Journal of Cancer Therapy, 2012, 3, 1170-1190
http://dx.doi.org/10.4236/jct.2012.36153 Published Online December 2012 (http://www.SciRP.org/journal/jct)

Monoclonal Antibodies: An Emerging Class of Therapeutics in Non Small Cell Lung Cancer

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Received July 21st, 2012; revsied August 23rd, 2012; accepted September 2nd, 2012

ABSTRACT

Lung cancer is the leading cause of cancer-related deaths in industrialized countries and non small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Cisplatin doublet based chemotherapy, which is the recommended regimen in first line therapy in advanced or metastatic NSCLC, improves survival but in low proportion. Monoclonal antibodies (mAbs) are a novel promising therapeutic class used with great results in inflammatory diseases such as rheumatoid arthritis. Antibodies are natural proteins with modular structure, specific pharmacodynamics and pharmacokinetics and possibly produced against any antigens, thus giving them several advantages over small drug therapeutics. In solid tumors, therapeutic mAbs improved progression free survival (PFS) and overall survival (OS) of patients with breast and colon cancers and had considerably changed the treatment in clinical practice. In NSCLC, bevacizumab, an anti-VEGF mAb, and cetuximab, an anti-EGFR mAb, are the most studied antibodies. Bevacizumab acts on angiogenesis and improved PFS of non squamous NSCLC but in low proportion as shown in two large phase III trials. It was approved by European Medicines Agency (EMEA) and Food and Drug administration (FDA) as a first line therapy in combination with cisplatin doublet chemotherapy. Cetuximab slightly enhanced OS but did not improve PFS in two large phase III trials. These results added to high adverse effect lead to cetuximab refusal by EMEA and FDA in NSCLC. At first glance, the results of mAbs in NSCLC are somewhat disappointing, in contrast to the benefits obtained with mAb treatments in other solid tumors. However, many other mAbs directed against novel targets, such as IGF1-R or CTLA-4, and new mAbs targeting VEGFR and EGFR pathways with different pharmacodymamical and pharmacokinetic properties are under evaluation and may change our vision of taking care of patients with NSCLC. In conclusion, it seems that mAbs therapy in NSCLC clearly marks the start of a new era in NSCLC treatment, with promises in improving patient survival and quality of life.

Keywords: Monoclonal Antibody; Targeted Therapy; Non Small Cell Lung Cancer; Immunoglobulin

1. Introduction

Cytotoxic agents and radiation therapy have been used to improve the survival and quality of life of patients with cancer, but they no longer increase patient survival and yield many side effects. The past few decades have seen huge progress in our understanding of the molecular mechanisms underlying tumor development and dissemination, and this has led to the development of specific therapies with reduced systemic toxicity and improved patient survival. Targeted therapies include small-molecule kinase inhibitors and biotherapeutics, including monoclonal antibodies (mAb). Antibodies have become major biodrugs for treating solid and hematological tumors. They are natural proteins that bind to one of a huge variety of molecular targets with great specificity. Their structure is multimodular, and each domain has a well-defined function. Therapeutic mAbs are not only specific, they also have pharmacodynamical and pharmacokinetic advantages over small molecule drugs, together with limited toxicity. This is why therapeutic mAbs are one of the fastest growing areas of the pharmacological/biotechnological industry, with applications in oncology, in immune and inflammatory disorders. Six therapeutic mAbs have now been approved by the US Food and Drug Administration (FDA) for treating solid tumors, whereas only one was available ten years ago.

Lung cancer is the leading cause of cancer fatalities in industrialized countries and non small cell lung cancer (NSCLC) accounts for 85% of all lung cancers [1]. The American Society of Clinical Oncology recommends cisplatin doublet based chemotherapy as the first-line treatment for NSCLC, but the increase in median survival time is modest [2]. Spiro *et al.* showed that the me-

dian survival time of patients with advanced NSCLC treated with cisplatin doublet based chemotherapy (8 months) was only 9 weeks longer than for patients given the best supportive care (5.7 months) [3]. Treatment with mAbs has greatly prolonged the survival of patients with solid tumors like breast and colon cancers [4,5]. They are therefore providing hope to patients with metastatic or locally advanced NSCLC who cannot be treated by surgery. Only one therapeutic antibody, bevacizumab targeting VEGF, is presently approved for treating NSCLC, but several others are under clinical investigation and may improve the survival and quality of life of NSCLC patients. The first part of this chapter summarizes the characteristics of therapeutic antibodies while the second part discusses clinical trials of mAbs designed to treat NSCLC.

2. Therapeutic Antibodies in Cancer: Rationale

Most monoclonal antibodies (mAb) used as therapeutics are full length IgGs, often of the IgG1 or IgG3 subclasses. They have a molecular weight of ~150 kDa and a valence of 2, which means that each molecule can bind two identical epitopes of the antigen. IgGs are composed of a Fab domain (fragment of antigen binding) containing the antigen binding site region, and an Fc region corresponding to the effector domain [6].

Paul Erhlich was the first to consider antibodies as therapeutics in his "magic bullet" theory in 1908 [7]. Achievement of this concept became possible with the development of mouse hybridoma technology by Köhler and Milstein, the first reliable source of monoclonal antibodies [8]. Despite the fact that they had overcome major technological problems, mouse mAb were disappointed in clinical studies. This was because the mouse mAb that were used had a short half-life in human serum and triggered immune responses in human subjects that limited the possibilites of repeated injections [9,10].

The human anti-mouse antibody responses (HAMA) was reduced by engineering mAbs that lacked most of the murine sequences, leading to chimeric mAbs and humanized mAbs [11-13]. In terms of immunogenicity, Hwang and Foote reported a significant decrease in marked anti-antibody response (AAR) when the Fc regions of murine mAbs were replaced with human sequences [14]. More recently, fully human mAbs have also been produced by transgenic animals or phage display technology and they are being used more and more in clinical trials. However, the improved safety of humanized and fully human mAbs in clinics is still being debated [10]. Getts *et al.* recently reviewed the clinical data for 38 human(ized) and 43 rodent-derived antibodies with contrasting indications and suggest that both types of mAbs trigger similar acute phase reactions and infusion reactions.

Therapeutic antibodies differ from small molecule drugs in their pharmacological properties. The mechanisms by which therapeutic mAbs act depend on their Fab and/or Fc domains and/or the cytotoxic agents conjugated to them (for summary, see **Table 1**). Therapeutic mAbs bind to their antigen through the Fab domain, usually with high affinity, specificity and selectivity [13]. Therapeutic antibodies may also act through their Fc domains that enable an antibody to interact with molecules such as complement or Fc receptors [15,16]. Indeed, an IgG bound to its target antigen can be recognized by specific Fc-receptors, FcγRs, which in turn can lead to the recruitment of immune cells effectors, such as natural killer (NK) cells, granulocytes, monocytes or macrophages. This cascade leads to phagocytosis and antibody-dependent cellular cytotoxicity (ADCC) [17]. After interacting with its antigen, mAb can also activate the complement system, leading to complement-dependent cytotoxicity (CDC) [16]. Most of the approved mAb can induce CDC *in vitro*, but the clinical relevance of this function remained unclear for a long time, with only indirect presumptions.

Therapeutic mAbs, in particular anticancer mAbs, may also act through a conjugated cytotoxic agent, such as radioisotopes and small chemotherapeutic molecules [18]. In this case, the mAb acts as a delivery vehicle, carrying the cytotoxic drug to the therapeutic site.

Monoclonal antibodies have other advantages over small (non-biological) molecules. First, their range of targets is almost limitless. Second, they are unlikely to have unexpected side-effects [19,20]. Their high selectivity reduces the potential of non-mechanism-based toxicity and their bioconversion is well-defined. Antibodies are metabolized to non-toxic peptides and amino acids by circulating phagocytic cells or by their target cells. Thera-

Table 1. Multi-faceted activity of therapeutic mAbs.

Mechanisms of action
Naked antibody—direct effects
• Neutralizing infectious agents
• Interfering with ligand-receptor interactions (antagonist activity)
• Receptor cross-linking (agonist activity)
• Sequestrating soluble mediators
• Antibody as immunogens (anti-idiotype)
Naked antibody—indirect effects
• Antibody-dependent cellular cytotoxicity (ADCC)
• Complement-dependent cytotoxicity (CDC)
Armed antibody
• Delivery of cytotoxic molecules (radionuclides, small chemotherapeutic drugs, toxins...)
• Immunomodulation (cytokine)

peutic mAbs are generally safe [19,20]. Hence, preclinical and clinical trials tend to be very successful. The tox icity of mAbs is mainly associated with excessive pharmacological activity and/or the presence of the targeted antigen in tissues where the therapeutic effect is useless [20]. Serious adverse effects of mAbs include anaphylaxis, a rare response to the first infusion (IgE-mediated), and the cytokine release syndrome (CRS) or cytokine storm [21].

Last, therapeutic antibodies differ from small molecule drugs in their pharmacokinetic (PK) profiles. The PK describes the outcome of injecting mAbs into the human body and is a critical parameter in describing their clinical actions. Various factors may contribute to the removal of a mAb, including the amount of the target antigen, immune reactions to the antibody, the delivery route and patient characteristics [22]. One of these factors, the FcRn receptor, plays a critical role regulating mAb pharmacokinetics [23]. Indeed, the FcRn protect IgGs from catabolism and mediates the transport of IgG across epithelial/endothelial cells [23]. It therefore plays a central role in the absorption and distribution of mAbs from the bloodstream to the tissues, and strongly influences their half-life in biological fluids [23].

Smaller structures derived from IgGs, containing an antigen binding domain (Fab) or a single chain variable fragment (scFv), have also been engineered. Their pharmacokinetics, distributions and pharmacological properties are different from those of intact IgGs [24].

A total of 30 monoclonal antibodies and three fragments are presently approved for sale around the world for treating human diseases and there are nearly 350 candidate mAbs in the pipeline. Several have achieved "blockbuster" status, with annual sales of over $1 billion. The majority of mAbs on the market or in clinical development are approved or evaluated as treatments for cancer or immunological diseases. Other indications include infectious and central nervous system diseases [25].

Due to advantages cited above, therapeutic antibodies are a hopefull potential therapy in NSCLC. Antibodies, which were or are currently evaluated in NSCLC, are detailed further.

3. Therapeutic Antibodies and Angiogenesis

3.1. Anti-VEGF Antibodies

Angiognesis has been known to play a role in cancer pathophysiology for over a century [26]. VEGF (also called VEGF A) is involved in angiogenesis and interacts with two related receptors, tyrosine kinase VEGFR-1 and VEGFR-2 [26]. These receptors are present on endothelial cells and hematopoietic cells, and are autophosphorylated once VEGF bound to them [26].

In NSCLC, overproduction of VEGF is associated with tumor progression and poor prognosis [27,28]. A recent meta-analysis showed that VEGF overproduction in NSCLC, assessed by immunohistochemistry, is associated with poor prognosis with a hazard ratio of 1.46 [29]. The high concentrations of VEGF in NSCLC led to the proposal of anti-VEGF antibody, as potential cancer treatments.

3.2. Bevacizumab: Current Concept

Bevacizumab is a recombinant humanized IgG1 directed against soluble VEGF [30]. In NSCLC, safety clinical trials showed that most adverse events observed with association of bevacizumab-chemotherapy were HTA, proteinuria, pulmonary hemorrhage and thrombosis [31-35]. Grade ≥ 3 HTA ranged from 0% to 16.7%, grade ≥ 3 proteinuria 0% to 3.2% and grade ≥ 3 thrombosis 5% to 14.7% [31-35]. Grade ≥ 3 Pulmonary hemorrhage ranged from 2% to 9.4% and was the most severe toxicity with significant grade 5 events [31,36]. Overall, bevacizumab was well tolerated in adenocarcinoma. Fatal pulmonary hemorrhages occured almost exclusively in squamous carcinoma [31], and led to exclusion for a long time of this histology from clinical trials. However, the recent BRIDGE study, conducted by Hainsworth *et al.*, showed that pulmonary hemorrhage was low in squamous carcinoma patients with no history of pulmonary haemorrhage [32].

Bevacizumab was approved by the Food and Drug Administration (FDA) as a first-line therapy for advanced or recurrent NSCLC without predominantly squamous cell histology in 2006. It was based on the results of the ECOG 4599 and AVAiL (Avastin in Lung) trials [37,38]. In both trials, bevacizumab was given together with chemotherapy to patients with advanced or recurrent non-small cell lung cancer. Bevacizumab treatment was given every 2 weeks and continued until the disease progressed. The chemotherapy was cisplatin plus gemcitabine in the European trial (AVAiL), while it was carboplatin plus paclitaxel in the American trial (ECOG 4599) [37,38]. In the ECOG and AVAiL trials, the median overall survival (OS) and progression free survival of the group given chemotherapy plus bevacizumab was significantly longer than patients given chemotherapy alone (**Table 2**) [37]. In AVAil trial, two doses of bevacizumab were tested 7.5 mg/kg and 15 mg/kg [38]. The progression-free survival time was significantly longer in the two groups treated with bevacizumab than for the chemotherapy alone patients with no difference between both dosages (**Table 2**). The follow-up was too short for overall survival (OS) analysis, but median survival times were unusually long, over 13 months, for all three patient groups.

Table 2. Phase III and IV clinical trials of bevacizumab combined with chemotherapy as first or second line therapy in NSCLC. PC: Paclitaxel/Carboplatin, Cis/Gem: Cisplatin/Gemcitabine. PFS: progression free survival. OS: overall survival. PH: pulmonary hemorrhage.

Authors	Drugs	Patients	Response rate	Grade ≥ 3 toxicity
Phase III [37]	Arm A: Bevacizumab 15 mg/kg + PC Arm B: PC alone	n = 818	PFS: Arm A = 12.3 months Arm B = 10.3 months OS: Arm A = 6.2 months Arm B = 4.5 months	HTA: 7% Proteinuria: 3.1% PH: 1.9%
Phase III [38]	Arm A: Cis/Gem alone Arm B: Bevacizumab 7.5 mg/kg + Cis/Gem Arm C: Bevacizumab 15 mg/kg + Cis/Gem	n = 1043	PFS: Arm A = 6.7 months Arm B = 6.5 months Arm C = 6.1 months No sufficient data for OS analysis	HTA: 6% (A), 9% (B) Bleeding: 4% (A), 4% (B) Proteinuria: <1%, 1% PH: 1.5% (4/5 grade 5) (A) 0.9% (all grade 5) (B)
Phase IV [39]	Various chemotherapy regimen + Bevacizumab	n = 2212		PH: 1% HTA: 6% Proteinuria: 3% Thrombosis: 8%

The final approval of bevacizumab by the FDA and EMEA required a phase IV study to assess its safety in "real life" with unselected patients. In agreement with safety clinical trials, the incidence of clinically significant (grade ≥ 3) adverse events of special interest with bevacizumab (7.5 or 15 mg/kg) was generally low in the SAiL study [39]. Thromboembolism occurred in 8%, hypertension in 6%, bleeding in 4%, proteinuria in 3% and pulmonary haemorrhage in 1%. Three percent died because of adverse events [39].

The profile of bevacizumab in patients 70 years of age or older was also a crucial question because elderly patients with an NSCLC are no longer uncommon considering the increase in life expectancy. Data obtained from subgroup analysis of ECOG 4599, AVAiL and SAiL studies showed a low benefit of bevacizumab compare to chemotherapy alone in elderly, with efficacy and safety profile of bevacizumab somewhat similar to young patients [40-42]. However, this result was not confirmed in a recent retrospective study of 4168 Medicare benificiaries aged from 65 years old and older [43].

3.3. Bevacizumab: Future Direction

3.3.1. Maintenance Therapy

Maintenance therapy is defined as therapy that is continued without a break after the end of first line therapy. Bevacizumab is, by definition, a maintenance therapy because it is given in NSCLC until disease progression. Bevacizumab combined with maintenance therapy (pemetrexed) is currently under evaluation in various clinical trials [44-48]. Preliminary results of AVAPERL trial showed better PFS (10.2 months) with pemetrexed/bevacizumab than bevacizumab maintenance (6.6 months) [48].

3.3.2. Targeted Therapy

Erlotinib is a HER-1/epidermal growth factor receptor tyrosine kinase inhibitor (TKI) that improves the survival time of patients with advanced NSCLC who have been given one or two prior chemotherapy regimens [49]. In theory, administering bevacizumab and erlotinib together may have additional clinical benefits because bevacizumab and erlotinib act on two different pathways. Combination of bevacizumab and erlotinib was well tolerated in clinical trials but did not improve OS (**Table 3**) [50-53]. The recent phase III trial ATLAS, assessing bevacizumab and erlotinib met its primary endpoint with a significant (28%) decrease in the risk of progression and an increase in the median PFS of 1.1 months comparing with erlotinib alone [54]. Data on overall survival have not yet been presented and are awaited with great interest.

3.3.3. Predictive Markers

Despite the benefit of bevacizumab in clinical studies, some patients do not response to this therapy. The greatest challenge in using bevacizumab to treat patients with NSCLC is to identify predictive biomarkers that may help discriminate patients most likely to respond to it. In metastatic colorectal cancer, Jubb *et al.* showed that adding bevacizumab to chemotherapy improved survival regardless the concentration of VEGF or thrombospondin-2, or the microvessel density [55]. In NSCLC, the ECOG 4599 trial reported that the baseline ICAM concentrations were prognostic for survival and predicted the response to chemotherapy with or without bevacizumab [56]. VEGF concentrations predicted only the response to bevacizumab but not survival. Overall, high blood pressure (>15/10) (HBP) by the end of first cycle may be the most reliable predictive marker. It was demonstrated that patients with HBP had better OS and PFS when they were treated with bevacizumab [57]. At the present time, bevacizumab is still given to NSCLC patients with no

selection and further studies are needed.

3.4. Other Antiangiogenic mAbs

In preclinical studies, ramucirumab, an antibody directed specifically against VEGFR-2, was combined with radiotherapy with interesting results [58]. In NSCLC patients, it is currently tested in phase II trial in combination with chemotherapy [59,60]. It is also tested in a phase III trial on NSCLC patients previously treated as second line therapy in combination with docetaxel [61]. This trial is still recruiting participants.Bavituximab is a vascular targeting antibody directed against phosphatidylserine which is restricted to the internal surface of the endothelial cell membrane [62]. In NSCLC, preliminary results with bavituximab combined with chemotherapy, showed an overall response rate of 52.4%, with a clinical complete response in 4.8% and a partial response in 47.6% [63]. The median progression-free survival time was 6.2 month. Two phase II trials have been set up, one to compare carboplatin/paclitaxel to carboplatin/paclitaxel/bavituximab in chemonaive NSCLC patients and the other one to compare docetaxel with docetaxel/bavituximab in previously treated NSCLC patients [64,65]. The primary endpoint for both studies is the objective response rate.

4. Anti-HER Antibodies

The epidermal growth factor (EGFR) family of molecules is a subclass I of the receptor tyrosine kinase (RTK) superfamily and has four members: EGFR, HER2, HER 3 and HER 4 [66]. EGFR is overexpressed in NSCLC and tumor cells produce the EGFR ligands which can activate cell surface receptor [67,68]. However, overproduction of EGFR does not seem to be associated with a poor prognosis in NSCLC, unlikely in other cancers [67]. Although HER2 does not interact with EGF-like ligands, it is the preferred heterodimer partner of the other three receptors [69]. HER2 is infrequently overproduced in NSCLC, but it seems to be associated with a poor prognosis [70]. HER2 overexpression in NSCLC ranges from 7% to 23% by immunohistochemistry and 2% to 23% by FISH [70-74].

4.1. Cetuximab: Current Concept

Cetuximab is an IgG1 mAb that targets EGFR and competitively inhibits endogenous ligand binding [75]. In NSCLC clinical trials, safety of cetuximab was over-all acceptable. The most reported adverse effects were skin rash and neutropenia [76-82]. Grade ≥ 3 skin rash ranged from 0% to 28%. [76,79] Grade ≥ 3 neutropenia was dependent on chemotherapy regimen used. It ranged from 0% to 44% [81,82]. Allergic reaction was reported in some trials [78,83] but was less common than in head and neck cancer patients. A recent meta-analysis estimated that cetuximab was associated with a higher incidence of hypomagnesemia (5.6%) compared with chemotherapy alone [84]. Despite this well tolerated profile, cetuximab did not improve PFS in phase III FLEX and BMS099 clinical trials [75,86] (**Table 4**). In these studies,

Table 3. Phase III clinical trial of bevacizumab combined with erlotinib. PFS: progression free survival. OS: overall survival.

Authors	Drugs	Patients	Response rate	Toxicity
Phase III [50]	Arm A: Bevacizumab 15 mg/kg + Erlotinib Arm B: Erlotinib alone (2^{nd} line)	n = 636	PFS: Arm A = 3.4 months Arm B = 1.7 months OS: Arm A = 9.2 months Arm B = 9.3 months	Similar between group

Table 4. Phase III clinical trials of cetuximab alone or combined with chemotherapy as first line therapy in NSCLC. Cetuximab was given with an initial dose of 400 mg/m^2 followed by weekly dose of 250 mg/m^2. Cis/Vin: cisplatin/vinorelbin; CT: carboplatin/taxane (paclitaxel or docetaxel). PFS: progression free survival; OS: overall survival.

Authors	Drugs	Patients	Response rate	Toxicity
Phase III [85]	Arm A: cetuximab + Cis/Vin Arm B: Cis/Vin alone	n = 1125	PFS: Arm A = 4.8 months Arm B = 4.8 months OS: Arm A = 10.1 months Arm B = 11.3 months	Grade ≥ 3 rash: Arm A: 10% Arm B: <1% Grade ≥ 3 febrile neutropenia: Arm A: 22% Arm B: 15%
Phase III [86]	Arm A: cetuximab + CT Arm B: CT alone	n = 676	PFS: Arm A = 4.4 months Arm B = 4.24 months OS: Arm A = 9.69 months Arm B = 8.38 months	Grade ≥ 3 rash: Arm A: 10.8% Arm B: 0% Grade ≥ 3 febrile neutropenia: Arm A: 4.6% Arm B: 3.4%

OS was enhanced by 1.2 and 1.3 months respectively with addition of cetuximab to chemotherapy [85,86]. However PFS reflected better than OS the efficacy of the first line therapy. OS is influenced by the treatment given after the first-line therapy and no data were provided about second line therapy in these studies. Based on these two trials, cetuximab was not approved by the EMEA or the FDA. EMEA considered that the drug had no convincing effect while the toxicity was considerable.

4.2. Cetuximab: Future Directions

4.2.1. Cetuximab and Other Targeted Therapies

Combining an anti-EGFR antibody and an EGFR TKI may enhance the inhibition of downstream signaling by blocking the different target sites on EGFR (extracellular and intracellular domains) [87]. Bortezomib which is the first drug of a new class of targeted drugs that are proteasome inhibitors may be also synergistic with cetuximab [88]. Despite the benefit in preclinical studies, association of cetuximab with TKI or bortezomid did not lead to objective response in phase II trials [88-93]. To the best of our knowledge, no phase III has yet started.

4.2.2. Cetuximab and Radiotherapy

The combination modality chemotherapy and radiotherapy conferred a small but significant survival advantage over radiotherapy alone in NSCLC [94]. Concomitant cetuximab and radiotherapy prolonged the survival of patients with locally advanced squamous cell carcinoma of the head and neck better than radiotherapy alone [95].

Combination of cetuximab and radiation resulted toxicity mainly in oesophagitis and pneumonitis as toxicity. Proportion of these adverse events was similar to those obtained with radiotherapy alone in previous clinical studies [96-102]. Only one trial compared directly cetuximab and chemoradiotherapy to chemoradiotherapy. A small but non significant benefit was observed for OS with association [102]. PFS was similar in both groups. A phase III trial is in progress to compare carpolatin/ paclitaxel followed by radiotherapy plus cetuximab and concurrent chemotherapy followed by radiotherapy in locally advanced NSCLC. Results may change clinical practice as it is actually done in head and neck cancer but are not expected before 2014 [97].

4.2.3. Aerosolized Cetuximab

Our group is investigating cetuximab delivery by airways in NSCLC. We previously showed that aerosolized cetuximab passed slowly and poorly in blood in mice [103]. It also significantly decreased tumor growth in an ectopic model of lung tumors. The benefit to deliver cetuximab compared to the systemic route is still under evaluation.

4.2.4. Cetuximab and Predictive Markers

As for bevacizumab, the main challenge is to discover predictive markers of the response to cetuximab in NSCLC. In colorectal cancer, it was shown that cetuximab was only active on wild type *KRAS* cancer [104]. The two large phase III clinical trials (BMS099 and FLEX) showed that EGFR and K-Ras mutations were not correlated with cetuximab response in lung cancer [86,105]. However a post-hoc analysis of the FLEX study collecting and quantifying the immunohistochemical EGFR activity in tumors found that EGFR expression in tumor may be a predictive marker [106]. In another post-hoc analysis of the FLEX study, skin rash at first cycle was associated with better PFS and OS in patients treated with cetuximab [107]. Identification of predictive markers is a crucial challenge and results of post-hoc analysis should be confirmed in a prospective study.

4.3. Other Anti-EGFR Antibodies

Several other anti-EGFR mAb were tested or are currently under evaluation in NSCLC. Matuzumab, an IgG1 mAb, binds EGFR with an affinity a little lower than that of cetuximab but, matuzumab has a longer half-life (6 - 8 days) [108,109]. Overall response rate of matuzumab combined with paclitaxel, as first line therapy, was 22%. EGFR expression and the KRAS mutation status seemed to predict a clinical response to matuzumab [110]. Pemetrexed/matuzumab as second line therapy seemed to be superior to chemotherapy alone (objective response 11% vs 5%) but difference was not statistically significant probably due to low patient inclusion (n = 148) [111].

Nimotuzumab was engineered to reduce human immunogenicity and slow clearance from the body [112]. In two clinical trials, nimotuzumab administered weekly was well tolerated with no notable skin toxicity [113, 114]. Objective response rate ranged from 47% to 66% [113,114]. Other clinical trials are in progress. The combination of gefitinib/nimotuzumab is being compared to gefitinib alone in NSCLC patients and results are due soon [115]. Another study is comparing the combination of nimotuzumab/liposomal paclitaxel/carboplatin to chemotherapy alone in NSCLC patients [116]. The results of this trial are expected in 2014.

Panitumumab, a fully humanized IgG2 directed against EGFR, was assessed in a phase I escalating dose clinical trial but the maximum tolerated dose was not reached [117,118]. Panitumumab in association with motesanib, a small-molecule antagonist of vascular endothelial growth factor receptors 1, 2, and 3, platelet-derived growth factor receptor, and Kit was assessed recently in a clinical trial [119]. No response was observed in patients treated with panitumumab associated to motesanib. Various clinical trials testing panitumumab in NSCLC are currently

in progress, one testing pre-operative chemoradiotherapy with or without panitumumab in advanced NSCLC patients [120] and two designed to evaluate the response rate to carboplatin/vinorelbin/panitumumab as first line therapy and the progression-free survival time for cisplatin/pemetrexed with or without panitumumab [121, 122].

Finally, necitumumab, a fully human IgG1 targeting the extracellular domain III of EGFR delivered alone did not show any therapeutic effect in NSCLC patients [123]. Necitumumab is being evaluated combined with cisplatin and gemcitabine in a phase III trial of advanced NSCLC [124]. Another phase III study comparing pemetrexed/cisplatin/necitumumab to chemotherapy alone in chemonaive NSCLC was stopped prematurely [125]. According to the press release from the company, the independent Data Monitoring Committee (DMC) decided that new or recently enrolled patients should stop treatment because of safety concerns related to thromboembolisms (blood clots) in the experimental arm of the study [126].

4.4. Anti-HER2 mAb

Trastuzumab is a humanized monoclonal antibody IgG1 directed against Her2 receptor [127]. While, trastuzumab seemed to have greater antitumor activity against NSCLC xenografts than against breast cancer xenografts, clinical results in NSCLC are less encouraging probably due to heterogeneity of HER2 overproduction and technical difficulties to quantify HER2 expression in lung tissues [128-133]. Overall clinical trials showed that trastuzumab was well tolerated but efficacy was low whether it was given alone or combined with chemotherapy.

Pertuzumab is a mAb with a particular mechanism of action. It inhibits HER2 dimerization [134,135]. A phase I clinical trial in which 43 NSCLC chemonaïve patients were treated with pertuzumab i.v. every 3 weeks found 9.3% grade ≥ 3 adverse events and no response [136]. Lastly, a phase II clinical trial assesses the response to F-18-fluorodeoxyglucose positron emission tomography of the combination of erlotinib and pertuzumab and results are pending [137].

5. Immune Modulating Antibodies

In human cancer, somatic gene mutations and epigenetically dysregulated genes lead to products which are potentially recognized as nonself-antigens [138]. Failure of the immune system to recognize these foreign antigens and eradicate tumor cells is probably a key mechanism in tumor development and recurrence [139]. Local immune suppression, induction of tolerance, and systemic dysfunction in T-cell signaling are described as mechanism implicated in immune system failure [140,141]. Several immunomodulatory molecules have been targeted to treat NSCLC. CTLA-4 is an immunoglobulin which is present on the surface of T cells. It binds to CD80 and CD86 on antigen-presenting cells [141]. Blocking the CTLA-4-mediated termination signal with antibodies should prolong anti-tumor immune responses, resulting in enhanced tumor suppression. Programmed death-1 (PD-1) is a key immune receptor expressed by activated T cells [142]. Ligation of PD-1 by B7-H1 (PD-L1), expressed on tumor cells, inhibits proliferation and cytokine production by activated T cells and prevents immune response against tumor cells. In NSCLC, PD-L1 does not seem to be correlated with survival [143].

5.1. Anti CTLA-4 Antibody

Ipilimumab, an antibody targeting CTLA-4, was combined to carboplatin/paclitaxel as sequencial treatment (given after chemotherapy) or concurrent treatment or placebo in chemonaive NSCLC patients [144]. The overall incidence of treatment related grade ≥ 3 adverse events was similar across arms. Sequential ipilimumab statistically improved PFS but not concurrent imipilmumab (4.1 vs 5.1 months). Immune related adverse events such as colitis, hypohysitis, hypopituitarism ranged from 15% to 20% with ipilimumab arm but 6% in control arm. A phase III trial comparing carboplatin/paclitaxel/ipilimumab to carboplatin/paclitaxel alone has just started [145]. The primary end point is overall survival. Tremelimumab (CP-675,206), an IgG2 specifically directed against CTLA-4 was recently assessed in a phase 2 clinical trial but results have not yet been published [146].

5.2. Anti-Programmed Death 1 Antibody

Safety of anti-PD-1 antibody in NSCLC was evaluated in two phase I clinical trials [147,148]. Overall, grade ≥ 3 immunological reaction was low. Autoimmunity adverse events were uncommon comparatively with ipilimumab (anti-CTLA-4 antibody). Objective response was promising and ranged from 17% to 18% in pretreated NSCLC patients. None of PD-L1 negative tumors had objective response [147,148]. One phase I clinical trial assessed safety of anti-PD-L1 antibody in NSCLC [149]. Overall, only 9% of patients developed grade ≥ 3 adverse events. Objective response occurred in 10% in pretreated patients [149].

6. Antibodies against the Insulin Growth Factor (IGF) Pathway

The IGF system comprises circulating ligands (IGF-1, IGF-2 and insulin) and cell-membrane receptors (IGF1R and IGF2R) [150]. IGF-1 is associated with higher risk of lung cancer [151]. IGF1R is overexpressed in NSCLC and implicated in resistance to therapy [152]. Moreover,

the presence of IGF1-R is associated with shorter disease-free survival times in NSCLC patients and is a potential target for NSCLC treatment [153].

Figitumumab (CP-751,871), an IgG2 antibody specific for IGF1-R was combined with paclitaxel/carboplatin or docetaxel in two clinical trials [154-156]. Compared to chemotherapy alone, figitumumab + paclitaxel/carboplatin led to more hyperglycemia (8% and 15% respectively). Objective response rate with the combination was 54% and 42% with chemotherapy alone. Baseline free IGF-1 concentration was correlated with the clinical benefit of figitumumab [157]. A phase III study in which NSCLC patients were given carboplatin/paclitaxel/figitumumab or chemotherapy alone was shut down early because of too many deaths linked to figitumumab therapy [158]. The results of the study indicated that the overall survival of patients given figitumumab plus chemotherapy (8.5 months) was worse than for those given chemotherapy alone (10.3 months) [159]. However, figitumumab/chemotherapy was associated with better overall survival than was chemotherapy alone in a subset of patients with high baseline circulating IGF1-R. A phase III trial that compared erlotinib/figitumumab and erlotinib alone as a second-line therapy for NSCLC patients was prematurely closed because there was no improvement in the progression-free survival time in intermediate analyses [160]. Dalotuzumab (MK-0646 or h7C10), directed against IGF-1R, was administered in 80 patients with various cancers and the treatment was well tolerated [161]. Another phase I/IIa trial assessed the safety of erlotinib/dalotuzumab in previously treated NSCLC patients [162]. Results are expected soon. The response to dalotuzumab combined with pemetrexed/cisplatin or gemcitabine/carboplatin is currently assessed [163,164]. Cixitumumab (IMC-A12), RG1507, Ganitumab, fully human IgG1 and BIIB022, a fully human IgG4 are currently evaluated in NSCLC combined with chemotherapy or targeted therapies [165-172].

7. TRAIL Agonist Antibodies

The tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), also known as Apo2L, is a member of the TNF ligand superfamily [173,174]. It induces apoptosis in many cancer cell lines, with little or no effect on most normal cells [173]. TRAIL mediates apoptosis through two death receptors, TRAIL-receptor 1 (TRAIL-R1) and TRAIL-receptor 2 (TRAIL-R2) expressed on cell surface. NSCLC patients have high tumor concentrations of TRAIL-R1 (in 67% to 99% of tumor biopsies) [175,176]. TRAIL-R2 was detected in 82% of NSCLC tumor biopsies [176]. Several antibodies which are TRAIL agonist have been developed [177].

In two NSCLC clinical trials, Mapatumumab, an agonist antibody of TRAIL R1 receptor, was well tolerated [178,179]. The most common grade ≥ 3 adverse event was back pain. Administered alone, no objective response was shown and combined with chemotherapy, it did not improve response rate or PFS in comparison of chemotherapy alone [178,179]. To the best of our knowledge, no phase III trial has yet been organized. Lexatumumab (HGS-ETR2), an agonistic high-affinity antibody that activates TRAIL-R2 (or death receptor 5), was assessed in 8 NSCLC patients among 31 cancer patients [180]. One patient given 10 mg/kg experienced a possibly dose-related toxicity of grade 3 hyperamylasemia. The outcome of the NSCLC patients was not given. Conatumumab (AMG 655), an agonistic antibody TRAIL-R2, did not lead to dose-limiting toxicities [181]. Only one patient with NSCLC had a confirmed partial response at week 32 (38% reduction in tumor size) [181]. This patient remains on conatumumab after 4.2 years with a sustained partial response [181]. Tigatuzumab (TRA-8), another agonist of TRAIL-R2 was well tolerated in 17 cancer patients, but no NSCLC patient was included [182]. The maximum tolerated dose was not reached. No clinical trial on lung cancer patients is planned.

8. Anti-IL-6 Antibody: ALD518

Inflammation is associated with 15% - 20% of all deaths from cancer worldwide and contributes to fragility of cancer patients [183]. IL-6 is an inflammatory cytokine which play an important role in NSCLC [184]. Elevated plasma IL-6 concentrations were associated with a poor prognosis in NSCLC [185]. ALD518 is a humanized IgG1 monoclonal antibody that binds with high affinity to human IL-6. The 124 NSCLC patients in a phase II study were given increasing doses of ALD518 [186,187]. The hemoglobin concentration was higher in the patients given ALD518 than in the placebo group. Moreover, the pooled subjects treated with ALD518 lost statistically less of lean body mass (LBM).

9. Anti-NeuGcGM3: Racotumomab

Neu-glycolyl-containing gangliosides (NeuGcGM3) are glycolipids that are not normally components of the cytoplasmic membranes of humans. But Neu-glycolyl-containing gangliosides are overproduced by several human tumors [188]. Racotumomab is an anti-idiotype murine monoclonal antibody which reacts with NeuGc-containing gangliosides. A group of 71 previously treated NSCLC patients were given racotumomab in a phase II trial with no serious adverse effects [189]. The median survival time of the 56 patients who entered the study with a partial response or a stable disease and with a PS 1 after the first line of chemo/radiotherapy was 11.50

months from starting treatment. In contrast, the median survival time calculated for patients who started treatment with progressive disease and/or a PS2 was 6.50 months.

10. Perspectives

To enhance antibody properties, several molecules have been conjugated to the antibodies. As discussed in the first part, conjugation of mAbs with radionuclides may enhance their anti-tumor efficacy. Several radiolabeled antibodies are being evaluated for treating NSCLC. Two clinical trials showed that the toxicity of radiolabeled monoclonal antibody mCC49 directed against tumor-associated glycoprotein-72 (TAG-72) was acceptable, but the conjugate compound was no better than the unconjugated mAb [190,191]. The radiolabeled cT84.66 monoclonal antibody directed against CEA (Carcino-embryonic antigen) will be assessed soon in patients with stage IIB, stage IIIA, or stage IIIB non-small cell lung cancer [192]. Conjugation of mAbs with cytotxic drugs were assessed in two phase II clinical studies on NSCLC patients. The first obtained some good results by giving SGN-15 (cBR96-doxorubicin conjugate) consisting of a chimeric murine monoclonal antibody that recognizes the Lewis Y antigen, conjugated to doxorubicin, in NSCLC patients [193]. In the second trial, ABR-217620 (naptumomab estafenatox), a recombinant fusion protein consisting of a mutated variant of the superantigen staphylococcal enterotoxin E (SEA/E-120) linked to a Fab fragment that recognizes the tumor-associated antigen 5T4, was given alone or in combination with docetaxel [194]. The treatment was well tolerated with evidence of immunological and antitumor activity.

Table 5. Status of therapeutic antibodies in NSCLC.

	Target	Type	Immunoglobulin sub-class	Status in NSCLC
Bevacizumab	VEGF	Humanized	IgG1	Approved
Ramucirumab	VEGFR-2	Fully human	IgG1	Phase III
Cetuximab	EGFR	Chimeric	IgG1	Phase III (Refusal)
Matuzumab	EGFR	Humanized	IgG1	Phase II
Nimotuzumab	EGFR	Humanized	IgG1	Phase II
Panitumumab	EGFR	Fully Human	IgG2	Phase II
Necitumumab	EGFR	Fully Human	IgG1	Phase III
Trastuzumab	HER2	Humanized	IgG1	Phase II
Pertuzumab	HER dimerization	Humanized	IgG1	Phase II
Figitumumab	IGF1-R	Fully human	IgG2	Phase III
Dalotuzumab	IGF1-R	Humanized	IgG1	Phase II
Cixitumumab	IGF1-R	Fully human	IgG1	Phase II
BIIB022	IGF1-R	Fully human	IgG4P	Phase I
RG1507	IGF1-R	Fully human	IgG1	Phase II
Ipilimumab	CTLA-4	Fully human	IgG1	Phase III
Tremelimumab	CTLA-4	Fully human	IgG2	Phase II
Anti-PD-1	PD-1	Fully human	IgG4	Phase I
Anti-PD-L1	PD-L1	Fully human	IgG4	Phase I
ALD518	IL-6	Humanized	IgG1	Phase II
Mapatumumab	TRAIL-R1 (agonist)	Fully human	IgG1	Phase II
Lexatumumab	TRAIL-R2 (agonist)	Fully human	IgG1	Phase I
Conatumumab	TRAIL-R2 (agonist)	Fully human	IgG1	Phase I
Tigatuzumab	TRAIL-R2 (agonist)	Humanized	IgG1	Phase I
Racotumomab	NeuGcGM3	Murin	Ab2	Phase II
Bavituximab	Phosphatidylserine	Chimeric	IgG1	Phase II

11. Conclusion

NSCLC is a cancer with a particularly poor prognosis that is generally refractory to anti-cancer treatments. Monoclonal antibodies offer new promising ways of treating NSCLC (**Table 5**). Only one antibody, bevacizumab, is presently approved for NSCLC, but the progression-free survival time is short. Another mAb, cetuximab, was evaluated in several clinical trials and showed a small increase of overall survival in combination with chemotherapy. However, the FDA and the EMEA considered the therapeutic benefit insufficient and refused to approve cetuximab for treating NSCLC. At first glance, the results for NSCLC are somewhat disappointing, in contrast to the benefits obtained with mAb treatments in other solid tumors, such as breast and colon cancers. However, we believe this is only the visible part of the iceberg. The first steps towards treating NSCLC with therapeutic mAbs have been taken. Research and development of mAbs and derived compounds are a great challenge for both industry and academic institutions and countless possibilities remain to be explored. As proof, many mAb that have been approved for other cancers and new mAbs are being clinically evaluated for use with NSCLC. Cetuximab and anti-EGFR mAbs have not yet been abandoned as NSCLC treatments. Indeed, cetuximab is currently being tested in combination with radiation in clinical trials. New anti-cancer targets are being discovered every year and mAb technology to engineer more efficient biologics continues to evolve. Thus, the development of monoclonal antibodies clearly marks the start of a new era in NSCLC treatment, although there is still a long way to go before those "magic bullets" find their optimal target in lung cancer.

12. Acknowledgements

This publication was funded by the French National Research Agency under the program "Investissements d'avenir" Grant Agreement LabEx MAbImprove: ANR-10-LABX-53. It was also supported by the "fond de dotation en santé respiratoire", "Cancéropôle Grand Ouest", "Région Centre" and "Association régionale d'aide aux insuffisants respiratoires".

The English text was edited by Dr Owen Parkes.

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