Keytruda: A Major Advance in Immuno-Oncology

Yuan Chen[1, a, †], Lanqing Liu[2, b, *, †], Yuemo Wang[3, c. †]

[1]The University of Adelaide, Adelaide, Australia

[2]China Pharmaceutical University, Nanjing, China

[3]Nanjing Tech University, Nanjing, China

[a]a1828691@student.adelaide.edu.au, [b]2020182337@stu.cpu.edu.cn, [c]regulus876142484@163.com

*Corresponding author: 2020182337@stu.cpu.edu.cn

[†]These authors contributed equally.

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Abstract: Cancer threatens the health of human beings around the world because of its high incidence, high fatality rate, and difficulty in treatment. Traditional treatment methods are mostly surgical treatment. However, the recurrence rate of cancer after surgery is still high. In recent years, more and more cancer treatment methods have emerged. Radiation therapy, chemotherapy, etc. Among them, immunotherapy is a hot topic of research in recent years. Pembrolizumab (Keytruda) is an immunotherapy drug used in cancer. A large number of studies have shown that keytruda is superior to conventional chemotherapy in all aspects, both as a single agent and in combination. Data show that keytruda is effective in NSCLC, which is resistant to standard chemotherapy and has rarely been treated before. In this review, we first briefly introduced CAR-T therapy and keytruda, focusing on analyzing and summarizing various experimental data related to keytruda and other oncology drugs. With the gradual understanding of the pathogenesis of tumors and the mechanism of action of various treatment methods, breakthroughs in tumor immunotherapy are expected to accelerate in the next few decades.

1. Introduction

Non-small-cell lung carcinoma, or NSCLC, accounts for the vast majority of lung cancer diagnoses (approximately 84 percent), and the vast majority of patients with NSCLC have advanced stage disease—stage IV. The absolute 5-year survival rates range from around 43 percent to 55 percent in situations where the tumor can be removed [1]. Advanced stage NSCLC could only be treated with systemic chemotherapy in the early 2000s, and patients' life times might be extended to 10-12 months. Targeted medicines and molecular diagnostics are now accessible.

Immuno-oncology has been the most popular among them. The treatment of is quickly improving, particularly with the use of immunotherapy. When immunotherapy and chemotherapy are used to treat NSCLC, healing characteristics are predicted. As a result, it becomes a contentious topic in anti-tumor research.

This review focuses on the therapeutic effects of Keytruda, as well as the pharmacological activity as evidenced by current studies, toxicity, and a comparison of Keytruda to other chemotherapeutic medications. Its superiority is proved by the results of many trials, which motivates clinical researchers to develop better NSCLC therapy.

2. The development of CAR-T therapy

Immune checkpoints act as positive and negative feedback mechanisms that limit T cell growth and function during the effector phase. They play an important role in autoantigen tolerance and lay the groundwork for fine-tuning the T-cell

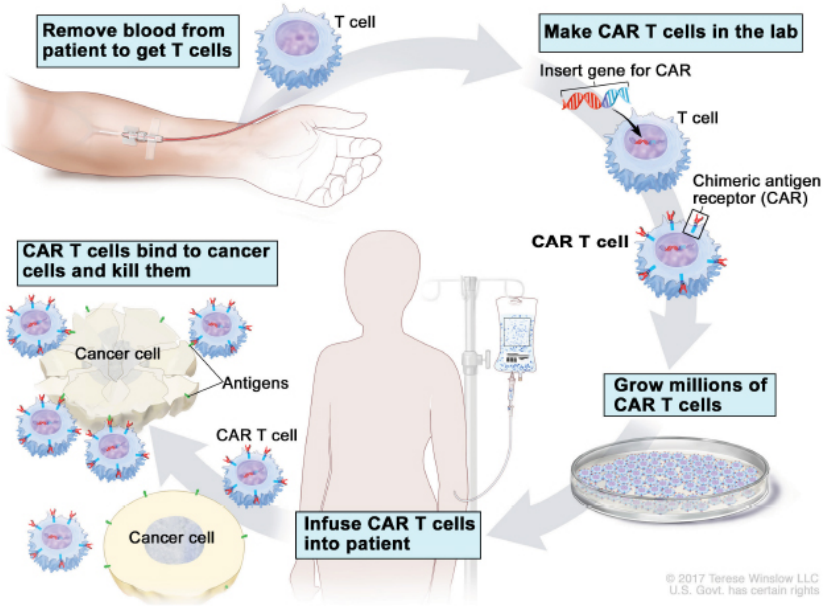

Figure 1. After the extraction of T cell from human blood, CAR-gene is imported into T cells and turns into CAR-T cells. The expanded and purified CAR-T cells can bind tumor cells and lead to apoptosis.

Response. CTLA4 is the prototype. CTLA 4, when expressed on T cells, interacts with CD80 and CD86 on antigen presenting cells (APCs) and other target cells to produce inhibitory signals. CD80 and CD86 are also ligands of CD28, a key T cell costimulant that enhances TCR signaling when TCR interacts with major histocompatibility complex proteins and contacts its target antigens.

CAR T-cell therapy was one of adoptive T-cell treatment that included TILs and TCR-engineered T cells, as well as tumor-infiltrating lymphocytes (TILs) (TCRT). TILs, on the other hand, were only detectable in a small percentage of tumors [2].

TCR recognition is confined to certain HLA repertoires because to the human leukocyte antigen (HLA)-restricted nature of TCR recognition. CAR T-cell treatment, fortunately, met the requirement for innovative and effective adoptive T-cell therapy.

3. Target identification and Validation of Keytruda

Because half-molecules may exchange amongst themselves, Keytruda, which belongs to the IgG4 subclass of human antibodies, can function in vivo. Pembrolizumab, or Keytruda, is a complex molecule with an asymmetrical Y structure. The tight packing of the Fab and Fc domains was verified by NMR studies. The hinge region, which spans residues Val218 through Gly236 and has an S228P mutation, connects the Fab domains to the Fc. The Fab-arm exchange in IgG4 is prevented by this single mutation. CH2 domain conformation in the Keytruda Fc was altered when compared to the PDB 1HZH Fc and an isolated IgG4 Fc. IgG interactions with the neonatal Fc receptor (FcRn) are vital for catabolism and protection of IgG from degradation.

4. KEYNOTE-001 experiment of Keytruda

The first trial to look into pembrolizumab (Keytruda) in NSCLC was KEYNOTE-001. This is a biomarker-driven early phase I/II trial to see if pembrolizumab is safe.

4.1 Conclusion of KEYNOTE-001 experiment

The KEYNOTE-001 NSCLC cohort's results were recently published. Patients with 50% or higher PD-L1 expression had a superior ORR, PFS, and OS than those with lower PD-L1 expression. This suggests that the drug may be effective. Furthermore, only 9.5 % of patients reach to grade III or higher adverse events (AEs), with pneumonia (1.8 %) being the most common [3]. This means that pembrolizumab has received preliminary approval for its safety.

4.2 Method and data of KEYNOTE-001 experiment to NSCLC

The research enrolled a total of around 500 patients, each of whom received one cycle of pembrolizumab treatment. In terms of dose, dosage form, and PD-L1 expression degree, the ORR was about 20%. The ORR for newly treated patients (n = 101) was about 25% and 18% respectively. Regardless of histology, dose, or timing, there were no variations in response between groups. At 0.02 g/kg Q3W (n = 6), pembrolizumab had an ORR of 33.3 percent, and at 0.01 g/kg Q3W (n = 287), it had an ORR of 19.2 percent. At 0.01 g/kg Q2W (n = 202), the ORR was 20 %. Nonsmokers had an ORR of 10.3 percent, while previous or current smokers had an ORR of 23 percent. The median duration of remission for all patients was 12.5 months at the time of the study (August 2014), 10.4 months for previously treated patients, and 23.3 months for patients who had not been treated. A median progression-free survival of 3.7 months was seen in all of the patients (95 percent confidence interval: 2.9-4.1). All of the patients had a 12-month median overall survival time [3].

5. The clinical effects of Keytruda

In the treatment of NSCLC, the appropriate treatment plan needs to be chosen according to the type of pathology of the patient. After determining the patient's cancer stage, it is necessary to first confirm whether the patient's NSCLC is squamous or non-squamous, followed by confirming whether the patient's driver gene is positively or negatively expressed, followed by confirming the patient's immunophenotyping, i.e. the patient's level of PD-L1. In general, immunotherapy with Keytruda is indicated for patients with advanced non-small cell lung cancer with negative driver gene expression and intermediate or high PD-L1 expression. The use of Keytruda alone is indicated as first-line treatment for PD-L1 (TPS 1%) in stage IV driverless NSCLC, while the use of Keytruda in combination with chemotherapy can be used as first-line therapy in patients with stage IV driverless NSCLC regardless of the level of PD-L1.

5.1 The therapeutic effect of Keytruda monotherapy on patients with PD-L1 TPS≧50%

In patients with TPS 50%, monotherapy with Keytruda can extend overall patient survival to about twice that of chemotherapy, with a superior safety profile.

The phase 3 clinical trial Keynote-024 (NCT02775435 on ClinicalTrials.gov) is a randomized, double-blind study. The goal of this study was to compare the efficacy and safety of Keytruda versus platinum-containing chemotherapy chosen by the investigators in newly treated advanced NSCLC patients with PD-L1, TPS50%, and no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) driver mutations. A total of 305 patients from 16 countries were randomly divided into two groups and treated with Pembrolizumab 200mg Q3W and Platinum-Doublet Chemotherapy (4-6 cycles) in this study [4].

The clinical trial began on May 2014, and results were first published on July, 2017, with a median follow-up time of 25.2 months. Median treatment duration was 7.9 months in the Keytruda group (n=154) and 3.5 months in the chemotherapy group (n=151). 82 patients in the chemotherapy arm received Keytruda cross-therapy. After 33 mouths therapy, a total of 169 patients died, and 73 and 96 patients in the Keytruda and chemotherapy groups were analyzed, respectively. The median OS of the two groups was 30 months and 14.2 months, respectively. The survival rates of the two groups at 12 months were 70.3% and 54.8%, respectively. At 24 months, survival was 51.5% and 34.5%, respectively. The median OS of Keytruda group was almost twice as high as in the chemotherapy group. The results undermine the dominance of chemotherapy in the treatment of advanced lung cancer.

In terms of safety, treatment-related adverse reactions in the palizizumab group were obviously lower than those in the chemotherapy group (76.6% versus 90%), and no new adverse reactions were found after long-term follow-up. From these results, for patients with TPS ≥ 50%, it appears that monotherapy with Keyruda has significant advantages over conventional chemotherapy.

5.2 The therapeutic effect of Keytruda monotherapy on patients with PD-L1 TPS≧1%

In patients with a TPS of less than 1%, keytruda monotherapy still outperforms chemotherapy in terms of safety and effectiveness. Keynote-042 (NCT02220894 on ClinicalTrials.gov) is a randomized, open-label phase 3 clinical trial that was undertaken at 213 medical centers throughout 32 countries.

A total of 1274 individuals with PD-L1 TPS 1% were included in the trial between December 2014 and March 2017, and were randomly assigned to either the pablizumab (n = 637) or chemotherapy (n= 6370) arms. There were 599 patients (47%) with a TPS of 50 % or higher, and 820 patients (65%) with a TPS of 20 % or higher. The median follow-up length was 12.8 months. In patients with TPS 50%, there was a difference between the keytruda and chemotherapy groups, with mOS of 20 months versus 12.2 months, respectively. Patients with a TPS of 20% had a median survival of 17.7 months compared to 13.0 months, while those with a TPS of 1% had a median survival of 16.7 months compared to 12.1 months. Patients with TPS 50% had a two-year survival rate of 45% and 30%, respectively, for the two groups. Patients with TPS 20% and TPS 1% had survival rates of 41% and 30%, respectively, and patients with TPS 20% had survival rates of 39% and 28%, respectively.

According to a safety study, the frequency of treatment-related adverse events (TRAEs) of any grade was 63% in the pablizumab group and 90% in the chemotherapy group (Table 2). In both groups, grade 3 or higher TRAEs were found in 18% and 41% of the time, respectively, with a 2% fatality rate related to TRAEs. Hypothyroidism (11%) and anemia (37%), respectively, were the common TRAEs in the pablizumab [5].

In the Chinese population sub-trial of Keynote-042, about 262 Chinese patients with IV non-small cell lung cancer lacking driver genes were included (ClinicalTrials.gov identifier: NCT03850444). For patients with TPS of 50%, mOS was 20 months in the Keytruda group versus 14.0 months in the chemotherapy group, and 19.9 months versus 10.7 months for patients with TPS of 1-49% in the Chinese subgroup. In the Keytruda group, the rate of grade III-V drug-related adverse events (AEs) was 17%. The findings of this study are congruent with those of the KEYNOTE-042 multinational investigation [6].

From this result, it is clear that Keytruda monotherapy has a significant advantage over chemotherapy for patients with TPS ≥ 50%, while as the TPS value decreases, the advantage of Keytruda is present but gradually becomes less significant. This suggests that people with low TPS will benefit less from Keytruda monotherapy. In people with TPS between 1% and 49%, treatment with Keytrueda monotherapy is slightly more effective than chemotherapy. The safety profile of monotherapy with Keytruda is also far greater than that of chemotherapy.

5.3 The therapeutic effect of Combination of Keytruda and Chemotherapy on patients with PD-L1≧1%

The use of keytruda in conjunction with chemotherapy for patients with TPS 1%, including squamous and non-squamous NSCLC, provides a significant benefit over chemotherapy alone. The Keynote-021 (NCT02039674) research is a combination Phase I-II trial assessing the safety of Keytruda in conjunction with chemotherapy in advanced NSCLC patients.In Keynote-021, patients older with stage IV non-small cell lung cancer without EGFR mutation or ALK rearrangement were screened for the study and assigned to group ABC (group A for any histological type of NSCLC, B and C for non-squamous NSCLC). The treatment regimens in each group are: A: Keytruda 2mg or 10mg/kg combined with paclitaxel carboplatin regimen, B: Keytruda 2mg or 10mg/kg combined with paclitaxel/carboplatin/bevacizumab, C: Keytruda 2mg or 10mg/kg combined with pemetrexed/ carboplatin regimen. The ORR of patients in groups A, B and C was 48% (12/25), 56% (14/25) and 75% (18/24) respectively, with 1 patient in each group achieving complete remission (CR) and the remainder achieving partial remission (PR). ORR rates were similar in all 3 groups for different PD-

L1 TPS subgroups (≥50%, 1-49% and <1%). 80%, 68% and 79% of patients in the 3 groups experienced disease progression or death with mPFS of 10.3, 7.1 and 10.2 months, respectively; 6-month PFS rates of 72.0%, 65.8% and 78.4%; 52%, 48% and 67% of patients died with mOS of 21.4 months, 16.7 months and 16.7 months, respectively; and 6-month OS rates of 87.7%, 79.2% and 87.5%, respectively. In this study, the Keytruda in combination with carboplatin paclitaxel bevacizumab regimen increased the incidence of specific AEs compared to other combination groups. Patients who received Keytruda immunotherapy in combination with chemotherapy had a considerably higher incidence of objective remission than those who had chemotherapy alone (55% vs 29%) [7]. The results of the trial in Groups A and C were better than those in Group B. The results of KEYNOTE-021 showed that Keytruda in combination with chemotherapy was as effective as or better than conventional chemotherapy, and this trial confirmed that Keytruda in combination with platinum-based drugs is a viable combination therapy. The poorer results in Group B compared to Groups A and C in this trial, and the high incidence of immune system-related AEs in Group B patients shown in the study, suggest that a four-drug combination may not be a good option.

The KEYNOTE-189 study (NCT02578680) was a phase III clinical trial that enrolled patients with primary EGFR mutation-negative or ALK-negative advanced cancer. Patients were randomly assigned in a 2:1 ratio to either pablizumab combined with pemetrexed and platinum (pablizumab 200 mg administered every 21days for 4 times) or placebo combined with pemetrexed and platinum (pablizumab 200 mg administered every 21days for 4 times Maintenance therapy with pablizumab or placebo in conjunction with pemetrexed can be continued for another 35 cycles if desired. If disease progression occurs, patients in the placebo-chemotherapy arm can switch to the pablizumab-chemotherapy arm.

Data are current as of May 2019, with a median follow-up duration of 31.0 (26.5 to 38.8) months with 17 patients in the pablizumab combination chemotherapy arm still receiving initial treatment compared to only one in the placebo combination chemotherapy arm. With 84 (40.8 %) patients in the placebo combination chemotherapy group switching to Keytruda monotherapy, Keytruda combination chemotherapy provided a significant overall survival (OS) benefit, with median OS of 22.0 months and 10.6 months in the two groups, respectively, with Keytruda combination chemotherapy lowering the risk of death by 44%. At two years, the two groups had 45.7 % and 27.3 % OS, respectively. Furthermore, independent of the patient's PD-L1 expression, Keytruda in conjunction with chemotherapy resulted in a substantial OS benefit.

In addition, Keytruda in conjunction with chemotherapy significantly improved progression-free survival (PFS), lowering the risk of disease progression or death by 51%. The median PFS in the pablizumab-combined chemotherapy arm was 9.0 months, compared to just 4.9 months in the placebo-combined chemotherapy arm. The two groups' 2-year PFS rates were 22.0 % and 3.4 %, respectively. Regardless of the patient's PD-L1 expression level, pablizumab in conjunction with chemotherapy resulted in a substantial PFS advantage [8]. This study found that Keytruda in conjunction with chemotherapy had a superior therapeutic impact than chemotherapy in patients with IV phase non-squamous NSCLC, regardless of PD L1 expression.

The results of the Japanese sub-trial of KEYNOTE-189 (ClinicalTrials.gov identifier: NCT02578680), a small trial with 40 Japanese subjects showed mOS of 16.5 months and 7.1 months in the Keytruda combined chemotherapy and chemotherapy groups, respectively, which were consistent with the results of international trials [9]. A total of 559 patients satisfied the inclusion criteria and were randomly allocated 1:1 to receive Keytruda 0.2 g or placebo, Q3W, for over 30 cycles in conjunction with 4 cycles of carboplatin, AUC 0.006 g/mL/min Q3W, and the investigator's choice of paclitaxel 0.2 g/m2 Q3W or albumin paclitaxel 0.1 g/m2 QW. The major study endpoints were OS and FPS, with ORR serving as a supplementary objective. The results showed that Keytruda in combination with chemotherapy improved the OS of patients regardless of whether they chose paclitaxel carboplatin or albumin paclitaxel carboplatin. HR 0.67 (0.48-0.93) for Keytruda in combination with paclitaxel carboplatin vs chemotherapy alone, and mOS was NR vs 12.6 months, HR 0.59 (0.36-0.98), respectively.

Similar to the OS results, Keytruda in combination with chemotherapy improved PFS regardless of whether patients chose paclitaxel carboplatin or albumin paclitaxel carboplatin. mPFS for Keytruda in combination with paclitaxel carboplatin vs chemotherapy alone was 6.4 vs 4.4 months, HR 0.52 (0.40-0.68), and mPFS for Keytruda in combination with albumin paclitaxel carboplatin vs chemotherapy alone was 6.4 vs 4.4 months, HR 0.52 (0.40-0.68). The mPFS was 6.5 vs 5.9 months, HR 0.65 (0.45-0.94) for pablizumab combined with paclitaxel carboplatin versus chemotherapy alone, respectively.

A similar pattern was observed for ORR comparisons, with both Keytruda combined with chemotherapy improving ORR, with Keytruda combined with paclitaxel carboplatin vs chemotherapy alone at 57.4% vs 37.7% and Keytruda combined with paclitaxel carboplatin vs chemotherapy alone at 58.7% vs 39.5%, respectively [10].

KEYNOTE-407 China sub-study (ClinicalTrials.gov identifier: NCT03875092) included 125 patients in mainland China, 65 in the pablizumab+chemotherapy group and 60 in the control group. Median OS in the Chinese population was 17.3 months and 12.6 months in the pablizumab combination chemotherapy and control groups, respectively, with an improvement of 4.7 months and a 56% reduction in risk of death in the combination group (HR=0.44), consistent with the overall global population results; 12-month OS rates were 79% and 55%, an improvement of 24%. In a subgroup analysis of the Chinese population, all subgroups (age, male, ECOG PS status, PD-L1 expression) could benefit from pabrolizumab in combination with chemotherapy. Median PFS was 8 months and 4 months in both groups, with a 68% reduction in the risk of disease progression, and a 37% improvement in 6-month PFS, similar to the overall population outcome of 71% and 34%, respectively [11]. The results of these trials show that Keytruda in combination with chemotherapy can provide better outcomes than chemotherapy for patients with stage IV squamous NSCLC.

Combining the results of the Keynote-189 and Keynote-407 trials, we can see that Keytruda in combination with chemotherapy can provide better results than chemotherapy alone, regardless of whether the patient has stage IV squamous or non-squamous non-small cell lung cancer. Overall, Keytruda in combination with chemotherapy is over to chemotherapy alone in terms of safety and efficacy, irrespective of economic factors.

6. Side effects

Keytruda has documented side effects on melanoma patients, but is treatable in most cases. The most common Adverse Events (AE) are fatigue, redness, itching, joint stiffness, elevated amylase. Individual cases of particular reactions, such as diabetes and heart failure, have been reported [12-13]. AE of grade 3 or higher is infrequent in KEYNOTE-001 patients.

KEYNOTE-006 study about melanoma showed that Pembrolizumab had lower side effects than Ipilimumab [13]. The safety of KEYNOTE-001 in lung cancer patients was comparable to that of melanoma patients. In the trial, 3.6 percent of the participants got pneumonia of some sort. In patients with NSCLC, no clear links between the risk of pneumonitis and previous or subsequent radiotherapy after progression on an anti-PD-1/PD-L1 medication have been found.

7. Conclusions

Pembrolizumab (Keytruda) is an immunotherapy drug. Pembrolizumab works by blocking the protein PD-1, which is found on the surface of some immune cells. T lymphocytes are triggered to seek out and kill cancer cells when PD-1 is blocked. Keytruda has demonstrated to be effective against NSCLC that has resisted standard chemotherapy, a disease that previously had few therapeutic alternatives. A large amount of data shows Keytruda as a single drug is significantly safer than chemotherapy. Clinical trials of Keytruda in combination with chemotherapy have shown that Keytruda is safer and more effective than chemotherapy alone. Despite the side effects, Keytruda still has fewer side effects than other drugs. NSCLCS with GENOMIC abnormalities of EGFR or ALK were not responding to specific therapy for those aberrations prior to acquiring pembrolizumab. To summarize, pembrolizumab's approval as the first PD-1 inhibitor was a watershed moment in immuno-

oncology. Immuno-oncology research is expected to accelerate in the coming decades as a result of this therapy.

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