

Drug discovery of PD-L1 inhibitor Atezolizumab

Xinying Guo ^{1, †}, Xinyi Sheng ^{2, *, †}

¹ The university of Strathclyde, G1 1XQ, UK

² The University of Melbourne, VIC 3010, Australia

* Corresponding author. Email: xinsheng@student.unimelb.edu.au

[†]These authors contributed equally.

Abstract. Immunotherapy, especially immune checkpoint inhibitors have made a tremendous breakthrough in NSCLC management. Over last decades, ICIs targeting the PD-1, PD-L1 and CTLA-4 have exhibited promising antitumor efficacy and durable response including NSCLC patients with advanced or refractory, metastatic disease. We will provide an overview of mechanism of cancer development and how current available ICIs can be employed to improve patients' outcome. This review also summarized the discovery process of atezolizumab which led to final FDA approval for its indication. Our major focus is on the significant survival benefit achieved by atezolizumab and taking into consideration of its advantages and disadvantages when we applied it into clinical setting. We hope to help patients and clinicians to better understand the mechanisms, clinical progress and future research direction of NSCLC atezolizumab in decision making.

Keywords: *Atezolizumab, PD-L1.*

1. Introduction

Cancer immunotherapies include immune checkpoint inhibitors, adoptive cell transfer (ACT) and cancer vaccines. The principle of immunotherapy is to reactive immune cells to recognize and kill tumors. Immune checkpoints express on the surface of lymphocytes to regulate their activation. Immune checkpoints on the T cell surface can be activated to attenuate T cell activation and proliferation. Two known immune checkpoints are CTLA-4 and PD-1, which can be targeted to prevent immune escape of tumors. Tumor cells express PD-L1 on the surface to interact with PD-1 expressed on T cells which can also leads to immune escape. Recent advances in immunotherapy especially antibodies interfered with those immune checkpoints such as PD-1, PD-L1 and CTLA-4 have been widely recognised to prolong survival rate in patients suffered from NSCLC.

Atezolizumab is a fully humanized IgG1 λ monoclonal antibody that binds to PD-L1 to stop PD-1 and PD-L1 interaction. It is discovered through a human phage display library. It not only blocks the binding of PD-1 and PD-L1, but the interaction of PD-L1 and B7-1. Atezolizumab has good efficacy on melanoma and non-small cell lung cancer (NSCLC). FDA approved atezolizumab as first-line treatment for NSCLC on May 18, 2020. The efficacy of atezolizumab is estimated through random trials in stage IV NSCLC patients. And these patients have high expression and infiltration of PD-L1. The result was revealed through overall survival (OS). Patients with atezolizumab have a significant improvement in OS compared to patients with platinum-based chemotherapy. Atezolizumab is also an approved treatment for urothelial carcinoma, triple-negative breast cancer (TNBC) and small cell lung cancer. It is specifically effective to treat tumors that have spread to other parts of body and can't be removed through surgery. Atezolizumab is an injection solution that can be used alone or as adjuvant medicine. The recommended dosage is 840mg every 2 weeks, 1200mg every 3 weeks or 1680mg every 4 weeks. There are phase 3 clinical studies to test the combined effects of Atezolizumab and chemotherapy such as oxaliplatin and leucovorin calcium for stage III clonal cancer. Although it's still in trials, the results are positive.

There are some challenges with ICBs that need to be solved. Firstly, this antitumour effect was not universally demonstrated in the trial by responder and nonresponder. Furthermore, some patients have been found to relapse after the initial treatment with ICBs. All might be attributed to resistance to ICBs based immunotherapies. As a result, it prompts an effective strategy to overcome resistance.

Moreover, cytotoxic T cells does not only attack tumor cells but also normal body cells. Therefore, the side effects of atezolizumab can be serious. 2.5% patients in clinical trials who received atezolizumab as a single agent got immune-mediated pneumonitis. It also causes immune-mediated hepatitis, colitis, endocrinopathies and other immune mediated adverse reaction. Additionally, infection, fever, shortness of breath and abdominal pain are some common symptoms. Therefore, the administration of atezolizumab should be monitored by doctors and the laboratory.

This review introduced atezolizumab and discussed the challenges with regards of its clinical application. The resistance to ICB based immunotherapy could also be observed in atezolizumab. This review explained immunotherapy resistance and current solution for it with major focus on atezolizumab. Certainly, a better understanding of the functional mechanism associated with atezolizumab, their limitation and current trend for combinational therapy would assist patients and doctors to make informed decision.

2. The mechanism of tumor progression

Cancer progression has been described in three sequential phases: elimination, equilibrium and escape [1]. In the elimination phase, the innate and adaptive immunity function properly to eradicate the growing tumor and its destruction is mainly performed by specific activated CD8⁺ effector T cells. The initial activation of naïve T lymphocyte takes place in secondary lymphoid organs, following tumor associated antigen presentation through the MHC on APC's surface and its recognition by TCR. Although this response is highly specific, tumor cells have constantly evolved to escape immune detection through immune editing. T cell activation is controlled by the interplay of stimulatory and inhibitory molecules. Interaction between CD28 on T cell with B7-1 and B7-2 on APC activates downstream mitogenic PI3K/Akt and Ras/MARK pathway, ultimately results in differentiation of naïve T cells into effector T cells (figure 1). In contrast, PD-1 is a 55kDa inhibitory monomeric transmembrane receptor, structurally related to CD28, usually appeared on the surface of activated T cells and many other tumors infiltrating lymphocytes (TILs), PD-1 contains an IgV domain in the extracellular, one ITIM and one ITSM in the cytoplasmic tail. ITSM is the major structure for the inhibitory pathway of T cells. PD-L1 contain IgG and IgV domains and binds to PD-1 through IgV domain. The ligation of PD-1 with its ligand PD-L1 triggers various pathways including SHP2, PI3K-Akt, Ras-MEK-ERK, leading to TCR signaling reduction (figure 2) hence secure normal tissue from excessive harmful inflammation and maintains immune tolerance to self-antigen under normal physiology. However, in the escape phase, tumors highly over-express PD-L1 to protect themselves from cytotoxic T cell mediated programmed cell death.

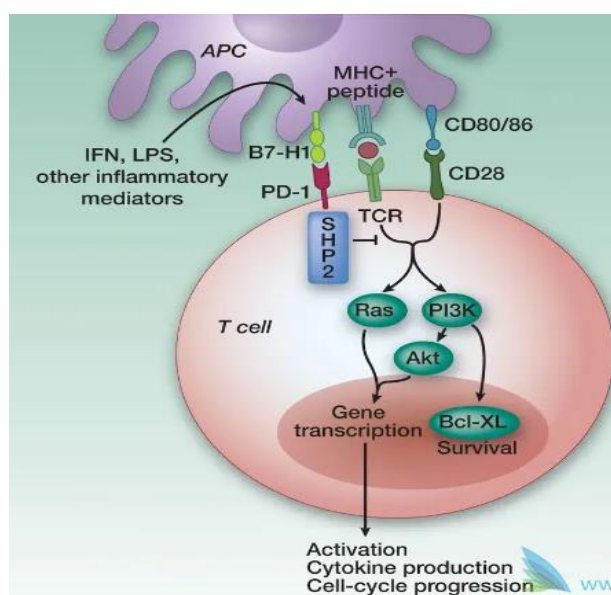


Figure 1. T cell activation [1].

3. PD-L1/PD-L2

Both PD-L1 and PD-L2 are able to bind to PD-1[1]. PD-1 and PD-L2 both express APC, DC, and other non-lymphoid cells. PD-L1 was discovered by Dong in 1999 and it belongs to the B7 family called B7-H1. Its expression is found to be highly induced in plenty of cancer cells including NSCLC. In oncogenic pathways, PTEN-PI3K and MAPK pathway take part in its expression on the cell surface post-transcriptionally while its transcriptional synthesis is regulated by IFN- γ and type 1 interferon. PD-L1 does not bind to CD-28, CTLA-4 or inducible co-stimulator, instead, it engages with inhibitory receptor PD-1 to down-regulate effector T cell function [2]. In addition, it also interacts with B7-1 to further suppress T cell mediated immunity.

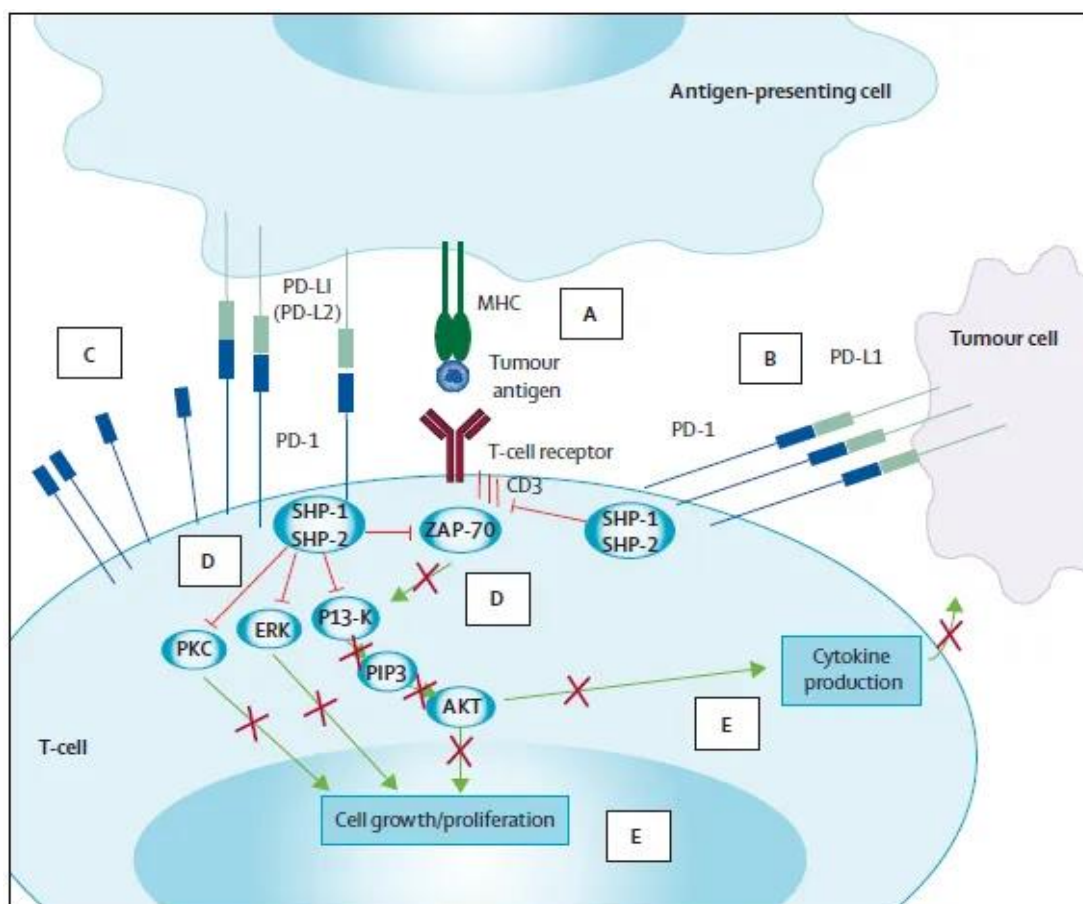


Figure 2. The ligation of PD-1 with its ligand PD-L1 triggers pathways.

PD-L2 (B7-DC) was first identified in 2001 with limited distribution among macrophages [1], dendritic cells and mast cells [1]. In normal situation, its basal expression is expected to be low, however its level would be raised upon various micro-environmental stimuli especially sensitive to Th2 cytokines. But the lack of 14 amino acids in PD-L2 is the main difference from PD-L1. PD-L2 has exerted its fundamental role in moderating severity of a hypersensitive condition caused by Th2, observed in an experimental asthma model. Currently, little information has been gathered about its immunosuppressive characteristics.

4. Anti-PD-1 antibodies/anti-PD-L1 antibodies

As demonstrated by figure 2, when PD-1 binds to its PD-L1 ligand, ITIM and ITSM are phosphorylated and Src homologous region 2 domain-containing phosphatase 2 SHP2 get instruction to dephosphorylate phosphatidylinositol 3-kinase (PI3k) and eventually it transmits inhibitory signals to motivation of T cells. Monoclonal antibodies called immune checkpoint inhibitors, targeting PD-1 and PD-L1 are practical way to restore effector T cell performance by disrupting the binding of PD-

L1 towards PD-1 as show by figure 3 [1]. Many preclinical and clinical trial has proved their ability to shrink tumors size and suppress tumors metastasis with limited toxicity.

Currently it is still not clear whether the PD-1 or PD-L1 inhibitors are more effective due to the fact that their function depends on patients' characteristics. Anti-PD-1 antibodies prevent both PD-L1 and PD-L2 from binding to PD-1 carried T cells it may be preferred for tumor that carries both ligands, However, in lung with high expression of PD-L2, direct PD-1 blockade has potential to raise the risk of inflammatory response compared to PD-L1 inhibitors. On the other hand, PD-1 might heighten the function of immunosuppressive regulatory T cell thereby argument Treg-mediated immunosuppression. Conversely, engagement of PD-L1 with B7-1 is able to render T cell inactive, for this reason, theoretically targeting PD-L1 may add anti-tumor response through inhibition of this pathway.

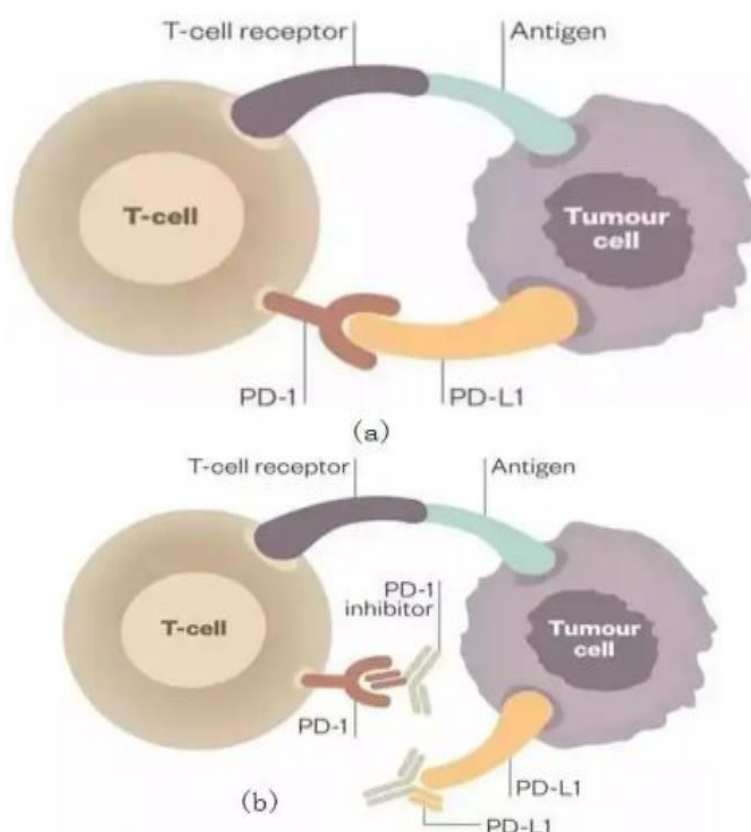


Figure 3. T cell performance by disrupting the binding of PD-L1 towards PD-1.

Pembrolizumab in October 2015 receive APF approval for recurrent metastatic NSCLCs patients with tumor cell expression of PD-L1 greater than or equal 1%. Shortly, nivolumab are indicated for the recurrent or advanced squamous and non-squamous NSCLC during or after platinum-based chemotherapy without PD-L1 expression restraint.

5. Atezolizumab – PD-L1 inhibitor

Generally, some monoclonal antibody medicines that target at PD-L1 are approved for various cancers treatment by FDA. For example, Atezolizumab (Tecentriq), Avelumab (Bavencio) and Durvalumab (Imfinzi) have been applied in patients. Avelumab is a fully humanized IgG1 λ antibody and the first FDA approved drug for metastatic Merkel cell carcinoma. Avelumab is also treatment for urothelial carcinoma and renal cell carcinoma [2]. The suitable dosage is 10mg/kg as intravenous infusion every two weeks. The common side effects are diarrhea, nausea, rash, and pain. Immune-mediated events happened in 10.3% of 1738 Merkel patients with Avelumab [3]. Immune checkpoint inhibitors have chances to induce immune mediated diseases. Durvalumab, a human immunoglobulin G1 κ , is approved first-line drug for advanced NSCLC that spreads to other parts of body and is unable

to remove. It is also combined with other therapies to treat extensive-stage small cell lung cancer and various types of bladder cancers [4]. 709 NSCLC patients divided into durvalumab group and placebo group in random to test the efficacy of durvalumab. The results show a higher response rate and longer median duration with durvalumab than placebo. And 15.4% patients have grade 3 or grade 4 adverse event. Cough, inflammation in lung, infection and shortness of breath are common side effects for NSCLC patients with durvalumab [5]. Nausea, hair loss and weakness are side effects for SCLC patients with Durvalumab.

Another PD-L1 inhibitor is atezolizumab, a high-affinity humanized IgG1 κ monoclonal antibody, which contains an engineered Fc domain [6]. It is separated from human phage display by targeting extracellular Fc domain of PD-L1 [7]. To prove the binding of atezolizumab and PD-L1 is fatal to PD-L1 overexpression cells, researchers substituted one amino acid at position 298 from Asn to Ala [7]. The substitution damaged the binding of atezolizumab to Fc receptor of PD-L1[7]. Engineered atezolizumab is unable to mediate antibody-induced cellular cytotoxicity in cell lines that transfected with PD-L1 [7].

To test preclinical pharmacokinetics and pharmacodynamics of atezolizumab, researchers used BALB/c mice and cynomolgus monkeys [8]. The binding residue of atezolizumab is engineered to murine Fc domain to generate an antibody that targets at murine PD-L1, called PRO304397. It minimized the immunogenicity in preclinical animal experiments. Atezolizumab and PRO304397 have similar binding affinity to human and murine PD-L1. Atezolizumab has commensurate affinity to human and monkey PD-L1. Administrate 1, 10 and 30 mg/kg PRO304397 to BALB/c mice through intravenous, and administrate 0.5, 5, 20 mg/kg atezolizumab to cynomolgus monkeys through intravenous. Then test serum concentration and saturation of PD-L1 on CD8⁺ and CD4⁺ T cells. The results show that complete saturation of PD-L1 attains at serum concentration above 0.5 μ g/ml [8]. Moreover, the non-linear PK reveals anti-therapeutic antibodies and target mediated drug disposition might present. Therefore, the efficacious dose might be higher than estimated value. The preclinical trial provides significant figures for clinical dosage and optimizes the development of atezolizumab.

Atezolizumab is approved by FDA for NSCLC and urothelial carcinoma treatment. In the treatment of NSCLC, atezolizumab is approved to be used after platinum chemotherapy in 2016 [9]. The approval depended on two international, open-label, and randomized clinical trials, POPLAR and OAK [10]. In these two trials, atezolizumab increased the survival rate compared to docetaxel. Furthermore, EGFR⁺ patients and anaplastic lymphoma kinase tumor patients are allowed to treat with atezolizumab [9]. Recently, FDA approved atezolizumab as first-line treatment for NSCLC. This relies on an international, open-label and randomized trial with stage IV NSCLC patients that overexpress PD-L1. The trial illustrates a better overall survival for atezolizumab treatment than platinum-containing chemotherapy. The most common side effect is weakness in this clinical trial. In the treatment of NSCLC, the recommended dosage of atezolizumab is 840mg/2 weeks, 1200mg/3 weeks, or 1680mg/4 weeks though intravenous administration over 60 minutes. In the treatment of urothelial carcinoma, atezolizumab is also approved to be applied in advanced or metastatic urothelial carcinoma treatment. It is based on a multi-center and single-arm trial that shows a good activity of atezolizumab in inhibiting immune checkpoint. With increasing expression of PD-L1, the response is stronger [11]. Although it has significant improvement in overall survival, the adverse effects are serious. The most common adverse effect is pneumonia [12].

Atezolizumab also has good effects as a combination drug in various cancer. Atezolizumab with bevacizumab combination stimulates antigen-specific T cells traffic into metastatic renal cell carcinoma [13]. Other clinical trials present the significant effect of atezolizumab in combination with bevacizumab, carboplatin, and paclitaxel (BCP) to treat NSCLC. Atezolizumab with BCP therapy has been approved in the EU, USA, and Japan [14]. The atezolizumab combination therapy presents clinical benefits, but it's not cost effective [15]. Moreover, Atezolizumab in combination with nab-paclitaxel significantly improved progression-free survival of triple negative breast cancer (TNBC) patients in a phase III clinical trial [16]. Although the overall survival of this combination is awaited, it is still an effective choice for advanced TNBC patients [16]. Another study evaluates the potential

effect of triplet combination therapy with ipatasertib (IPAT), atezolizumab and paclitaxel as first-line treatment for TNBC [17]. And the result of triplet regimen trial shows positive anti-tumor activity, but further investigation is required [17]. The combination of atezolizumab and cabozantinib is in phase 1b clinical trials for urothelial carcinoma patients that previously received platinum-based chemotherapy [18]. Data illustrates an inspiring clinical benefits and acceptable safety in advanced urothelial carcinoma [18].

6. Challenge

Despite the use of atezolizumab having achieved desirable outcomes in NSCLCs, resistance has been observed in atezolizumab treated patients which could interfere with its efficacy in prolonging survival benefit. There are three type of resistance based on the assessed clinical presentation: long-term responders whose response last until now, primary resistance (no response from start) and secondary resistance (initial response but loss disease control over long period). Development of resistance might be attributed to impairment of immune system with effector T cells mainly account for anti-tumor response.

Firstly, common cold tumors are scare of T lymphocyte nor inflammatory signal. Its presence thought to participate in primary resistance against atezolizumab. The absence of specific T lymphocytes in the tumor microenvironment (TME) or lack of TCR molecules for neoantigens from disturbance antigen presentation, ultimately will lead to failure of immune response. In another circumstances, T cell has received activation signaling from antigen presenting, cells, after leaving the node, unfavorable tumor microenvironment would prevent infiltration of activated T cell into tumor eventually. For example, IDO released by tumor has ability to eliminate T lymphocyte from the tumor area. Hence it is hypothesized that addition of IDO inhibitors to atezolizumab may overcome ICIs resistance. Another example from the compression of vasculature system in TME caused by VEGF mediated fibrosis formation and over-abundant cancer cells compresses lead to decreased immune cell delivery to the targeted tumor.

Compared to cold tumors, hot tumors with infiltration of immune cells particularly T lymphocytes are usually associated with better survival rate from immune checkpoint inhibitor. Although current available immunotherapy are designed to mount effector T cells' immunity against cancer, in some case, acquired or adaptive resistance still appeared in hot tumors. It is because other immune cells are also involved in immunity against tumor cells, it should be noted that myeloid cells including MDSCs and tumor-associated macrophages substantially influence treatment outcome in a negative direction while dendritic cells and anti-tumor form of TAMs play a key role in enabling cytotoxic T lymphocyte to execute tumor killing.

Myeloid-derived suppressor cells displaying strong protumoral potency, will transform into activated form upon stimulation by cytokines and growth factors within TME. In addition to its direct contact with effector T cells, the hypoxia and acidic TME in cooperation with myeloid cells are capable of recruiting immunosuppressive regulatory T cells and restraining proliferation and stimulation of cytotoxic T cell. Moreover, TAMs attach to tumors by macrophage chemoattractants or by CSF-1 and drive tumor progression through exhibiting a immunosuppressive M2 phenotype. Most importantly It is discovered that Infiltration, phenotypic, functional differentiation and survival of myeloid cells are modulated by Colony-stimulating factor-1 (CSF-1). CSF-1/R antibody has been able to sensitize tumor to ICBs, as shown by some preclinical studies through lowering penetration of immunosuppressive myeloid cells and shifting myeloid cells to immunostimulatory state.

High infiltration of regulatory T cells responsible for poor survival across various cancer type. Tregs are specialized double positive CD4 and CTLA-4 cells, which is applied in maintaining balance between immune homeostasis and self-tolerance. In tumor cells, they are required for tumor growth through inhibition of interaction between APCs and cytotoxic T cells. CTLA-4 blockage originally managed to reactivate cytotoxic T cells and it is recently realized its survival benefit mainly comes from the concomitant inhibition of CTLA_4-expressing Tregs. Thus, Tregs emerged as a potential

target in cancer treatment. One limitation in terms of elimination of systemic Tregs is inflammatory adverse effects as it is necessary for curtailing overactive cytotoxic T cell response in the face of atezolizumab.

VEGF signaling attract more attention in exploring practical treatment against NSCLCs., as described above, hypoxia condition created by VEGF assist with the upregulation of immune checkpoint and traveling of immunosuppressive regulatory T cells and MDSCs and pro tumor TAMs into the tumor while restraining dendritic cells and anti-tumor TAMs and cytotoxic T cells. A phase III clinical trial was conducted in patients with metastatic non-squamous NSCLCs and it provided evidence for the efficacy of combination of atezolizumab with anti-angiotensin agent bevacizumab in prolonging survival and reflected VEGF pathway's relationship with immunotherapy resistance including atezolizumab.

7. Conclusion

Immune checkpoint inhibitors are hot in immunotherapies. The blockade of PD-1 and PD-L1 triggers multiple signal pathway and enhances immune cells activity to kill tumor cells. Atezolizumab as a PD-L1 inhibitor is approved by FDA as first line or second line treatment for various metastatic cancers. The good clinical data of overall survival is the basis of approval. Some international, open label randomized clinical trials of NSCLC, urothelial carcinoma and TNBC illustrate an inspiring clinical activity of atezolizumab. It also functions as adjuvant drug with platinum-containing chemotherapy or other monoclonal antibodies to fight against tumor.

Plenty of clinical and preclinical trials have revealed that abnormal TME can compromise the efficacy of immunotherapy across different types of cancers. This problem also observed in the use of atezolizumab. There is an emerging filed for the application of combination therapy in NSCLCs to strengthen immunotherapy including atezolizumab. Different combination strategies could achieve this goal through promotion of cytotoxic T lymphocyte infiltration and functional normalization, enhancement of APCs recruitment and proliferation and conversely depletion of Tregs and MDSCs regarding their presence and function. However, combination therapies such must be carefully chosen in a context-dependent manner to avoid alternative resistance mechanism. Hence dosing, timing and sequence of drug administration and the host-organ response must be considered when clinician attempt to generate a treatment plan. For example, VEGF blockage would normalize vascular system and it enable clinicians to reduce dose of atezolizumab from enhanced drug delivery to avoid adverse effect.

Secondly, Immunotherapy has been effective in NSCLC treatment, but the response rate remains suboptimal. PD-L1 expression in both TCs and ICs has been approved by FDA as a biomarker for initiation of ICIs, however, it was identified that some highly PD-L1 carriers failed to respond to ICIs whereas some patients without PD-L1 expression have demonstrated reasonable benefit toward ICIs, it was supposed the same issue would happen to atezolizumab treated population, It calls for the need of a predictive biomarker for immunotherapy resistance in treatment selection and therapeutic option maximization.

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