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Monoclonal antibodies in non-small-cell lung cancer: Light at the end of the tunnel

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Abstract

Lung cancer is the leading cause of death and non-small cell lung cancer (NSCLC) is considered as the most common type of lung cancer. Several conventional therapies, such as surgery, radiation, and chemotherapy are used for the treatment of lung cancer. But, these therapies could have multiple undesirable side effects. Therefore, there is an urgent need for therapeutic agents to improve the clinical outcomes for cases with NSCLC. Recently, therapeutic antibodies have shown promise for NSCLC treatment. The aim of this review is to discuss FDA-approved antibodies such as durvalumab, pembrolizumab, necitumumab and nivolumab in the treatment of NSCLC as well as Onartuzumab, a monoclonal antibody against c-MET, that was discontinued due to its lack of clinical activity. Furthermore, the aim of this manuscript is to give a brief overview about NSCLC therapeutic mAbs.

Introduction

Lung cancer is considered as a heterogeneous and complex disease [1]. Non-small cell lung cancer (NSCLC), the most common type of lung cancer, accounts for approximately 85 percent of all lung cancers and is classified as nonsquamous carcinoma and squamous NSCLC [2,3]. The primary treatment for patients with stage I, II, or IIIA NSCLC could be surgery. But, long-term survival of NSCLC cases after surgery alone might be largely unsatisfactory [4]. Though patients who receive adjuvant chemotherapy after complete resection of localized NSCLC could have an absolute survival advantage of about 5% at 5 years, there is still a relatively high risk of relapse even for early-stage NSCLC cases [5]. Furthermore, it has been indicated that third-generation chemotherapy regimens in NSCLC cases who have a good performance status could moderately improve survival at one and two years [6,7]. It has been shown that immunotherapy with monoclonal antibodies including nivolumab and pembrolizumab has improved the survival of cases with metastatic NSCLC [8]. Since many monoclonal antibodies against programmed cell death (PD-1) have been introduced to enhance anticancer immune responses and cause tumor cell death, targeting PD-1 pathway is considered as a new anticancer strategy [9]. It has been reported that response rates in cases with pretreated, advanced NSCLC were higher and more durable with PD-1 blockade therapy in comparison with chemotherapy. Thus, PD-1 inhibitors including nivolumab and pembrolizumab were approved for squamous and nonsquamous lung cancer in the pretreated patients [10]. Pembrolizumab could improve survival as first- and second-line therapy compared to chemotherapy in cases with PD-L1 expressing advanced NSCLC [11]. Moreover, blockade of the epidermal growth factor receptor (EGFR) by monoclonal antibodies can improve outcome in cases with NSCLC [12]. Immune checkpoint inhibitors including nivolumab, pembrolizumab and durvalumab are at the forefront of immunotherapy [13]. Till now, the efficacy and toxicity of immune checkpoint inhibitors in elderly patients is unclear since related studies involved a low number of elderly cases [14]. At present, four therapeutic monoclonal antibodies have been approved for the treatment of non-small-cell lung cancer and many monoclonal antibodies are currently being tested in clinical trials (Table 1) (Figure 1).

Durvalumab

Durvalumab (MEDI4736), a high-affinity human IgG1 monoclonal antibody, was approved for the treatment of non-small cell lung cancer (NSCLC). It could bind to both programmed death protein 1 (PD-1) and CD80. As well as, programmed cell death ligand 1 (PD-L1) was blocked [15]. It has been indicated that durvalumab had encouraging antitumor activity, by allowing T cells to recognize and induce tumor cell death. Both chemotherapy and radiotherapy could up-regulate PD-L1 expression in tumor cells, which can be a predictive factor for a response to durvalumab. Thus, it has been suggested that durvalumab could be beneficial after chemoradiotherapy [16]. Currently, durvalumab is in many clinical trials alone or in combination with other agents, such as anti–CTLA-4 and anti–PD-1, as well as IDO, MEK, BRAF, and EGFR inhibitors [17]. The combination of both durvalumab and tremelimumab potentiates their antitumor activity in patients with advanced NSCLC, regardless of PD-L1 tumor status [18]. Till now, no immunogenicity that impacts pharmacokinetics/ pharmacodynamics of durvalumab has been observed at the 10 mg/kg (every 2 weeks) selected dose [19].

Pembrolizumab

Pembrolizumab (Keytruda (®)) is a humanized monoclonal antibody that was approved on October 2, 2015 for the treatment of cases with

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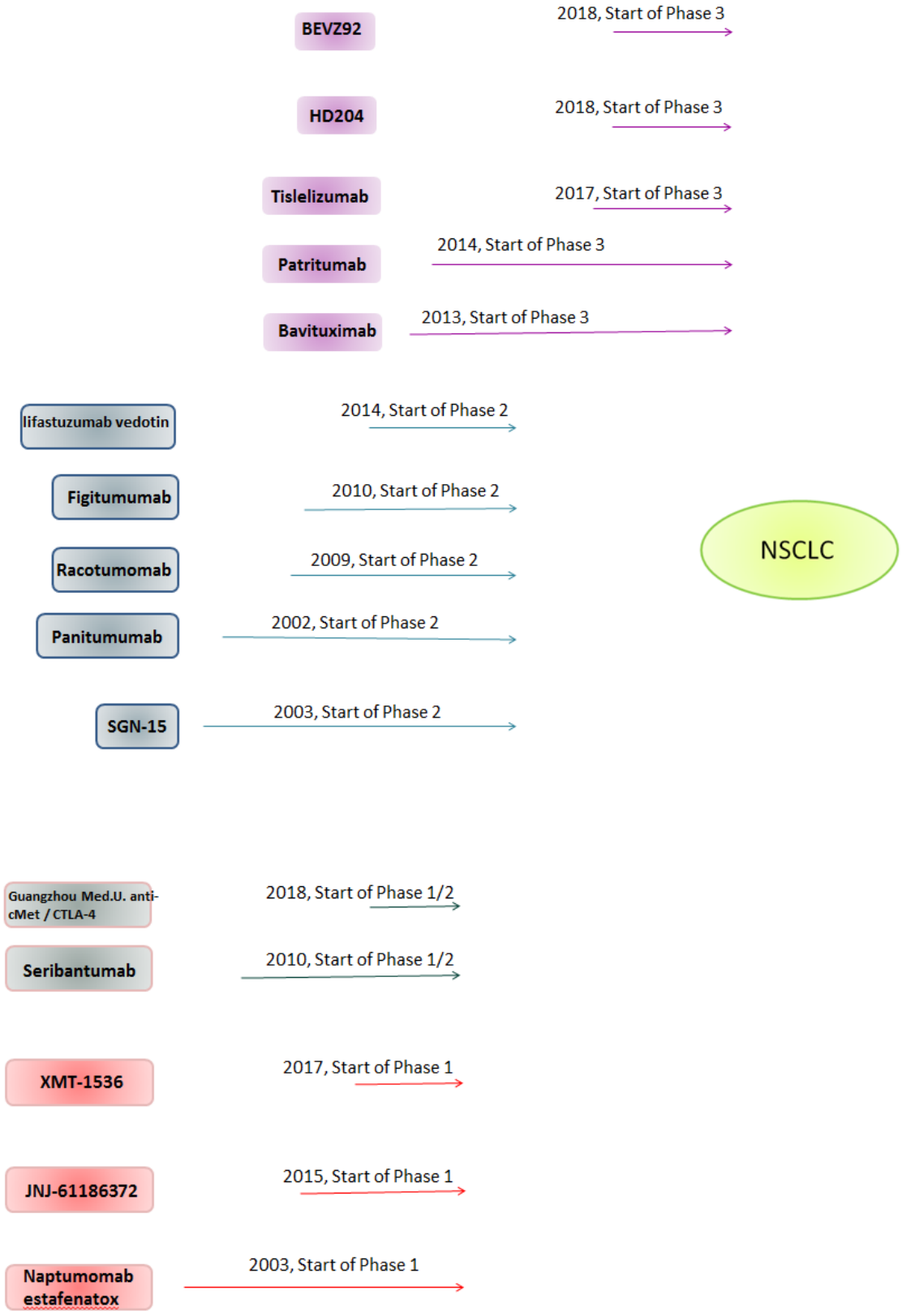

Figure 1. Non-small cell lung cancer monoclonal antibodies in clinical trials

Table 1. A brief overview of non-small cell lung cancer (NSCLC) antibodies. Monoclonal antibodies are in clinical trials for treatment of NSCLC and various malignancies

Antibody	Internal name	Antigen	Company	Phase	Condition	Antibody type
BEVZ92	MB02	Vascular endothelial growth factor A	mAbxience S.A.	2014, Start of Phase 1 2018, Start of Phase 3	Cancer Lung cancer (non-small cell)	Antibody
Guangzhou Anjie Biomed. Tech. anti-Muc1 CAR	Guangzhou Anjie Biomed.Tech. anti-Muc1 CAR	Mucin 1	Guangzhou Anjie Biomedical Technology Co.Ltd.	2018, Start of Phase 1/2	Lung cancer (non-small cell)	Chimeric antigen receptor
HD204	HD204	Vascular endothelial growth factor A	Prestige BioPharma Pte Ltd	2018, Start of Phase 3	Lung cancer (non-small cell)	Antibody
JNJ-61186372	EM1-mAb	cMet Receptor, Epidermal growth factor receptor	Genmab A/S, Janssen Biotech Inc	2015, Start of Phase 1	Lung cancer (non-small cell)	Bispecific antibody
SGN-15	SGN-15, BMS-182248, BR96-DOX	Lewis y/b antigen	Bristol-Myers Squibb, Seattle Genetics	2003, Start of Phase 2	Lung cancer (non-small cell)	Chimeric human/mouse, Antibody drug conjugate
XMT-1536	XMT-1535, XMT-1536	NaPi2b	Mersana Therapeutics	2017, Start of Phase 1	Lung cancer (non-small cell)	Antibody drug conjugate
Bavituximab	ch3G4	Phosphatidyl serine	Peregrine Pharmaceuticals, Inc.	2013, Start of Phase 3 2008, Start of Phase 2 2005, Start of Phase 1	Lung cancer (non-small cell) Breast cancer Solid tumors	Chimeric human/mouse Antibody
Figitumumab	CP-751871, CP-751,871	Insulin-like Growth Factor 1 Receptor	Amgen, Pfizer, Schering-Plough	2010, Start of Phase 2 2007, Start of Phase 1 2003, Start of Phase 1	Lung cancer (non-small cell) Breast cancer Multiple myeloma	Human - from transgenic mouse Antibody
lifastuzumab vedotin	RG7599, DNIB0600A	NaPi2b	Genentech Inc. Seattle Genetics	2014, Start of Phase 2	Lung cancer (non-small cell)	Human, Antibody drug conjugate
Naptumomab estafenatox	ABR-217620	Trophoblast glycoprotein	Active Biotech Research	2007, Start of Phase 2/3 2003, Start of Phase 1	Renal cell carcinoma Lung cancer (non-small cell)	Mouse, Other
Panitumumab	ABX-EGF, clone E7.6.3, Pmab, 139	Epidermal growth factor receptor	Abgenix (Amgen), Amgen	2006, Approved 2002, Start of Phase 2 2000, Start of Phase 1	Colorectal cancer Lung cancer (non-small cell) Head and neck cancer	Human - from transgenic mouse Antibody
Patritumab	AMG 888, U3-1287	Receptor tyrosine-protein kinase erbB-3	Amgen, Daiichi Sankyo, Inc, U3 Pharma GmbH	2014, Start of Phase 3 2010, Start of Phase 2	Lung cancer (non-small cell) Cancer	Human - from transgenic mouse Antibody
Racotumomab	1E10	Ganglioside GM3	Recombio	2009, Start of Phase 2	Lung cancer (non-small cell)	Mouse Antibody
Seribantumab	MM-121, SAR256212	Receptor tyrosine-protein kinase erbB-3	Merrimack Pharmaceuticals Inc, Sanofi-aventis	2011, Start of Phase 2 2010, Start of Phase 1/2	Breast cancer Lung cancer (non-small cell)	Human - from phage display Antibody
Tislelizumab	BGB-A317	Programmed Cell Death 1	BeiGene Ltd, Celgene Corporation	2017, Start of Phase 3 2017, Start of Phase 1/2 2015, Start of Phase 1	Lung cancer (non-small cell) Solid tumors Cancer	Humanized undefined source Antibody

metastatic NSCLC whose tumors express PD-L1 as well as patients who have disease progression on or after platinum- based chemotherapy or targeted therapy against anaplastic lymphoma kinase (ALK) or epidermal growth factor receptor (EGFR) [20,21]. Pembrolizumab showed antitumor activity in cases with advanced NSCLC. It has been indicated that PD-L1 expression in at least 50 percent of tumor cells could be related to improved efficacy of pembrolizumab [22]. It has been demonstrated that a combination of pembrolizumab, carboplatin, and pemetrexed can be an effective and tolerable first-line treatment option for advanced non-squamous NSCLC [23]. In another study, the addition of pembrolizumab to standard chemotherapy of pemetrexed and a platinum containing drug could result in longer overall survival (OS) and progression-free survival (PFS) than chemotherapy alone in cases with previously untreated metastatic non-squamous NSCLC without EGFR/ALK mutations [24].

Necitumumab

Necitumumab, a fully human IgG1 monoclonal antibody, was approved in 2015 for the treatment of NSCLC [25]. It could target and bind to the EGFR to prevent the interactions between the receptor and its ligands [26]. The most common necitumumab treatment adverse events were infusion reactions, hypomagnesemia, diarrhea, and dermatological toxicities [26]. Though it has been considered as a safe and effective drug for squamous NSCLC, the clinical utility of necitumumab could be limited due to the high cost of the drug and toxic effects occurred when combined with both cisplatin and gemcitabine. Moreover, many clinical studies are ongoing to investigate the utilization of necitumumab [26]. It is indicated that both necitumumab and cetuximab are internalized to a low-pH compartment more quickly than panitumumab in NSCLC cells [27]. In NSCLC cell lines such as HCC827, NCI-H1650 and EKVX, both necitumumab and cetuximab

could induce more rapid internalization and degradation of epidermal growth factor receptor (EGFR) in comparison with that reported with panitumumab [28]. Moreover, it has been reported that necitumumab may induce ADCC against non-small cell lung cancer cell lines, and the intensity of ADCC was correlated with the level of EGFR expression on the cell surface [28]. It has been demonstrated that combination of necitumumab and standard chemotherapy (cisplatin+gemcitabine), can increase overall survival in chemo-naı¨ve cases with metastatic confirmed squamous cell histology [29].

Nivolumab

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune-checkpoint–inhibitor antibody which is approved in NSCLC in 2015 [25,30]. It can disrupt the negative signal that mediates T-cell activation and proliferation via binding to PD-1 on activated immune cells in order to selectively block the interaction of the PD-1 receptor with its two programmed death ligands (PD-L1 and PD-L2) [30]. Nivolumab was active in advanced NSCLC in first- and second-line settings. Furthermore, it was superior to docetaxel with respect to overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) in squamous cell and nonsquamous cell NSCLC [31]. Tumor PD-L1 overexpression has been related to higher ORR, but nivolumab could be active among cases with PD-L1 expression less than 1% and nonsquamous histology [31]. It has been indicated that among cases with advanced nonsquamous NSCLC who had progressed during or after platinum-based chemotherapy, OS was reported to be longer with nivolumab than with docetaxel [32]. Nivolumab monotherapy has been shown to produce durable responses and encouraging survival rates in cases with heavily pretreated NSCLC. Moreover, randomized clinical studies with nivolumab in advanced NSCLC are ongoing [33]. It has been shown that the combination of both PD-1/PD-L1 and CTLA-4 antibodies can increase toxicity more than PD-1/PD-L1 blockade alone in cases with advanced NSCLC, but further investigation is needed [34]. Recently, the PD-L1 immunohistochemistry (IHC) assay is used in late-stage nivolumab clinical trials of multiple indications such as NSCLC [35]. The clinical validation of the assay and its utility in identifying cases for nivolumab treatment have been indicated in 2 phase III studies in previously treated non-small cell lung cancer with distinct histology. Moreover, the clinical utility of PD-L1 IHC assay is being further investigated in NSCLC clinical studies in the first-line setting [35]. It has been shown that the combination of nivolumab and platinum-based doublet chemotherapy (PT-DC) could provide benefit beyond single-modality chemotherapy. Thus, this can be a treatment option for cases with rapidly progressing disease or patients whose tumors do not express PD-L1 [36].

Onartuzumab

Onartuzumab is derived from the 5D5 antibody previously indicated to bind the MET Sema domain [37]. Onartuzumab entered phase 3 in 2012 in *non-small cell lung cancer but discontinued in 2014 [25].* Onartuzumab can block hepatocyte growth factor (HGF) α-chain binding to the receptor tyrosine kinase MET. Thus, targeting MET could be a promising therapeutic strategy [37]. After promising results obtained from both preclinical and phase I studies, a randomized phase II trial was designed in advanced NSCLC in 2nd or 3rd line treatment. 128 cases have been randomized between an association of erlotinib plus placebo and erlotinib plus Onartuzumab (15 mg per kg IV every 3 weeks) until progression or toxicity [38]. It has been indicated that cases with overexpression of Met in immunohistochemistry had a progression-free survival and an overall survival two-fold and three-fold longer, respectively, than cases with negative immunohistochemistry score. Moreover, it has been reported that the erlotinib plus onartuzumab can have a worse effect on both SSP and OS than the control arm in cases with negative immunohistochemistry [38].

Conclusion

Most lung cancer cases still die from their disease. Thus, there is an urgent need for more effective therapies. With 15 monoclonal antibodies in clinical trials as well as four FDA-approved drugs, it is obvious that this is becoming an attractive approach for NSCLC treatment. It has been indicated that monoclonal antibodies against vascular endothelial growth factor receptor (VEGFR) or epidermal growth factor receptor (EGFR) might enhance the survival compared to chemotherapy alone. PD-1 inhibitors including nivolumab and pembrolizumab had been widely used in advanced cancers. Furthermore, PD-L1 expression in at least 50 percent of cancer cells can be related to improved efficacy of pembrolizumab. In previously treated cases with advanced, refractory, squamous NSCLC, nivolumab has a favorable safety profile and might restore antitumor immunity. Moreover, both PD-1 and PD-L1 antibodies, with a good safety profile and manageable side effects, show durable responses in non-small cell lung cancer. Thus, it seems that monoclonal antibodies can improve the outcome including survival in NSCLC patients.

Conflict of interests

The author declared no conflict of interests.

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