The application of PD-L1 Inhibitors Atezolizumab in three different cancer treatment

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Abstract: Currently, checkpoint inhibitors, which function by triggering patients' own T cells to combat tumor, are revolutionizing treatment for various types of cancer. Atezolizumab, a monoclonal antibody targeting PD-L1 proteins, has shown a much lower mortality rate and a significantly longer survival rate, resulting in its being approved as a reliable treatment for TNBC, NSCLC, and bladder cancer, etc. However, there still exists immune-related adverse events that may affect patients' recovery in different ways and ought to be carefully assessed. This review mainly focused on analyzing the efficacy of atezolizumab in different stages for the treatment of TNBC, NSCLC, and bladder cancer.

1. Introduction

Programmed Cell Death protein 1, also known as PD-1 or Cluster of Differentiation 279, is a surface receptor. The ligand PD-L1 is mainly expressed in CD4+, CD8+ T cells, B cells, natural killer cells and other immune cells, while the ligand PD-L1 is mainly expressed in tumor cells. Its main function is to inhibit the immune response of the body, down-regulate the immune system and promote tolerance by inhibiting the inflammatory activity of T cells. When PD-1 binds to its ligand, PD-L1, it prevents T cells from killing other cells, including cancer cells, because cancer cells develop mechanisms for the PD-L1 ligand to grow on the surface of cancer cells. If immune cells bind to PD-L1, cancer cells can escape the immune system. Therefore, the development of anti-PD-1 inhibitors can prevent T or B cells from being inactivated by cancer cells.

PD-1/PD-L1 pathway is demonstrated as a major cause for cancer immune escape and a vital mechanism of immune evasion in tumor site, which is an important hallmark of cancer, and its blockage therapy also exerts tremendous influence in clinical trials for cancer immunotherapy.

Atezolizumab is a monoclonal antibody that targets the PD-L1 protein. Atezolizumab binds to PD-L1 expressed on tumor cells and tumor infiltrating immune cells, blocking its interaction with B7.1 and PD-L1 receptors. By inhibiting PD-L1, T cells can be activated to destroy normal cells. Tecentriq, also known as T-drug, was the first approved PD-L1 inhibitor to be approved by the FDA for metastatic / recurrent urinary tract cancer. Up to now, atezolizumab has also been approved for the treatment of different indications of lung cancer and breast cancer, and is also being tested in some other kinds of cancer.

This article presented the using of atezolizumab in the treatment of TNBC (Triple Negative Breast Cancer), Non-small Cell Lung Cancer (NSCLC) and Bladder Cancer.

2. Triple negative breast cancer

2.1 Introduction of TNBC and current trials

Breast cancer is a breast cells' cancer, especially the malignant cancer of epithelial cells. There are four main types of breast cancers and TNBC refers to the subtypes of breast cancer that do not have the expression of progesterone receptors (PRs), human epidermal growth factor receptor-2 (HER-2), and estrogen receptors (ERs)[5]. It accounts for 10% to 10.8% of all breast cancer pathology types. There are about one million new cases of breast cancer around the world every year, and more than 170000 of them are TNBC. Young women are at higher risk of developing TNBC, which has an average age of 50 years old, compared with 60 years old for other kinds of breast cancer.

The grading of TNBC is high, the tumor is invasive and the edge is vulnerable to attack. TNBC is mostly associated with lymphocyte invasion and central fibrosis, while central fibrosis and small part of lymphocyte invasion lead to its easily distant metastasis. The prognosis of TNBC is extremely poor, with a five-year survival rate which is less than 15%. It recurs easily and the peak of death is within 5 years after diagnosis. Patients have a high incidence of brain metastasis, which can lead to death due to the rapid distant metastasis. Compared with patients with other cancers, DFS in TNBC patients was associated with tumor size (2 cm or <2 cm, p.02), lymph node status (positive or negative, p.0.0001) and menstrual status (postmenopausal or premenopausal, p.0.001).

The lack of antigens for common breast cancer led TNBC to be unresponsive to endrocrine therapy and targeted treatment for HER-2. As a result, the routine treatment for TNBC is chemotherapy, and although TNBC is sensitive to chemotherapy, it has a limited response and a very poor prognosis. It was clear that TNBC urgently needed new treatments. The FDA accelerated approval of atezolizumab combined with nab-paclitaxal for first-line treatment of PD-L1+ TNBC and metastasis TNBC.

2.2 IMpassion130 (NCT02425891)

The study was a randomized, double-blind, placebo-controlled international multicenter phase III study (NCT02425891). The enrolled 902 untreated metastatic TNBC patients were given nab-paclitaxal (100 mg/m2, per week, one week suspended every three weeks) and atezolizumab (840 mg, every two weeks) (experimental group, n=451 cases) as randomized assignment at 1:1 or placebo (control group, n=451) until the disease develops or the toxicity is not tolerate. The stratification was based on whether received paclitaxel new adjuvant therapy or adjuvant treatment, whether or not liver metastasis at enrollment, and the positive or negative expression of PD-L1. The main study points were PFS (ITT population and PD-L1 positive subgroups) and OS (ITT population; PD-$L1^+$ subgroup if significant).

The first reported PFS in the experimental and control groups were 7.2 and 5.5 months (HR 0.8), respectively, whereas in the PD-$L1^+$ patient population the difference of PFS between experimental and control group was more pronounced. Although the OS data are immature currently, it has shown a trend towards greater OS differences consistent with previous immunotherapy. In the ITT population, the OS of control group and experimental group are 17.6 and 21.3 months separately, and have more significant difference in PD-L1+ populations. The study updated the results of further follow-up of OS, and the maturity of the data was further improved, at the ASCO in 2019. The second interim analysis of OS data showed that no significant statistical differences were observed in the population, but in PD-L1+ patients, the Atezolizumab + nab-paclitaxel group compared the placebo + nab-paclitaxel group with median OS of 25 and 18 months respectively and 7 months of significant improvement [1, 2].

IMpassion130 studies show that the Atezolizumab + nab-paclitaxel group is tolerated and has a clinical benefit against the placebo group for the treatment of TNBC without compromising health-related quality of life (HRQoL), physical and social function [3]. Moreover, the consistent results of the two interim analyses confirmed a clinically meaningful OS benefit of Atezolizumab + nab-paclitaxel in untreated patients with PD-L1+ metastatic TNBC.

2.3 IMpassion031（NCT03197935）

IMpassion031 was a randomized, double-blind, placebo-controlled international multicenter phase III study, evaluated the safety and efficacy of atezolizumab in combination with chemotherapy for nab-paclitaxel, followed by using doxorubicin and cyclophosphamide) compared with placebo in

combination with chemotherapy. The study enrolled 333 stage II-III untreated TNBC patients (age≥18, tumor>2 cm), 1:1 randomized to two group. The experimental group received 12-week Atezolizumab (840mg, IV, q2w) with Nab-P (125mg / m2, IV, qw) and sequential 8-week Atezolizumab (840mg, IV, q2w) with polirubicin (60mg/m2,IV,q2w) + cyclophosphamide (600mg/m2,IV,q2w), and the control group received a 12-week placebo combined with Nab-P (125mg / m2, IV, qw), with a sequential 8-week placebo combined with Dororubicin (60mg/m2,IV,q2w) + cyclophosphamide (600mg/m2,IV,q2w). All patients were subsequently operated on and their complete pathological remission was assessed, stratified by the clinical stage of breast cancer and PD-L1 expression of tumor-infiltrating immune cells. The original study endpoint was the ITT or the pCR rate in PD-L1+ patients (IC≥ 1%), and the secondary study endpoint included OS, EFS, DFS and quality of life indicators. The median follow-up time between the experimental and control groups was respectively 20.6 and 19.8 months, and the PCR rate increased by 16.5% (57.6% VS 41.1%, P=0.0044) and 19.5% (68.8% VS 49.3%, P= 0.021) in PD-L1+ patients.

IMpassion031 studies showed that Atezolizumab increased pCR rate in TNBC patients significantly, independent of PD-L1 expression and well safe. Neoadjuvant therapy with Atezolizumab + chemotherapy provides a clinically meaningful pCR benefit in patients with stage II-III TNBC.
In addition to these two studies already approved, there are many finished or ongoing studies related to TNBC and atezolizumab (Ttable1).

In conclusion, compared with chemotherapy alone, atezolizumab combined with neoadjuvant chemotherapy significantly improves OS, PCR rate, PFS et al. in patients with early TNBC. It also got good safety, and the patient has a good prognosis. The treatment has been approved for clinical application now. Many progress is evident in other ongoing studies on atezolizumab, which suggests that atezolizumab has good promise in the treatment of TNBC.

Table 1. A summary table of related studies.

Early stages	
IMpassion031(NCT03197935)	Atezolizumab+ T-AC neoadjuvant chemotherapy vs neoadjuvant chemotherapy, phase III study
IMpassion030(NCT03498716)	Atezolizumab + T-AC neoadjuvant chemotherapy vs neoadjuvant chemotherapy, phase III study
NSABP B-59(NCT03281954)	Atezolizumab +TCb-AC neoadjuvant chemotherapy vs neoadjuvant chemotherapy, phase III study
Advanced stages	
IMpassion130(NCT02425891)	Atezolizumab +Nab-paclitaxel vs Nab-paclitaxel Phase III study of the first-line treatment of advanced TNBC
IMpassion131(NCT03125902)	Atezolizumab +paclitaxel vs paclitaxel Phase III study of the first-line treatment of advanced TNBC
IMpassion132(NCT03371017)	Atezolizumab + chemotherapy (Gemcitabine(GCB)+ Carboplatin (CBP)or capecitabine (GEM)) vs chemotherapy Clinical study of recurrent TNBC within 1 year of first-line adjuvant therapy

3. Non-small Cell Lung Cancer

3.1 Overview of NSCLC

Lung cancer is of great concern because of its high mortality rate and poor prognosis, and is usually diagnosed as advanced. Current chemotherapy for non-small cell lung cancer (NSCLC), which accounts for nearly 85% of all types, has shown limited benefit in lung cancer treatment. Recent advances in cancer immunotherapy, especially antibody blocking of the PD-1/PD-L1 pathway, are considered to be an effective treatment for non-small cell lung cancer.

3.2 Clinical Trials of Atezolizumab in NSCLC

Immunotherapeutic efficacy of the atezolizumab monotherapy was accessed in phase II FIR and Birch trials, and phase II and phase III studies compared with docetaxel as well, with much fewer adverse events (AEs) than traditional chemotherapy.

3.3 FIR (NCT01846416) and BIRCH (NCT02031458)

Both the Phase II FIR study and the Phase II BIRCH study evaluated PD-L1 selected NSCLC patients receiving atezolizumab monotherapy at a fixed dose. The primary endpoint of FIR and BIRCH, the objective response rate (ORR) assessed by the investigator, was obtained at this stage according to imprecise. The original data expiration date for the FIR study was January 7, 2015, and the original data expiration date for BIRCH was May 28, 2015.Patients with NSCLC were included in three cohorts. Progression-free survival (PFS) was a secondary endpoint of FIR and BIRCH. The 6-month PFS rates of FIR were 39%, 35% and N/A, respectively, while BIRCH's median PFS were 7.3, 2.8 and 3.0 months [6].In phase II FIR and BIRCH studies, the most common treatment-related AEs were nausea, fatigue, and loss of appetite, which occurred in approximately 67% of patients. Together, phase II FIR and BIRCH's clinical data demonstrate that, while their AEs cannot be ignored, they may improve patient survival.

3.4 POPLAR (NCT01903993) and OAK (NCT02008227)

Both the randomized Phase II POPLAR and Phase III OAK trials evaluated atezolizumab monotherapy versus docetaxel. PD-L1 untreated NSCLC patients aged 20 years were enrolled in both phases to receive 1000 mg atezolizumab every 2 weeks, excluding previously treated docetaxel patients. The main finish in POPLAR and OAK was OS, a significant improvement on Docetaxel's OS. In Phase II POPLAR, atezolizumab had a median OS of 12 months compared to 9 months for Docetaxel. In Stage III, atezolizumab had a median OS of 13 months, also significantly higher than docetaxel's 9 months. The clinical data demonstrate that Atezolizumab may significantly improve median OS compared to docetaxel, providing possible consideration for further anti-PD-L1 immunotherapy studies. The secondary endpoint for POPLAR and OAK was PFS, but there was no significant difference between Atezolizumab and Docetaxel. In POPLAR, the median progression-free survival was 3 months in the Atezolizumab group and 3 months in the docetaxel group, while the median progression-free survival was 3 months in the OAK group and 4 months in the Docetaxel [6] group. In addition, atezolizumab showed no significant difference in ORR between Docetaxel and POPLAR [7] in both POPLAR and OAK Phase II trials. Therefore, these data demonstrate that atezolizumab and Docetaxel are not significantly different in terms of median PFS and ORR.

Table 2. Phase II and III trials with Atezolizumab in NSCLC.

Trial	Phase	Line of Therapy	Treatment	Primary Endpoint	Primary Endpoint Data	Secondary Endpoints
FIR	II	First/ second or further/second or further with brain metastases	Atezolizumab monotherapy	ORR	First line: 29% Second or further line: 17% Second or further line with brain metastases: 17%	6-month PFS rate: 39%, 35%, N/A
BIRCH	II	First/ second/ further	Atezolizumab monotherapy	ORR	First line: 24% Second line: 19% Third or further line: 19%	Median PFS: 7.3, 2.8, 3.0 months
POPLAR	II	Second or further	Atezolizumab vs. Docetaxel	Median OS	Atezolizumab: 12.6 months Docetaxel: 9.7 months	Median PFS: 2.7 vs. 3.4 months for atezolizumab vs. docetaxel ORR: 15.3% vs. 14.7%
OAK	III	Second or further	Atezolizumab vs. Docetaxel	Median OS	Atezolizumab: 13.8 months Docetaxel: 9.6 months	Median PFS: 2.8 vs. 4.0 months for atezolizumab vs. docetaxel ORR: 14% vs. 13%

4. Atezolizumab in Bladder cancer treatment

4.1 Introduction of bladder cancer and its second-line treatment- atezolizumab

Bladder cancer is the ninth most common cancer worldwide and the fifth most common cancer in developed countries. Approximately 20% of patients are diagnosed with muscular invasive disease at the time of initial presentation, which will require multiple treatment modalities due to the high rate of disease recurrence, progression and disease-specific mortality [8].In addition, about 30% of patients had muscle invasive disease, suggesting a poor prognosis due to its potential metastasis [9].Traditionally, first-line therapy for metastatic urothelial carcinoma (mUC) has remained cisplatin based combination therapy for the past several decades [9]. Other treatment options include radiotherapy and radical cystectomy for clinically localized disease, and systemic chemotherapy for patients with metastatic disease [8]. Atezolizumab, an anti-PD-L1 immune checkpoint inhibitor (ICI), has been approved by the FDA as a new immunotherapy for second-line treatment of bladder cancer due to intravesical resistance to BCG treatment in some patients [10]. The therapeutic perspective of Atezolizumab as a second-line treatment and in combination with chemotherapy is phosphorus.

4.2 Atezolizumab used as second-line treatment for bladder cancer following with platinum-based chemotherapy

Patients with metastatic urothelial carcinoma have limited treatment options after resistance or failure of platinum-based chemotherapy [11]. The observation of higher neoantigen load, antigen-binding affinity, and select T effector signature has been identified as biomarkers to predict whether

patients can evoke a durable response towards immune checkpoint inhibitor therapy [11]. Based on these rationales, using Atezolizumab as a second-line treatment of bladder cancer becomes promising for clinical investigation.

Atezolizumab in patients with locally advanced or metastatic or urothelial bladder cancer was initially approved based on the Phase II, single-arm IMvigor210 clinical trial [12]. The first experiment is part of another study and included treatment-naive, cisplatin ineligible patients. A larger sample was obtained in the second group of patients who received Atezolizumab during and after a previous platinum-based chemotherapy regimen. In both coves, patients were given 1200mg doses every three weeks and continued until disease progression, loss of clinical benefit, or uncontrolled toxicity. Compared with the overall response rate of 10% in the primary analysis versus the previous historical control, there was a significant improvement in the racist V1.1 objective response rate of 15% in all patients, the most robust response in the IC2/3 group [4]. Median overall survival was 11.4 months for the IC2/3 group, 8 months for the IC2/3 group, and 7-9 months for the entire cohort. The most common adverse events occurring at any level of treatment were fatigue, followed by nausea, decreased appetite, pruritus, fever, diarrhea, rash, and joint pain. In addition, the incidence of immune-mediated adverse events at any level was 7%. Treatment-related adverse events occurred in 16% of grade 3/4 patients, and all-cause immune-mediated adverse events occurred in 5%.No immune-mediated nephrotoxicity was observed.

Preliminary results from the Phase III IMvigor010 trial do not show that adjuvant atezolizumab improves disease-free survival compared to observations [13], but it provides additional data to support atezolizumab as an adjuvant therapy for uroepithelial carcinoma. The trial included over 900 patients with metastatic urothelial carcinoma who had not previously received platinum-based chemotherapy and were randomized to atezolizumab or chemotherapy (vflunine, paclitaxel, or docetaxel). Despite of no difference in ORR, atezolizumab's median response lasted about twice as long compared to chemotherapy. In addition, atezolizumab was shown to have a higher response rate in patients with increased PD-L1 expression, suggesting that PD-L1 expression level can be used as a biomarker to determine the efficacy of response rate in patients. Atezolizum was restricted for use in first-line patients with high PD-L1 expression who were not eligible for cisplatin. In the ABACUS Phase II trial, over 90 MIBC patients were enrolled, and baseline biomarker analysis showed that the presence of existing activated T cells was associated with prognosis, but tumor mutation load did not predict prognosis [14].

Atezolizumab has not been widely used as a first-line treatment for metastatic urothelial carcinoma due to its relative cost-effectiveness in combination with chemotherapy. Cost-benefit analysis helps determine drug prices and reflects the efficiency and benefits of drugs for patients and the healthcare system. Atezolizumab in combination with platinum-based chemotherapy as first-line treatment is not cost-effective for mUC patients. Although atezolizumab prolongs PFS and does not increase the incidence of AEs, it is not considered the best first-line treatment option for patients with mUC. Lowering the price is most likely to improve the cost-effectiveness of Atezolizumab in patients with mUC [15].

In conclusion, Atezolizumab induces a durable antitumor response as second-line or adjunctive therapy for advanced urothelial carcinoma that progresses during or after platinum-based chemotherapy. Low incidence of clinically relevant treatment-related adverse events makes Atezolizumab widely applicable that often have multiple comorbidities and/or renal impairment.

Table 3. Selected clinical trials using atezolizumab in treating.

Trial	Regimen	Outcome(s)
IMvigor130	Gemcitabine/ Platinum+ Atezolizumab	Improvement in PFS 8.2 vs 6.3 months HR 0.82; p=0.007 OS 16 vs 13.4 months
IMvigor210	Cisplatin+ Atezolizumab	Median follow-up time 14.4 months mPFS 2.1 mos ORR 23.5% (16.2-32.2)

		Complete response 6.7% Partial response 16.8%
ABACUS	Atezolizumab	1-Year RFS 79% cpRR 37%, 95% IC:21-55% pCR 31%
IMvigor211	Platinum-based chemotherapy+ Atezolizumab	HR 0.87, 95% CI 0.63-1.21 AEs 20%

4.3 Atezolizumab used as combined therapy in treating bladder cancer

Bacillus Calmette - Guérin (BCG) was first used as immunotherapy for bladder cancer in 1976 with nine patients with superficial bladder tumors. The exact mechanism of BCG anti-tumor response induction activity-whether BCG directly induces an anti-tumor response to specific tumor cells or whether the general BCG-induced immune response is responsible for the anti-tumor activity.

Results are organized according to patients' risk categories, from primary low-grade small single tumors with a 5-year recurrence risk of 31% to the highest risk categories with 5-year recurrence and progression rates of 78% and 45%.

Side effects of intravesical BCG are generally mild and shared, including dysuria and haematuria up to approximately 85%. Due to the high frequency of adverse effects, only 19% of patients received the full-dose maintenance schedule. In addition, there are no significant differences in side effects with reduced dose or duration, which leads to 8-21% of patients cease the treatment [16].

5. Conclusion

In this review, we analyzed the effectiveness of atezolizumab as a treatment for TNBC, NSCLC, and bladder cancer. Atezolizumab is a fully-humanized IgG1 mAb designed to interfere with the binding of PD-L1 ligand to its two receptors, PD-1 and B7.1. It has shown reliable efficacy in significantly reducing mortality rate and improving survival rate. In the review, through analysis of clinical trials of the application of atezolizumab in three types of cancer, it is suggested that atezolizumab combined with neoadjuvant chemotherapy shows improved OS, PCR rate, PFS et al. in early TNBC patients. In addition, NSCLC patients being treated with atezolizumab offers more prolonged median OS and survival rates despite the non-negligible AEs. The use of atezolizumab as second-line treatment for bladder cancer following by platinum-based chemotherapy has been proven effective in inducing a durable anti-tumor response in patients with advanced urothelial carcinoma, and its relatively low AEs makes it applicable to a larger population. Currently, atezolizumab has been chiefly used as a second-line treatment for TNBC, NSCLC, and bladder cancer due to the relatively low cost-effectiveness of first-line therapy compared with chemotherapy. Price reduction of atezolizumab is expected to improve the cost-effectiveness of atezolizumab. Furthermore, clearer biomarkers to indicate the prognosis of atezolizumab treatment are desired to widen the range of application of atezolizumab and enhance its safety and effectiveness.

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