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PEMBROLIZUMAB IN LUNG CANCER : LITERATURE REVIEW

R. Chacha* Department of Oncology Mohammed VI University Hospital-Oujda , Morocco
*Corresponding Author

S. Afqir Department of Oncology Mohammed VI University Hospital-Oujda , Morocco

ABSTRACT Lung cancer is the first cause of death cancer in the worldwide. There is an important development of agents which aimed the PD-1/PD-L1 axis and that d has a great influence on the strategy of the treatment of lung cancer in first and second line. Pembrolizumab is approved by the U.S. FDA for the treatment of advanced NSCLC progressed after other therapies and with expression of PD-L1. This review highlights the results of recent clinical trials on pembrolizumab for the treatment of non-small cell lung cancer.

KEYWORDS : immunotherapy, lung cancer, PD-1/PD-L1

INTRODUCTION

Lung cancer is the first cause of cancer death for men and women [1]. The treatment based on platinum has presented an important efficacy [2] . Some targeted therapies had as result superior results in comparison to standard chemotherapy in NSCLC [3] as gefitinib, erlotinib, or afatinib , which are recommended as first-line therapy for patients with mutation in epidermal growth factor receptor (EGFR) and crizotinib is indicated as first-line treatment for patients who anaplastic lymphoma kinase (*ALK*) gene rearrangement [4] For vaccines, interleukin-2, and interferon had limited efficacy and they had important toxicities [5]. Anti-CTLA-4 antibody ipilimumab and anti-PD-1 antibodies pembrolizumab and nivolumab, were approved for advanced melanoma. and clinical trials showed activity of anti-PD-1/PD-L1 antibodies in lung cancer [5]. This review discuss the role of immune response in cancer , the mechanisms of immune checkpoint inhibitors, clinical trials and their results

PROGRAMMED DEATH PATHWAY AND LUNG CANCER

PD-1 has two known ligands PD-1 ligand 1 (PD-L1) and PD-1 ligand 2 (PD-L2) The interaction inhibits the proliferation , and effector function of $CD8^+$ cytotoxic T-lymphocyte (CTL), T-cell receptor-mediated effector functions [6] . Nivolumab and pembrolizumab have been evaluated in clinical trials and have the US Food and Drug Administration (FDA) approval in NSCLC, in melanoma, in renal cell cancer and Hodgkin lymphoma . In this review, we focus on pembrolizumab in NSCLC.

PHARMACOLOGY OF PEMBROLIZUMAB

1- Mechanism of action

Pembrolizumab is a anti-PD-1 humanized monoclonal IgG4 kappa isotype antibody which inhibits the interaction between PD-1 and PD-L1. On October 2016, it was approved by the US FDA in the first-line setting for metastatic NSCLC patients whose tumors have high PD-L1 expression, tumor proportion score (TPS) $\geq$ 50% , and in second line for metastatic NSCLC patients whose tumors express PD-L1 with TPS $\geq$ 1% progressing on or after platinum-based chemotherapy.

2- Metabolism and elimination

There is no specific mechanism of metabolism and elimination reported for pembrolizumab. It is possible that phagocytes break down monoclonal antibodies into small fragments which are renally eliminated. The cytochrome P-450 system has not direct involvement in the metabolism of IgG monoclonal antibodies. [7]

3- Drug-drug interactions

Any drug that alterate T-cell function or immune responses may have a negative impact on pembrolizumab's efficacy[8]. For example, methotrexate which downregulate Fcγ receptors so that could potentially affect monoclonal antibody clearance [9].

4- Pharmacodynamics

PD-1 is expressed on activated T-cells (CD8+ and Cd4+), natural killer (NK) cells, antigen presenting cells (APC), monocytes and B-cells. Inflammatory cytokines produced by these cells induce expression of PD-L1 and PD-L2 on APCs.And PD-1/PD-L1 , PD-1/PD-L2 interactions induce inhibitory signal to T- and B-cells, leading to reducing cytokine production and decreased antibody formation, and as result to inhibition of anti-tumor immunity.[10]

5- Pharmacokinetics

The pharmacokinetics of pembrolizumab were similar to other monoclonal antibodies. The clearance of pembrolizumab was low with 0.22 L/day [11] based on results of study data pooled by Ahamadi et al (2016) of 2195 patients who were treated for different types of cancer using pembrolizumab at intravenous doses of 1 to 10 milligrams per kilogram bodyweight and in intervals of two or three weeks. Data were collected from three trials: KEYNOTE-001, KEYNOTE-002 and KEYNOTE-006. [12]

CLINICAL EFFICACY OF PEMBROLIZUMAB

1- Pembrolizumab as monotherapy

KEYNOTE 024 is Phase 3, multicenter, open-label, in which evaluate the safety and efficacy of pembrolizumab in comparison to standard-of-care platinum-based chemotherapies in the first-line treatment of Stage IV NSCLC, it compared pembrolizumab at 200 mg every 3 weeks (n = 154) to the investigator's choice of five different platinum-based chemotherapy regimens (n = 150) in patients with the both type of histology squamous and non-squamous Stage IV NSCLC who are chemotherapy naives and have PD-L1 expression on ≥50% . Treatment with pembrolizumab and platinum-based chemotherapy was continued for a total of 35 cycles and 4–6 cycles, respectively, or until a radiologic disease progression or unacceptable toxicity. Pemetrexed maintenance was done for patients with non-squamous type . The primary end point was PFS and mPFS was longer for pembrolizumab versus chemotherapy (10.3 versus 6.0 months) and disease progression or death was significantly better for pembrolizumab (HR 0.50 $p < 0.001$). The 6-month OS for pembrolizumab versus chemotherapy was 80.2 and 72.4%, respectively (p = 0.005). Pembrolizumab had modest toxicities of any grade compared to chemotherapy (73.4 versus 90.0%), less grade 3–5 TRAEs (26.6 versus 53.3%), and had higher rates of immune-TRAEs (29.2 versus 4.7%). [13]

KEYNOTE-001 is a , multicohort, Phase I that evalute pembrolizumab in patients with advanced tumors primarily melanoma and NSCLC [14]. This phase I trial studies both groups pretreated and non-pretreated patients, 495 patients received at least one cycle of pembrolizumab, at a dose of 2 mg/kg once every 3 weeks (n=6), 10 mg/kg Q3W (n=287) or 10 mg/kg Q2W (n=202). The objective response rate (ORR) was 19.4% , progression free survival (PFS) was 3.7 months and OS 12.0 months . Naive patients had a higher ORR of 24.8% compared to pretreated patients: 18.0% . And, we note a significant difference between smokers (ORR 22.5%) and non-smokers (ORR 10.3%).

KEYNOTE-010 trial phase II/III evaluates the effect of two doses(2 mg/kg Q3W or 10 mg/kg Q3W) of pembrolizumab or docetaxel (75 mg/m2 Q3W) in pretreated patients with NSCLC who expressed PD-L1. As result, the ORR was 18% in both pembrolizumab groups compared to 9% in the docetaxel group . And , the PFS was different

between pembrolizumab 10 mg/kg and docetaxel (Hazard Ratio (HR : 0.79 , p=0.004), but not between pembrolizumab 2 mg/kg and docetaxel (HR : 0.88 , p=0.07) for patients who had tumors expressing ≥1% of PD-L1. Median OS was 10.5 months in the 2 mg/kg and 13.4 months in the 10 mg/kg group, in comparaison to docetaxel (median 8.6 months) . The 24 months OS was 30.1% and 37.5% in both pembrolizumab groups, which is significantly higher than in the docetaxel group 14.5%. Thus it was concluded that pembrolizumab was more efficacious in all patients with PD-L1 expression, although more in those who had a tumor PD-L1 expression score ≥50%.

KEYNOTE-025 is a Phase Ib study that evaluates the safety and efficacy of pembrolizumab at the dose of 10 mg/kg intravenously every 3 weeks for up to 2 years in PD-L1-positive advanced NSCLC. But the study is now closed, and results are awaited.

2-Combination therapy

KEYNOTE 021 is Phase I/II trial about eight cohorts which evaluates the safety, tolerability, and efficacy of pembrolizumab in combination with other therapies in treatment-naïve advanced NSCLC. The patients received pembrolizumab with cytotoxic chemotherapy such as carboplatin/pemetrexed or carboplatin/paclitaxel (cohorts A, B, C, and G), bevacizumab (cohort B), tyrosine kinase inhibitor : gefitinib or erlotinib (cohorts E and F), or anti-CTLA-4 antibody : ipilimumab (cohorts D and H). Preliminary results from cohorts A–C (pembrolizumab + chemotherapy) and D and H (pembrolizumab + ipilimumab). Patients received pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks plus either carboplatin + paclitaxel (cohort A; any histology), carboplatin + paclitaxel + bevacizumab (cohort B, nonsquamous type), or carboplatin + pemetrexed (cohort C; nonsquamous type) for four cycles, followed by maintenance pembrolizumab (cohort A), pembrolizumab + bevacizumab (cohort B), or pembrolizumab + pemetrexed (cohort C) [15]. After 12 months of follow-up , 74 patients (25 in cohort A, 25 in cohort B, and 24 in cohort C) had been treated. ORR was 25%, and 40% of stability. Median PFS was 6 months. Grade 3–4 treatment-related AEs occurred in 36%, 46%, and 42% of patients in cohorts A, B, and C, respectively. For the combination ipilimumab and pembrolizumab, the dose of pembrolizumab was reduced from 10 mg/kg to 2 mg/kg and that of ipilimumab from 3 mg/kg to 1 mg/kg based on toxicities observed in a study done in advanced NSCLC witch associated nivolumab and ipilimumab. One treatment-related death was noted. So it seems that the combination of pembrolizumab and ipilimumab in pre-treated advanced NSCLC demonstrated an important toxicities and an ORR similar to that of pembrolizumab alone.

KEYNOTE-189 is a randomized, Phase III study evaluating the efficacy and safety of platinum doublet (carboplatin or cisplatin with pemetrexed) with or without pembrolizumab every 3 weeks in first-line treatment of patients with metastatic nonsquamous NSCLC . Both groups receive four cycles of the platinum with pemetrexed chemotherapy . The control arm will receive pemetrexed for maintenance, while the experimental arm will receive pemetrexed and pembrolizumab for maintenance. If progression on the control arm, participants may receive pembrolizumab. The primary and secondary end points are PFS and ORR, respectively, as assessed by RECIST Version 1.1. Another secondary outcome measure is PFS as assessed by investigator immune-related RECIST .

KEYNOTE-407 is randomized, Phase III trial which compares the efficacy of platinum doublet chemotherapy (carboplatin with paclitaxel or nab-paclitaxel) alone or in combination with pembrolizumab in first-line for patients with metastatic squamous NSCLC. Patients will receive either pembrolizumab 200 mg (experimental arm) or placebo (control) prior to platinum doublet chemotherapy. The duration of platinum doublet is four cycles, however pembrolizumab (experimental arm) and placebo (control arm) will be continued for a total of 35 cycles. PFS and OS are the primary endpoints, while ORR is the secondary endpoint.

3- PD-L1 expression and efficacy

In the **KEYNOTE-010** study only patients with PD-L1 expression with at least 1% were studied. In this study 2222 patients were evaluable for their PD-L1 status, we find 747 with PD-L1 negative (TPS <1%). The cut-off was TPS ≥50%. The number of patients with TPS ≥50% was similar in the three groups , we find 139 patients in the 2 mg/kg group, 151 in the 10 mg/kg group and 152 in the docetaxel group.As results , ORR was 30% vs 29% vs 8% respectively, which was higher compared to the total group (ORR: 18%, 18% and 9% respectively). PFS in both pembrolizumab groups was superior in comparison to the docetaxel group with HR 0.59 (p=0.0001) and HR 0.59 (p<0.0001), respectively. Hazard Ratios for OS were significantly lower in the pembrolizumab groups compared to the docetaxel group as well: 0.54 (p=0.0002) and 0.50 (p<0.0001), with a median OS of 14.9 months and 17.3 months in the pembrolizumab groups, versus 8.2 months in the docetaxel group [16].

In the **KEYNOTE-021** trial [17] studies 2 arms pembrolizumab with chemotherapy and chemotherapy alone , the stratification is based on PD-L1 status, PD-L1 negative if (<1%), or PD-L1 positive if (1%-49% or ≥50%). Patients who had a TPS ≥50% (n=20) had a higher (ORR 80%), compared to the TPS 1-49% group (ORR 26%) and PD-L1 negative tumors (ORR 57%), and compared to chemotherapy alone (ORR 35%).

In the **KEYNOTE-024** trial [18] patients who express TPS ≥50% were included. As results an ORR of 44.8% in pembrolizumab group and 27.8% in chemotherapy arm .

SAFETY AND TOLERABILITY

1-Pembrolizumab as monotherapy

The **KEYNOTE-001** trial reported moderate toxicity of pembrolizumab. Toxicities of any grade were reported in 70.9% of patients. Grade 3 was reported in 9.5% of patients. And most reported imAEs were hypothyroidism (6.9%), pneumonitis (3.6%). we note one case of death because of this serious immunotherapy related toxicity.[19]

The **KEYNOTE-010** trial reported that 81% of toxicity in the docetaxel group, which was higher than both pembrolizumab groups (63% in the 2 mg/kg group and 66% in the 10 mg/kg group).Grade 3 to 5 adverse of toxicities were reported in 13% and 16% of patients in the 2 mg/kg and 10 mg/kg groups, respectively, and in 35% of patients in the docetaxel group. The incidence of imAEs was similar in both pembrolizumab groups: 20% in the 2 mg/kg group and 19% in the 10 mg/kg group.

KEYNOTE-024 trial comparing pembrolizumab to chemotherapy it reported a diarrhea as the most frequent adverse event in both treatment groups (14.3% and 13.3% respectively) and pneumonitis was reported in 5.8% of patients treated with pembrolizumab.[20]

2- Pembrolizumab in combination therapy

In the **KEYNOTE-021** compared chemotherapy plus pembrolizumab to chemotherapy alone.The toxicities of any grade were reported in 90% and 93% respectively in the both groups. Grade 3 to 5 toxicities were reported in 39% and 26% of treated patients. The incidence of imAE was higher in the pembrolizumab combination arm (22% versus 11%, respectively).

3-Quality of life

Patients receiving pembrolizumab reported less deterioration about quality of life compared to docetaxel (30% versus 39%). The hazard ratio (0.66, p=0.029) for time to deterioration was in favor of pembrolizumab as well

Biomarkers Associated With Disease Outcome

The biomarker investigations for PD-1/PD-L1 agents has based on the tumor microenvironment and, specifically, the expression of the ligands of PD-1, PD-L1. Most studies showed that patients whose tumors express PD-L1 have higher response rates to PD-1/PD-L1 blockade [21] . Patients who do not express PD-L1 can have impressive responses to PD-1 blockade and should be considered eligible for PD-1–blocking approaches. [22]

APPROVAL OF FDA

In October 2015 the FDA approval based on the KEYNOTE-001 trial indicate pembrolizumab as treatment of patients with metastatic NSCLC in progression on or after platinum containing chemotherapy. In October 2016 the FDA expanded the approval of pembrolizumab to first line treatment of patients with NSCLC with PD-L1 (TPS ≥50%) and this was based on the KEYNOTE-010 and KEYNOTE-024 trials.

RECOMMANDATIONS

1- NCCN

Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1

receptors are expressed on activated cytotoxic T-cells. Nivolumab and pembrolizumab inhibit PD-1 receptors. Atezolizumab inhibits PD-L1. Immune checkpoint inhibitors are associated with a delay in benefit when compared with targeted therapy or cytotoxic chemotherapy. Nivolumab, pembrolizumab, and atezolizumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated. Pseudoprogression has been reported; therefore, traditional RECIST criteria may not be applicable

2- ESMO

Lung cancer has been historically considered poorly immunogenic, with no established benefit from cytokine modulation or vaccines. Nevertheless, the recent development of checkpoint inhibitors provided a promising new approach for immunotherapy in patients with NSCLC. Immune checkpoints are inhibitory pathways that maintain self-tolerance and protect peripheral tissues by restricting the immune responses. The two checkpoint targets that have been studied more extensively in lung cancer are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and the PD-1 receptor. Among the antibodies against PD-1, nivolumab, a fully IgG4 PD-1 immune checkpoint inhibitor, was the first to be investigated in phase III trials, as reported below.Pembrolizumab is another anti-PD-1 monoclonal antibody that has recently received European Medicines Agency (EMA) approval for the treatment of any histological type of NSCLC after failure of first-line therapy in patients with tumours expressing PD-L1

CONCLUSION

Pembrolizumab is an effective treatment for patients with advanced NSCLC. It has demonstrated durable response and prolonged overall survival (OS) and a good tolerance, however clinicians have to be careful about monitoring for the symptoms of IrAEs and manage them correctly.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
2. Goldstraw P, Ball D, Jett JR, et al. Non-small-cell lung cancer. Lancet. 2011;378(9804):1727–1740
3. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol. 2011;12(2):175–180.
4. Janku F, Stewart DJ, Kurzrock R. Targeted therapy in non-small-cell lung cancer – is it becoming a reality? Nat Rev Clin Oncol. 2010;7(7):401–414.
5. Langer CJ. Emerging immunotherapies in the treatment of non-small cell lung cancer (NSCLC): the role of immune checkpoint inhibitors. Am J Clin Oncol. 2015;38(4):422–430.
6. Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non–small-cell lung cancer: American society of clinical oncology clinical practice guideline update. J Clin Oncol. 2015;33(30):3488–3515.
7. Ettinger DS, Wood DE, Akerley W, et al. Non–Small cell lung cancer, version 6.2015. J Natl Compr Cancer Netw. 2015;13(5):515–524.
8. Shaw AT, Ou SI, Bang Y, et al. Crizotinib in ROS1-rearranged non–small-cell lung cancer. N Engl J Med. 2014;371(21):1963–1971.
9. Tabrizi MA, Tseng C-M L, Roskos LK. Elimination Mechanisms of Therapeutic Monoclonal Antibodies. Drug Disc Today. 2006;11:81–88.
10. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450–461
11. Ahamadi M, Freshwater T, Prohn M, Li CH, de Alwis DP, de Greef R, Elassaiss- Schaap J, Kondic A, Stone JA. Model-Based Characterization of the Pharmacokinetics of Pembrolizumab: A Humanized Anti-PD-1 Monoclonal Antibody in Advanced Solid Tumors. CPT: pharmacometrics & systems pharmacology. 2016
12. Al-Moundhri M, O'Brien M, Souberbielle BE. Immunotherapy in lung cancer. Br J Cancer. 1998;78(3):282–288
13. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med. 2015;372(21):2018–2028
14. Chatterjee M, Turner DC, Felip E, Lena H, Cappuzzo F, Horn L, Garon EB, Hui R, Arkenau HT, Gubens MA, Hellmann MD, Dong D, Li C, Mayawala K, Freshwater T, Ahamadi M, Stone J, Lubiniecki GM, Zhang J, Im E, De Alwis DP, Kondic AG, Flotten O. Systematic evaluation of pembrolizumab dosing in patients with advanced non-small-cell lung cancer. Annals of oncology : official journal of the European Society for Medical Oncology. 2016;27:1291-8
15. Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A, Yang JC, Gubens M, Sequist LV, Awad MM, Fiore J, Ge Y, Raftopoulos H, Gandhi L. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The Lancet Oncology. 2016;17:1497-508
16. Herbst RS PB, Jose Luis Perez-Gracia, Enriqueta Felip, Dong-Wan Kim, Ji-Youn Han, Julian R. Molina, Joo-Hang Kim, Catherine Dubos Arvis, Myung-Ju Ahn, Margarita Majem, Mary J. Fidler, Veerle Surmont, Gilberto Castro, Marcelo Garrido, Yue Shentu, Marisa Dolled-Filhart, Ellie Im, Edward B. Garon. Archival vs new tumor samples for assessing PD-L1 expression in the KEYNOTE-010 study of pembrolizumab vs docetaxel for previously treated advanced NSCLC.J Clin Oncol 34, 2016
17. Papadimitrakopoulou V, Patnaik A, Borghaei H, et al. Pembrolizumab (pembro; MK-3475) plus platinum doublet chemotherapy (PDC) as front-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohorts A and C. J Clin Oncol. 2015;33(15_suppl):8031
18. Brahmer JR. Health-Related Quality of Life for Pembrolizumab vs Chemotherapy in Advanced NSCLC with PD-L1 TPS ≥50%: Data from KEYNOTE-024 (ID 7213). Abstract, as presented at the WCLC december 2016 in Vienna. 2016.
19. Khoja L, Butler MO, Kang SP, Ebbinghaus S, Joshua AM. Pembrolizumab. Journal for mmunotherapy of cancer
20. Costa R, Carneiro BA, Agulnik M, Rademaker AW, Pai SG, Villaflor VM, Cristofanilli M, Sosman JA, Giles FJ. Toxicity profile of approved anti-PD-1 monoclonal antibodies in solid tumors: a systematic review and meta-analysis of randomized clinical trials. Oncotarget. 2016.
21. Allison JP. Immune checkpoint blockade in cancer therapy: the 2015 Lasker-DeBakey clinical medical research award. JAMA. 2015;314(11):1113–1114
22. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–264.