for the treatment of unresectable or metastatic melanoma in March 2011(21, 22).

Recently, a phase II clinical study was conducted to evaluate the efficacy of Ipilimumab in stage IIIB-IV NSCLC patients. The study was double blinded, randomized and enrolled 204 patients. The patients were randomly assigned into 3 groups: control, concurrent Ipilimumab and phased Ipilimumab (1:1:1). All the enrolled patients received standard chemotherapy with paclitaxel and carboplatin for 6 cycles. Concurrent Ipilimumab group received four doses of Ipilimumab (10 mg/kg) plus chemotherapy followed by two doses of placebo plus chemotherapy and phased Ipilimumab group received two doses of placebo plus chemotherapy followed by four doses of Ipilimumab (10 mg/kg) plus chemotherapy. Control group received six doses of placebo with chemotherapy. Treatment was administered intravenously every 3 weeks for ≤ 18 weeks as induction therapy (along with chemotherapy cycles). Eligible patients continued Ipilimumab or placebo every 12 weeks as maintenance therapy. Immune related (ir) response criteria and WHO criteria were considered for evaluation. The results observed were in favor of phased Ipilimumab group. Phased Ipilimumab group had improved irPFS compared with the control group, no significant improvement was observed in the concurrent Ipilimumab group. Similarly significant improvement was seen in median irPFS and median PFS as well (phased Ipilimumab, concurrent Ipilimumab, and control group had irPFS of 5.7, 5.5, and 4.6 months, respectively, median PFS of 5.1, 4.1, and 4.2 months, respectively). Phased Ipilimumab group showed significantly improvement in median OS of 12.2 compared to 9.7 and 8.3 months of concurrent Ipilimumab and control group respectively. The overall incidence of treatment related grade 3 and 4 AEs were almost similar among all groups (control, concurrent and phased AEs of 37%, 41%, and 39% respectively) (23). The rationale of comparing the concurrent and the phased schedule for the initiation of Ipilimumab therapy is based on the notion that the most appropriate timing of the Ipilimumab addition is not clear. The concurrent schedule may give Ipilimumab the opportunity to be present at the earliest phase of CT induced tumor necrosis; whereas the phased schedule is thought to contribute a CTLA-4 blockade after the occurrence of tumor necrosis to activate the immune response (24).

The productive result of this phase II clinical trial supported the initiation of phase III clinical trial of Ipilimumab in SCLC, which will enroll 920 patients of stage IV or recurrent NSCLC (squamous). This trial had excluded patients with brain metastasis and immune disorder. The trial is estimated to complete in June 2016. The patients will be randomly assigned to two groups (study and control). Study group will receive standard chemotherapy with paclitaxel and carboplatin for 6 cycles along with the Ipilimumab, whereas control group will receive standard chemotherapy along with placebo. Dosage form of Ipilimumab mentioned in this trial is different than what was seen in earlier mentioned phase II trial. IV solution of 10 mg/kg of Ipilimumab over a period 90 minute infusion will be injected to patients once every 3 weeks for 4 doses and then every 12 weeks beginning at week 24 along with 6 doses of standard chemotherapy with paclitaxel and carboplatin for 6 cycles. Despite of better responses observed with phased Ipilimumab, the ongoing trial has modified the dosage form. The primary measure considered is OS and the secondary measured are PFS and best overall response rate (clinicaltrials.gov, identifier: NCT01285609). Beside this trial, a phase I trial is conducted to evaluate the increment in the number of patients with detectable circulating T cells with specificities against tumor associated antigens after combination of neoadjuvant plus Ipilimumab (clinicaltrials.gov, identifier: NCT01820754).

Bevacizumab

Bevacizumab belongs to MAb therapy, which is directed to act against Vascular Endothelial Growth factor (VEGF) thus inhibiting angiogenesis, thereby impeding tumor growth and survival (25; 26). VEGF is the single most commonly upregulated angiogenic factor in both grafted and naturally occurring tumors, thus is considered as a prime target for antivasular therapy (27). The therapy is already approved by the FDA for treatment of various cancer including advanced stage lung cancer patients in combination with chemotherapy (7). Cui et al. performed a metanalysis and showed that Bevacizumab as a adjuvant therapy with chemotherapy had significant improvement in response rate (RR), PFS, and OS among chemotherapy-naïve patients compared to other targeted drugs in the treatment of NSCLC patients (28). Similarly, lots of clinical trials (phase II/III) suggested the efficacy of Bevacizumab in lung cancer. In a recent phase II clinical study, efficacy and safety of Bevacizumab was demonstrated in 180 patients (Japanese population) with stage IIIB/IV or recurrent NSCLC. The patients were randomly assigned to receive chemotherapy (carboplatin-paclitaxel) with bevacizumab or chemotherapy alone

in a ratio of 3:1. The result revealed hazard ratio of 0.61 for PFS of chemotherapy with Bevacizumab group versus chemotherapy alone ($p=0.0090$; median 6.9 versus 5.9 months). Chemotherapy with bevacizumab had higher objective response (OR) than that of chemotherapy alone (60.7% versus 31.0%). Median OS was more than 22 months for both the groups (25). A study was conducted to assess the efficacy and safety of Bevacizumab combined with platinum-based chemotherapy as first-line treatment in Asian patients with advanced NSCLC. The patients were randomized to receive Bevacizumab 7.5 mg/kg, Bevacizumab 15 mg/kg or placebo along with cisplatin and gemcitabine. Total patients enrolled were 1043 enrolled, among them 105 were asian and were included in the subgroup analysis. The study revealed Bevacizumab at a dose of 7.5 mg/kg improves the duration of OS when combined with cisplatin-gemcitabine in asian patients. This study showed the therapy was well tolerated (26). A study conducted in elderly patients (age more than 70 years) of advanced stage NSCLC, revealed higher response rate (RR) and higher PFS in patients treated with Bevacizumab in combination with chemotherapy than those treated with chemotherapy alone (29). To evaluate the safety profile of the Bevacizumab, a group of researchers, performed sub analysis of data from SAIL. SAIL is a single-arm phase IV study, was conducted to evaluate the Bevacizumab in routine oncology practice. 2212 patients were evaluated; bleeding AEs (any grade) occurred in 38.2% of patients. But in majority of cases, bleeding episodes were resolved or improved (88.6%) (30). Despite these promising outcomes, this highly anticipated drug failed to show efficacy in some studies. Old aged patients did not benefit with addition of Bevacizumab (29). In the phase III AVAIL trial, addition of Bevacizumab with cisplatin and gemcitabine did not show any survival benefit compared to treatment with only cisplatin and gemcitabine (31). Further this study was confined to patients with non squamous NSCLC.

A different approach to access the efficacy of Bevacizumab in 600 patients is being undertaken in a phase IIIB randomized study. The aim of the study is to evaluate the continuation of Bevacizumab beyond disease progression in patients with advanced non-squamous NSCLC after first-line treatment with Bevacizumab plus platinum-based chemotherapy. Patients with advanced non-squamous NSCLC whose disease has progressed after 4-6 cycles of first-line treatment with Bevacizumab plus a platinum-based doublet and a minimum of two cycles of Bevacizumab are enrolled for study. They are randomly categorized in 2 arms; arm 1 will receive Bevacizumab 7.5 or 15 mg/kg intravenously on day

1, every 21 days along with second-line therapy (limited to pemetrexed, docetaxel, or erlotinib) and subsequent lines of treatment. Patients belonging to arm 2 will receive investigator's choice of agents alone indicated for use in second-line therapy and subsequent lines of treatment, but no further Bevacizumab treatment. The primary endpoint of this study is OS. Secondary endpoints include the 6-month, 12-month, and 18-month OS rates, PFS, and time to progression at second and third progressive disease (PD), response rate (RR), disease control rates, and duration of response at second and third PD. The study is expected to complete in September 2015 (clinicaltrials.gov, identifier: NCT01351415).

Cetuximab

Cetuximab is a chimeric human-mouse anti-EGF receptor monoclonal antibody that binds competitively and with high affinity to the EGFR. Binding of the antibody to the EGFR prevents stimulation of the receptor by endogenous ligands and results in inhibition of cell proliferation, enhanced apoptosis, and reduced angiogenesis, invasiveness and metastasis. Binding of cetuximab to the receptor also results in internalization of the antibody-receptor complex which leads to an overall downregulation of EGFR expression (32, 33). Cetuximab has shown good clinical outcome in treating patients with advanced stage NSCLC(34).

In a phase III study, the efficacy of cetuximab in combination with chemotherapy as first-line treatment of advanced NSCLC was evaluated in 676 patients. This was multicenter, open-label study. The patients were randomly assigned to cetuximab with chemotherapy or chemotherapy alone group. Chemotherapy included paclitaxel or docetaxel and carboplatin. Cetuximab 400 mg/m² was injected on day 1 of week 1 followed by weekly doses of 250 mg/m². The result demonstrated Median PFS was 4.40 months with cetuximab and chemotherapy versus 4.24 months with chemotherapy. For cetuximab patients Median OS and over all RR were 9.69 months and 25.7% respectively, while those for chemotherapy alone group were 8.38 months and 17.2% respectively. The regime combination was well tolerated (35). A phase II clinical study also favored use of cetuximab. In this study, the efficacy of cetuximab was evaluated in combination with chemo-radiotherapy in unresectable stage III NSCLC patients. Median follow-up was 21.6 months. Response rate was 62%, median survival was 22.7 months, and 24-month OS was 49.3%. Adverse reactions observed were hematologic toxicities, esophagitis, pneumonitis etc. Majority of patients had hematologic toxicities (20%) (36). In a recent study, the efficacy and safety of the addition of cetuximab to first line chemotherapy with

carboplatin and docetaxel in patients with advanced NSCLC was evaluated. The result revealed the 1-year rates for PFS and OS were 11.2% and 64.4%, respectively. Median PFS was 4.8 months and median OS 12.9 months. Adverse events were mainly grades 1-2, mainly skin toxicity, dyspnea and anemia (37).

Lots of clinical trials of Cetuximab are in progress. A phase II trial is on operation to study the association of Cetuximab plus pemetrexed in combination with concurrent radiotherapy. The study will enroll 100 patients with unresected stage III NSCLC. The primary goal of the study is to assess disease control rate and OS (clinicaltrials.gov, identifier: NCT01102231). Furthermore a phase III clinical study is in progress to assess the combined effect of 2 MABs; Bevacizumab plus cetuximab treating patients with stage IV or recurrent NSCLC. The study will enroll 1546 patients. The patients will be randomized to receive Bevacizumab plus cetuximab with chemotherapy or Bevacizumab with chemotherapy. OS and PFS will be the primary aim. The study is scheduled to complete in June 2012(clinicaltrials.gov, identifier: NCT00946712)

Necitumumab

Necitumumab is a fully human immunoglobulin G, subclass 1 MAB targeting the EGFR, engineered to bind to the EGFR with high affinity and block the binding of relevant EGFR. Necitumumab neutralizes ligand-induced EGFR phosphorylation; blocking signaling pathways in multiple tumor cell lines, and thus inhibiting or degrading proliferation of EGFR-dependent tumor cells. In addition, this MAB is expected to result in a decreased potential for hypersensitivity and increased potential to mediate efficient ADCC by human peripheral blood mononuclear cells to EGFR-expressing cancer cells. The antitumor effect of Necitumumab is established in many human xenograft tumor models, and potentiates the antitumor effects of irinotecan and oxaliplatin in a panel of colorectal cancer models (38, 39). In addition, Necitumumab induces potent ADCC against NSCLC tumor cells. Patel et al. reported that, cetuximab elicits similar ADCC against EGFR expressing tumor cells as compared to Necitumumab (40). Infact most of the authors believe that the antitumor effects of Necitumumab in preclinical studies were either comparable with or superior to those observed with cetuximab.

The Phase I clinical trial of Necitumumab evaluated pharmaco-kinetics and preliminary anti-tumor activity of the agent in 60 patients with advanced solid malignancies, including NSCLC (39). Necitumumab was administered intravenously in flat doses of 100, 200, 400, 600, 800 and 1000 mg. The

study suggested that Necitumumab is associated with preliminary evidence of antitumor activity, and achieves biologically relevant concentrations throughout the dosing period. The recommended dose of Necitumumab for further clinical study is 800 mg (flat dose) weekly or every 2 weeks (39).

At present, the efficacy of Necitumumab is being evaluated in 2 different phase III clinical trials. In a randomized, multicenter, open-label phase 3, Necitumumab in combination with gemcitabine-cisplatin chemotherapy as first-line treatment of patients with stage IV squamous NSCLC is being studied. The trials will include 1097 patients. All the patients will be randomized on a 1:1 basis to receive first-line Necitumumab plus chemotherapy consisting of gemcitabine and cisplatin in study group, or gemcitabine-cisplatin chemotherapy alone in compare group. The dose of Necitumumab is 800 mg I.V. infusion on Days 1 and 8 of every 3 week cycle, as suggested by phase I study (39). The primary goal of study is OS along with PFS, ORR, and time to treatment failure (clinicaltrials.gov, identifier: NCT00981058). The study is estimated to complete on December 2014. In a different randomized, multicenter, open-label phase III clinical trial, the drug of study i.e. Necitumumab is evaluated in combination with Pemetrexed-Cisplatin, comparing to Pemetrexed-Cisplatin alone. The study will enroll 634 Patients with Stage IV Nonsquamous NSCLC. The anti-tumor efficacy of Necitumumab will be evaluated as first line therapy. OS is the primary goal of the study and PFS, ORR, and time to treatment failure remain the secondary aim. The study is expected to complete on December 2013 (clinicaltrials.gov, identifier: NCT00982111).

Racotumomab

Racotumomab also known as 1E10 is an anti-idiotypic MAb designed to mimic the NeuGc-GM3 ganglioside. This monoclonal antibody (mAb) is an Ab2-type-antibody which recognizes the Ab1 antibody called P3; the latter is a monoclonal antibody that reacts specifically with gangliosides. Gangliosides are a broad family of glycosphingolipids found on the outer cell membrane, involved in cell communication, regulation of the immune response, and cancer progression (41, 42). NeuGcGM3 has been described as a tumor antigen for non-small cell lung cancer (NSCLC) in humans (43, 44). So it is hypothesized that targeting NeuGcGM3 gangliosides Racotumomab would prolong the survival of patients with lung cancer. Because of being anti-idiotypic antibodies is a useful strategy to elicit an immune response toward a ganglioside and also is used as vaccine despite being a MAb, making this therapy superior to other MAb. This MAb is found to induce

tumor apoptosis and antiangiogenic effects in a metastatic lung carcinoma (45) and when combined with other therapeutic modality, is expected to potentiate the therapeutic effect (46, 47).

In a phase I clinical trials enrolling patients in small cell lung cancer, efficacy and safety profile of Racotumomab were analyzed. The result showed prolonged survival with no major side effects (48). Similarly phase I study of Racotumomab in NSCLC patients (34 stage IIb and 37 stage IV) were conducted. All the patients were treated with Racotumomab vaccine, after being treated standard chemotherapy and radiotherapy. Racotumomab vaccine was injected at dose of 1 mg bi-weekly for 5 times then, other 10 (1mg) doses at 28-day intervals and patients showing good performance status continuously received injection of 1mg at 28-day intervals. No evidence of unwanted side effects was observed (49).

Currently a phase III, randomized, open label, parallel-group, multicenter study is conducted to evaluate the efficacy and safety of racotumomab plus best supportive care versus best supportive care in patients with advanced NSCLC. The study will enroll 1082 patients who have achieved an OR (Partial or Complete Response) or SD with standard first-line treatment. The study will also evaluate immunological parameters such as IgM and IgG antibody titers against N-Glycolil-GM3 ganglioside, IFN- γ , Treg cell, reactivity of the antibodies against the patients tumoral tissue, pro-inflammatory and anti-inflammatory cytokines etc. The study is scheduled to complete by September 2015 (clinicaltrials.gov, identifier: NCT01460472).

Nivolumab

Nivolumab also widely known as BMS-936558 is MAb targeted to inhibit or suppress Programmed Death (PD)-1 pathway. The PD-1 pathway is also an important regulator of T-cell activation. The PD-1 receptor binds with its ligand (PD-L1/B7-H1), causing T-cell inhibition and downregulation of T-cell responses (50). This pathway is one specifically co-opted by tumors through tumor expression of PD-L1 on the cell surface. This allows tumors to directly suppress antitumor cytolytic T-cell activity, known as adaptive resistance (51). Blocking this binding by blocking PD-1 or PD-L1 via monoclonal antibodies causes augmentation of the T-cell response (52).

In a Phase Ib study, the antitumor activity and safety of BMS-936558 was assessed in advanced cancer. The study enrolled 296 patients, including patients with NSCLC. All patients with NSCLC were randomly assigned to 1, 3, and 10 mg/kg to include equal numbers of squamous and nonsquamous cell histology at each dose level. Among NSCLC patients

18 % cumulative response rates was observed where as squamous variety had 33% OR. Common treatment-related adverse events included fatigue, rash, diarrhea, pruritis, decreased appetite, and nausea with grade 3 or 4 treatment-related adverse events (14%) and drug-related serious adverse events (11%) (53). Currently lots of phase II and phase III clinical trials are recruiting patients to evaluate the efficacy of nivolumab in patients with NSCLC and also evaluate the safety profile of the drug. Single-Arm Phase II Study of nivolumab is designed enrolling 100 patients with advanced or metastatic squamous cell NSCLC who have received at least two prior systemic regimens. The study is estimated to complete on February 2014 and the primary goal is to evaluate the ORR (clinicaltrials.gov, identifier: NCT01721759). With a view to evaluate the efficacy of nivolumab in a different approach an open-label randomized phase III trial of nivolumab versus docetaxel in previously treated advanced or metastatic non-squamous cell NSCLC, enrolling 574 patients is under operation. The primary goal of the trial is to study OR and PFS and the study will complete on November 2014 (clinicaltrials.gov, identifier: NCT01673867).

BMS-936559

BMS-936559 is the first anti-PD-L1 monoclonal antibody. The significance of blocking PD-L1 pathway has been discussed in previous section. A multicenter phase I trial was conducted to evaluate the efficacy of BMS-936559. The study enrolled 207 patients with advanced cancer among with 75 were NSCLC. The drug was administered intravenously at escalating doses ranging from 0.3 to 10 mg per kilogram of body weight to patients, every 14 days in 6-week cycles for up to 16 cycles or until the patient had a complete response or confirmed disease progression. Treatment related grade 3-4 side effects were 9%. 5 of 49 (10 %) with NSCLC had objective response. Tumor response was seen in squamous (1/13 patients, 8%) and non-squamous (4/36 patients, 11%) variety. An additional six patients (12%) had stable disease for at least 6 months (54). To our knowledge, this MAb is not included in any clinical trials.

Discussion

Data and result of clinical trials are promising and encouraging. Bevacizumab and cetuximab, in large no of studies, have demonstrated a potential to improve RR or OS of patients with NSCLC; when they were added to a chemotherapy regimen (25, 28, 35, 36). In a report by Ribas, the efficacies of anti-PD-1 antibody and anti-PD-L1 antibody have been highlighted quoting that widely applicable immunotherapy agents have broken the

ceiling of durable tumor response rates of 10 to 15% (the highest rate of antitumor activity of the many immunotherapy approaches tested in the clinic for the treatment of cancer during the past 30 years)(55). However, these MAb along with high efficacy in eliminating tumor also carries some AEs. Drug related AE's are special concern. Recently, some authors have reported immune related AE's in patients being treated with ipilimumab (21). In a recently study, combination of Bevacizumab and erlotinib in combination with first-line chemotherapy, followed by Bevacizumab and erlotinib monotherapy as maintenance had shown survival benefit compared to therapy only with chemotherapy. Further, combinational therapy with Bevacizumab and erlotinib had better safety profile compared to Bevacizumab and erlotinib taken individually (56). A meta-analysis comprising five studies including 2,100 patients showed erlotinib in combination with other targeted therapy had better ORR and disease control rate compared to erlotinib alone. Also no significant differences were observed in relation to adverse effects (57). These studies advocate that combining 2 or more MAbs would potentiate the therapeutic efficacy of the drug with minimizing the AEs.

Technical questions are not answered. Defining the optimal dose and timing of administration of MAb is still a major problem. For example, in case of Ipilimumab, the result observed in phase II clinical trials showed different efficacy with change in timing of administration of Ipilimumab (Phased Ipilimumab effective than concurrent Ipilimumab) (24). So modifications in clinical trials are urgently needed to formulate the optimum dose and exact time of administration. Again most of the clinical trials conducted in lung cancer, enrolls advanced stage NSCLC patients. But most of the clinicians and researchers, they do believe that early staged resected lung cancer patients are good candidate for MAb. So refinement in clinical trials are needed to include patients of early stage (I-II). Further, some immune related markers along with conventional prognostic modalities (e.g. radiology) should be developed to assess the efficacy of therapy. Some study included immune markers as in Ipilimumab study (irPFS evaluation), immunological parameters detection in racotumomab study (such as IgM and IgG antibody titers against N-Glycolil-GM3 ganglioside, IFN- γ , Treg cell) which also need further development.

Despite these limitations, some had shown encouraging response in NSCLC. With positive results of ongoing phase III clinical trials, in next 5 years, more effective MAbs will be available for patients and their treating oncologist to treat patients

with NSCLC. Not a single treatment modality but in combination therapy including use of either single MAb or combination of 2 or more MAbs with conventional therapy (surgery, chemotherapy and radiotherapy) should be enough to experience some progress in management of patients with NSCLC.

***Corresponding Author:**

Yusheng Li,
Department of neurology, The first affiliated hospital
of Zhengzhou university, Zhengzhou, 450052, Henan,
China

Email: yushengli1970@163.com

References:

- [1] GLOBOCAN FAST STATS. 2008
<http://globocan.iarc.fr/factsheet.asp>
- [2] Lehtiö J, De Petris L. Lung cancer proteomics, clinical and technological considerations. *Journal of Proteomics* 2010; 73(10):1851-63
- [3] Tsuboi M, Ohira T, Saji H et al. The present status of postoperative adjuvant chemotherapy for completely resected non-small cell lung cancer. *Ann Thorac Cardiovasc Surg* 2007; 13(2):73-7.
- [4] Wu YI, Huang ZF, Wang SY et al. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer* 2002; 36(1):1-6.
- [5] Belani CP, Wang W, Johnson DH et al. Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer. *J Clin Oncol* 2005; 23(16):3760-7.
- [6] Sandler A, Yi J, Dahlberg S, Kolb MM et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/ carboplatin for advanced non-small-cell lung cancer. *J Thorac Oncol* 2010; 5(9):1416-23.
- [7] FDA Approval for Bevacizumab (<http://www.cancer.gov/cancertopics/druginfo/faq-bevacizumab>)
- [8] Golay J, Introna M. Mechanism of action of therapeutic monoclonal antibodies: promises and pitfalls of in vitro and in vivo assays *Arch Biochem Biophys*, 526 (2012), pp. 146–153
- [9] Weiner L.M., Surana R., Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy *Nat Rev Immunol*, 10 (2010), pp. 317–327
- [10] Kawaguchi Y, Kono K, Mimura K ET AL. Cetuximab induce antibody-dependent cellular cytotoxicity against EGFR-expressing esophageal squamous cell carcinoma. *Int J Cancer*. 2007;120(4):781-7.
- [11] Klapper LN, Vaisman N, Hurwitz E, et al. A subclass of tumor-inhibitory monoclonal antibodies to ErbB-2/ HER2 blocks crosstalk with growth factor receptors. *Oncogene* 1997;14(17):2099-109
- [12] Trail PA, King HD, Dubowchik GM. Monoclonal antibody drug immunoconjugates for targeted treatment of cancer. *Cancer Immunol Immunother* 2003;52(5):328-37.
- [13] González JE, Barquinero JF, Lee M et al. Radiosensitization induced by the anti-epidermal growth factor receptor monoclonal antibodies cetuximab and nimotuzumab in A431 cells. *Cancer Biol Ther* 2012;13(2):71-6.
- [14] O'Mahony D, Bishop MR. Monoclonal antibody therapy. *Front Biosci* 2006;11:1620-35.
- [15] Baselga J, Norton L, Masui H et al. Antitumor effects of doxorubicin in combination with anti epidermal growth factor receptor monoclonal antibodies. *J Natl Cancer Inst* 1993;85(16):1327-33
- [16] Jones PT, Dear PH, Foote J et al. Replacing the complementarity-determining regions in a human antibody with those from a mouse. *Nature*. 1986;321(6069):522-5.
- [17] Queen C, Schneider WP, Selick HE et al. A humanized antibody that binds to the interleukin 2 receptor. *Proc Natl Acad Sci U S A*. 1989;86(24):10029-33.
- [18] Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* 1996;271:1734-6.
- [19] Tesniere A, Apetoh L, Ghiringhelli F et al. Immunogenic cancer cell death: a key-lock paradigm. *Curr Opin Immunol* 2008;20:504-11.
- [20] Ramakrishnan R, Assudani D, Nagaraj S et al. Chemotherapy enhances tumor cell susceptibility to CTL-mediated killing during cancer immunotherapy in mice. *J Clin Invest* 2010; 120: 1111-24.
- [21] Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; 363: 711-23.
- [22] FDA Approval for Ipilimumab (<http://www.cancer.gov/cancertopics/druginfo/faq-ipilimumab>).
- [23] Lynch TJ, Bondarenko I, Luft A et al. Ipilimumab in Combination With Paclitaxel and Carboplatin As First-Line Treatment in Stage IIIB/IV Non-Small-Cell Lung Cancer: Results From a Randomized, Double-Blind, Multicenter Phase II Study. *J Clin Oncol* 2012; 30(17):2046-

- 54.
- [24] Genova C, Rijavec E, Barletta G et al. Ipilimumab (MDX-010) in the treatment of non-small cell lung cancer. *Expert Opin Biol Ther* 2012; 12(7):939-48.
- [25] Niho S, Kunitoh H, Nokihara H et al. Randomized phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. *Lung Cancer* 2012; 76(3): 362-7.
- [26] Mok TS, Hsia TC, Tsai CM et al. Efficacy of bevacizumab with cisplatin and gemcitabine in Asian patients with advanced or recurrent non-squamous non-small cell lung cancer who have not received prior chemotherapy: a substudy of the Avastin in Lung trial. *Asia Pac J Clin Oncol* 2011; 7 Suppl 2:4-12.
- [27] Keshet E, Ben-Sasson SA. Anticancer drug targets: Approaching angiogenesis. *J Clin Invest* 1999;104:1497-501
- [28] Cui J, Cai X, Zhu M et al. The Efficacy of Bevacizumab Compared with Other Targeted Drugs for Patients with Advanced NSCLC: A Meta-Analysis from 30 Randomized Controlled Clinical Trials. *PLoS One* 2013; 16; 8(4):e62038.
- [29] Ramalingam SS, Dahlberg SE, Langer CJ et al. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. *J Clin Oncol* 2008;(1)26:60-5
- [30] Dansin E, Cinieri S, Garrido P et al. MO19390 (SAiL): Bleeding events in a phase IV study of first-line bevacizumab with chemotherapy in patients with advanced non-squamous NSCLC. *Lung Cancer* 2012; 76(3):373-9.
- [31] Reck M, von Pawel J, Zatloukal P et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAiL. *J Clin Oncol* 2009;27(8):1227-34.
- [32] Carillio G, Montanino A, Costanzo R et al. Cetuximab in non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2012;12(2):163-75.
- [33] Harding J, Burtneess B. Cetuximab: an epidermal growth factor receptor chemeric human-murine monoclonal antibody. *Drugs Today (Barc)* 2005;41(2):107-27
- [34] Grigorescu AC, Bala C. Phase II study of erlotinib plus gemcitabine in first-line treatment of poor prognosis, advanced non-small cell lung cancer patients. *J BUON*. 2013;18(1):188-94.
- [35] Lynch TJ, Patel T, Dreisbach L et al. Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter phase III trial BMS099. *J Clin Oncol* 2010;28(6):911-7.
- [36] Blumenschein GR Jr, Paulus R, Curran WJ et al. Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. *J Clin Oncol* 2011;29(17):2312-8.
- [37] Fischer JR, Griesinger F, Fink T et al. Docetaxel-carboplatin chemotherapy combined with cetuximab in patients with locally advanced or metastatic non small-cell lung cancer (NSCLC)-Results of the nonrandomised phase II study TaxErb. *Lung Cancer* 2012;75(3):348-52.
- [38] Liu M, Zhang H, Jimenez X, et al. Identification and characterization of a fully human antibody directed against epidermal growth factor receptor for cancer therapy. *Proc Am Assoc Cancer Res* 2004;45:abstract 706.
- [39] Kuenen B, Witteveen PO, Ruijter R et al. A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies *Clin Cancer Res*. 2010;16(6):1915-23.
- [40] Patel D, Saxena B, Zhou Q et al. Differential induction of antibody-dependent cellular cytotoxicity (ADCC) against human EGFR-expressing NSCLC cell lines by necitumumab, cetuximab, and panitumumab. *Proc Am Soc Clin Oncol* 2011;29:abstract e21075
- [41] Patra S. K. Dissecting lipid raft facilitated cell signaling pathways in cancer. *Biochim. Biophys. Acta* 2008; 1785(2):182–206.
- [42] Lopez R. H., Schnaar R. L. Gangliosides in cell recognition and membrane protein regulation. *Curr. Opin. Struct. Biol.* 2009; 19(5):549–57.
- [43] van Cruijsen H, Ruiz M G, van Der Valk P et al. Tissue micro array analysis of ganglioside N-glycolyl GM3 expression and signal transducer and activator of transcription (STAT)-3 activation in relation to dendritic cell infiltration and microvessel density in non-small cell lung cancer. *BMC Cancer* 2009; 9: 180.
- [44] Blanco R, Rengifo C E, Cedeño et al. Immunoreactivity of the 14F7 Mab (raised against N-glycolyl GM3 ganglioside) as a positive prognostic factor in non-small-cell lung cancer. *Patholog. Res. Int.* 2012:235418.
- [45] Diaz Y, Gonzalez A, Lopez A et al. Anti-ganglioside anti-idiotypic monoclonal antibody-based cancer vaccine induces apoptosis and antiangiogenic effect in a metastatic lung carcinoma. *Cancer Immunol Immunother* 2009; 58(7):1117-28.

- [46] Reece DE, Foon KA, Bhattacharya-Chatterjee M et al. Use of the anti-idiotypic breast cancer vaccine 11D10 in conjunction with autologous stem cell trans-plantation in patients with metastatic breast cancer. *Clin Breast Cancer* 2003; 3(Suppl 4):S152–7.
- [47] Honeychurch J, Glennie MJ, Illidge TM. Cyclophosphamide inhibition of anti-CD40 monoclonal antibody-based therapy of B cell lymphoma is dependent on CD11b⁺ cells. *Cancer Res* 2005; 65(16):493–7501.
- [48] Neningen E, Diaz R M, de la Torre A et al. Active immunotherapy with 1E10 anti-idiotypic vaccine in patients with small cell lung cancer: report of a phase I trial *Cancer Biol. Ther* 2007;6(2): 145–50.
- [49] Alfonso S, Diaz R M, de La Torre A et al. 1E10 anti-idiotypic vaccine in non-small cell lung cancer: experience in stage IIIb/IV patients. *Cancer Biol. Ther* 2008; 6(12):1847–52.
- [50] Chen L. Co-inhibitory molecules of the B7-CD28 family in the control of T-cell immunity. *Nat Rev Immunol* 2004; 4(5):336–47.
- [51] Taube JM, Anders RA, Young GD et al. Colocalization of inflammatory response with B7–h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med* 2012;4(127):127ra37.
- [52] Brahmer JR, Drake CG, Wollner I et al. Phase I study of single-agent anti-programmed death-1 (MDX-1106) in refractory solid tumors: Safety, clinical activity, pharmacodynamics, and immunologic correlates. *J Clin Oncol* 2010;28(19):3167–75.
- [53] Topalian SL, Hodi FS, Brahmer JR. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366(26):2443–54.
- [54] Brahmer JR, Tykodi SS, Chow LQ et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366(26):2455–65.
- [55] Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med*; 366(26):2517–9.
- [56] Boutsikou E, Kontakiotis T, Zarogoulidis P. Docetaxel-carboplatin in combination with erlotinib and/or bevacizumab in patients with non-small cell lung cancer *OncoTargets and Therapy* 2013;6:125–34.
- [57] Pan G, Ke S, Zhao J. Comparison of the efficacy and safety of single-agent erlotinib and doublet molecular targeted agents based on erlotinib in advanced non-small cell lung cancer (NSCLC): a systematic review and meta-analysis. *Target Oncol.* 2013; 8(2):107–16.