

Clinical studies of Atezolizumab contributing to FDA approvals

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Abstract. PD-1/PD-L1 pathway mediates human self-tolerance, but tumours can achieve immune resistance by usurping PD-1/PD-L1 pathway and inhibiting antitumor response in vivo. PD-L1 antibody is proved to enhance immune function in tumour tissue by blockade of PD-1/PD-L1 interaction. Genentech inc. developed MPDL3280A (atezolizumab), a humanized monoclonal PD-L1 antibody with reduced Fc effector function via a single amino acid substitution. PD-L1 antibody drugs generally have good curative effects and less adverse events comparing to PD-1 antibody drug, but there're prerequisites such as PD-L1 expression and T cell infiltration in tumor tissues. PD-L1 won't induce ideal antitumour activity in most of the cases lacking proper pathological conditions. This review aims at providing an overview for crucial clinical stages of atezolizumab before its approvals, as a reference for future development of atezolizumab or other PD-L1 antibodies development. Patient populations, methods, results and safety information of one basic phase I clinical trial and three specialized phase III clinical trials that has led to the three approvals of atezolizumab by FDA were summarized and stated briefly.

Keywords: Atezolizumab, Clinical, Treatment.

1. INTRODUCTION

Immune checkpoints mean a plethora of inhibitory pathways playing a significant role in self-tolerance and physiological immune responses in peripheral tissues. Among all the checkpoints discovered, CTLA-4 was firstly found as a negative regulator of T cells and a co-inhibitor receptor, inhibiting T cell proliferation by delivering inhibitory signals. While programmed death 1 (PD-1) protein, as one of the immunoinhibitory receptors belonging to the CD28/CTLA-4 family and expressed on surfaces of chronically stimulated CD4⁺ and CD8⁺ T cells, expresses during early stage of T cell activation and upregulates its expression during chronic infection. It's confirmed that tumours achieve immune resistance by dysregulating the expression of immune-checkpoint proteins, particularly against T cells [1][2]. Mediation of PD-1 and PD-L1 interaction was presented to be capable of curing cancer [3], demonstrating that blocked PD-L1 can enhance immune function (such as T-cells responses) in vitro and mediates anti-tumour activity in preclinical models [4][5]. Many new cancer treatments are based on this principle, and Atezolizumab is no exception.

Atezolizumab, designed and studied by Genentech inc., is a human monoclonal immunoglobulin-G1 antibody with reduced Fc effector function via G298A. The modification of a crystallizable fragment (Fc) domain disables antibody lacking N-linked oligosaccharides to bind to human Fcγ receptors so that it could eliminate the cellular cytotoxicity. As is shown in affinity measurements using surface plasmon resonance, Atezolizumab can specifically bind to PD-L1 to prevent the interaction between PD-1 and PD-L1 receptor while leaves the intact interaction of PD-1 with alternative ligand PD-L2 [6]. In preclinical research, mice that had the syngeneic tumour implanted were treated with Atezolizumab and the treatment inhibited the growth of tumour and induce immune memory that resist the tumour cells again. Besides, PD-L2 is significant in the reduction of AHR, possibly by reduction of immune cells like eosinophils and macrophages [6]. After a complete series of clinical trials, according to announcements on FDA official website [7], Atezolizumab has received three approvals up to now, due to three respective and specific phase III clinical trials which are called IMpower133, IMpassion130 and IMpower150. All the approvals are in the form of combination with other antitumour drugs and were granted priority review.

However, in a majority of cancer cases, PD-L1 antibody fails to induce responses. It's demonstrated that tumor PD-L1 expression are prerequisites for responding to PD-L1 blockade [8][9].

PD-L1 antibody might not work in patients without enough PD-L1 expression on cancer cell or immune cells. Moreover, sufficient T cell infiltration in tumor tissues is necessary too. For instance, activation of the WNT/ β -catenin signaling pathway contributes noninflamed TME development, and in melanoma with active WNT/ β -catenin signaling pathway, PD-L1 antibodies are of less efficacy than ones without this kind of oncogene [10]. Due to the absence of T cells in cancer tissue caused by oncogene or other impacts, patients with similar situation may not respond to PD-L1 antibody therapy. It's also the case that if during a treatment period the tumour is not completely cleaved, the patient would stop responding to PD-L1 antibody treatment for the outbreak of T cells usually only occurs once.

This review focused on intuitively summarizing the detailed information about phase 3 clinical trials that those 3 FDA approvals based on and significant relevant analysis that were published. As supplementary, there would also be a brief description about phase 1 clinical trial conducted by Genentech inc. and the phase 2 clinical trials that led to three Phase 3 clinical trials.

2. MPDL3280A study

After the engineered anti-PD-L1 antibody MPDL3280A (Atezolizumab) was generated, a phase I clinical trial was conducted in patients with solid tumours of various types to investigate the PD-L1 expression on various tumours, drug safety, adverse event, and the association between response to MPDL3280A and expression of tumour-infiltrating immune cells [8].

In the first step of the basic phase I study, due to the principle of PD-L1 antibody drug, researchers analyzed the PD-L1 expression in human tumours and the association with PD-L1 expression and clinical benefit in advance. As a result of this advanced investigation, it was proved that the response of MPDL3280A treatment is positively associated with the tumour-infiltrating immune cell PD-L1 expression instead of the one in tumour cell, in a statistical way.

In the second step, a variety of patients with different spreading tumours were given MPDL3280A administration. Among all the tumour types involved in the trial such as the NSq NSCLC, Melanoma, RCC and other tumours, the objective response rate by patient IHC (IC) status reached 36 (21) % in all patients. Also, it was possible that the tumour IHC status have relevance to median progression-free survival. Besides from the IHC, IC and biomarker status, they conducted other examinations and generally showed that PD-L1 inhibition did not induce the existence of tumour-infiltrating immune cells.

As for the treatment-related adverse events (AEs), 70% of all the patients have any AE of any grades. Those AEs include fatigue, decreased nausea, rash, pyrexia, arthralgia, diarrhoea, pruritus, chills, influenza-like illness, asthenia, dyspnea, pain, myalgia, anaemia, dry skin, night sweats, vomiting are the most common ones with few cases of grade 3-4.

These phase I studies and its expansion study set the foundation of former clinical studies by confirming the potential of atezolizumab to treat various types of cancers that was found PD-L1 positive in both tumour-infiltrating immune cells and tumour cells. Primary indications from the preclinical stage to approval were provided by this study.

3. Lung cancer

Atezolizumab is now used with other drugs treats patients with 2 kinds of lung cancers, atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin for metastatic NSq NSCLC with no EGFR or ALK genomic tumor aberrations and atezolizumab in combination with carboplatin and etoposide for ES-SCLC.

4. Metastatic NSq NSCLC

Traditional treatments of NSq NSCLC cover the combination of monoclonal antibody drug and chemotherapy, however, the prognosis wasn't ideal and later study showed that the addition of Atezolizumab may bring more benefits.

As the continuing of IMpower150 trial I (NCT02366143) mainly focused on the effect of VEGF blockade on the efficacy of immunotherapy with Atezolizumab involved and the combination of atezolizumab and chemotherapy [12]. Impower150 trial was built under the premise that a GP28328 study (NCT01633970) had confirmed the safety and efficacy of Atezolizumab plus first-line chemotherapy regimens in multiple tumor types [13]. It basically enrolled patients whose tissue is available for biomarker testing and that had stage IV or recurrent metastatic NSq NSCLC but hadn't been treated with chemotherapy. Also, Patients were randomly divided into ACP, BCP and ABCP group and assessed the PD-L1 expression via IHC. The first-step induction last for 4 or 6 21-day cycles and the administration was conducted on the day 1.

The basic PFS study results were shown in WT population without EGFR or ALK genetic alterations and teff-high WT population. In both of these two populations, a higher percentage of patients in in BCP group resulted in progression or death. ABCP group not only had a higher PFS rate, but also had a longer PSF period. For the next several months of observation, these differences remain significant (Figure1).

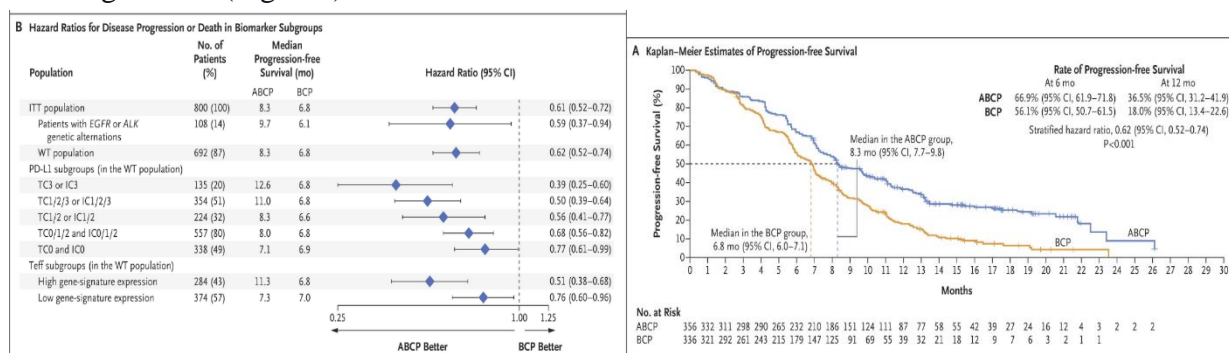


Figure 1. Comparison of ABCP and BCP Progression-free Survival

In secondary analysis, it's found that in ABCP group, patients with EFGR mutations or ALK translocations, patients with low or negative or high PD-L1 expression all had higher PFS rate and longer PFS. Adverse events due to ABCP treatment happened in 94.4% of the patients, while the ones in BCP group happened in 95.4% of the patients. The former ones are usually light as grade 1-2 and included no grade 5 events. The most common grade 3-4 adverse events were neutropenia, decreased neutrophil count, febrile neutropenia, and hypertension. Some adverse events such as rash, stomatitis, febrile neutropenia, and hemoptysis in ABCP group were higher but not up to 10%. The key subgroup analysis also indicated that improved survival of the ABCP treatment group [14]. IMpower150 study demonstrated that regardless of PD-L1 expression and EGFR or ALK genetic alteration status, the ABCP treatment had a better PFS and survival than BCP treatment, which acted as the base of FDA approval. It not only focus on the addition of atezolizumab, but also studied the replacement between monoclonal antibody and their synergy.

5. ES-SCLC

ES-SCLC is an aggressive neuroendocrine tumour, highly malignant, difficult to treat and of poor prognosis [15]. SCLC's 5-year survival rate is less than 5%. Platinum-based chemotherapy with etoposide is a standard regimen for SCLC.

IMpower133(NCT02763579) was based on a phase Ia trial on ES-SCLC demonstrating a tolerable safety profile with no new safety signals for Atezolizumab which also showed encouraging single-agent activity [16] [17]. IMpower133 compared the therapeutic effect of atezolizumab + carboplatin + etoposide (atezolizumab + chemotherapy) to placebo + carboplatin + etoposide (placebo +

chemotherapy) in patients with untreated ES-SCLC regardless of positive or negative PL-L1 expression. The patients were assigned by 1:1 ratio into 2 group to get atezolizumab or placebo with chemotherapy and were subdivided by gender. IMpower133 had two endpoints, the primary one being PFS and secondary ones being ORR and DOR. Administration of TECENTRIQ (atezolizumab) was permitted beyond RECIST-defined disease progression [18].

In all patients, PFS of atezolizumab + chemotherapy group was longer than placebo + chemotherapy group. The death rate of atezolizumab + chemotherapy group was lower. Percentage of all responders and partial response in placebo + chemotherapy group was higher but atezolizumab + chemotherapy group had higher complete response rate. Atezolizumab + chemotherapy group also had higher DOR. IMpower133 provided reliable information about the combination of atezolizumab and traditional first-line chemotherapy.

6. PD-L1 positive unresectable locally advanced or metastatic TNBC

Atezolizumab is used in adult patients with TNBC whose tumor expresses PD-L1 in combination with paclitaxel protein. TNBCs are a heterogeneous disease that lacks expression of the three prognostic and predictive biomarkers: estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor type 2 (HER2) which are routinely used in clinical management [19]. It's an aggressive disease with poor clinical outcome because they do not respond to endocrine agents or targeted agents. Both unresectable locally advanced TNBC and metastatic TNBC are aggressive and expect poor outcomes. And nab-paclitaxel is an albumin-bound paclitaxel, a new generation of docetaxel and is differentiated by its capability to bind to albumin, which could avoid castor oil as the traditional solvent causing allergic reaction. More importantly, glucocorticoid premedication with solvent-based paclitaxel may affect immunotherapy activity, which will have negative influences on the research [20].

IMpassion130 (NCT02425891) included 902 patients with unresectable locally advanced or metastatic TNBC [21]. It was generally based on a phase 1b trial for metastatic TNBCs which provided manageable a safety profile and antitumour responses of the joint administration of Atezolizumab and nab-paclitaxel [15].

In IMPasion130, TNBCCS patients were assigned in a 1:1 ratio to receive intravenous atezolizumab plus NAb-paclitaxel or placebo plus Nab-paclitaxel to explore the effects of the addition of ATEzolizumab. The two primary endpoints were PFS and overall survival and objective response rate and duration (DOR).

Regardless of PD-L1 expression status, a higher percentage of patients in placebo-nab-paclitaxel group ended in progression or death and PFS of atezolizumab-nab-paclitaxel group was also longer. The rate of overall objective response was 56.0%, 10.1% higher than the placebo–nab-paclitaxel group. It's worth noting that this rate was higher in PD-L1-positive population. Median DOR was also higher in Atezolizumab-nab-paclitaxel group. The rate of any grade of treatment-related adverse events is 57.3% in atezolizumab-nab-paclitaxel group. The events of any grade were alopecia, nausea, cough, peripheral neuropathy, neutropenia, pyrexia and hypothyroidism.

To summarize, this trial showed the efficacy of atezolizumab-nab-paclitaxel treatment compared to placebo-nab-paclitaxel especially in PD-L1-positive TNBC patients and demonstrated that the safety characteristic was acceptable, which served as strong evidence for FDA approval.

7. limitation and future development

PD-L1 antibody, including atezolizumab has been proved to have impressive curative effects on many kinds of cancers. Especially when atezolizumab was added into combination with other first-line chemotherapy drugs, sometimes the combination with atezolizumab could result in longer PFS, higher PFS rate, higher ORR, longer DOR than combination without atezolizumab or with other kinds of PD-L1 antibodies, which basically led to first-line usage among larger amounts of patients.

Atezolizumab treatment still have limitations though. Firstly, the antitumour activities of atezolizumab treatment correlated with PD-L1 immunohistochemistry expression. Therefore, an absence of immune cells inside tumour tissues may happen on a considerable population of cancer patients, which negatively effects the of atezolizumab treatment after administration. Secondly, although some of the clinical trials have proved that in some specific kinds of cancers, regardless of PD-L1 expression, atezolizumab treatment show benefits in all subtypes, it is still predictive for atezolizumab benefit. Thirdly, in situations of relapse, PD-L1 antibody can only do limited effects. That is because although PD-L1 antibodies can activate the function of tumour-infiltrating immune cells in a short period of time, they will still decline and resulted in T-cell exhaustion. Patients whose tumors are not completely cleared during the one-time treatment window often do not have a lasting effect, even with continued use of antibodies.

In the future, there're a few ways to solve the problems of atezolizumab and other PD-L1 antibodies treatment. Combination therapies play an important role in this field. For one thing, the combination of chemotherapy and antibody therapy, as the three methods stated above, can enhance the curative effects. For another, tumour vaccine and cell therapy may also help overcome tumor resistance to checkpoint blockade. The vaccines can help immune cells better recognize tumor cells and enter the tumor microenvironment while cell therapy means artificially introducing immune cells into tumour tissue. For instance, targeting necrosis factor superfamily member LIGHT by antibody can increase the chemokines that recruit T cells, and create a T cell-inflamed microenvironment [22].

8. Conclusion

Among the immune checkpoints and their ligands, administration of PD-L antibodies that blocked the interaction of PD-1, PD-L can enhance immune function (such as T-cells responses) and mediates antitumour activity. PD-L1 antibodies such as atezolizumab has been designed to act as promising strategies for specific tumour immunotherapy. The primary problem for atezolizumab and its relevant immunotherapy against tumours is the low response rate in a large number of cases because several factors count: there must be PD-L1 expression in tumour, immune inhibition caused by PD-L1 in tumour tissue, sufficient T cell infiltration in tumor tissues and so on. Also, the possibility of causing T-cell exhaustion also will negate the immunotherapy. In the approvals of three first-line combination treatments of atezolizumab as well as other antitumour drugs, the phase I study made an initial conclusion that atezolizumab is effective in suppressed pre-existing immunity patients. Phase II and III clinical trials about treating specific types of cancers with the combination of atezolizumab as well as other first-line drugs were launched. For three approvals made by FDA, IMpower150, IMpassion130 and IMpower133 provided the most meaningful phase III information on PFS, survival, ORR, DOR, adverse events and so on. Up to know atezolizumab have been applied in metastatic NSq NSCLC, ES-SCLC, and PD-L1 positive unresectable locally advanced or metastatic TNBC. Until now there're still some atezolizumab treatments in stages of phase I or II clinical trials, which possibly presents more atezolizumab combination treatment to meet the unmet medical needs [23]. And except for immunotherapy and chemotherapy, methods to improve the microenvironment where drugs have their effects, such as cell therapy also have potential to join the combination treatment.

IMpassion130 studied the benefits of combination of atezolizumab and nab-paclitaxel in metastatic or unresectable locally advanced TNBCs. Its primary endpoints were PFS & overall survival and secondary endpoints were DOR and ORR. IMpassion130 found that regardless of PD-L1 expression status, atezolizumab-nab-paclitaxel had significantly better curative effects on population enrolled.

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