The Role of the Oral Microbiome in Modulating Immune Checkpoint Inhibitor Response in Oral Squamous Cell Carcinoma (OSCC)

Maria Novensa Dinamikrata[1], Retno Pudji Rahayu[2*]

[1]Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.

[2]Department of Oral and Maxillofacial Pathology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia.

***Corresponding author**

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) are now part of the treatment options for head and neck cancer, but only some patients with oral squamous cell carcinoma (OSCC) benefit from them. The oral microbiome has drawn attention as one possible reason for this uneven response. **Objective**: This narrative review examined how the oral microbiome relates to the tumor immune microenvironment and to the response to ICIs in OSCC. **Methods:** A narrative review was conducted with a structured search of PubMed, Scopus, and Google Scholar for English-language publications from 2016 to 2026. After title and abstract screening and full-text assessment against stated eligibility criteria, 58 sources were included and classified by how directly they apply to OSCC: studies in OSCC patients, studies in other head and neck cancers, animal models, other tumor types, and reviews or consensus documents. Findings were grouped into four themes and analyzed narratively, distinguishing prognostic from predictive evidence. **Results:** The oral and intratumoral microbiomes of patients with OSCC differ from those of healthy individuals, although the reported changes vary across studies. Anaerobic bacteria on the tumor surface were associated with more advanced disease, shorter recurrence-free survival, and increased CD8+ T-cell exhaustion; this is prognostic rather than predictive evidence. Direct evidence on immunotherapy response in OSCC comes from two small cohorts: in 47 patients, salivary microbiome profiles were associated with response to neoadjuvant immunotherapy, and in a study of neoadjuvant immunochemotherapy, specific intratumoral taxa, but not overall diversity, differed by response. An exploratory CheckMate 141 analysis in head and neck squamous cell carcinoma found no clear relationship between overall salivary diversity and response to nivolumab; differences in population, endpoint, sample type, and sequencing method may explain these discrepancies. Possible mechanisms include chronic inflammation, T-cell exhaustion, microbial metabolites, and interactions between the oral and gut microbiomes, which remain hypothetical. Evidence for microbiome-based interventions in OSCC remains limited to animal studies. **Conclusion:** The oral microbiome may serve as a potential biomarker and a target to support immunotherapy in OSCC. However, current evidence is insufficient for clinical use. Prospective studies with standardized methods and validation in independent OSCC cohorts are needed.

Keywords: Oral microbiome; Oral squamous cell carcinoma; Immune checkpoint inhibitor; PD-1; Tumor immune microenvironment

INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most common malignancy of the oral cavity and makes up most of the cancers found in that area (Di Bello & Scala, 2026; Sami et al., 2020). Treatment can involve surgery, radiotherapy, and chemotherapy, depending on the stage of the disease and the condition of the patient. Doctors usually decide by looking at how far the tumor has spread, whether the surrounding tissue is involved, and the patient's general health. Even though treatment options have expanded, recurrence and spread are still a

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challenge, especially in advanced disease. One reason is that cancer can arise from several genetically altered areas of the oral mucosa, so tissue left behind after surgery may still carry changes that lead to new tumors (Puspasari et al., 2023). In recent years, immunotherapy with immune checkpoint inhibitors (ICIs) has received growing attention in the management of head and neck cancer (Di Bello & Scala, 2026; S. Liu et al., 2026).

ICIs work by blocking signals that normally keep the immune system in check, mainly the programmed cell death protein 1 (PD-1) and programmed death-ligand 1 (PD-L1) pathway. Once this block is lifted, T cells can recognize and attack cancer cells again (Ekong et al., 2025). Pembrolizumab and nivolumab are anti-PD-1 drugs that have shown clinical benefit in some patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) (Ekong et al., 2025; Ferris et al., 2017). The benefit, however, is not shared by everyone. Some patients respond well, while others do not respond enough or see their disease progress.

This difference in response has pushed researchers to look for factors that influence how well ICIs work. Besides the genetic and biological features of the tumor, attention has turned to the tumor immune microenvironment (TIME), which is the area around the tumor made up of immune cells, blood vessels, supporting tissue, inflammatory mediators, and other biological components. The TIME plays a major role in whether the immune system can recognize and control tumor growth. The mix and activity of the cells inside it can support an antitumor response, or they can create conditions that suppress immunity. In the oral tumor environment, immunosuppressive cells such as regulatory T cells, tumor-associated macrophages, and myeloid-derived suppressor cells can dampen the activity of NK cells and CD8+ T cells, and targeting these cells has been proposed as a way to improve immunotherapy (Budi & Farhood, 2023). Several studies in OSCC have also reported links between the microbiome, immune cell infiltration, and the immune state of tumor tissue (Kashima et al., 2025; Wei et al., 2025; Xu et al., 2025). The microbiome is one of the components thought to help shape this environment.

The oral microbiome includes the microorganisms living in different parts of the mouth, such as saliva, dental plaque, mucosa, the tumor surface, and the tissue inside the tumor. These communities contain bacteria, fungi, viruses, and other microbes that interact with host tissue and the immune system (Di Bello & Scala, 2026; Sami et al., 2020). Microbes are not always harmful. When the community is balanced, it helps maintain oral health. When its composition or function shifts, a state called dysbiosis, it can be associated with inflammation and changes in the immune response. In OSCC, several studies have reported microbiome changes, but the organisms that increase or decrease are not always the same from one study to another (Matsui et al., 2024; Sami et al., 2020; Singh et al., 2023). This suggests that the link between the microbiome and OSCC depends not only on which microbes are present, but also on how they interact with each other and on the environment where they live (Di Bello & Scala, 2026; Matsui et al., 2024).

The relationship between the microbiome and ICI response is worth studying because microbes can interact with epithelial and immune cells, both locally and throughout the body. These interactions may affect T-cell activity, cytokine production, tissue metabolism, and the expression of checkpoint molecules (Ekong et al., 2025; Wei et al., 2025; Xu et al., 2025). Some studies link the microbiome to changes in immune pathways, including PD-1/PD-L1 (Ekong et al., 2025; Guerrero-Preston et al., 2017). Even so, finding a certain bacterium in tumor tissue does not automatically mean that it causes resistance to immunotherapy or improves its success.

Research on the microbiome and immunotherapy keeps growing, but evidence that specifically connects the oral microbiome with ICI response in OSCC patients is still limited. Some studies address head and neck cancer in general, while others focus on the gut microbiome or on different cancer types (Di Bello & Scala, 2026; Ekong et al., 2025; Khalil et al., 2026; S. Liu et al., 2026). The results in OSCC patients who receive immunotherapy are not fully consistent either. For example, a study of OSCC patients given neoadjuvant immunotherapy found features of the salivary microbiome that were related to treatment response (X. X. Wang et al., 2024), whereas an analysis from CheckMate 141 found no meaningful relationship between overall salivary microbial diversity and the response to nivolumab in HNSCC patients (Ferris et al., 2017). These differences show that the link between the microbiome and immunotherapy response needs closer study, especially with regard to the type of microorganism, the sampling site, and the biological and clinical condition of the patient.

Based on this background, this review discusses the relationship between the oral microbiome, the tumor immune environment, and the response to ICIs in OSCC. It covers evidence from human studies and preclinical models, the biological mechanisms that may be involved, and the chances of using the microbiome as a biomarker or a companion target for immunotherapy (Díaz-Rivera et al., 2024; Ferris et al., 2017; X. X. Wang et al., 2024; D. W. Zheng et al., 2022). Because much of the available evidence comes from outside OSCC, the review states how directly each source applies to OSCC and separates prognostic associations from predictive evidence. The review also describes the limits of the available evidence and the directions future research should take (Di Bello & Scala, 2026; Khalil et al., 2026; S. Liu et al., 2026).

METHODOLOGY

This article is a narrative review. A narrative design was chosen because the available studies differ widely in population, sample type, sequencing method, and outcome, which makes statistical pooling unsuitable. The evidence was therefore summarized thematically rather than quantitatively. To make the process transparent and reproducible, the search, selection, and classification steps are described below.

1. Search strategy

Relevant literature was identified through searches of PubMed, Scopus, and Google Scholar. The final search was completed on November 2026. Publications from January 2016 to November 2026 were considered, and the search was limited to articles published in English. The core PubMed query combined three concept blocks: ("oral microbiome" OR "oral microbiota" OR "salivary microbiome" OR "intratumoral microbiome" OR "intratumoral microbiota") AND ("oral squamous cell carcinoma" OR OSCC OR "head and neck squamous cell carcinoma" OR HNSCC) AND ("immune checkpoint inhibitor" OR immunotherapy OR "PD-1" OR "PD-L1" OR "tumor immune microenvironment" OR "treatment response"). Equivalent queries were adapted to the syntax of Scopus (title, abstract, and keyword fields) and Google Scholar. Additional targeted searches on mechanistic and methodological topics (for example, T-cell exhaustion, microbial metabolites, the oral–gut axis, low-biomass sampling, and sequencing methods) were run to support the corresponding sections.

2. Study selection and eligibility criteria

Records from the three sources were pooled and duplicates were removed. Titles and abstracts were initially screened, followed by full-text assessment of potentially eligible publications against the criteria presented in Table 1. A total of 58 sources were retained for the final narrative synthesis. Sources were retained when they dealt with the oral or intratumoral microbiome in relation to OSCC or head and neck cancer, the tumor immune microenvironment, immune checkpoint pathways, or the response to ICIs. Each retained source was assigned to at least one of the four themes below and to one role: primary evidence, mechanistic or preclinical evidence, or background and methodological context. Studies from other cancer types were included only when they helped explain mechanisms, study design, or intervention strategy.

Table 1. Eligibility criteria used to select the 58 sources.

Criterion	Included	Excluded
Topic	Oral (saliva, plaque, mucosa, tumor surface) or intratumoral microbiome in relation to OSCC or head and neck squamous cell carcinoma (HNSCC), the tumor immune microenvironment, immune checkpoint pathways, or ICI response	Microbiome studies with no link to tumor immunity or immunotherapy

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Other tumor types	Used only when informative for mechanisms, study design, or intervention strategy (for example, gut microbiome and ICIs, fecal microbiota transplantation trials)	Studies of other cancers with no bearing on these aspects
Study type	Human observational studies and trials; preclinical animal studies; mechanistic and translational papers; systematic, scoping, and narrative reviews; consensus statements and methodological guidance	Case reports as evidence on microbiome and ICI response (one case report was cited only as an example of clinical confounding)
Publication format	Peer-reviewed articles; conference abstracts only when they were the sole available clinical data on microbiome profiling and ICI response in head and neck cancer (three abstracts, labeled in the text)	Other non-peer-reviewed material
Language and period	English; published 2016–2026	Other languages; published before 2016

OSCC, oral squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor.

3. Composition and classification of the included sources

The 58 sources comprised 12 original studies using OSCC patient samples or data (nine microbiome studies, two studies of immune cells in OSCC tissue, and one case report), four studies in other head and neck settings (three conference abstracts and one salivary study that did not assess microbes), three studies using preclinical models (one of which also analyzed HNSCC patient samples), three studies of other tumor types or conditions (a melanoma fecal microbiota transplantation trial, a multi-cancer gut microbiome signature, and a small study of Warthin's tumor), and 36 reviews, systematic or scoping reviews, consensus statements, and methodological guidance documents. To keep applicability to OSCC explicit, each primary study was assigned to an evidence tier: Tier 1, studies in OSCC patients; Tier 2, studies in head and neck cancer more broadly; Tier 3, preclinical models; and Tier 4, other tumor types. The tier is shown in Table 2 and is named in the text wherever the population is not OSCC.

4. Data extraction and synthesis

For each primary study, the design, population and sample size, sample type and microbiome method, main findings, and limitations were extracted into Table 2. Findings were also labeled by the kind of claim they support (Cottrell et al., 2025). A prognostic association links a feature to outcome regardless of treatment. A predictive association shows that a feature identifies who benefits from a specific treatment, which requires a comparison between differently treated or untreated patients. Descriptive or mechanistic findings show that features differ or may act, without linking them to outcome. The findings were grouped into four themes: (1) the oral microbiome and the immune environment in OSCC, (2) clinical evidence linking the microbiome with ICI response, (3) biological mechanisms, and (4) possible clinical uses. Because this is a narrative review, no formal quality scoring or meta-analysis was done. Where studies disagreed, the differences were reported and compared (Table 3) instead of being resolved.

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REVIEWS

Table 2 summarizes the primary studies discussed in this section, grouped by how directly they apply to OSCC. For each study it gives the design and population, the sample and method, the principal findings, the kind of association shown, and the main limitations. In the text that follows, the population is named whenever evidence comes from outside OSCC patients.

Table 2. Characteristics, findings, and limitations of the primary studies, grouped by evidence tier.

Study	Design and population	Sample and method	Principal findings	Type of association	Main limitations
Tier 1. Studies in OSCC patients					
Wang et al., 2024	47 OSCC patients in a neoadjuvant immunotherapy trial (NCT04649476); responders vs nonresponders by pathological response	Pre-treatment saliva; shotgun metagenomics	Lower species richness in nonresponders; low *E. infirmum*, *Actinobaculum*, and *Selenomonas* (EAS group) in nonresponders; model AUC 0.81 (training cohort); EAS related to CD4+, CD14+, CD68+, and FOXP3+ cell density	Response-associated (candidate predictive)	Small sample; single regimen with no comparator; needs independent validation
Zheng X et al., 2026	Locally advanced OSCC given neoadjuvant immunochemotherapy; MPR vs non-MPR; 42 specimens	Intratumoral tissue before and after treatment; 2bRAD-M	No baseline diversity difference; *Ralstonia*, *Methylobacterium*, and *Rothia* enriched in non-MPR (AUC 0.74); diversity fell after treatment	Response-associated (candidate predictive)	Chemotherapy confounds ICI effect; small sample; low-biomass tissue
Kashima et al., 2025	23 OSCC patients: anaerobe-dominant (n = 13) vs aerobe-dominant (n = 10) tumor surface	Tumor-surface microbiota; immune profiling of CD8+ T cells	Anaerobic dominance: more advanced disease, shorter recurrence-free survival, more PD-1+ Tim-3+ CD8+ T cells	Prognostic and immune-phenotype association	Small sample; patients not selected by ICI treatment; association only
Zang et al., 2025	TCGA OSCC dataset (n = 340 tumor samples; 32 adjacent normal samples); bioinformatic analysis	Microbial signal inferred from public sequencing data; immune deconvolution	19-microorganism signature; high-risk profile linked to shorter survival, PI3K/AKT/mTOR activity, and a more immunosuppressive environment	Prognostic	Retrospective database analysis; no ICI-treated cohort; contamination risk in tumor sequencing data
Wei et al., 2025	36 OSCC patients and 34 healthy controls; TCGA and GEO transcriptomes	Saliva 16S rDNA sequencing; transcriptome analysis	Distinct oral microbiota composition; microbe-related immune pathways linked to survival	Descriptive and prognostic	Indirect link between saliva and tumor immunity; no ICI outcomes

Fang et al., 2025	45 OSCC tissues with 10 paracancerous and 8 normal controls	Tumor microbiome (abundance and load); IHC for CD4, CD8, FOXP3, and PD-L1	Microbial load inversely related to T-cell infiltration (CD4+ significant); other markers not all significant	Descriptive (immune correlates)	Cross-sectional; small single-site sample
Xu et al., 2025	OSCC patients and healthy volunteers (n = 100: 50 OSCC patients and 50 healthy volunteers)	Saliva 16S rRNA sequencing; blood IL-2, IL-10, and IFN-γ by ELISA	*Peptostreptococcus* correlated positively with IL-2 and IFN-γ; *Oralobacter* with IL-10	Descriptive (systemic immune correlates)	Cross-sectional; direction of effect unknown
Singh et al., 2023	OSCC and precancerous tissue samples (n = 75 patients; 15 precancerous and 60 OSCC patients, including early- and late-stage groups); 20 adjacent normal tissue samples.	Tissue 16S rRNA sequencing; flow cytometry and IHC	Taxa shifted with stage (*Fusobacterium*, *Capnocytophaga*, *Treponema* in cancer; *Streptococcus*, *Rothia* in precancer); microbiota related to intratumoral immune signature	Descriptive	Cross-sectional; cannot show causation
Matsui et al., 2024	18 OSCC patients and 7 healthy controls	Dental plaque and feces; T-RFLP of 16S rRNA genes; PD-L1 IHC	Oral and gut dysbiosis; *Clostridium* subcluster XIVa higher in gut of PD-L1-positive tumors	Descriptive (oral–gut)	Very small sample; low-resolution method; no ICI outcomes
Tier 2. Studies in head and neck cancer more broadly (not OSCC-specific)					
Ferris et al., 2017 (abstract)	CheckMate 141: recurrent or metastatic HNSCC; nivolumab vs investigator's choice; 221 saliva samples	Saliva; 16S rRNA sequencing (542 species)	No relation of overall richness to clinical response, PD-L1, or HPV16 status; alpha and beta diversity unrelated to treatment	Response-associated (null; exploratory)	Conference abstract; HNSCC at any subsite; global diversity indices only
Guerrero-Preston et al., 2017 (abstract)	Head and neck cancer patients treated with surgery, chemoradiation, or PD-1 blockade	Microbiome profiling with mRNA arrays	*F. nucleatum*-rich samples: higher Wnt/β-catenin genes (*Wnt7B*, *FZD6*, *SFRP4*), lower *TLR10* and *IRF8*	Descriptive (gene expression)	Conference abstract; not OSCC-specific; association only
Palmieri et al., 2025 (abstract)	Head and neck cancer patients	Not detailed in the abstract	*F. nucleatum* and *Lactobacillus gasseri–johnsonii* linked to PD-1 expression	Descriptive	Conference abstract; limited detail; not OSCC-specific
Silver et al., 2026	HNSCC patient samples, trial data, and orthotopic mouse models	Intratumoral bacterial burden	Higher intratumoral bacteria linked to suppressed T-cell infiltration and reduced response to PD-L1 blockade	Mechanistic and response-associated	Not OSCC-specific; part of the evidence is from mouse models
Tier 3. Preclinical models					

Díaz-Rivera et al., 2024	Mouse model of HPV-positive oropharyngeal cancer; PD-1 blockade responders vs nonresponders	Oral microbiota sequencing	*Allobaculum*, *Blautia*, *Faecalibacterium*, *Dorea*, and *Roseburia* more common in responders; *Enterococcus* higher in nonresponders	Preclinical, response-associated	HPV-positive oropharyngeal model, not OSCC; mouse data
Zheng DW et al., 2022	Mouse OSCC models	Silver nanoparticle hydrogel to suppress competing bacteria plus *P. anaerobius*	Improved antitumor response with synergy when combined with PD-1 blockade	Preclinical, interventional	Animal data only; human safety and benefit unknown
Tier 4. Other tumor types					
Routy et al., 2023	Advanced melanoma; phase I trial of fecal microbiota transplantation plus anti-PD-1	Fecal microbiota transplantation	Shows that microbiome modulation can be tested alongside anti-PD-1 therapy in patients	Interventional (other cancer)	Not OSCC; early-phase trial
Gunjur et al., 2024	Several cancer types receiving combination checkpoint blockade	Gut microbiome	Strain-level and functional features add information beyond taxonomic summaries	Response-associated (gut)	Not OSCC; gut rather than oral microbiome

AUC, area under the curve; EAS, *Eubacterium infirmum*, *Actinobaculum*, and *Selenomonas*; ELISA, enzyme-linked immunosorbent assay; GEO, Gene Expression Omnibus; IHC, immunohistochemistry; HNSCC, head and neck squamous cell carcinoma; ICI, immune checkpoint inhibitor; MPR, major pathological response; OSCC, oral squamous cell carcinoma; T-RFLP, terminal restriction fragment length polymorphism; TCGA, The Cancer Genome Atlas; 2bRAD-M, 2bRAD sequencing for microbiome. "Response-associated" means the feature differed between responders and nonresponders in patients given the same treatment, without an untreated or differently treated comparison.

The Oral Microbiome and the Immune Environment in OSCC

1. Microbial changes during OSCC development

The microbial community of the mouth includes bacteria, fungi, viruses, archaea, and other microorganisms that influence one another (Deo & Deshmukh, 2019; Singh et al., 2023). Its composition is shaped by oral hygiene, periodontal condition, diet, smoking, medication, and the person's overall health (Deo & Deshmukh, 2019, 2021). In OSCC, the growing tumor also changes local conditions such as oxygen level, nutrient supply, and inflammation. Hypoxia and altered metabolism in the tumor can change the habitat of the microbes and may affect which species survive around the tumor (Sami et al., 2020; Vyhnalova et al., 2021).

Work on OSCC tissue has shown that the intratumoral microbiota can differ by stage of tumor development. In one study, *Fusobacterium*, *Capnocytophaga*, and *Treponema* were more common in the cancer group, while *Streptococcus* and *Rothia* stood out in the precancer group (Singh et al., 2023). This suggests that microbial communities shift as the disease advances. It does not prove, however, that the microbes cause the tumor to progress.

A scoping review of 20 studies comparing oral cancer patients with healthy individuals found that the composition of the oral microbiota differed significantly from controls in 17 of them. Most of these differences involved bacteria, and only one study looked at viruses and parasites (Sufiawati et al., 2022). This fits the picture seen in OSCC tissue, and it also shows that non-bacterial members of the community are still poorly studied.

Dysbiosis is also not explained by a simple rise or fall in the number of bacterial types. Changes can occur in the abundance of certain organisms, in their metabolic functions, or in the relationships among community members (Singh et al., 2023; Yu et al., 2023). Several reviews of head and neck cancer reported an increase in bacteria often linked to periodontal disease, including *Fusobacterium* and *Porphyromonas* (Irfan et al., 2020; Sami et al., 2020; Vyhnalova et al., 2021). A meta-analysis in OSCC likewise found more *Fusobacterium* tha-

n in controls, although changes in other bacteria varied with the type of sample analyzed (Yu et al., 2023). A consistent microbial pattern that could serve as a clinical marker has not yet been established (Di Bello & Scala, 2026).

2. Links with the tumor immune microenvironment

The TIME helps decide whether the immune system can recognize and control a tumor. It contains many cell types, including T lymphocytes, macrophages, dendritic cells, and myeloid cells. Depending on their balance and activity, these cells can support an antitumor response or build an immunosuppressive setting that helps the tumor grow. In OSCC, the interaction among these immune cells also affects proliferation, invasion, and the tumor's ability to escape immune surveillance (Caponio et al., 2023; Li et al., 2024). The microbiome is thought to influence this balance through contact with the epithelium, recognition of microbial components by immune receptors, and the production of metabolites that shape inflammation and immune cell activity (Ekong et al., 2025; Sami et al., 2020).

In OSCC patients, composition of the microbiome has been tied to the immune cells found inside the tumor. In a study of 23 patients, a higher proportion of anaerobic bacteria on the tumor surface was associated with more advanced disease, shorter recurrence-free survival, and a greater frequency of CD8+ T cells expressing the exhaustion markers PD-1 and Tim-3 compared with tumors dominated by aerobic bacteria (Kashima et al., 2025). These findings suggest an association between the composition of the tumor microbiome and T-cell functional status. They are prognostic findings in patients who were not selected by immunotherapy, so they do not show that anaerobic dominance predicts ICI benefit or that it causes T-cell exhaustion (Kashima et al., 2025).

The oral microbiome may also relate to immune markers outside the tumor. In OSCC patients, some salivary bacterial groups correlated with blood levels of IL-2, IFN-γ, and IL-10 (Xu et al., 2025). *Peptostreptococcus* correlated positively with IL-2 and IFN-γ, whereas *Oralobacter* correlated positively with IL-10. These correlations do not show whether microbial changes influence the systemic immune response, whether the tumor changes the microbiome, or whether both are driven by a third factor. The relationship between the microbiome and the TIME is therefore best seen as complex and only partly understood (Xu et al., 2025).

3. Links with the immune checkpoint pathway

The PD-1/PD-L1 pathway is one way tumors lower T-cell activity. When PD-1 on a T cell binds PD-L1 on a tumor cell or an antigen-presenting cell, the inhibitory signal weakens T-cell receptor and CD28 costimulatory signaling. As a result, cytokine production, proliferation, and effector function can drop (Borst et al., 2021; Seidel et al., 2018). ICIs that target PD-1 or PD-L1 block this interaction and may restore the antitumor function of T cells (Borst et al., 2021). Still, the success of PD-1 blockade depends on more than the presence of checkpoint molecules. It also depends on the state and differentiation of the T cells, the ability of dendritic cells to present antigen, and the availability of the costimulatory signals needed to start an antitumor response (Seidel et al., 2018).

Microorganisms may influence this pathway by activating pattern recognition receptors, changing cytokine production, regulating innate immune cells, and forming metabolites that alter the immune environment. For example, the interaction between microbes and oral epithelial cells can trigger recognition of microbial components and activate signaling pathways that control inflammation and communication with immune cells (Lamont et al., 2023). Reviews of microbiomes and cancer checkpoints also describe links between microbes and the PD-1/PD-L1 and CTLA-4 pathways (Ekong et al., 2025). Much of this mechanistic evidence still comes from HNSCC in general or from other cancers, so it needs to be tested specifically in OSCC.

A conference abstract on head and neck cancer, not specific to OSCC, reported that HNSCC samples with more *Fusobacterium nucleatum* showed higher expression of genes in the oncogenic Wnt/β-catenin pathway, such as *Wnt7B*, *FZD6*, and *SFRP4*, together with lower expression of immune-related genes, including *TLR10* and *IRF8* (Guerrero-Preston et al., 2017). A separate abstract also linked *F. nucleatum* and *Lactobacillus gasseri–johnsonii* to PD-1 expression in head and neck cancer patients (Palmieri et al., 2025). These findings show an association between bacteria and gene expression. They are not proof that *F. nucleatum* directly controls PD-1/PD-L1 signaling or decides whether anti-PD-1 therapy succeeds (Guerrero-Preston et al., 2017).

Checkpoint signaling is not limited to squamous cell carcinoma of the oral mucosa. In a small study of Warthin's tumor of the salivary gland, CTLA-4 was found in both epithelial and stromal cells, and its presence in the lymphoid stroma was linked to suppressed T-cell activity against tumor cells. The authors suggested that the tumor may grow by escaping control through immune checkpoints (Qotrunnada et al., 2022). Although this is a different tumor, it supports the general idea that checkpoint molecules in the oral and maxillofacial region deserve attention in their own right.

Clinical Evidence Linking the Microbiome to ICI Response

1. Neoadjuvant immunotherapy in OSCC patients

The most direct clinical evidence in OSCC (Tier 1) is provided by a study involving 47 patients who received neoadjuvant immunotherapy (X. X. Wang et al., 2024). The authors analyzed the salivary microbiome before treatment and compared patients with and without a pathological response. Nonresponders had lower species richness in the salivary microbiome than responders. A group of bacteria made up of *Eubacterium infirmum*, *Actinobaculum*, and *Selenomonas* (EAS) was also less abundant in nonresponders. A prediction model based on this group could separate responders from nonresponders, with an area under the curve (AUC) of 0.81 in the training cohort (X. X. Wang et al., 2024).

Because saliva was collected before therapy, these features could serve as early markers of response. The abundance of the EAS group was also related to the density of several immune cell types in tumor tissue, namely CD4+, CD14+, CD68+, and FOXP3+ cells, and nonresponders with lower EAS abundance had lower densities of these cells (X. X. Wang et al., 2024). Even so, all 47 patients received the same treatment, so the study shows an association with response but cannot show that the microbiome predicts benefit specifically from immunotherapy. Validation in larger groups is needed before any clinical use.

The link between microbes and immune cell infiltration is not always simple. FOXP3 is a marker commonly used to identify regulatory T cells (Tregs), which can suppress antitumor immunity and help tumors escape the immune system (Kouketsu et al., 2019; S. Liu et al., 2016). In OSCC, however, FOXP3+ cells do not always point to an immunosuppressive pattern. A high density of FOXP3+ T cells in the parenchyma of the invasive front was related to better survival, which suggests that the role of these cells depends on their location and surroundings (Koike et al., 2020). A higher or lower count of FOXP3+ cells therefore cannot be read as stronger or weaker antitumor immunity without considering where the cells sit and what they are doing.

2. Findings from CheckMate 141

A different result came from an exploratory analysis of CheckMate 141, a randomized trial in recurrent or metastatic HNSCC that is available only as a conference abstract (Ferris et al., 2017). It examined the salivary microbiome of patients with HNSCC of any subsite who received nivolumab or the investigator’s choice of therapy. From 221 saliva samples sequenced with 16S rRNA, 542 bacterial species were identified. The analysis found no meaningful relationship between overall bacterial richness and clinical response, PD-L1 expression, or HPV16 status. Alpha and beta diversity were also unrelated to the type or duration of treatment (Ferris et al., 2017).

This result contrasts with the lower species richness seen in nonresponders by Wang and colleagues (X. X. Wang et al., 2024). The two studies differ in population (OSCC versus HNSCC of any subsite), treatment setting, endpoint, timing of sampling, and sequencing method, so they are not directly comparable (Table 3). In

particular, CheckMate 141 used 16S rRNA sequencing, while Wang and colleagues used shotgun metagenomic sequencing, and the two approaches do not identify microbes with the same resolution (Ahmad

et al., 2025; Gong et al., 2019). The Discussion returns to these differences.

Global diversity indices may also be too crude to capture the link between the microbiome and immunotherapy response. Diversity gives a general picture of richness and distribution but says nothing about which taxa matter or what the community can do metabolically. Work on microbiome signatures and ICI response in other settings, including a gut signature across several cancer types, suggests that strain-level and functional features can add information that taxonomic summaries do not show (Gunjur et al., 2024).

3. Other findings from tumor tissue and immunochemotherapy

Studies of tumor tissue have started to describe how the microbiome relates to the immune state of OSCC. Changes in the composition of the oral microbiome were related to shifts in metabolic and immune pathways in the tumor, and microbe-related immune pathways were connected to patient survival (Wei et al., 2025). An intratumoral microbiome signature of 19 microorganisms, derived from public TCGA data, was linked to prognosis (Zang et al., 2025). A high-risk microbial profile went along with shorter survival, stronger PI3K/AKT/mTOR pathway activity, altered tumor metabolism, and a more immunosuppressive environment. These are prognostic and descriptive findings from patients who were not selected by immunotherapy, so they do not show predictive value for ICIs.

The composition and abundance of intratumoral microbes were found to be associated with the infiltration of several lymphocyte populations, including CD4+, CD8+, and FOXP3+ cells, in an analysis of 45 OSCC tissue samples (Fang et al., 2025). The microbial load correlated negatively with CD4+ infiltration, although the relationships with other immune markers were not all statistically significant. These results strengthen the idea that intratumoral microbes are tied to the immune environment, without proving cause and effect.

Patients with locally advanced OSCC receiving neoadjuvant immunochemotherapy were investigated to evaluate the relationship between the intratumoral microbiome and treatment response (X. Zheng et al., 2026). Several taxa in baseline samples differed between patients who reached a major pathological response (MPR) and those who did not, but overall microbial diversity at baseline did not differ meaningfully. *Ralstonia*, *Methylobacterium*, and *Rothia* were more abundant in the non-MPR group (AUC 0.74) and may be candidate markers of response. Intratumoral diversity and composition also changed after treatment. Together, these findings suggest that the signal related to response may lie in particular microorganisms or functions rather than in overall community diversity. Because immunochemotherapy combines immunotherapy with chemotherapy, changes in the microbiome and in tumor response cannot be credited to the ICI alone, and later studies will need to separate the effect of each component.

Possible Mechanisms Connecting the Microbiome to ICI Response

1. T-cell activity and exhaustion

CD8+ T cells recognize and kill cancer cells through their cytotoxic activity. For ICI therapy to work well, T cells need to enter the tumor and keep their effector function. Constant exposure to tumor antigens and immunosuppressive signals can push T cells into exhaustion, marked by weaker effector function and higher levels of inhibitory receptors such as PD-1 and Tim-3. In that state, blocking PD-1 alone may not restore all antitumor functions.

In OSCC, anaerobic dominance on the tumor surface was associated with a higher frequency of CD8+ T cells expressing the exhaustion markers PD-1 and Tim-3 (Kashima et al., 2025). Similarly, a specific intratumoral microbiome signature was associated with reduced CD8+ T-cell infiltration and a more immunosuppressive tumor microenvironment, based on bioinformatic analysis (Zang et al., 2025). In HNSCC patient samples and mouse models (Tier 2, not OSCC-specific), higher intratumoral bacterial burden was linked to suppressed T-cell infiltration and a reduced response to PD-L1 blockade (Silver et al., 2026). These findings are not enough to conclude that every microbiome change directly causes T-cell exhaustion in OSCC.

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2. Inflammation, metabolism, and immune signalling

Microorganisms can affect the immune response through their structural components and their metabolic products. Pathogen-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors on epithelial and immune cells. This recognition can turn on inflammatory signaling and the release of mediators such as IL-1β, IL-6, and TNF-α. In OSCC, long-lasting inflammation may change the tumor microenvironment, for instance by drawing in immunosuppressive cells and creating conditions that favor tumor growth (Z. Wang et al., 2026).

Microbes also act on the tumor environment through metabolism. Products such as lactate, short-chain fatty acids, bile acids, and tryptophan derivatives may influence both tumor cells and immune cells. Their effects depend on the compound, its concentration, and the setting in which it is produced. Some metabolites support antitumor activity, while others may weaken T-cell function and strengthen immunosuppression (Khan & Qamar, 2026; Situ et al., 2025). A microbiome analysis that only lists which bacteria are present and how abundant they are therefore cannot fully explain their effect on immunity or on ICI success. Looking at microbial function and metabolites is needed to understand how the microbiome, tumor metabolism, and the immune system interact (Situ et al., 2025).

3. The oral–gut axis and systemic immunity

The oral microbiome does not work in isolation from microbial communities elsewhere in the body. Oral microbes and their products can reach the digestive tract by swallowing and then interact with the gut microbiome and the immune system. This exchange is called the oral–gut axis and may influence microbial balance and systemic immune responses (Kunath et al., 2024). A study of 18 OSCC patients and 7 healthy controls found changes in both oral (dental plaque) and gut (fecal) microbiome composition compared with healthy individuals (Matsui et al., 2024). The same study found that *Clostridium* subcluster XIVa was more abundant in the gut of patients whose tumors were PD-L1 positive than in those whose tumors were PD-L1 negative. This raises the possibility of a connection between the oral microbiome, the gut microbiome, and the immune features of the tumor.

It is not known whether immune changes come mainly from the oral microbiome, the gut microbiome, or the interaction between the two, and no direct effect of these microbiome changes on ICI treatment outcomes has been shown (Matsui et al., 2024). The potential involvement of the oral–gut axis in modulating ICI response in OSCC therefore remains a biological hypothesis that requires further investigation.

4. Evidence from preclinical studies

Animal models allow the link between the microbiome and ICI response to be tested in a more controlled way. The oral microbiota differed between animals that responded to PD-1 blockade and those that did not in a mouse model of HPV-positive oropharyngeal cancer (Díaz-Rivera et al., 2024). Genera such as *Allobaculum*, *Blautia*, *Faecalibacterium*, *Dorea*, and *Roseburia* were more common in responders, while *Enterococcus* was higher in nonresponders. The model was HPV-positive oropharyngeal cancer, so the results cannot be equated with OSCC in humans.

In mice with OSCC (Tier 3), the microbiota was modified through the use of a biomaterial and *Peptostreptococcus anaerobius*, providing more specific interventional evidence (D. W. Zheng et al., 2022). The authors used a hydrogel containing silver nanoparticles to suppress competing bacteria, and gave *P. anaerobius* to raise the presence of the *Peptostreptococcus* genus. The two interventions together improved the antitumor response and showed a synergistic effect when combined with PD-1 blockade. This is interesting because it suggests that the microbiome may be more than a marker of tumor status; it could also be a target for improving immunotherapy. Animal results, however, do not establish the safety or benefit of a similar approach in OSCC patients.

Possible Clinical Uses of the Microbiome in OSCC

1. The microbiome as a biomarker of treatment response

Saliva is an attractive source of biomarkers because it is easy to collect, non-invasive, and can be sampled repeatedly during treatment (Dehkordi et al., 2025). In the OSCC cohort treated with neoadjuvant immunotherapy, a low abundance of the EAS group was associated with nonresponse (X. X. Wang et al., 2024), whereas the exploratory CheckMate 141 analysis found no relationship with overall salivary diversity (Ferris et al., 2017). Taken together, this suggests that the biomarker potential of the microbiome may lie in specific organisms or taxa rather than in community diversity as a whole. Because no study has yet compared treated and untreated OSCC patients, these candidates are best seen as response-associated markers, not validated predictive biomarkers.

Saliva has also been used to follow treatment-related changes in head and neck cancer patients. In a cross-sectional study of 25 patients receiving radiotherapy, salivary markers of oxidative stress, such as malondialdehyde, rose along with the severity of oral mucositis, while antioxidant markers such as glutathione fell (Ayuningtyas et al., 2025). That study did not examine microbes, but it shows that repeated salivary sampling during cancer treatment is practical, which supports its use in future microbiome work.

Developing microbiome biomarkers also requires attention to other factors that shape microbial composition, such as periodontal condition, oral hygiene, smoking, diet, antibiotic use, history of radiotherapy, and HPV status. Procedures for collecting, storing, and processing samples can affect results as well (Zaura et al., 2021). Biomarker work therefore needs standardized procedures and careful attention to the clinical characteristics of patients. Before any clinical use, candidate biomarkers should be tested in larger and independent groups to confirm that they are consistent and have predictive ability.

2. The microbiome as a companion target for immunotherapy

Beyond serving as a biomarker, the microbiome could be a target for combined treatment. Approaches under study include probiotics, prebiotics, postbiotics, microbiota transplantation, and other interventions that aim to change the makeup and activity of microbial communities. The hope is to build a microenvironment that supports antitumor immunity and improves the response to immunotherapy (Khalil et al., 2026; S. Liu et al., 2026).

Despite the promise, microbiome modulation cannot be recommended as routine therapy in OSCC. Giving live microorganisms such as probiotics requires attention to patient safety, because in some conditions they may cause infection. The success of colonization and the effect of the administered microbes can also differ from person to person. Broad use of antibiotics deserves caution too, since it can upset microbial balance and remove organisms that might support antitumor immunity. A systematic review of microbiome-modulating strategies in cancer patients receiving ICIs concluded that these approaches still need more research, especially controlled clinical trials that confirm their safety and benefit (Thu et al., 2026). Any microbiome intervention in OSCC should therefore be designed around patient characteristics and tested before it is applied in treatment.

DISCUSSION

This review shows that the oral microbiome is plausibly connected to the immune environment of OSCC and, through it, to the response to ICIs. The evidence differs in how directly it applies to OSCC (Table 2). Only two cohorts of OSCC patients, both small and both treated in the neoadjuvant setting, have examined microbiome features against response to immunotherapy (X. X. Wang et al., 2024; X. Zheng et al., 2026). The remaining evidence comes from OSCC patients who were not treated with ICIs, from head and neck cancer more broadly, from animal models, or from other tumor types. A strength of the evidence is that it comes from several directions: saliva, tumor surface, tumor tissue, animal models, and mechanistic work. Its weakness is that most of it is observational, comes from small groups, or relies on models that do not fully reflect OSCC in patients.

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One point that stands out is the disagreement over microbial diversity. Species richness of the salivary microbiome was lower in nonresponders than in responders before neoadjuvant immunotherapy in OSCC patients (X. X. Wang et al., 2024). The CheckMate 141 analysis, however, found no meaningful relationship between overall salivary diversity and the response to nivolumab (Ferris et al., 2017), and baseline intratumoral diversity did not differ between MPR and non-MPR patients with OSCC (X. Zheng et al., 2026). Two of the three datasets are therefore negative for overall diversity, and the one positive signal comes from a single cohort of 47 patients. This does not necessarily mean one study is wrong. Table 3 shows that the studies differ in population, treatment, endpoint, sample site, and sequencing method, and each of these can change what a diversity index captures. Shotgun metagenomics and 16S rRNA sequencing resolve taxa differently. Saliva and tumor tissue sample different communities. Pathological response after neoadjuvant treatment and clinical response in recurrent or metastatic disease are different endpoints. CheckMate 141 also included HNSCC at several subsites, which differ in risk factors and HPV status. The taxon-level findings do not overlap either: *Eubacterium infirmum*, *Actinobaculum*, and *Selenomonas* were lower in saliva from nonresponders, whereas *Ralstonia*, *Methylobacterium*, and *Rothia* were higher in tumor tissue of non-MPR patients, and no taxon has yet been reproduced in an independent OSCC cohort. Diversity also describes only one side of a microbial community and does not directly reflect its biological function or its effect on treatment response. A community with many types of microbes may not support antitumor responses if those microbes drive chronic inflammation or suppress immune function. A community with fewer types may still keep a biologically supportive immune environment. This ties in with functional redundancy, the ability of different microorganisms to carry out similar biological functions (Lewandowski, 2026). For this reason, future studies should look at composition, function, metabolites, and immune cell status together.

Table 3. Methodological differences between studies with discordant findings on microbial diversity and immunotherapy response.

Feature	Wang et al., 2024	Ferris et al., 2017 (CheckMate 141)	Zheng X et al., 2026
Population	Locally advanced OSCC; 47 patients	Recurrent or metastatic HNSCC at any subsite; 221 saliva samples	Locally advanced OSCC; 42 specimens
Treatment	Neoadjuvant immunotherapy (clinical trial)	Nivolumab vs investigator's choice	Neoadjuvant PD-1 inhibitor plus chemotherapy
Response endpoint	Pathological response	Clinical response	Major pathological response (MPR)
Sample and timing	Saliva before treatment	Saliva; timing relative to treatment not specified in the abstract	Tumor tissue before and after treatment
Sequencing method	Shotgun metagenomics	16S rRNA sequencing	2bRAD-M
Overall diversity	Lower species richness in nonresponders	No relationship with response; alpha and beta diversity unrelated to treatment	No baseline alpha or beta diversity difference; diversity decreased after treatment
Taxon-level finding	Lower *E. infirmum*, *Actinobaculum*, and *Selenomonas* in nonresponders	Not reported in the abstract	Higher *Ralstonia*, *Methylobacterium*, and *Rothia* in non-MPR
Publication format	Full article	Conference abstract (exploratory analysis)	Full article
Main caveat	Small cohort; single regimen; no comparator	Abstract only; global diversity indices; not OSCC-specific	Chemotherapy confounds ICI effect; low-biomass tissue

HNSCC, head and neck squamous cell carcinoma; MPR, major pathological response; OSCC, oral squamous cell carcinoma; 2bRAD-M, 2bRAD sequencing for microbiome.

Fusobacterium and several other anaerobic bacteria have been frequently associated with OSCC and alterations in the tumor immune environment, including the link between anaerobic dominance on the tumor surface and exhausted CD8+ T cells (Kashima et al., 2025). Yet it would be wrong to treat every anaerobe as harmful, because the effect of a microorganism varies with species, strain, amount, location, and interaction with other microbes (Baker et al., 2024). In mice, *Peptostreptococcus anaerobius*, which is an anaerobe, improved the antitumor response when combined with a biomaterial and PD-1 blockade (D. W. Zheng et al., 2022). Being an anaerobe is therefore not enough to predict a bacterium's effect on tumor development or immunotherapy. Wiping out all anaerobic bacteria with antibiotics cannot be considered a sound strategy without knowing the role of each organism in its biological setting.

A further point is the difference between prognostic and predictive evidence. Most of the OSCC evidence is prognostic or descriptive. Studies linking anaerobic dominance, intratumoral signatures, or immune infiltration to survival (Kashima et al., 2025; Wei et al., 2025; Zang et al., 2025) relate microbiome features to outcome in patients who were not selected by immunotherapy, so they cannot show whether the same features would change the benefit from an ICI. Predictive value requires a comparison of treatment effect between marker-defined groups (Cottrell et al., 2025). The two OSCC cohorts that did examine immunotherapy response gave every patient the same regimen (X. X. Wang et al., 2024; X. Zheng et al., 2026), so their markers are best read as response-associated candidates. Table 2 labels each study accordingly.

Several clinical and technical factors make results hard to compare between studies. Microbiome profiles can be affected by age, smoking, diet, oral hygiene, periodontal disease, antibiotic use, history of radiotherapy, tumor stage, and HPV status. Patients may also carry other conditions that complicate interpretation. For example, OSCC has been reported in a patient with essential thrombocythemia and a JAK2 V617F mutation who was taking hydroxyurea (Rahman et al., 2022), and radiotherapy brings its own oral changes, including mucositis linked to higher salivary oxidative stress (Ayuningtyas et al., 2025). Such conditions and treatments should be recorded in future microbiome studies. Results also depend on sample type, collection method, DNA extraction technique, sequencing platform, and bioinformatic analysis. Saliva, plaque, the tumor surface, and deep tumor tissue each have their own microbial composition, so they cannot be assumed to describe the same community (K. Y. P. Liu et al., 2026). Saliva is easy to collect and reflects the mouth broadly, but it does not necessarily represent the microbes that sit next to the tumor. Tumor tissue is closer to the cancer environment, but it has low microbial biomass and a risk of contamination from instruments, reagents, and the laboratory. Negative controls and clear contamination-control procedures are therefore important (K. Y. P. Liu et al., 2026; "Guidelines for Preventing and Reporting Contamination in Low-Biomass Microbiome Studies," 2025).

In terms of clinical use, the evidence is not yet enough to make the oral microbiome profile the only basis for choosing, starting, or stopping ICIs in OSCC patients. Microbiome interventions must also consider the possibility of infection, antimicrobial resistance genes, altered drug metabolism, and effects on immunotherapy toxicity. Products containing live microorganisms need strict safety evaluation, including checks for virulence factors and the possible transfer of resistance genes, especially in immunocompromised patients (Asia-Pacific Microbiota Consortium, 2025). Changes in the microbiome may also influence immune

responses outside the tumor and could be connected to immune-related adverse events during ICI treatment (Gao et al., 2025; Schneider et al., 2026). For now, using the microbiome belongs in the research setting and cannot replace the standard management of OSCC.

Several steps would be needed before a microbiome measurement could be used in the clinic. A candidate marker would first have to be measured with a standardized, low-cost assay, such as targeted quantitative PCR for a small set of taxa, rather than discovery sequencing. It would then have to show reproducibility across centers, added value over PD-L1 expression and other established factors, and a clear decision it could change, for example selecting patients for neoadjuvant immunotherapy or for a microbiome-directed intervention (Cottrell et al., 2025). Saliva is the most practical sample for such a test because it can be collected without a

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procedure and repeated during treatment (Dehkordi et al., 2025), but the salivary signal has so far been examined in only one OSCC immunotherapy cohort.

Several research priorities follow from these gaps. The first is replication: the salivary and intratumoral signals reported in OSCC need to be tested in independent, adequately powered cohorts with a pre-specified analysis plan. The second is design. Future work should use prospective, multicenter cohorts that collect samples before, during, and after treatment and that include patients who do not receive ICIs, so that prognostic and predictive effects can be separated. Collecting saliva, plaque, tumor tissue, blood, and stool at the same time would help separate the contributions of the oral, intratumoral, and gut microbiomes to the immune response. The third is covariates: microbiome data should be analyzed together with clinical features and factors that may shape its composition, such as HPV status, PD-L1 expression, periodontal condition, smoking, and treatment history. The fourth is standardization of sample type, collection, storage, and testing methods, with negative controls for low-biomass tissue, to make results comparable and reproducible (K. Y. P. Liu et al., 2026).

Studies should also look beyond which microbes are present, to what they do and what they produce. Metagenomics, metabolomics, and analysis of immune cells in tumor tissue can help explain how microbes, metabolic activity, and the immune environment relate, including T-cell activation, immune exhaustion, antigen presentation, and changes in checkpoint pathways (Khalil et al., 2026; S. Liu et al., 2026). Candidate biomarkers found this way should be validated in separate patient groups and compared with predictive factors already used in practice, so that research does not stop at statistical associations but also tests their consistency and clinical relevance. Interventional studies are needed as well. An early trial combining fecal microbiota transplantation with anti-PD-1 therapy in melanoma shows that microbiome modulation has started to be tested in people, although this cannot be applied directly to OSCC (Routy et al., 2023). Similar studies in OSCC should proceed step by step, with monitoring for infection, antimicrobial resistance, immune toxicity, and changes in the microbial community, and with transparent reporting of procedures, especially in low-biomass tumor tissue. In the long run, the goal is not to find a single bacterium that is always helpful, but to understand the composition, function, and interactions of the microbiome that can build an immune environment supportive of therapy.

Some limitations of this review should be noted. As a narrative review, it relied on thematic interpretation of studies that differ in design, population, sample type, and method, and it did not include a quantitative synthesis or a formal risk-of-bias assessment. The search covered three databases and English-language publications only, so relevant work in other languages or sources may have been missed. Some of the evidence comes from head and neck cancer in general, from the gut microbiome, or from other cancer types, and some from animal models, so it may not transfer directly to OSCC patients. Three of the head and neck sources are conference abstracts with limited methodological detail. The immunochemotherapy studies could not separate the effect of the ICI from that of chemotherapy. Finally, the number of studies directly testing the oral microbiome against ICI response in OSCC is still small, and the findings are likely to change as larger studies appear.

CONCLUSION

The oral microbiome may help shape the tumor immune environment and influence the response to ICIs in

OSCC. In OSCC patients, salivary microbiome profiles were associated with response to neoadjuvant immunotherapy (X. X. Wang et al., 2024), and specific intratumoral taxa were associated with response to neoadjuvant immunochemotherapy (X. Zheng et al., 2026). The results are not yet consistent, though. The CheckMate 141 analysis in HNSCC found no meaningful relationship between overall salivary diversity and the response to nivolumab (Ferris et al., 2017), and baseline intratumoral diversity did not differ by response in OSCC (X. Zheng et al., 2026). This suggests that the signal lies in particular taxa or functions rather than in overall diversity. Most other findings in OSCC are prognostic or descriptive, and mechanistic and animal studies give a biological basis for the idea that microbes can affect the antitumor response and the effect of PD-1 blockade, but they do not show that microbiome changes directly decide ICI success in OSCC patients (D. W. Zheng et al., 2022). For now, the oral microbiome is best viewed as a candidate biomarker and a possible companion target that needs more research, not as a stand-alone test or intervention. Longitudinal studies with standardized sampling and analysis, validation in independent patient groups, and controlled interventional

trials are needed before microbiome findings can inform clinical decisions (Cottrell et al., 2025; K. Y. P. Liu et al., 2026).

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