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Pembrolizumab in the Precision Immunotherapy of Sinonasal Malignancies

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Abstract:

Sinonasal carcinoma constitutes a rare subset of head and neck tumors. The majority of patients are diagnosed at a locally advanced stage, and the prognosis following recurrence or metastasis is extremely poor. Pembrolizumab is a humanized monoclonal antibody that targets programmed death-1 (PD-1) and reactivates T-cell-mediated antitumor immunity by disrupting the PD-1/PD-L1 signaling axis. This review systematically summarizes the research progress of this agent in treating these malignancies, focusing on its mechanism, key clinical data, current indications, and safety management. Published evidence indicates that combining this antibody with chemotherapy yields encouraging efficacy as frontline therapy for recurrent/metastatic sinonasal squamous cell carcinoma (SSCC). A phase II trial demonstrated that 12 of 20 patients achieved a response, resulting in an objective response rate (ORR) of 60% and a disease control rate (DCR) of 100%, with a median progression-free survival (PFS) of 12.2 months. Individuals with a PD-L1 combined positive score (CPS) ≥20 derived more pronounced benefit, and the overall toxicity was manageable. Future efforts should aim to refine biomarker-driven strategies, explore combination regimens, and accumulate evidence for rare pathological subtypes, thereby advancing precision immunotherapy for these tumors.

Keywords: Pembrolizumab; Sinonasal carcinoma; PD-1/PD-L1.

1. Introduction

Sinonasal cancer originates from the nasal cavity and paranasal sinuses—maxillary, ethmoid, frontal, and sphenoid. It represents approximately 3% to 5% of head and neck neoplasms, with an annual incidence of about 0.5 to 1 per 100,000, classifying it as a rare disease. Squamous cell carcinoma (SCC) is the predominant histology, accounting for 50% to 70%, followed by adenocarcinoma, malignant transformation of inverted papilloma, mucosal melanoma, and NUT carcinoma [1,2]. Because of the concealed anatomical location, early manifestations such as unilateral nasal obstruction, bloody rhinorrhea, or facial swell-

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ing are nonspecific; consequently, most patients present with locally advanced disease, namely T3 to T4. Although early-stage cases can achieve favorable outcomes with surgery plus radiotherapy, the 5-year survival rate for locally advanced or recurrent/metastatic disease remains only about 43%, underscoring the urgent demand for novel therapies. In recent years, immunotherapy, especially PD-1/PD-L1 inhibitors, has revolutionized the management of head and neck SCC. Pembrolizumab, as the first such inhibitor approved for first-line use in this setting, has been shown to significantly improve survival in the recurrent/metastatic population.

However, owing to the rarity of sinonasal primaries, dedicated prospective immunotherapy trials have been lacking, and treatment approaches have largely been extrapolated from data on oral cavity and laryngeal cancers. In 2025, the first phase II trial evaluating this drug plus chemotherapy for recurrent/metastatic SSCC was published, delivering pivotal evidence for immunotherapy in this rare tumor. This article reviews the molecular mechanism, clinical data, application scenarios, and safety considerations for this agent. Importantly, this review provides a novel and systematic summary of the latest phase II data specific to sinonasal SCC, with a particular focus on the predictive value of PD-L1 CPS and the therapeutic implications for rare subtypes, offering a reference for practice.

2. Molecular Mechanism of the PD-1/PD-L1 Pathway and the Basis of Pembrolizumab's Action

2.1 Physiological role of PD-1/PD-L1

Immune checkpoints are a set of regulatory molecules on the T-cell surface. By engaging their respective ligands, they fine-tune the threshold for T-cell activation, proliferation, and effector functions, maintaining immune homeostasis and preventing autoimmunity. PD-1, encoded by the PDCD1 gene, is a key inhibitory checkpoint that restrains T-cell activity [3]. Under normal physiology, T cells recognize antigens presented by antigen-presenting cells via the T-cell receptor, triggering an immune response and upregulating PD-1 expression. When PD-1 binds to its ligands—PD-L1 (encoded by CD274) or PD-L2—on antigen-presenting or tissue cells, it recruits the phosphatase SHP-2. This enzyme dephosphorylates critical components of the T-cell receptor signaling pathway, such as ZAP70 and PI3K, thereby suppressing T-cell proliferation, cytokine release, and cytotoxic function [4].

2.2 Tumor immune escape.

Tumor cells hijack this suppressive circuitry during evolution to achieve immune escape. Extensive research has shown that many solid tumors and myeloid cells within the tumor microenvironment (TME) overexpress PD-L1. By engaging PD-1 on tumor-infiltrating lymphocytes, they chronically deliver inhibitory signals, pushing T cells into a state of functional exhaustion—a process known as adaptive immune resistance. Specifically, inflammatory factors in the TME, especially interferon-γ, induce tumor cells and infiltrating myeloid cells to upregulate PD-L1. These molecules then interact with PD-1 on T cells, triggering an SHP-2-mediated cascade that halts T-cell expansion, reduces secretion of effector molecules (interferon-γ, perforin, granzyme), and promotes exhaustion or apoptosis, thereby forging an immunosuppressive microenvironment.

2.3 Mechanism of pembrolizumab

Pembrolizumab is a humanized IgG4 monoclonal antibody that precisely interferes with the binding of PD-1 to both PD-L1 and PD-L2. High-resolution crystallography reveals that it attaches with very high affinity to the extracellular domain of PD-1, at a site that overlaps considerably with the PD-L1 binding region. Through steric hindrance, it competitively blocks the PD-1/PD-L1 interaction, achieving dual-ligand inhibition [4-6]. This blockade releases T cells from inhibitory restraint, terminates the SHP-2-mediated negative cascade, and restores their proliferative and cytotoxic abilities, thereby activating effective antitumor immune responses.

3. Clinical Research and Evidence of This Agent in Sinonasal Cancer

3.1 Phase II trial of pembrolizumab plus chemotherapy

In 2025, Qian et al. reported in Clinical Cancer Research a prospective, single-arm phase II trial (ChiCTR2200057343) that, for the first time, systematically assessed the efficacy and safety of pembrolizumab combined with chemotherapy as first-line treatment for recurrent/metastatic SSCC [7,8]. The study enrolled 20 histologically confirmed patients, with a median age of 59 years. The regimen comprised pembrolizumab 200 mg, nab-paclitaxel 260 mg/m², and a platinum agent (cisplatin 75 mg/m² or carboplatin AUC 5) every 3 weeks for 6 cycles, followed by pembrolizumab maintenance. The results demonstrated an ORR of 60% (12 of 20 patients responded, including 2 complete and 10 partial responses)

and a DCR of 100%. Median PFS was 12.2 months (95% confidence interval, 9.0 months to not reached); median overall survival (OS) was not reached, and the 18-month OS rate approximated 70%. Regarding safety, grade 3/4 adverse events occurred in 30% of patients, all hematological (neutropenia and thrombocytopenia). The most frequent immune-related adverse event was hypothyroidism (60%), all grade 1–2; no treatment-related deaths were recorded.

3.2 Biomarker analysis: PD-L1 CPS and mutations

In the biomarker analysis, CPS was used to correlate PD-L1 expression with outcome. Stratified results showed that the 10 patients with CPS ≥20 had an ORR of 80% and median PFS not reached; in contrast, the 7 evaluable patients with CPS <20 had an ORR of only 28.6% and median PFS of 7 months, a statistically significant difference. This indicates that high PD-L1 expression is a strong predictive marker for the efficacy of this combination. Mutation profiling revealed frequent alterations in TP53, EGFR, and CDKN2A; 11q13 amplification (involving CCND1, FGF19, FGF4, FGF3) was also common. The median tumor mutational burden was 4 mutations per megabase, which showed no significant association with efficacy.

3.3 Real-world evidence

Beyond prospective trials, real-world cases provide additional support. Nair et al. described a 65-year-old male with recurrent/metastatic SSCC who progressed after surgery and radiotherapy and then achieved a durable response with pembrolizumab monotherapy. He developed grade 3 immune-related pneumonitis, managed with glucocorticoids; therapy was later resumed at a lower dose, and the response has persisted for over 10 months [9]. This case illustrates that even for patient's intolerant of chemotherapy, single-agent pembrolizumab can yield clinical benefit, and that severe immune-related events, after appropriate management, do not necessarily mandate permanent discontinuation-though this requires confirmation in larger studies.

4. Application Scenarios of This Drug in Sinonasal Cancer

Based on the positive phase II data, pembrolizumab plus nab-paclitaxel and platinum may serve as a first-line option for recurrent/metastatic SSCC. This regimen is especially appropriate for patients with recurrent/metastatic disease naive to systemic therapy, those developing distant metastases after surgery or radiotherapy, and those with advanced disease unsuitable for local treatments such as further surgery or radiation. For individuals with CPS ≥20, this approach offers greater benefit and can be prioritized. For patients who progress on or are intolerant to first-line chemotherapy, pembrolizumab monotherapy represents a second-line alternative. The National Comprehensive Cancer Network (NCCN) Guidelines for Head and Neck Cancers list PD-1 inhibitors as a recommended second-line option for head and neck SCC, a recommendation applicable to sinonasal cancer [10]. Monotherapy has a favorable toxicity profile and is suited for patients with poor performance status.

In locally advanced disease, the combination of pembrolizumab and radiotherapy is under exploration. The rationale is that radiation can provoke immunogenic cell death, release tumor antigens and activating antigen-presenting cells, thereby augmenting the antitumor effect of PD-1 inhibitors. The ongoing NeoPeSino study (NCT05925491) is evaluating neoadjuvant pembrolizumab plus chemotherapy in locally advanced sinonasal undifferentiated carcinoma [11].

5. Safety Assessment and Management of Adverse Reactions

Based on available trial data, adverse reactions to pembrolizumab plus chemotherapy fall into chemotherapy-related and immune-related categories. Chemotherapy-related toxicities are mainly hematologic: grade 3 neutropenia occurs in about 30% and grade 3 thrombocytopenia in about 20%; these are managed with granulocyte colony-stimulating factor, dose adjustments, or platelet transfusions. Non-hematologic toxicities include fatigue (~25%) and rash (~15%), mostly grade 1–2, manageable with supportive care. Immune-related adverse reactions stem from hyperactivation of the immune system against normal tissues. Hypothyroidism is the most frequent (60%), readily controlled with thyroid hormone replacement, and usually does not require discontinuation of pembrolizumab.

For other immune-related events, the management principles are early recognition, severity-graded intervention, timely glucocorticoid use, and multidisciplinary collaboration. Grade 1–2 skin toxicities can be treated with topical steroids; grade ≥3 events warrant holding therapy and administering oral glucocorticoids. Mild diarrhea is treated with antidiarrheals, while moderate-to-severe diarrhea or colitis calls for systemic steroids. The most concerning toxicity is immune-related pneumonitis, presenting with dry cough and dyspnea and confirmed by high-resolution

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CT. When grade ≥2 pneumonitis is diagnosed, pembrolizumab should be permanently discontinued, and high-dose glucocorticoids (e.g., methylprednisolone 1–2 mg/kg/day) started immediately [12].

For special populations, data on patients aged ≥75 years are limited, but current evidence supports acceptable safety; standard dosing with close monitoring is recommended. Pembrolizumab is not metabolized via the liver or kidneys, so no dose adjustment is needed for hepatic or renal impairment; however, concurrent chemotherapy agents (platinum, taxanes) require dose modification according to organ function. In patients with comorbid autoimmune conditions, caution is necessary because therapy may trigger disease flares; individualized decisions should be made collaboratively with a rheumatology specialist.

6. Future Perspectives and Directions

Although PD-L1 CPS is the most established predictive biomarker, its assessment requires tissue and is confounded by heterogeneity; moreover, some CPS-negative patients can still benefit. Future avenues include exploring T-cell-inflamed gene signatures, dynamically tracking PD-L1 status through circulating tumor DNA-based liquid biopsies, and evaluating pan-cancer markers such as tumor mutational burden and microsatellite instability in sinonasal cancer. Regarding combination strategies, dual checkpoint blockade with anti-CTLA-4 agents has shown synergy in melanoma and renal cancer but remains untested in sinonasal cancer. Combining this antibody with anti-angiogenic drugs like bevacizumab may relieve TME hypoxia and enhance immunotherapy responses, while partnering with targeted agents against EGFR or HER2 requires careful management of overlapping toxicities.

Sinonasal cancer comprises multiple rare subtypes whose immunotherapeutic profiles are still unclear. Sinonasal undifferentiated carcinoma is highly aggressive and chemo resistant; the NeoPeSino study is assessing the neoadjuvant value of pembrolizumab plus chemotherapy [11]. NUT carcinoma is rare and carries an extremely poor prognosis, with a median survival of about 12.4 months; anecdotal case reports show responses to PD-1 inhibitors, but prospective data are absent. Mucosal melanoma typically shows low PD-L1 expression and limited immunotherapy benefit, and novel targets such as PRAME are being explored. Beyond the PD-1/PD-L1 axis, next-generation checkpoint inhibitors (e.g., anti-LAG-3, anti-TIGIT) have demonstrated therapeutic potential, and their role in sinonasal cancers warrants further investigation.

7. Conclusions

Pembrolizumab plus chemotherapy is an effective first-line treatment for recurrent/metastatic SSCC, yielding an ORR of 60%, a DCR of 100%, and a median PFS of 12.2 months. The benefit is especially notable in patients with CPS ≥20 (ORR 80%). The regimen has a manageable safety profile, with hypothyroidism and hematologic toxicities being the most common adverse events. For those unable to tolerate chemotherapy, pembrolizumab monotherapy remains a second-line option. Future work should focus on refining combination strategies, optimizing biomarker-driven selection, and gathering evidence in rare subtypes like sinonasal undifferentiated and NUT carcinomas, to propel the development of precision immunotherapy for these malignancies.

Limitations, despite the promising findings, several limitations must be acknowledged. The phase II trial cited was a single-arm, non-randomized study with a small sample size (n=20) and no control group, which may introduce selection bias. Median overall survival has not yet been reached, and long-term efficacy data remain immature. The optimal cutoff for PD-L1 CPS (≥20) requires validation in larger, multicenter prospective cohorts. Furthermore, evidence for rare histological subtypes such as sinonasal undifferentiated carcinoma, NUT carcinoma, and mucosal melanoma is still derived from case reports or small series, limiting generalizability. Future research should address these gaps through randomized controlled trials and real-world registries.

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