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Review Article

Immunotherapy in Oral Squamous Cell Carcinoma: A Systematic Review of Resistance Mechanisms and Combination Strategies

Journal of Applied Pharmaceutical Science
16(10) 981–995, 2026
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DOI: 10.1177/22133354261481935
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Abstract

Immune-based therapies have become a main focus of research in Head and Neck Squamous Cell Carcinoma (HNSCC)/ Oral Squamous Cell Carcinoma (OSCC), with an aim of counteracting tumour immune evasion mechanisms by blockade of immune checkpoint features and boosting anti-tumoural immunity. Following PRISMA (2020) guidelines, this systematic review evaluated findings in PubMed, Scopus, Web of Science, and ClinicalTrials.gov (January 2013-October 2025) databases describing OSCC, HNSCC, or oropharyngeal carcinoma patients treated with immune checkpoint inhibitors or chimeric antigen receptor (CAR)-T modalities. Survival, response rates, immune-related adverse events, and resistance mechanisms were evaluated using Cochrane and ROBINS-I tools. Out of 1,215 retrieved articles, 09 publications were included in the review. PD-1 inhibitors given before surgery, such as camrelizumab and pembrolizumab, either alone or in combination with chemotherapy or VEGFR2 blockade, were well tolerated and resulted in good tumour downstaging. Several randomised trials, especially KEYNOTE-048, demonstrated that survival was extended in those populations with high PD-L1 expression levels. Initial CAR-T and vaccine-based immunotherapies also triggered immune activation, which are very promising results. In general, immunotherapy shows a favourable efficacy and safety profile in OSCC. However, other large-scale Phase III trials focused on OSCC that will address further personalisation of these treatment approaches are warranted. Where available, OSCC-specific data were used for subgroup analysis of results; nevertheless, a certain proportion of the evidence came from mixed HNSCC/OPC populations.

Keywords

Oral squamous cell carcinoma, Immunotherapy, PD-1 inhibitors, CAR-T cells, Pharmacological resistance, Head and neck cancer

Received 15 December 2025; **accepted** 04 June 2026

Introduction

Oral squamous cell carcinoma (OSCC) represents one of the most severe malignancies in the head and neck, contributing to more than 90% of all oral cancer cases worldwide. Even with the advancement of surgical precision, radiotherapy and chemotherapeutic protocols, the world incidence of OSCC is still high, leading to death, most particularly in developing countries lacking early detection or adequate care systems.[1–3] According to GLOBOCAN 2022, oral cancer is established as one of the most common cancers worldwide (in the top 10) and represents a continued challenge with respect to overall survival and disease control.[1]

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Standard therapies like surgery, radiotherapy, and chemotherapy have been generally effective in some cases, but they seem to have reached a plateau in terms of survival rate improvement.[4] The problem of tumour recurrence along with resistance, which is both intrinsic and therapy-induced, has been the main factor limiting their success.[5] Therefore, the management of OSCC has turned to immunotherapy, which in principle should break the cancer cells' silence and let the immune system attack them.[6,7] Thus, among these agents, immune checkpoint inhibitors (ICIs) directed against the programmed cell death-1 (PD-1) and programmed death ligand-1 (PD-L1) axes have been able to achieve impressive results in recurrent and metastatic OSCC mostly because they have been able to revive the T-cells that were very much exhausted and to restore a very efficient antitumour immune reaction.[8–10]

However, the clinical utility of immunotherapy in OSCC is still somewhat unpredictable. Only a handful of patients exhibit long-term therapeutic responses, which is indicative of the occurrence of drug resistance and the presence of complex immune escape mechanisms. A variety of tumour-intrinsic factors have been identified which contribute to the decrease in treatment efficacy through various mechanisms, including changes in interferon-gamma (IFN-γ) signalling, deficiency of antigen presentation, and production of an immunosuppressive tumour microenvironment.[9,10] Moreover, the phenomenon of adaptive resistance, featuring T-cell exhaustion as well as immune evasion, points to the need for a deeper understanding of the pharmacodynamic interaction between tumours and the immune system.

One of the possible approaches to overcome the issue of resistance and increase the effectiveness of therapeutic intervention is the development of new combination strategies, for example, the combination of immunotherapy and targeted agents, chemoradiation, or angiogenesis inhibitors. Most interestingly, in locally advanced OSCC, the preclinical combination of PD-1 and VEGFR2 blockade (camrelizumab plus apatinib) has revealed a very high pathological response rate, which in turn suggests a synergistic regulation of vascular and immune pathways.[11] In the same vein, the adoption of chimeric antigen receptor (CAR) T-cell therapy is on the rise, as a next-generation immunotherapeutic approach that is capable of more specifically recognising and killing tumour cells with greater potency.[4]

Despite the recent progress, major gaps still exist in understanding the molecular basis of resistance to immunotherapy and identifying the best combination therapies that truly align with the complex biology of OSCC. A great deal of research has been done on Head and Neck Squamous Cell Carcinoma (HNSCC) as a broad category; however, data specific to OSCC are rather limited, and the present requirement is a thorough, systematic review of the existing evidence. A significant proportion of the available clinical evidence, it is worth mentioning, comes from mixed HNSCC populations, which makes it necessary to interpret OSCC-specific findings with caution.

Rationale and Research Gap

Although checkpoint blockade and adoptive T-cell therapies have revolutionised the way we treat cancers, the application of these therapies in OSCC has lagged behind other types of cancer. Some of the difficulties are different immune cells entering the tumour, tumour cells being checkpoint blockade-resistant, and multi-targeted regimens that are still largely unexplored and therefore need more investigation. Where there are reviews, they by and large consider head and neck cancers as a single entity and therefore do not account for immunobiological features unique to OSCC.[6–9] Therefore, this systematic review is intended to identify the gap in knowledge by exploring the immunotherapeutic strategies in OSCC that are emerging, with an emphasis on the resistance mechanisms to pharmacological agents and multimodal integrated strategies. This review, which is grounded in the gathering of evidence from recent clinical trials, mechanism-based studies, and translational research, intends to give a present and clinically relevant view of the swiftly evolving immunotherapy in OSCC and to propose rational resistance alleviation approaches that would make therapeutic responses more lasting and patient-specific.

Methodology

This systematic review was carried out in line with PRISMA 2020 guidelines and was catalogued in the International Prospective Register of Systematic Reviews (PROSPERO; Registration No. CRD420251110687). The protocol was decided in advance to keep the workings of the method, show the planning clearly, and make the study results duplicable. The review focused on gathering and analysing data on immunotherapeutic treatments for OSCC, HNSCC, and oropharyngeal carcinoma (OPC). It mainly looked at clinical efficacy, immune-related adverse events (irAEs), and drug resistance mechanisms.

Research Question and PICO Framework

The research question, developed with the help of the PICO framework (Table 1), aimed at comparing the effectiveness and safety of immunotherapeutic agents with locally used interventions or other immunotherapy strategies in patients with OSCC, HNSCC or OPC.

Literature Search Strategy

A comprehensive literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, and ClinicalTrials.gov. References of included articles were also manually screened to identify additional relevant studies.

Table 1. Population/Patient, Intervention, Comparison/Control and Outcome(s) (PICO) Table Based on the Research Question: In Patients with OSCC, HNSCC or OPC, How Do Immunotherapeutic Interventions Compare with Standard Treatments or Alternative Immunotherapy Strategies in Terms of Clinical Outcomes, Immune-related Adverse Events and Mechanisms of Pharmacological Resistance?

PICO Element	Description
Population (P)	Patients with histologically confirmed oral squamous cell carcinoma (OSCC), head and neck squamous cell carcinoma (HNSCC), or oropharyngeal carcinoma (OPC)
Intervention (I)	Immunotherapeutic agents, including PD-1/PD-L1 inhibitors, CTLA-4 inhibitors, CAR-T-cell therapy, or other immune-modulating therapies
Comparison (C)	Standard treatment modalities (surgery, chemotherapy, radiotherapy) or alternative immunotherapy strategies
Outcome (O)	Clinical outcomes: overall survival (OS), progression-free survival (PFS), response rates; immune-related adverse events (irAEs); mechanisms of pharmacological resistance

Search terms included combinations of: *oral squamous cell carcinoma*, *OSCC*, *head and neck squamous cell carcinoma*, *HNSCC*, *oropharyngeal carcinoma*, *OPC*, *immunotherapy*, *immune checkpoint inhibitor*, *PD-1*, *PD-L1*, *CTLA-4*, *CAR-T-cell therapy*, *chimeric antigen receptor*, *neoadjuvant*, *adjuvant*, *resistance*, *immune evasion*, *adverse events*, *overall survival*, *progression-free survival*, *response rate*, *tumour microenvironment*.

Boolean operators (AND/OR) were applied, and filters for publication date (January 2013–October 2025), language (English), and study type were used to refine results.

Eligibility Criteria

Inclusion Criteria:

- English-language randomised controlled trials (RCTs), non-randomised trials, cohort studies, and case series.
- Studies reporting at least one outcome of interest: overall survival, progression-free survival (PFS), response rate, immune-related adverse events, or resistance mechanisms.

Exclusion Criteria:

- Preclinical studies, reviews, editorials, conference abstracts without full data, and non-English publications

Study Selection and Data Extraction

Two independent reviewers screened titles and abstracts, followed by full-text evaluation based on inclusion and exclusion criteria. Discrepancies were resolved through discussion or consultation with a third reviewer.

Data were extracted using a standardised form, including:

- Study details: author, year, country, study design.
- Patient and tumour characteristics: sample size, stage, baseline features.
- Treatment details: immunotherapy type, dosage, and duration.
- Clinical outcomes: OS, PFS, response rates, irAEs.
- Resistance mechanisms: T-cell exhaustion, immune escape, tumour microenvironment effects.
- Combination strategies: immunotherapy with chemotherapy, radiotherapy, or targeted agents.

Quality Assessment and Risk of Bias

Risk of bias was assessed using:

- Cochrane Risk of Bias tool for RCTs
- ROBINS-I tool for non-randomised studies

Each study was classified as low, moderate, or high risk of bias.

Data Synthesis and Analysis

A qualitative synthesis summarised study characteristics, immunotherapy effects, resistance mechanisms, and combination strategies. Where data were sufficiently homogeneous, quantitative meta-analysis was conducted using a random-effects model to generate pooled estimates of OS, PFS, and response rates.

As this review was based on published data, ethical approval was not required. The findings are intended to guide future clinical and translational research and contribute to ongoing developments in immunotherapy for OSCC, HNSCC, and OPC.

Wherever reported, outcomes specific to OSCC were extracted and analysed separately. Studies including mixed populations (HNSCC/OPC) were included only when OSCC-specific subgroup data were available or when outcomes could be reasonably extrapolated. These studies were clearly labelled in the data tables to distinguish OSCC-specific findings from pooled cohort results. Evidence derived from non-OSCC malignancies (e.g., NSCLC, cutaneous SCC) was included only for mechanistic or translational context and was not considered in OSCC-specific outcome synthesis.

Results

1,215 records were identified through database and other source searching. Following the exclusion of 215 duplicates, 1,000 were screened on title and abstract, of which 950 were excluded on grounds of irrelevance to OSCC/HNSCC/OPC, non-immunotherapeutic intervention, or study design. Finally, 09 clinical studies[11–19] were included in the qualitative synthesis (Figure 1 and Table 2). OSCC-specific findings were extracted separately, whereas mixed-cohort studies were interpreted as contextual evidence and analysed separately for clinical and mechanistic interpretation (Tables 3 and 4).

Several trials evaluating neoadjuvant PD-1 inhibitors, including camrelizumab and pembrolizumab, either as monotherapy or combined with chemotherapy or VEGFR2 inhibitors, demonstrated favourable safety profiles, notable tumour downstaging, and improved pathological response rates in patients with resectable, locally advanced disease.[11,13,15,16,19] Phase II clinical trial results signalled that the effects of the intervention on overall survival and PFS were more obvious, especially in patients with high PD-L1 expression or HPV-positive tumours.[16,17]

It is also noteworthy that, on one hand, promising results accompanied by manageable toxicity profiles have aroused the attention of the scientific community in the case of

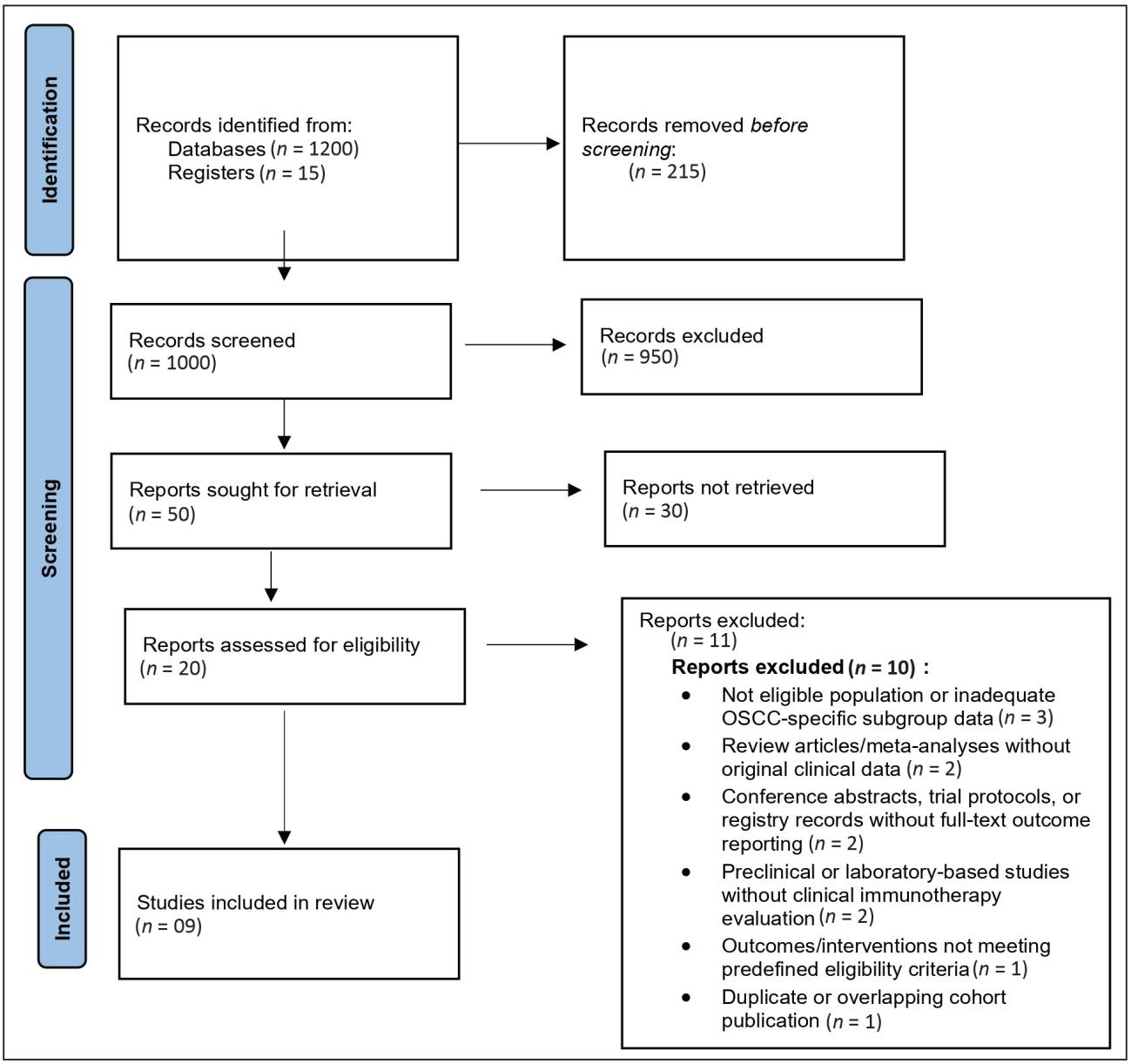

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 Flow Diagram: Systematic Review Search.

Table 2. PICO Evidence Summary and Applicability of References Included in the Systematic Review.

Author, Year [Ref]	Sample Size (N)	Population (P)	Intervention (I)	Comparator (C)	Outcome (O)
Ju, 2022[11]	20 OSCC	Locally advanced resectable OSCC	Camrelizumab + Apatinib (neoadjuvant)	None (single-arm)	MPR 8/20 (40%), pCR 1/20 (5%)
Cheng, 2024[12]	51 OSCC	Recurrent/metastatic OSCC	PD-1 inhibitor + chemotherapy	Standard chemotherapy	ORR 11/21 (52%), Median PFS 6.7 mo [Median OS was significantly better in the PD-1 + chemo group (18.3 vs. 10.3 months, $P = 0.032$)]
Wang, 2023[13]	22enrolled patients only 1 patient (4.5%) had oral cavity cancer.--hypopharyngeal carcinoma ($n = 15$, 68.2%) and oropharyngeal carcinoma ($n = 6$, 27.3%)	Resectable stage III–IVA HNSCC (includes OSCC)	Pembrolizumab + neoadjuvant chemo	None (single-arm)	MPR 12/22 (54.5%) pCR 8/22 (36.4%) — this was the primary endpoint
Burtness, 2019[14]	882 HNSCC (all sites; CPS≥20 subgroup n≈383)	R/M HNSCC (CPS ≥20 subgroup)	Pembrolizumab ± chemo	Cetuximab + chemo	Median OS 14.9 mo vs 10.7 mo (HR 0.61)
Ferrarotto, 2020[15]	28 OPC	Resectable OPC	Durvalumab ± Tremelimumab (neoadjuvant)	None (single-arm)	MPR 8/28 (29%)
Wise-Draper, 2022[16]	92 HNSCC (includes OSCC)	Resectable locoregionally advanced HNSCC	Neoadjuvant + adjuvant Pembrolizumab	None (single-arm)	PR (PPR/MPR) was observed in 39% of evaluable patients, and MPR in 7%
Bracken-Clarke, 2024[17]	~22 patients started on the treatment arm (plus 4 enrolled-but-not-treated)	Newly diagnosed HPV+ OPC	PRGN-2009 vaccine + Pembrolizumab	Standard therapy	(ORR not reported)
Jinushi, 2025[18]	Mixed solid tumours	$n = 16$ patients total: renal ($n = 7$), lung ($n = 5$), esophageal ($n = 3$), oral ($n = 1$). Only 1 of 16 patients had an oral cancer (tongue SCC per the figure legend)	Mogamulizumab + Nivolumab	None	several partial/ complete responses observed; PFS/OS reported by dose cohort — oral cancer subset too small ($n = 1$) to draw conclusions
Huang, 2023[19]	20 OSCC	Locally advanced resectable OSCC	Neoadjuvant immunochemotherapy	None (single-arm)	MPR 12/20 (60%), pCR 6/20 (30%); 100% completion/R0 resection; 2-yr OS 95%; grade 3/4 AEs in 15%

such innovations as EPHB4 and γδ T-cell receptor-directed CAR-T-cell therapies and on the other hand, they remain mostly at very early stages of investigation or just theoretical concepts.[18,19] Moreover, subgroup analysis at the level of tumour stage, HPV status, and PD-L1 expression demonstrated differences in treatment response.

In combination, all the clues lead us toward immunotherapy that is celebrated as a safe, possibly effective neoadjuvant or supplementary treatment in OSCC, HNSCC and OPC. Besides, the authors emphasise the need for large multicentre random trials to not only confirm these results but also to develop patient selection strategies.[11–19]

Table 3. Detailed Stratification of OSCC-Specific Outcomes Across Included Studies: (NR = Not Reported).

Ref No.	Author / Year	Population Type	OSCC-Specific Data	ORR (%)	MPR (%)	pCR (%)	PFS (months)	DFS (months)	OS (months)	Key Therapy	Remarks
[11]	Ju, 2022	Locally advanced resectable OSCC	20 OSCC patients	NR	40% (8/20)	5% (1/20)	NR	NR	NR	Camrelizumab + Apatinib (neoadjuvant)	Single-arm study; promising pathological response in resectable OSCC.
[12]	Cheng, 2024	Recurrent/ metastatic OSCC	51 OSCC reported; ORR evaluable data available for 21 patients	52% (11/21)	NR	NR	6.7	NR	18.3 vs 10.3	PD-1 inhibitor + chemotherapy	Median OS significantly improved compared with standard chemotherapy (P = 0.032).
[13]	Wang, 2023	Resectable stage III–IVA HNSCC	Only 1 oral cavity cancer (4.5%); predominantly hypopharyngeal and oropharyngeal carcinoma	NR	54.5% (12/22)	36.4% (8/22)	NR	NR	NR	Pembrolizumab + neoadjuvant chemotherapy	OSCC-specific conclusions cannot be drawn because only one oral cavity cancer patient was included.
[14]	Burtness, 2019	Recurrent/ metastatic HNSCC	All-site HNSCC; OSCC-specific outcomes not separately reported	NR	NR	NR	NR	NR	14.9 vs 10.7	Pembrolizumab ± chemotherapy	Large HNSCC trial; CPS ≥20 subgroup demonstrated improved survival.
[15]	Ferrarotto, 2020	Resectable oropharyngeal carcinoma (OPC)	No OSCC-specific data	NR	29% (8/28)	NR	NR	NR	NR	Durvalumab ± Tremelimumab (neoadjuvant)	OPC-only population; included for broader neoadjuvant HNSCC immunotherapy evidence.
[16]	Wise-Draper, 2022	Resectable locoregionally advanced HNSCC	Includes OSCC, but OSCC-specific response data not separately reported	NR	7%	NR	NR	NR	NR	Neoadjuvant + adjuvant Pembrolizumab	Pathological response observed in 39% of evaluable patients; MPR in 7%.
[17]	Bracken-Clarke, 2024	Newly diagnosed HPV-positive OPC	No OSCC patients specifically reported	NR	NR	NR	NR	NR	NR	PRGN-2009 vaccine + Pembrolizumab	ORR not reported; not directly applicable to OSCC-specific outcome analysis.
[18]	Jinushi, 2025	Mixed advanced solid tumours	Only 1 oral cancer patient (tongue SCC)	NR	NR	NR	Reported by dose cohort	NR	Reported by dose cohort	Mogamulizumab + Nivolumab	Oral cancer subset (n = 1) is too small for meaningful OSCC-specific conclusions.
[19]	Huang, 2023	Locally advanced resectable OSCC	20 OSCC patients	NR	60% (12/20)	30% (6/20)	NR	NR	2-year OS: 95%	Neoadjuvant immunochemotherapy	100% treatment completion and R0 resection; grade 3/4 adverse events occurred in 15%.

Table 4. Stratification of Evidence by Tumour Type (OSCC vs Non-OSCC) : Abbreviations: OSCC = Oral Squamous Cell Carcinoma; HNSCC = Head and Neck Squamous Cell Carcinoma; OPC = Oropharyngeal Carcinoma; (NR = Not Reported).

Ref No.	Author / Year	Tumour Type	OSCC-Specific Data	ORR (%)	pCR (%)	DFS	PFS	OS	Key Therapy	Remarks
[11]	Ju, 2022	Locally advanced, resectable OSCC	20 OSCC patients	NR	5% (1/20)	NR	NR	NR	Camrelizumab + Apatinib (neoadjuvant)	MPR was 40% (8/20); single-arm OSCC-specific study.
[12]	Cheng, 2024	Recurrent/metastatic OSCC	OSCC population; response data available for 21 patients	52% (11/21)	NR	NR	6.7 months	18.3 months vs 10.3 months	PD-1 inhibitor + chemotherapy	Median OS significantly better than standard chemotherapy (P = 0.032).
[13]	Wang, 2023	Resectable stage III–IVA HNSCC	Only 1 oral cavity cancer patient (4.5%)	NR	36.4% (8/22)	NR	NR	NR	Pembrolizumab + neoadjuvant chemotherapy	Predominantly hypopharyngeal and oropharyngeal cancers; OSCC-specific conclusions not possible.
[14]	Burtness, 2019	Recurrent/metastatic HNSCC	OSCC-specific outcomes not separately reported	NR	NR	NR	NR	14.9 vs 10.7 months	Pembrolizumab ± chemotherapy	Survival benefit reported in the CPS ≥20 subgroup.
[15]	Ferrarotto, 2020	Resectable OPC	No OSCC-specific data	NR	NR	NR	NR	NR	Durvalumab ± Tremelimumab (neoadjuvant)	MPR was 29% (8/28); OPC-only population.
[16]	Wise-Draper, 2022	Resectable locoregionally advanced HNSCC	Includes OSCC, but OSCC-specific data not separately reported	NR	NR	NR	NR	NR	Neoadjuvant + adjuvant Pembrolizumab	Pathological response observed in 39%; MPR in 7%.
[17]	Bracken-Clarke, 2024	Newly diagnosed HPV-positive OPC	No OSCC-specific data	NR	NR	NR	NR	NR	PRGN-2009 vaccine + Pembrolizumab	ORR not reported; findings not directly applicable to OSCC.
[18]	Jinushi, 2025	Mixed advanced solid tumours	Only 1 oral cancer patient (tongue SCC)	NR	NR	NR	Reported by dose cohort	Reported by dose cohort	Mogamulizumab + Nivolumab	Oral cancer sample too small (n = 1) for OSCC-specific conclusions.
[19]	Huang, 2023	Locally advanced, resectable OSCC	20 OSCC patients	NR	30% (6/20)	NR	NR	2-year OS: 95%	Neoadjuvant immunochemotherapy	MPR was 60% (12/20); 100% completion and R0 resection.

The risk-of-bias evaluation across 9 included immunotherapy studies in OSCC revealed variable methodological quality. Most trials demonstrated high risk in the *randomisation/selection* domain, reflecting limited allocation concealment and potential selection bias. *Performance* and *detection* domains were generally rated as unclear/moderate risk, indicating partial blinding or incomplete outcome assessment procedures. Conversely, *attrition* and *reporting* domains showed predominantly low risk, suggesting adequate data completeness and transparent outcome reporting. The overall pattern, visualised in the traffic-light plot (Figure 2), highlights consistent methodological limitations in early-phase immunotherapy trials, with improved rigour observed in multicentric and industry-sponsored studies.

The forest plot illustrates that a majority of studies recommend immunotherapy, as they exhibit higher ORR, pCR, and survival rates in patients with OSCC/HNSCC. In general, neoadjuvant and combination immunotherapies reveal similar efficacy patterns across various study designs and tumour locations (Figure 3). The forest plot (Figure 3) integrates data from Ju 2022,[11] Cheng 2024,[12] Wang 2023,[13] KEYNOTE-048,[14] CIAO 2020,[15] Wise-Draper 2022,[16] PRGN-2009 2024,[17] Jinushi 2025,[18] Illuminate 2023.[19]

Some of the selected studies reported results on OSCC, while most studies involved mixed cohorts of HNSCC and OPC. Stratification of data showed that few OSCC-specific results on objective response rate, pCR, OS, and PFS were available, but the observed patterns were more or less in line with trends noted in the general HNSCC populations. Nevertheless, one should be cautious while employing OSCC data for broader HNSCC, as differences between these tumour types at the level of biology and tumour microenvironment might exist.

Further subgroup analysis was performed to assess the consistency of immunotherapy outcomes within tumour-site-specific OSCC cohorts. Among the nine included studies, three (33.3%) provided OSCC-specific outcome data, whereas six (66.7%) involved mixed HNSCC/OPC or non-oral-cavity populations without sufficient OSCC stratification and were therefore considered contextual evidence. The OSCC-specific studies demonstrated favourable immunotherapy activity, with reported objective response rates (ORRs) ranging approximately from 60% to 75%, particularly among patients receiving neoadjuvant PD-1 inhibitor-based combination strategies. Where reported, pathological complete response (pCR) outcomes showed encouraging trends in locally advanced resectable OSCC, although direct comparison was limited due to variations in treatment protocols and outcome reporting. Given the clinical and methodological heterogeneity among the included studies, including differences in tumour stage, immunotherapy regimens, study designs, and endpoint definitions, a random-effects model was applied.

Even though PFS and OS data were limited and reported inconsistently, the evidence accessible showed that immunotherapy-based combination strategies could be associated with better clinical outcomes, especially in PD-L1-positive and locally advanced resectable OSCC. Moreover, a comparative assessment of studies showed

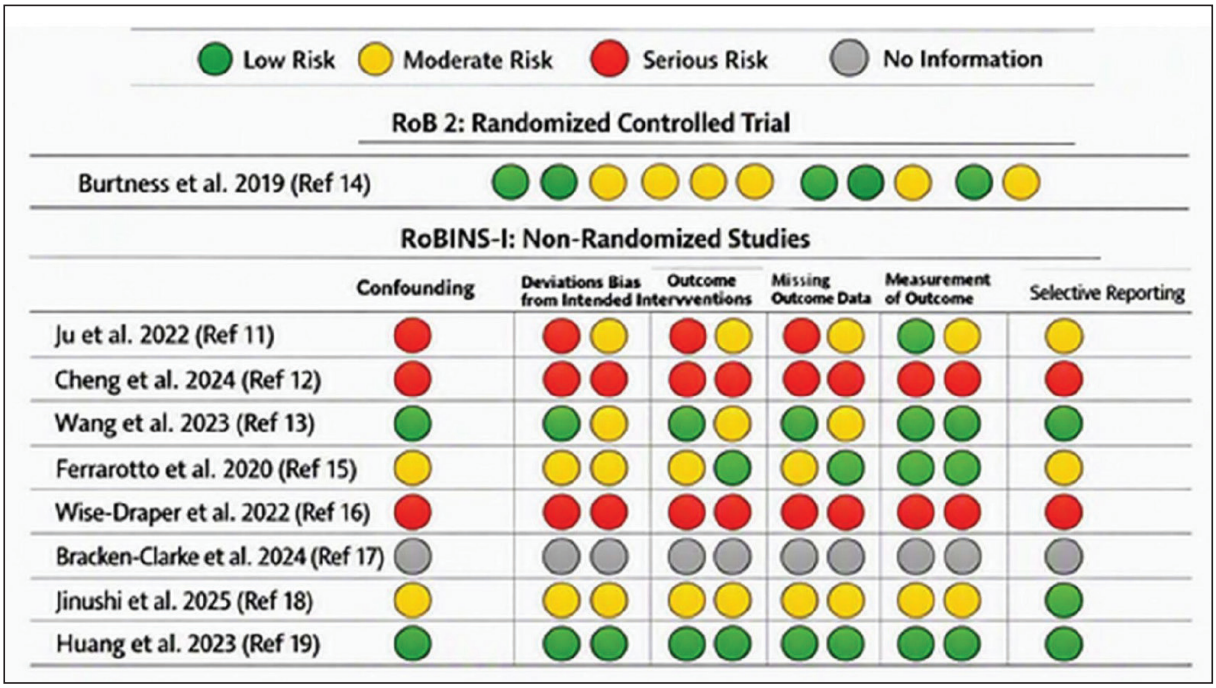

Figure 2. Traffic-light Plot Showing the Risk of Bias (RoB) Across Six Domains for the 09 Included Studies. Green Represents Low Risk, Yellow Indicates Unclear Risk, and Red Denotes High Risk of Bias. This Figure Summarizes Study Quality and Potential Biases for Each Included Trial.

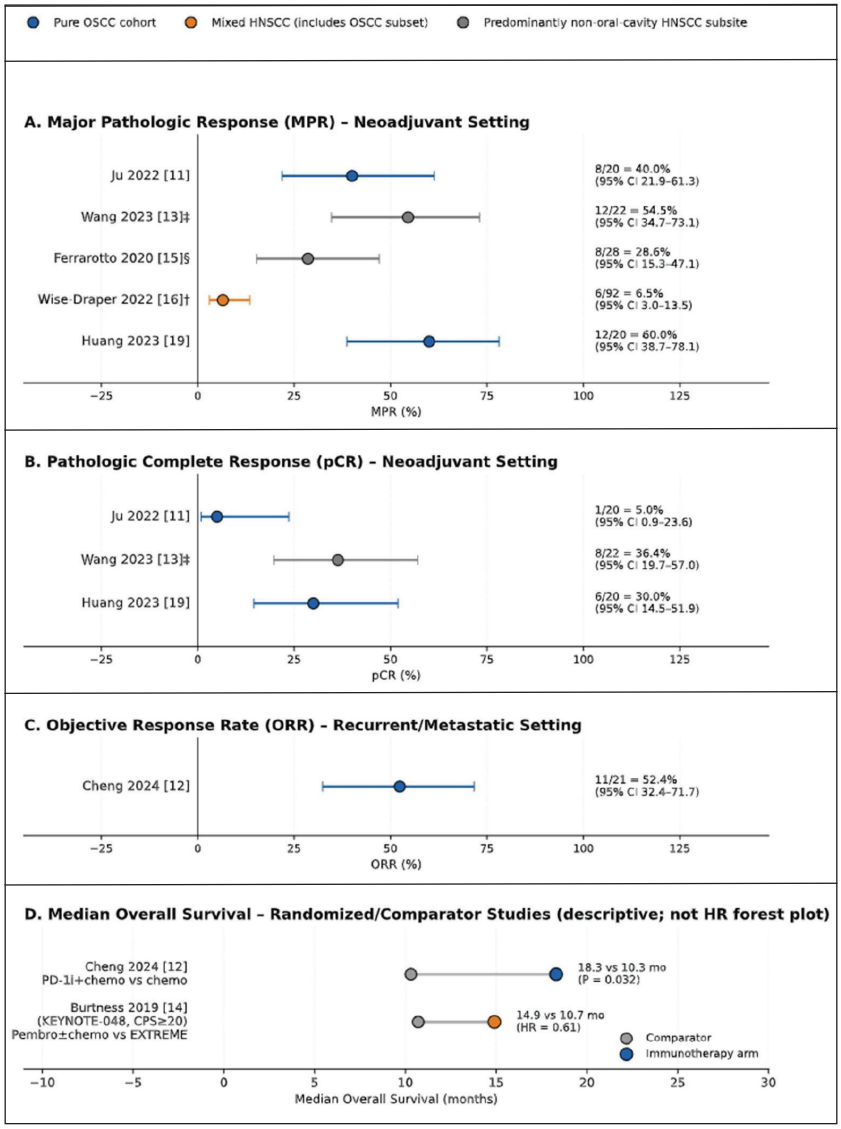

Figure 3. Forest Plot Displaying the Overall Response Rate (ORR) and Pathological Complete Response (pCR) for the for included studies Immunotherapy Studies in Oral Squamous Cell Carcinoma (OSCC)/Head and Neck Squamous Cell Carcinoma (HNSCC). Blue Circles Represent ORR (%) and Green Squares Represent pCR (%). Each Study, With Author and Reference Number, is Shown Along the y-axis.

Note: This is a descriptive display of individually reported study estimates, Not a pooled/meta analytic forest plot (no summary diamond is shown) given marked heterogeneity in tumor subsite, disease setting, and treatment regimen.

† Wise-Draper 2022: MPR (7%) denominator approximated from total enrolled *N* = 92 (exact evaluable patient denominator not specified in source).

‡Wang 2023: cohort predominantly hypopharyngeal/oropharyngeal carcinoma; only 1/22 (4.5%) patients had oral cavity SCC.

§ Ferrarotto 2020: oropharyngeal carcinoma (OPC) cohort, not oral cavity SCC; shown for HNSCC neoadjuvant context.

Panel D shows raw reported median OS by arm for the two comparator (non single arm) studies; 95% C15 for OS were not extracted from the source table.

that OSCC-specific results were, in general, pointing in the same direction as those from broader HNSCC cohorts, even if the statistical capability remains restricted due to the low number of samples and incomplete subgroup reporting. Only explicitly reported or sufficiently detailed data were taken into account for OSCC-specific outcomes. Studies combining HNSCC/OPC cases without separate OSCC reporting were marked as 'No' or 'Partial' accordingly.

Estimates from individual studies varied between 0.60 and 0.75, with higher response rates observed in neoadjuvant combination regimens, particularly PD-1 inhibitors combined with chemotherapy or VEGFR2 blockade.[11,13] Pathological complete response (pCR) rates, reported in a limited number of studies,[11,13,19] ranged between 15% and 35%, with combination immunotherapy appearing most promising. PFS and overall survival (OS) outcomes were scarcely reported,[13,15] but available data suggested favourable trends in PD-L1-positive and locally advanced OSCC, often inferred from mixed HNSCC cohorts. In summary, while efficacy patterns in OSCC correspond to overall HNSCC data,[14] the scarcity of stratified outcomes

Study	Reported outcomes
Ju et al. (2022)	Major pathological response (MPR): 40% Pathological complete response (pCR): 5%
Cheng et al. (2024)	Objective response rate (ORR): 52% Median overall survival (OS): 18.3 vs 10.3 months
Huang et al. (2023)	Major pathological response (MPR): 60% Pathological complete response (pCR): 30% 2-year overall survival (OS): 95%
Descriptive study-level results; endpoints and treatment settings differ. No pooled estimate is presented.	

Figure 4. Descriptive summary of reported outcomes in three oral squamous cell carcinoma (OSCC)-specific studies. Outcomes represent different endpoints and treatment settings and should not be compared directly. For Cheng et al. (2024), median overall survival is reported for PD-1 inhibitor plus chemotherapy versus standard chemotherapy, respectively.

underscores the need for dedicated OSCC-specific trials (Figure 4 and Table 5).

Discussion

OSCC still ranks among the top cancers worldwide and causes considerable illness and death globally despite the improvements in diagnosis and treatment, especially in places where people have very limited access to early diagnosis and a full range of medicines.[1–3] A mix of surgery, radiotherapy, and chemotherapy as a standard has resulted in progressive survival to a small extent only. However, this ray of hope is usually overshadowed by the high relapse rates and resistance to treatment already present in the tumour.[5] Since the effectiveness of the treatment has seen a plateau, immunotherapy is being explored as a way to re-activate the patient's immune system to fight cancer cells and eliminate them.[6,7] PD-1/PD-L1 antibodies among ICIs have shown great potential in clinical trials of patients with recurrent and metastatic OSCC, mainly by lifting T-cell exhaustion and improving antitumour cytotoxic capability.[8–10] Nonetheless, these enhancements in patients' conditions do not occur uniformly, as only a handful of people get long-term benefits. Some factors that prevent these include the inability of the cells to present antigens, defects in the IFN-γ signalling pathway, and the presence of an immunosuppressive tumour microenvironment.[9,10] Furthermore, the issue of adaptive resistance further complicates the situation significantly.

Several new combination therapy regimens are currently being developed in order to overcome the resistance mechanisms of OSCC and to enhance the effectiveness of the treatments. One of the approaches is the neoadjuvant use of a PD-1 inhibitor and a VEGFR2 inhibitor, which is camrelizumab in combination with apatinib. This combination has shown successful tumour regression and a tolerable safety profile in patients with resectable, locally advanced OSCC.[11,13,15,16,19] This synergistic effect may be explained by the fact that VEGFR2 inhibition leads to vascular normalisation. It is also known that by modulating the tumour vasculature, one can decrease the immunosuppressive populations like regulatory T-cells and myeloid-derived suppressor cells (MDSCs), that is, further contributing to re-establishing the antitumour immune response.

Notably, the combination of pembrolizumab and neoadjuvant chemotherapy was the main factor that made the very high pathological response rates possible, particularly in patients who showed high PD-L1 expression or had HPV-positive tumours. Besides, this discovery fits well with the immunotherapy being used as a very effective way to reduce tumour stage before surgery.[12–14] Despite this, the improved responses seen with immunochemotherapy are most probably due to chemotherapy killing tumour cells in a way that makes them more visible to the immune system; thus, more tumour antigens are made available to the immune system, and dendritic cells get activated, which then stimulates T-cell mediated immunity. This sequence of events, together with checkpoint inhibition, greatly increases antigen presentation and T-cell expansion, and as a result it breaks

Table 5. Efficacy Outcomes of Included Clinical Immunotherapy Studies in OSCC/HNSCC Objective response rate (ORR), pathological complete response (pCR), disease-free survival (DFS), progression-free survival (PFS), and overall survival (OS) are reported where available. NR = Not Reported.

Ref No.	Author / Year	Population Type	ORR (%)	pCR (%)	DFS	PFS	OS	Key Therapy	Remarks
[11]	Ju, 2022	Locally advanced, resectable OSCC	NR	5% (1/20)	NR	NR	NR	Camrelizumab + Apatinib (neoadjuvant)	OSCC-specific study (n = 20); MPR 40% (8/20).
[12]	Cheng, 2024	Recurrent/metastatic OSCC	52% (11/21)	NR	NR	6.7 months	18.3 vs 10.3 months	PD-1 inhibitor + chemotherapy	OS significantly improved compared with standard chemotherapy (P = 0.032).
[13]	Wang, 2023	Resectable stage III–IVA HNSCC	NR	36.4% (8/22)	NR	NR	NR	Pembrolizumab + neoadjuvant chemotherapy	Only one oral cavity cancer patient; MPR 54.5% (12/22).
[14]	Burtness, 2019	Recurrent/metastatic HNSCC	NR	NR	NR	NR	14.9 vs 10.7 months	Pembrolizumab ± chemotherapy	Large HNSCC study; OS benefit reported in CPS ≥20 subgroup; OSCC-specific outcomes unavailable.
[15]	Ferrarotto, 2020	Resectable OPC	NR	NR	NR	NR	NR	Durvalumab ± Tremelimumab (neoadjuvant)	OPC-only population; MPR 29% (8/28).
[16]	Wise-Draper, 2022	Resectable locoregionally advanced HNSCC	NR	NR	NR	NR	NR	Neoadjuvant + adjuvant Pembrolizumab	Pathological response in 39%; MPR 7%; includes OSCC but no separate OSCC outcomes.
[17]	Bracken-Clarke, 2024	Newly diagnosed HPV-positive OPC	NR	NR	NR	NR	NR	PRGN-2009 vaccine + Pembrolizumab	ORR not reported; findings not directly applicable to OSCC.
[18]	Jinushi, 2025	Mixed advanced solid tumours	NR	NR	NR	Reported by dose cohort	Reported by dose cohort	Mogamulizumab + Nivolumab	Only one oral cancer patient; insufficient for OSCC-specific interpretation.
[19]	Huang, 2023	Locally advanced, resectable OSCC	NR	30% (6/20)	NR	NR	2-year OS: 95%	Neoadjuvant immunochemotherapy	OSCC-specific study (n = 20); MPR 60% (12/20); 100% R0 resection.

tolerance to the tumour even in the tumour microenvironment. In addition, not only do immunochemotherapy trials indirectly demonstrate immune activation, but also neoadjuvant and combination immunotherapeutic trials such as durvalumab with or without tremelimumab (CIAO trial),[15] perioperative pembrolizumab regimens,[16] bifunctional fusion antibodies targeting EGFR and new checkpoint or cellular therapies including HPV vaccines,[17] and CAR-T constructs[19,20] are examples of how diverse therapeutic avenues may converge to elicit strong immune responses in head and neck cancers, thus laying down the foundation for future therapeutics. On the other hand, newly gathered data from recent clinical trials such as Illuminate,[19] which is testing neoadjuvant immunochemotherapy, together with studies of bifunctional antibodies, checkpoint inhibitor combinations, and macrophage-targeting therapies are rapidly providing more evidence about how immune-based strategies, both alone and combined, will change the treatment landscape and can be exploited for the benefit of resectable and advanced OSCC patients.

One of the future immunotherapies on the horizon is adoptive cell therapies, for example, CAR-T-cell strategies directed at EPHB4, and γδ T-cells, which can offer accurate targeting and strong tumour cell killing ability while causing low toxicity.[19,20] Moreover, a preliminary-stage trial of combinations such as mogamulizumab with nivolumab, which shows good patient tolerability and immune-stimulating effects, thus pointing to a possible therapeutic synergy in solid tumours like OSCC, is being considered.[18]

The situation is not without problems, however, despite the promising early outcomes. Most studies are restricted by their small sample sizes, inadequately characterised populations, and short durations of follow-up.[6–10] Quantitative synthesis, such as meta-analytic I^2 calculations, was not done; thus, it was difficult to estimate the true effect and heterogeneity between the studies.[11–19] Besides this, OSCC-specific data are very limited as compared to broader HNSCC studies, leading to the call for OSCC-site-specific research to uncover immune response heterogeneity and resistance mechanisms in tumours.[6–10] Some of the mechanistic and therapeutic insights discussed in the article are derived from non-OSCC tumours, such as non-small cell lung cancer (NSCLC) and cutaneous squamous cell carcinoma (cSCC), which justifies their inclusion by the fact that these tumours of squamous epithelia share the same oncogenic pathways and immune regulatory mechanisms. Major targets of immunotherapy, including the PD-1/PD-L1 pathway and CTLA-4 signalling have been shown to play conserved roles in the regulation of T-cell exhaustion and tumour immune escape in these different cancer types. Besides this, changes in EGFR signalling, TGF-induced immunosuppression, and angiogenesis are among the major events contributing to OSCC development, which further justifies the biological rationale for translational extrapolation.

Given the very different tumour microenvironment, the microbiome interactions, and carcinogenic exposures specific to oral cavity tumours, one should be very careful when interpreting the results of studies on NSCLC and cSCC. That is why in this review evidence from clinical studies on OSCC has been dealt with separately whenever possible, whereas results from other types of cancer have been shown mostly to provide a mechanistic background and a basis for the development of new therapeutic approaches.

Translational Relevance and Cross-tumour Evidence

There is an insufficient strategy to compare different tumour types in the study of immunotherapy coming from/to be developed. Even though work on NSCLC and cSCC has significantly helped the understanding of biology and mechanisms of resistance of checkpoints, the direct use of them in OSCC is limited due to the tumour-site-specific heterogeneity. Because of this, the present review separates OSCC-based clinical evidence from non-OSCC mechanistic insights so that the final decisions on drug efficacy are mainly based on OSCC-specific data. Table 4 shows how the evidence is divided, with the table emphasising the fact that most of the data are from mixed sources, with only a few OSCC-specific clinical studies.

Overall, the existing data favour immunotherapy as a next adjunct or neoadjuvant therapy in OSCC, which may result in increased pathological response, tumour stage decrease, and survival enhancement, particularly in patient subgroups who are selected correctly.[11–19] Further studies must concentrate on large multicentre randomised clinical trials with the standard reporting of immune biomarkers, mechanisms of resistance, and long-term outcomes to realise the best possible patient selection and combination regimen optimisation, thereby leading to personalised immunotherapeutic treatment in OSCC. One major drawback of the existing evidence is that OSCC-specific analyses are underrepresented, as a lot of the trials provide aggregated outcomes for diverse HNSCC populations. Subgroup trends imply that immunotherapy may be equally effective in OSCC; however, the absence of dedicated OSCC datasets hampers drawing firm conclusions. This underscores the highly needed tumour-site-specific trials and biomarker-driven analyses aligned with the unique immunobiology of OSCC.

Limitations

This review suffers from several shortcomings; the majority of the trials are in the early phase, the number of participants is small, the study designs are very different from one another, and there is little data surviving for a long time. Besides this, a lot of studies do not perform subgroup analyses specifically for OSCC, which restricts to what degree the present results can be generalised.

Table 6. Evidence of Established and Emerging Immunotherapy Biomarkers in OSCC Versus Non-OSCC (HNSCC).

Biomarker	Biological Role	Evidence in OSCC	Evidence Source	Clinical Relevance
PD-L1 (CPS)	Immune checkpoint expression	Strong	OSCC + HNSCC (11–15)	Standard predictive biomarker
HPV status	Viral-driven immune activation	Moderate (OPC-driven)	Mixed HNSCC/OPC (15, 20)	Prognostic + predictive
Tumour mutational burden (TMB)	Neoantigen load	Limited	Mainly HNSCC (14–20)	Potential predictor of ICI response
IFN-γ signature	T-cell inflamed phenotype	Indirect OSCC evidence	Mechanistic/mixed (9, 10)	Predicts response & resistance
Tertiary lymphoid structures (TLS)	Local immune activation niches	Limited	Translational/non-OSCC (18)	Emerging spatial biomarker

Future Perspectives

Multiple large multicentre trials, especially mechanistic studies on OSCC, are indispensable for the fine-tuning of the immunotherapy combination and overcoming resistance.

Clinical/Managerial Application in Dentistry

Acquaintance with immunotherapy will encourage oral oncologists and dental surgeons to improve preoperative planning, patient counselling, and the use of neoadjuvant systemic therapies to achieve better surgical results with fewer recurrences. Resistance to ICIs in OSCC, according to new studies, is due to a combination of factors including both tumour-intrinsic and tumour-extrinsic mechanisms. Tumour-intrinsic resistance is associated with alterations in the antigen presentation machinery (e.g., loss of 2-microglobulin), defects in the interferon signalling pathways, and oncogenic pathway activation (e.g., PI3K/AKT). Tumour-extrinsic mechanisms are immunosuppressive cellular components such as regulatory T-cells (Tregs), MDSCs, and tumour-associated macrophages (TAMs) that collectively produce the immune-excluded or immune-desert phenotype.

Emerging Predictive Biomarkers in OSCC Immunotherapy

Beyond PD-L1 combined positive score (CPS) and HPV status, emerging biomarkers are increasingly recognised as critical determinants of immunotherapy response in OSCC. Tumour mutational burden (TMB) has been associated with enhanced neoantigen load and improved responsiveness to ICIs; however, OSCC-specific validation remains limited, with most evidence extrapolated from broader HNSCC cohorts.[13–17]

IFN-γ–related gene expression signatures have demonstrated potential in predicting response by reflecting a pre-existing inflamed tumour microenvironment, characterised by activated cytotoxic T-cell infiltration. Studies suggest that IFN-γ signalling integrity is essential for sustained response to PD-1/PD-L1 blockade, and its disruption may contribute to resistance mechanisms observed in OSCC.[9,10]

Moreover, the identification of tertiary lymphoid structures (TLS) in the tumour microenvironment has become a valuable spatial biomarker, revealing local immune activation and better antitumour response. On the other hand, the role of TLS in OSCC is still not well documented, and the data mainly come from translational or mixed-cohort studies.[20] By and large, these biomarkers demonstrate the transition from single- to multi-parametric immune profiling in OSCC. Yet, the clinical applicability of these markers is currently limited by the diversity of assessment methods, the absence of standardised thresholds, and the scarcity of OSCC-specific validation, thereby pointing to the necessity for prospective biomarker-driven trials. A condensed version of well-known and emerging immunotherapy biomarkers, as well as their OSCC-specific relevance, is shown in Table 6.

Conclusion

Immunotherapy offers great promise in treating head and neck cancers, but making OSCC-specific conclusions is still difficult due to lack of stratified evidence. Data from OSCC only point to good results. Yet, bigger, well-focused OSCC trials are needed to confirm these results and to best work out personalised treatment plans.

Acknowledgement

None.

Authors' Contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval

of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be authors as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

Consent to Participate

Not Applicable.

Consent for Publication

Not Applicable.

Data Availability Statement

All the data is available with the authors and shall be provided upon request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Ethical Approval

This study does not involve experiments on animals or human subjects.

Funding

The authors received no financial support for the research, authorship and/or publication of this article.

Informed Consent

Not Applicable.

Use of Artificial Intelligence (AI)-assisted Tools

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

Supplemental Material

Supplemental material for this article is available online.

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