Research Article

Efficacy and Safety of Pembrolizumab Monotherapy for Recurrent/Unresectable/Metastatic Oral Squamous Cell Carcinoma: A Single-Center Study in China

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Background. Although pembrolizumab is recommended as a first-line treatment for advanced recurrent/unresectable/metastatic (R/U/M) head and neck squamous carcinoma, the differences in its efficacy among different populations need to be investigated.

Methods. We reviewed 15 consecutive patients with R/U/M oral squamous cell carcinoma (OSCC) treated with pembrolizumab monotherapy at the Affiliated Hospital of Qingdao University between February 2021 and May 2022. All the 15 patients had known programmed death-ligand 1 expression and received multiple cycles of pembrolizumab monotherapy as first-line treatment. We evaluated and analyzed patients’ basic characteristics, time to first remission, the clinical efficacy of pembrolizumab monotherapy, and treatment-related adverse reactions.

Results. The objective response rate of the 15 patients was 60%. Six patients (40.0%) achieved partial response, while three patients (20.0%) achieved complete response. In our study, the objective response status of the patients was observed in two to five cycles (mean, 3.6 cycles). For patients who responded well to immunotherapy, the mean Karnofsky Performance Status (KPS) score after treatment was significantly higher than that before treatment ($P < 0.001$). The progression-free survival rates were 66.9% and 50.1% at 6 months and 1 year, respectively. Eight adverse events were observed, comprising four cases of rash and one case each of hypothyroidism, interstitial pneumonia, cheilitis, and cerebral thrombosis.

Conclusion. Our study suggests that pembrolizumab is beneficial to the most responsive patients with R/U/M OSCC in our single-center study and may shed light on the management of OSCC.

1. Introduction

Oral squamous cell carcinoma (OSCC) is a common subtype of head and neck squamous cell carcinoma (HNSCC), with a 5-year survival rate of approximately 50% [1, 2]. In the past decade, cetuximab plus platinum-fluorouracil chemotherapy has been the primary first-line treatment option for recurrent or metastatic OSCC as it helps in local control and improves overall survival in some patients; however, the overall prognosis of patients with advanced OSCC remains poor [3–6]. Therefore, for patients with advanced recurrent/unresectable/metastatic (R/U/M) OSCC, prolonging life expectancy and improving quality of life remains challenging for oncologists.

Immunotherapy has caused a paradigm shift in cancer treatment. In particular, immune checkpoint inhibitors targeting programmed cell death 1 (PD-1) have been effective in treating certain cancer types. Presently, immunotherapy has shown good efficacy for more than 10 solid tumors, including melanoma and lung cancer [7, 8]. A KEYNOTE-024 randomized controlled trial (pembrolizumab) conducted on patients with metastatic nonsmall-cell lung cancer indicated that the 5-year survival rate of patients treated with pembrolizumab significantly
improved from 16.3% to 31.9% compared to those subjected to platinum-based chemotherapy [9].

Recently, the clinical benefits of immunotherapy in patients with HNSCC have been reported. In a KEYNOTE-048 prospective randomized controlled study on patients expressing programmed death-ligand 1 (PD-L1), pembrolizumab monotherapy or a combination of chemotherapy was reportedly superior to the EXTREME regimen in terms of meaningful improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) [10]. According to the 2021 National Comprehensive Cancer Network guidelines for Head and Neck Cancer (published on November 9, 2020), pembrolizumab was first proposed as the first-line treatment for advanced R/U/M HNSCC [11]. Subsequently, pembrolizumab monotherapy was approved by the National Medicine Products Administration (NMPA) of China for treating patients with advanced R/U/M HNSCC and PD-L1 combined positive score (CPS) ≥ 20. Although immunotherapy has revolutionized HNSCC treatment, the efficacy and safety of pembrolizumab varies by geographic region and ethnicity [10, 12]. Moreover, limited data are available on pembrolizumab efficacy in the Chinese population with HNSCC, especially OSCC. In the present study, we evaluated 15 patients with advanced R/U/M OSCC who were treated with pembrolizumab to evaluate its antitumor efficacy and safety among the Chinese OSCC population. We hope that the results of our study will be a useful reference for the immunotherapy of patients with advanced OSCC.

2. Materials and Methods

2.1. Patients and Treatments. Based on the NCCN guidelines (Version 1.2021), the inclusion criterion of R/U/M was summarized as follows: R, loco-regional recurrence (recurrence of the primary tumor or the draining lymph nodes) or persistent disease; U, newly diagnosed T4b, N0–3, M0, or unresectable nodal disease, or unfit for surgery; M, distant metastases [11]. In our study, we reviewed 15 consecutive patients with R/U/M OSCC who were treated with pembrolizumab monotherapy at Affiliated Hospital of Qingdao University between February 2021 and May 2022. All the patients were histopathologically confirmed to have OSCC and tested positive for PD-L1 expression based on CPS (≥ 20) [13]. All the patients received first-line pembrolizumab monotherapy (200 mg) intravenously every 3 weeks [10, 14]. The treatment regimen was re-evaluated when any of the following issues were noted: grade 4-5 adverse reactions (AEs), progressive disease, or no positive response by the fifth cycle. In addition, 20 patients with no surgery or radiotherapy option received the conventional chemotherapy regime (platinum and 5-fluorouracil or paclitaxel) with or without cetuximab in the CPS of 1 or more populations. These populations with chemotherapy were used as the control group for the evaluation of PFS without pembrolizumab in our study. All the patients were followed up until the end of the study (May 1, 2022). This study was approved by the review board of the Affiliated Hospital of Qingdao University and conducted in accordance with the Declaration of Helsinki (1964). This manuscript is available as a preprint at https://www.researchsquare.com/article/rs-1708624/v1 [15].

2.2. Data Collection and Evaluation. Patients’ demographic and clinical data, medical history, PD-L1 expression, and Karnofsky performance status (KPS) score were obtained [16]. Follow up was conducted regularly by telephone calls or during clinic visits. Patients’ quality of life (QoL) was evaluated using the KPS scale, which had a maximum score of 100; the higher the score, the better the health status of the patient [16]. Response to pembrolizumab monotherapy was assessed by regular imaging examination and observation of objective tumor response according to the suggestions of the multidisciplinary team (MDT) and Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) [17]. Data were collected from the initiation of pembrolizumab monotherapy to the end of our study on May 1, 2022. Immune-related adverse events (irAEs) were evaluated according to the Common Terminology Criteria for Adverse Events, version 5.0 [18].

3. Results

3.1. Demographic and Clinical Data of Patients. Fifteen patients (five female and ten male) with OSCC who were receiving pembrolizumab monotherapy as first-line treatment were enrolled in the study (Figure 1). The median age was 69 years (range: 48–89 years). The primary sites of the OSCC were the tongue (n = 4, 26.7%), gingiva (n = 6, 40.0%), buccal mucosa (n = 3, 20.0%), floor of mouth (n = 1, 6.7%), and hard palate (n = 1, 6.7%). Among the 15 patients, four cases were of recurrent OSCC, nine of unresectable primary OSCC, and two of metastatic OSCC. Thirteen patients had a CPS ≥ 20 while two patients had 1 ≤ CPS ≤ 19.

3.2. Efficacy of Pembrolizumab as First-Line Treatment. PFS analysis showed that four patients (26.7%) had disease progression at 6-months posttreatment and five patients (33.3%) had disease progression at 1-year posttreatment. The PFS rates were 66.9% and 50.1% at 6 months and 1 year, respectively (Figure 2). Additionally, we found that the PFS rates in the chemotherapy group were 58.7% and 37.3% at 6 months and 1-year posttreatment, respectively. When compared with the chemotherapy group (patients who received conventional chemotherapy without pembrolizumab), the pembrolizumab alone group did not observe significantly improved PFS in the PD-L1 CPS of 1 or more population (P = 0.906; Figure 2). Nine of 15 patients
responded well to single-agent immunotherapy with a median follow-up duration of 9.6 months (range: 3–13.5 months). For the total patients (15/15) with immunotherapy, the median follow-up duration was 6.4 months (range: 2.8–13.5 months). Until the end of the study, the fifteen included patients were all alive and follow-up studies were ongoing. A swimmer plot of outcomes for each of the 15 patients is displayed in Figure 3. The ORR was 60% (9/15). Nine patients started showing positive response to pembrolizumab monotherapy (time to first remission) between two to five cycles (mean: 3.6). The imaging examinations and biopsies after treatment showed that three patients (20%) achieved a complete response, whereas six patients (40%) achieved a partial response (PR). Among them, one patient each transitioned to progressive disease status on the 12th and 18th cycles, respectively. For the patients who responded well to immunotherapy, the mean KPS score after treatment was significantly higher than that before treatment (58.89 ± 13.64 to 85.56 ± 10.14; \( P < 0.001 \)).

3.3. Pembrolizumab Treatment-Related Adverse Events. The adverse reactions observed during the immunotherapy are listed in Table 1. Eight adverse events were observed: four (26.7%) cases of rash and one case each of hypothyroidism, interstitial pneumonia, cheilitis, and cerebral thrombosis (each 6.7%). Among these adverse events, one patient suffered concurrent rash and interstitial pneumonia, whereas another had concurrent rash and cheilitis. The emergency management of severe irAEs should be given attention because it would be life-threatening for patients. In our study, one patient developed breath-holding and coughing.

**Figure 1:** Treatment schema roadmap of all patients in our study. The efficacy of monotherapy in patients with OSCC was assessed according to Response Evaluation Criteria in Solid Tumors version 1.1. CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; DOR = duration of response; irAEs = immune-related adverse events; C/T = chemotherapy; R/T = radiotherapy; S/T = surgical treatment; and T/T = targeted therapy.

**Figure 2:** Kaplan–Meier survival curves for progression-free survival of patients with recurrent/unresectable/metastatic oral squamous cell carcinoma treated with pembrolizumab or chemotherapy.
and was admitted with grade IV interstitial pneumonia after seven cycles of pembrolizumab. The patient’s symptoms were significantly alleviated after 1-week of treatment with the intervention of a high dose of intravenous methylprednisolone and maintenance of airway patency. This patient maintained PR status even after cessation of anti-PD-1 immunotherapy (Figure 4). In another case of severe irAE, the patient had a history of thrombosis and developed symptoms of cerebral thrombosis on the seventh treatment cycle. Despite the permanent cessation of anti-PD-1 immunotherapy, the recurrence of either vascular thrombosis or tumor was not observed during the follow-up of this patient.

4. Discussion

Patients with R/U/M OSCC have a poor prognosis, with a median survival of 6–12 months [3, 20]. In recent years, the benefits of immunotherapy in HNSCC have caused a paradigm shift in the treatment of OSCC. On December 11, 2020, pembrolizumab monotherapy was approved by the NMPA of China for treating patients with advanced R/U/M HNSCC with PD-L1 expression (CPS ≥ 20). However, the efficacy and safety of pembrolizumab in Chinese patients with R/U/M HNSCC, especially OSCC, has not been reported adequately due to the relatively short clinical treatment duration. Hence, our case series evaluated the efficacy and safety of pembrolizumab for OSCC treatment in a single-center in China.

Immunotherapy allows the re-establishment of the immune system and is a promising therapy for advanced OSCC. In a KEYNOTE-048 study on HNSCC, 23% (31/133) participants showed an objective response (OR) were reported in the pembrolizumab alone group with PD-L1 expression (CPS ≥ 20). However, the efficacy and safety of pembrolizumab in Chinese patients with R/U/M HNSCC, especially OSCC, has not been reported adequately due to the relatively short clinical treatment duration. Hence, our case series evaluated the efficacy and safety of pembrolizumab for OSCC treatment in a single-center in China.

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regimens for patients receiving single-agent immunotherapy. According to MDT evaluations and our single-center experiences with pembrolizumab, combination therapy may be recommended if patients show no positive response to the single-agent immunotherapy by the fifth cycle.

The management of cancer patients aims to prolong life expectancy and improve QoL. So far, none of the studies have concluded that immunotherapy can significantly improve the PFS and OS of oral cancer patients. In our study, the longest follow-up period for the single-agent immunotherapy was more than 18 cycles (13 months) in patients with good responses. Although there were no PFS benefits by comparing the pembrolizumab group with the chemotherapy group without pembrolizumab in the PD-L1 CPS ≥ 1 population in our study, our patients with pembrolizumab treatment showed a better PFS than those subjected to the chemotherapy regimen in an open-label Phase II trial reported by Chang [24]. Due to the lack of data on the long-term follow-up of efficacy, it is insufficient to evaluate OS. Indeed, to a certain extent, the QoL of patients with OSCC is considered as important as survival. Advanced oral cancer significantly impacts patients’ QoL by adversely influencing their communication and appearance and inducing intractable pain and dysphagia [25–27]. In recent years, immunotherapy has significantly improved QoL for patients with different cancers. In the KEYNOTE-024 study, patients with advanced non-small cell lung cancer who received pembrolizumab showed better PFS and OS than those who received cytotoxic chemotherapy

**Figure 4:** Patient No. 7 experienced tumor recurrence on the right maxilla and an invasion into the pterygoid plate ((a); (c) red arrow). Partial response occurred after four cycles of pembrolizumab treatment ((b); (d) green arrow). Interstitial pneumonia in both lungs was observed after seven cycles of pembrolizumab treatment ((e) chest radiograph; (g) chest computed tomography). The serial images indicate that the immune-related adverse events were controlled following seven days of methylprednisolone treatment ((f) chest radiograph; (h) chest computed tomography).
pembrolizumab was useful for improving or maintaining QoL by relieving symptoms such as cough, chest pain, and dyspnea in lung cancer patients, compared to chemotherapy [28]. In patients responding well to single-agent immunotherapy, the mean KPS score before and after treatment improved from $58.89 \pm 13.64$ to $85.56 \pm 10.14$ ($P < 0.001$), suggesting that immunotherapy significantly improved their physical and mental health.

Although immunotherapy has led to a paradigm shift in OSCC treatment, the risk of irAEs in immunotherapy cannot be avoided completely. In our study, we found that mild irAEs (grades 1-2) were predominant compared to severe irAEs (grades 3–5). For patients undergoing immunotherapy, the emergency management of severe irAEs should be established, because they would be life-threatening for patients. Pneumonitis, organizing pneumonia, interstitial pneumonitis, and nonspecific interstitial pneumonia, have been underscored as grade 3–5 irAEs in case reports and clinical studies [29, 30]. Immune-related pneumonitis is a rare but life-threatening adverse reaction that accounts for 35% of PD-1/PD-L1 inhibitor-related deaths [31]. Once PD-1 inhibitor-related pneumonitis is recognized, treatment should be immediately stopped and glucocorticoid administration should be considered [32]. In our study, one patient developed severe respiratory failure after seven cycles of pembrolizumab and was diagnosed with immune-related pneumonitis (interstitial pneumonitis). The patient’s symptoms were significantly alleviated after administering high doses of intravenous methylprednisolone and maintaining airway patency for one week. In addition, immunotherapy may increase the risk of irAEs, such as thrombosis. Although the correlation between thrombosis and immunotherapy has not been well reported in recent years, it has been reported that checkpoint blockers in patients with cancer could induce accelerated inflammation and lead to an increased risk of thromboembolism and cardiovascular complications [33–36]. In our study, a patient with a history of thrombosis developed symptoms of cerebral thrombosis on the seventh treatment cycle. Despite the permanent cessation of anti-PD-1 immunotherapy, the recurrence of either vascular thrombosis or tumor was not observed during the follow-up period. Our case may contribute to the expanding evidence for the correlation between anti-PD-1-related immunotherapy and the risk of thrombosis.

5. Conclusion

MDT is important for single-agent immunotherapy in patients with R/U/M OSCC and should be recommended throughout the treatment period. Existing data lacks a long-term follow-up to conclusively evaluate the efficacy or OS. However, in our study, patients responding well to anti-PD-1 single-agent immunotherapy showed obvious improvement in QoL. The emergency management of severe irAEs should be established because the risk of irAEs in immunotherapy cannot be avoided completely. Nevertheless, some limitations should be acknowledged in our study. Since our findings came from a single-center study, clinically relevant differences may be found among hospitals. Additionally, a larger sample size should be designed to increase the significance of the results. Overall, we hope that our data can provide a clinical reference for immunotherapy in Chinese patients with R/U/M OSCC.

Data Availability

No data were used to support this study.

Ethical Approval

Ethics approval for this study was provided by the Research Ethics Board of Qingdao University.

Consent

A written informed consent was obtained from each patient before treatment.

Disclosure

This manuscript has been presented in Research Square as a preprint according to the following link: https://www.researchsquare.com/article/rs-1708624/v1.

Conflicts of Interest

The authors declare there are no conflicts of interest.

Authors’ Contributions

Jieying Li and Zongxuan He contributed equally to this study.

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References

[1] M. N. M. R. Petruzzi, K. Cherubini, F. G. Salum, and M. A. Z. de Figueiredo, “Role of tumour-associated macrophages in oral squamous cells carcinoma progression: an update on current knowledge,” Diagnostic Pathology, vol. 12, no. 1, p. 32, 2017.
[2] D. Baraniya, V. Jain, R. Lucarelli et al., “Screening of health-associated oral bacteria for anticancer properties in vitro,” Frontiers in Cellular and Infection Microbiology, vol. 10, Article ID 575656, 2020.
[3] J. B. Vermorken, R. Mesia, F. Rivera et al., “Platinum-based chemotherapy plus cetuximab in head and neck cancer,” New England Journal of Medicine, vol. 359, no. 11, pp. 1116–1127, 2008.
[4] Y. Wang, W. Zhang, P. Sun et al., “A novel multimodal NIR-II nanoprobe for the detection of metastatic lymph nodes and targeting chemo-photothermal therapy in oral squamous cell carcinoma,” Theranostics, vol. 9, no. 2, pp. 391–404, 2019.
[5] Q. Tang, M. Xie, S. Yu et al., “Periodic oxaliplatin administration in synergy with PER2-mediated PCNA transcription
repression promotes chronochemotherapeutic efficacy of OSCC,” *Advanced Science*, vol. 6, no. 21, Article ID 1900667, 2019.

[6] R. Wang, X. Lu, and R. Yu, “miRNA MALAT1 promotes EMT process and cisplatin resistance of oral squamous cell carcinoma via PI3K/AKT/m-TOR signal pathway,” *Onco-Targets and Therapy*, vol. 13, pp. 4049–4061, 2020.

[7] K. Margolin, M. S. Ernstorff, O. Hamid et al., “Pembrolizumab in patients with melanoma and brain metastases: an open-label, phase 2 trial,” *The Lancet Oncology*, vol. 13, no. 5, pp. 459–465, 2012.

[8] A. S. Mansfield, R. S. Herbst, G. de Castro et al., “Outcomes with pembrolizumab monotherapy in patients with programmed death-ligand1-positive NSCLC with brain metastases: pooled analysis of KEYNOTE-001, 010, 024, and 042,” *JTO Clinical and Research Reports*, vol. 2, no. 8, Article ID 100205, 2021.

[9] F. Li and X. Dong, “Pembrolizumab provides long-term survival benefits in advanced non-small cell lung cancer: the 5-year outcomes of the KEYNOTE-024 trial,” *Thorac Cancer*, vol. 12, no. 23, pp. 3085–3087, 2021.

[10] B. Burtness, K. J. Harrington, R. Greil et al., “Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study,” *Lancet*, vol. 394, no. 10212, pp. 1915–1928, 2019.

[11] D. G. Pfister and S. Spencer, “NCCN clinical practice guidelines in head and neck cancers,” *Official Journal of the National Compressive Cancer Network*, vol. 18, 2020.

[12] R. Mehra, T. Y. Seiwert, S. Gupta et al., “Efficacy and safety of pembrolizumab in recurrent/metastatic head and neck squamous cell carcinoma: pooled analyses after long-term follow-up in KEYNOTE-012,” *British Journal of Cancer*, vol. 119, no. 2, pp. 153–159, 2018.

[13] D. Evrard, M. Hourreau, A. Couvelard et al., “PD-L1 expression in the microenvironment and the response to checkpoint inhibitors in head and neck squamous cell carcinoma,” *OncoImmunology*, vol. 9, no. 1, Article ID 1844403, 2020.

[14] E. B. Baron, N. A. Rivi, R. Hui et al., “Pembrolizumab for the treatment of non-small-cell lung cancer,” *New England Journal of Medicine*, vol. 372, no. 21, pp. 2018–2028, 2015.

[15] J. Li, Z. He, Y. Tao, X. Yang, S. Ge, and H. Xu, “Efficacy and Safety of Pembrolizumab Monotherapy for Recurrent/unresectable/metastatic Oral Squamous Cell Carcinoma: A Single-Centre Study in China,” *Research Square*, Preprint, 2022.

[16] A. H. Friendlander and R. L. Ettinger, “Karnofsky performance status scale,” *Special Care in Dentistry*, vol. 29, no. 4, pp. 147–148, 2009.

[17] E. A. Eisenhauer, P. Therasse, J. Bogaerts et al., “New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1),” *European Journal of Cancer*, vol. 45, no. 2, pp. 228–247, 2009.

[18] M. Lv, M. Chen, R. Zhang et al., “Manganese is critical for antitumor immune responses via cGAS-STING and improves the efficacy of clinical immunotherapy,” *Cell Research*, vol. 30, no. 11, pp. 966–979, 2020.

[19] G. Raffa, M. C. Quattropani, G. Marzano et al., “Mapping and preserving the visuospatial Network by repetitive nTMS and DTI tractography in patients with right parietal lobe tumors,” *Frontiers Oncology*, vol. 11, Article ID 677172, 2021.

[20] A. Argiris, K. J. Harrington, M. Tahara et al., “Evidence-based treatment options in recurrent and/or metastatic squamous cell carcinoma of the head and neck,” *Frontiers Oncology*, vol. 7, p. 72, 2017.

[21] J. S. O’Donnell, M. W. L. Teng, and M. J. Smyth, “Cancer immunoeediting and resistance to T cell-based immunotherapy,” *Nature Reviews Clinical Oncology*, vol. 16, no. 3, pp. 151–167, 2019.

[22] A. Kalbasi and A. Ribas, “Tumour-intrinsic resistance to immune checkpoint blockade,” *Nature Reviews Immunology*, vol. 20, no. 1, pp. 25–39, 2020.

[23] G. Herbreteau, A. Vallée, A.-C. Knol et al., “Circulating tumor DNA early kinetics predict response of metastatic melanoma to anti-PD1 immunotherapy: validation study,” *Cancers*, vol. 13, no. 8, p. 1826, 2021.

[24] P. M. H. Chang, H. J. Lu, L. W. Wang et al., “Effectiveness of incorporating cetuximab into docetaxel/cisplatin/fluorouracil induction chemotherapy and chemoradiotherapy for inoperable squamous cell carcinoma of the oral cavity: a phase II study,” *Head & Neck*, vol. 39, no. 7, pp. 1333–1342, 2017.

[25] J. Breeze, A. Rennie, D. Dawson et al., “Patient-reported quality of life outcomes following treatment for oral cancer,” *International Journal of Oral and Maxillofacial Surgery*, vol. 47, no. 3, pp. 296–301, 2018.

[26] M. K. Oba, L. M. A. R. Innocentini, G. Viani et al., “Evaluation of the correlation between side effects to oral mucosa, salivary glands, and general health status with quality of life during intensity-modulated radiotherapy for head and neck cancer,” *Supportive Care in Cancer*, vol. 29, no. 1, pp. 127–134, 2021.

[27] D. Adkins, J. Ley, P. Oppelt et al., “Impact on health-related quality of life of induction chemotherapy compared with concurrent cisplatin and radiation therapy in patients with head and neck cancer,” *Clinical Oncology*, vol. 31, no. 9, pp. e123–e131, 2019.

[28] J. R. Brahmer, D. Rodriguez-Abreu, A. G. Robinson et al., “Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial,” *The Lancet Oncology*, vol. 18, no. 12, pp. 1600–1609, 2017.

[29] V. Leroy, C. Templier, J. B. Faivre et al., “Pembrolizumab-induced pneumonitis,” *ERJ Open Research*, vol. 3, no. 2, pp. 00081–2016, 2017.

[30] S. L. Topalian, F. S. Hodi, J. R. Brahmer et al., “Safety, activity, and immune correlates of anti-PD-1 antibody in cancer,” *New England Journal of Medicine*, vol. 366, no. 26, pp. 2443–2454, 2012.

[31] D. Y. Wang, J. E. Salem, J. V. Cohen et al., “Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis,” *JAMA Oncology*, vol. 4, no. 12, pp. 1721–1728, 2018.

[32] M. Nishino, N. H. Ramaiya, M. M. Awad et al., “PD-1 inhibitor-related pneumonitis in advanced cancer patients: radiographic patterns and clinical course,” *Clinical Cancer Research*, vol. 22, no. 24, pp. 6051–6060, 2016.

[33] J. Roopkumar, S. Swaidani, A. S. Kim et al., “Increased incidence of venous thromboembolism with cancer immunotherapy,” *Medicus Plus*, vol. 2, no. 4, pp. 423–434.e3, 2021.

[34] J. Tsukamoto, M. Monteiro, S. Vale et al., “Thromboembolic events related to treatment with checkpoint inhibitors: report of two cases,” *Case Rep Oncol*, vol. 11, no. 3, pp. 648–653, 2018.
[35] C. Fu, G. Wang, and W. Yang, "Vascular thrombosis and anti-PD-1 therapy: a series of cases," *Cancer Management and Research*, vol. 13, pp. 8849–8853, 2021.

[36] Y. Ando, T. Hayashi, R. Sugimoto et al., "Risk factors for cancer-associated thrombosis in patients undergoing treatment with immune checkpoint inhibitors," *Investigational New Drugs*, vol. 38, no. 4, pp. 1200–1206, 2020.