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Immunotherapeutic strategies in HPV-positive and HPV-negative recurrent/metastatic oropharyngeal squamous cell carcinoma: From PD-1 blockade to EGFR-directed bispecifics and therapeutic HPV vaccines

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ABSTRACT

Oropharyngeal squamous cell carcinoma (OPSCC) comprises two biologically distinct entities, HPV-positive and HPV-negative disease, which differ in etiology, immune microenvironment, molecular drivers, and clinical behavior. This narrative review summarizes current evidence on immunotherapeutic strategies in OPSCC, focusing on subtype-specific biological rationale and emerging treatment approaches. A literature search of PubMed/MEDLINE, Embase, Cochrane Library, ClinicalTrials.gov, and major oncology meeting abstracts was conducted for studies published from January 2000 to February 2026. PD-1/PD-L1 inhibitors represent the current standard of care in recurrent/metastatic disease, with HPV-positive tumors generally showing more favorable outcomes, likely reflecting a more inflamed and antigen-rich tumor microenvironment. However, HPV status remains primarily a prognostic rather than a validated predictive biomarker for checkpoint inhibitor benefit. In contrast, HPV-negative OPSCC is more frequently characterized by immune exclusion, EGFR dependence, hypoxia, and activation of MET/HGF and TGF-β pathways, supporting the development of EGFR-centered and bifunctional strategies to overcome resistance. Emerging agents such as ficerafusp alfa, petosemtamab, and amivantamab have demonstrated promising early clinical activity, particularly in biomarker-enriched or post-immunotherapy settings. In HPV-positive disease, therapeutic vaccines targeting E6/E7 oncoproteins have shown encouraging immunogenicity and preliminary antitumor activity, especially when combined with PD-1 blockade. Overall, the immunotherapeutic landscape of OPSCC is evolving toward a biomarker-driven framework integrating viral status, immune contexture and pathway activation to enable more precise and personalized treatment strategies.

1. Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) comprises two major biological entities, HPV-positive and HPV-negative disease, which differ in etiology, molecular drivers, immune microenvironment, and clinical behavior. The introduction of PD-1/PD-L1 inhibitors has transformed the management of recurrent/metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), including OPSCC, establishing pembrolizumab-based regimens as a first-line standard of care for PD-L1 positive disease (Burtness et al., 2019).

Evidence from clinical and translational studies indicates that HPV-positive tumors are generally characterized by a more inflamed and antigen-rich tumor microenvironment, whereas HPV-negative tumors more frequently display features of immune exclusion and distinct molecular alterations. Despite these biological differences, treatment selection in clinical practice remains largely driven by clinical parameters

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and PD-L1 expression, rather than by HPV status or underlying tumor biology (Succaria et al., 2021).

Although immune checkpoint inhibitors (ICIs) have improved outcomes in a subset of patients, a substantial proportion fail to achieve durable responses, highlighting the need for more effective and biologically tailored therapeutic strategies. In this context, novel immunotherapeutic approaches are being developed to overcome resistance mechanisms and to exploit subtype-specific vulnerabilities.

Several systematic reviews and meta-analyses have examined individual aspects of HNSCC, including the role of immunotherapy and the prognostic implications of HPV status (Wang et al., 2019). In parallel, broader narrative overviews have described the biological and clinical features of HPV-associated OPSCC (Lechner et al., 2022; Sun and Colevas, 2025). However, these studies predominantly address emerging therapeutic approaches or the biological features of HPV-associated disease in parallel, rather than within a unified, clinically oriented framework. As a result, the integration of HPV-stratified tumor biology into therapeutic decision-making in the recurrent/metastatic OPSCC setting remains insufficiently developed.

At the same time, the rapid expansion of therapeutic options has generated a growing body of clinical and translational evidence that remains only partially integrated into a coherent, subtype-specific framework.

Accordingly, this review addresses three key questions: (1) how HPV-positive and HPV-negative OPSCC differ in terms of clinical outcomes and response to immunotherapy; (2) which therapeutic options are available after progression on immune checkpoint inhibitors and how their activity differs according to HPV status; and (3) which emerging immunotherapeutic strategies may further reshape the treatment landscape, with particular attention to differences between HPV-positive and HPV-negative disease.

The structure of this review reflects these objectives, with separate sections addressing ICIs, post-immunotherapy strategies, therapeutic HPV vaccines, and emerging bispecific or pathway-directed approaches.

2. Methods

This narrative review was designed to provide a clinically and biologically integrated overview of immunotherapeutic strategies in recurrent/metastatic OPSCC, with particular attention to differences between HPV-positive and HPV-negative disease. A narrative rather than systematic approach was chosen because the available literature is highly heterogeneous in terms of study design, population composition, anatomical site specificity, biomarker definitions, therapeutic settings, and reported endpoints, thereby limiting the feasibility of a formal quantitative synthesis focused specifically on OPSCC.

A literature search was conducted in MEDLINE/PubMed, Embase, and the Cochrane Library for studies published from January 2000 to February 2026. This was supplemented by searches of ClinicalTrials.gov and major oncology meeting abstracts, including ASCO, ESMO, ESMO-IO, and AACR, to capture emerging data not yet available as full-text publications. Search terms included combinations of the following concepts: “oropharyngeal squamous cell carcinoma” or “OPSCC”, “head and neck squamous cell carcinoma”, “HPV” or “p16”, “PD-1”, “PD-L1”, “EGFR”, “cetuximab”, “bispecific antibodies”, “bifunctional antibodies”, “TGF-β”, “MET/HGF”, and “therapeutic HPV vaccine”, including peptide-, DNA-, mRNA-, and viral vector-based platforms.

The search strategy was specifically structured to address the predefined research questions, including differences in immunotherapy outcomes according to HPV status, therapeutic strategies after progression on ICIs, and emerging immunotherapeutic approaches in recurrent/metastatic OPSCC.

The full PubMed search strategy is provided in Appendix 1.

Eligible evidence included prospective clinical trials, retrospective clinical studies, meta-analyses, systematic reviews, and translational or preclinical studies considered informative for biological rationale. Case reports, very small case series, and studies focused exclusively on locoregional disease without relevance to recurrent/metastatic OPSCC were excluded. When studies enrolled mixed HNSCC populations, OPSCC-specific data were preferentially extracted when available; otherwise, findings were interpreted cautiously in light of anatomical heterogeneity. Priority was given to studies with validated HPV assessment, more recent evidence, and datasets with greater clinical relevance to the review objectives.

Study selection was based on relevance to the predefined research questions and clinical applicability to the recurrent/metastatic OPSCC setting.

Data extraction focused on HPV status, disease setting, study design, treatment line, biomarker information, efficacy outcomes (including objective response rate, progression-free survival, overall survival, and duration of response), and safety. Evidence was synthesized qualitatively and organized according to disease setting (immunotherapy-naïve vs post–ICI), HPV status, and therapeutic class, and interpreted according to study maturity, sample size, methodological robustness, and consistency across available datasets.

When a primary study was already represented in a systematic review or meta-analysis, emphasis was placed on the most informative and methodologically relevant source according to the specific question addressed. In the presence of overlapping meta-analyses, priority was given to the most recent and clinically relevant synthesis, while avoiding redundant interpretation of the same datasets.

Given the narrative nature of the review, no formal quantitative synthesis or meta-analysis was performed. Statistical outcomes, including objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and duration of response (DoR), defined as the time from first documented objective response to disease progression or death, whichever occurred first, were interpreted in the context of study design, sample size, clinical setting, and consistency across studies.

Consistent with the narrative design of this review, no formal PRISMA flow diagram, duplicate independent screening procedure, or study-level risk-of-bias assessment was performed. Therefore, the findings should be interpreted as a qualitative, clinically oriented synthesis rather than as a fully reproducible systematic review or meta-analysis.

3. Systemic therapeutic strategies in recurrent/metastatic OPSCC

The therapeutic landscape of recurrent/metastatic HNSCC has evolved from chemotherapy-based regimens established by the EXTREME trial (Vermorken et al., 2008) to PD-1–based strategies defined by KEYNOTE-048 (Burtness et al., 2019), and is now entering a third phase characterized by biologically informed and rational combination approaches. This evolution can be conceptualized into three major therapeutic phases, providing a framework for interpreting current evidence and future therapeutic strategies in OPSCC. Historically, this transition reflects a shift from empiric cytotoxic therapy to broadly applied immune checkpoint blockade and, more recently, to biomarker-enriched strategies aimed at overcoming resistance in biologically defined subgroups. Within this context, OPSCC represents a particularly relevant model given its biologically distinct HPV-defined subtypes.

The following sections provide a structured overview of systemic therapeutic strategies in R/M OPSCC, integrating clinical evidence with underlying biological rationale and HPV-related differences. First, we examine the role of ICIs as the current standard of care, highlighting differences in clinical outcomes according to HPV status. We then discuss therapeutic options following progression on PD-1/PD-L1 blockade, with a focus on EGFR-directed strategies and their biological rationale in HPV-negative disease. Finally, we review emerging immunotherapeutic approaches, including therapeutic HPV vaccines and novel bispecific or bifunctional agents, with particular attention to

subtype-specific mechanisms and clinical development.

3.1. Immune checkpoint inhibitors

PD-1–targeting ICIs are a cornerstone of treatment for R/M OPSCC, with activity in both HPV-positive and HPV-negative disease, consistently associated with more favorable survival outcomes in HPV-positive tumors. Pembrolizumab-based regimens, alone or combined with platinum chemotherapy, represent the first-line standard of care for R/M HNSCC regardless of HPV status, based on the KEYNOTE-048, in which long-term follow-up confirmed a sustained survival tail versus the EXTREME regimen, with signals of greater benefit in HPV-positive patients in exploratory subgroup analyses (Harrington et al., 2023). In routine practice, treatment selection is primarily driven by PD-L1 CPS, disease burden, and performance status rather than HPV status (Cramer et al., 2019). Importantly, OPSCC-specific prospective datasets are scarce: most evidence informing these recommendations derives from anatomically mixed R/M HNSCC trials and subsequent subgroup analyses, and therefore HPV- and site-stratified inferences should be interpreted cautiously (Table 1).

From a biological perspective, HPV-positive tumors generally present a more inflamed tumor microenvironment (TME) with greater T-cell infiltration, which may partially explain their slightly enhanced responsiveness to immunotherapy (Succaria et al., 2021). Nevertheless, despite these biological insights, the difference in clinical efficacy between HPV-positive and HPV-negative patients remains uncertain, and HPV status is not currently used to guide therapeutic decision-making (Machiels et al., 2020).

In a large retrospective cohort of patients receiving first-line pembrolizumab-based therapy, HPV-positive status was significantly associated with improved overall survival in both treatment groups, as identified in multivariable analyses. However, this finding should be interpreted cautiously, as the study included anatomically heterogeneous HNSCC populations (Black et al., 2023).

Data from meta-analyses indicate that HPV-positive status is associated with improved outcomes in patients with HNSCC receiving ICIs; however, whether this reflects a true predictive effect or underlying prognostic differences remains uncertain. In the meta-analysis by Wang et al. (2019), including 589 patients from 6 clinical trials, HPV-positive patients showed improved OS (HR = 0.71) and a higher ORR (21.9% vs 14.1%) compared with HPV-negative counterparts, independently of PD-L1 expression and tumor mutational burden, suggesting that viral neoantigens and a pre-existing inflamed microenvironment may prime the immune system for anti-PD-1 blockade (Wang et al., 2019). These findings were corroborated by Xu et al. (2021), who analyzed 814 patients from seven studies and reported a higher likelihood of response (OR = 1.77) and a reduced risk of death (HR = 0.77) in HPV-positive disease (Xu et al., 2021). In contrast, HPV-negative tumors more frequently exhibit an "immune-excluded" or "cold" phenotype, characterized by limited T-cell infiltration and immunosuppressive features, which likely contributes to the lower response rates and survival outcomes observed in these patients. Overall, the current body of evidence supports HPV status primarily as a prognostic marker, with HPV-negative disease consistently associated with inferior outcomes, while its role as a standalone clinically actionable predictive biomarker for ICI benefit has not yet been definitively established. Notably, HPV-positive tumors often exhibit higher CPS, yet clinical benefit from ICIs is observed even in some cases with low CPS, suggesting that virus-driven immune inflammation may act as an independent driver of response, beyond PD-L1 expression alone.

More recent evidence supports these findings. In a meta-analysis including 3509 patients with recurrent/metastatic HNSCC treated with ICIs, HPV-positive status was associated with longer overall survival compared with HPV-negative disease (20.7 vs 12.2 months in the first-line setting); however, these data derive from anatomically heterogeneous populations and do not establish a predictive role for HPV status (Park et al., 2025).

Most HPV-stratified analyses derive from post hoc or pooled datasets within mixed HNSCC populations, and dedicated prospective OPSCC-restricted trials incorporating formal treatment-by-HPV interaction analyses remain lacking. Consequently, extrapolation of HPV-stratified outcomes to OPSCC-specific therapeutic decision-making should be interpreted with caution.

Taken together, these data suggest that HPV status functions predominantly as a prognostic biomarker rather than a determinant of treatment selection.

3.2. Therapeutic options after anti–PD-1 failure in R/M HNSCC: revisiting EGFR-targeted therapy

After progression on anti–PD-1 therapy, treatment options for R/M disease remain limited, with no clear standard of care universally established.

In routine practice, salvage strategies commonly include chemotherapy (taxanes, platinum compounds, fluoropyrimidines) with or without cetuximab. Notably, mounting evidence indicates that sensitivity to EGFR inhibition is restricted to biologically defined subgroups characterized by distinct TME features (Llop et al., 2024).

A pivotal study analyzing 40 patients with R/M HNSCC treated with chemotherapy plus cetuximab identified a subset of long-term responders (defined as mPFS 19 months) whose tumors displayed strong baseline EGFR signaling activity coupled with a pronounced hypoxic

Table 1
Summary of included studies evaluating PD-1/PD-L1 inhibitors in recurrent/metastatic HNSCC, stratified by HPV status, with OS and ORR outcomes.

Author, year	Regimen (anti-PD-1/PD-L1)	Population specificity	Number of trials (n; phase distribution)	Number of patients	N patients (HPV+/ HPV−)	OS (HPV+ vs HPV−)	ORR HPV+ vs HPV−	Risk of bias (AMSTAR-2)
Wang 2019	Mixed: nivolumab, pembrolizumab, durvalumab, others, monotherapy in R/M setting	Mixed HNSCC population; HPV analyzed across entire cohort; OPSCC not analyzed separately.	6 (1 phase III, 5 phase I–II)	589	192 / 397 (301 unknown)	OS HR 0.71 (0.53–0.94)	21.9% vs 14.1% OR = 1.79 (95% CI 1.13–2.83; p = 0.01)	Critically low
Xu 2021	Mixed: anti-PD-1/PD-L1 monotherapy in R/M setting (first-/second-line)	Mixed HNSCC population; HPV analyzed across entire cohort; OPSCC not analyzed separately.	7 (2 phase III, 5 phase I–II)	814	217 / 454 (139 unknown)	OS HR 0.77 (0.60–0.99)	21.5% vs 13.7% OR 1.77 (95% CI: 1.14–2.74; P = 0.01)	moderate
Park et al. 2025	Mixed ICI-based regimens (anti-PD-1/PD-L1; mono- and combination therapies) in R/M setting (first-/second-line)	Mixed HNSCC population; HPV-stratified across included studies; OPSCC not analyzed separately	10 (5 phase II, 2 phase Ib, 3 phase III)	3509	837 / 2672	20.7 (1 L); 11.1 (≥2 L)	NR	moderate

differentiation program (Bossi et al., 2016).

These observations are further supported by gene and protein expression profiling analyses performed on large HNSCC cohorts, which consistently demonstrate that hypoxia-related signatures such as the 15-gene hypoxia classifier and the expression of key hypoxia markers including HIF1A, GLUT1, and ASPH are significantly enriched in OPSCC HPV-negative tumors (Linge et al., 2016). Collectively, these data provide a strong biological rationale for the preferential activity of EGFR-targeted therapies in HPV-negative disease and, conversely, for the limited efficacy of EGFR blockade in HPV-positive populations, particularly in the post–ICI setting. They also underscore the critical importance of integrating hypoxia and pathway-based biomarkers into future patient selection strategies for anti-EGFR therapies.

In line with this biological framework, multiple retrospective studies have suggested that cetuximab-based regimens administered in the second-line setting after progression on ICI may retain unexpected antitumor activity, with response rates apparently higher than those historically reported in ICI-naïve populations (Vermorken et al., 2007). However, it must be emphasized that robust prospective evidence supporting this strategy remains limited.

One of the most informative findings in this context derives from the control arm of the INTERLINK-1 trial. Notably, the ORR observed with placebo plus cetuximab in the HPV-negative analysis set of INTERLINK-1 was higher than anticipated, reaching 23.9%, compared with historical ORRs ranging from 6.5% to 14.5% reported with cetuximab monotherapy in similar populations. Similarly, mOS was 8.6 months, compared with 5.9 months reported in prior studies of cetuximab monotherapy in the same setting (Fayette et al., 2025).

These findings support the hypothesis of a re-sensitization to EGFR blockade after exposure to ICI, potentially mediated by an ICI-induced remodeling of the TME. Nevertheless, consistent with the concept that ICI blockade may reshape the TME and influence subsequent treatment response, emerging prospective data suggest that cetuximab-based regimens can retain clinically meaningful activity in the post–ICI setting.

The phase II PACE-ACE trial specifically investigated the combination of paclitaxel and cetuximab in patients with R/M HNSCC progressing after failure of ICIs. In this biologically and clinically challenging population, the combination demonstrated substantial antitumor activity, with an ORR of 47.4% (95% CI, 34.0%–61.0%), including 8 complete responses (14.0%). The median DoR was 5.5 months, and disease control was achieved in 42 patients, corresponding to a disease control rate (DCR) of 71.9% (95% CI, 58.5%–83.0%). mPFS was 5.9 months (95% CI, 5.4–8.2), while mOS reached 14.0 months (95% CI, 10.8–20.5) (Fuereder et al., 2024).

However, the study does not provide robust efficacy estimates for the HPV-negative oropharyngeal subgroup, highlighting the need for site-specific analyses.

Within the therapeutic landscape of post–ICI R/M HNSCC, increasing attention has been directed toward strategies aimed at overcoming resistance to EGFR-directed therapies.

Among these, ficlatuzumab, a humanized monoclonal antibody targeting hepatocyte growth factor (HGF), the ligand of the c-MET receptor, has emerged as a biologically rational agent designed to counteract MET-driven resistance to cetuximab.

The clinical activity of ficlatuzumab was first evaluated in a randomized phase II trial enrolling heavily pretreated patients with R/M HNSCC who were resistant to platinum, cetuximab, and anti–PD-1 therapy. Patients were randomized to receive ficlatuzumab with or without cetuximab. In the combination arm, mPFS was 3.7 months (lower bound of the 90% CI: 2.3 months), with an ORR of 19% (6/32 patients), including two complete and four partial responses. Notably, a striking enrichment of clinical benefit was observed in the HPV-negative subgroup, in which median PFS increased to 4.1 months and ORR reached 38% (6/16 patients) (Bauman et al., 2023).

The ongoing phase III FIERCE-HN trial represents the first large-scale prospective attempt to definitively validate the MET/HGF axis as a biomarker-enriched therapeutic target to restore sensitivity to EGFR inhibition in exclusively HPV-negative disease (NCT06064877). This trial is enrolling patients with R/M HPV-negative HNSCC who have progressed after platinum and anti–PD-1 therapy and who have not previously received cetuximab in the R/M setting. Patients are randomized to receive ficlatuzumab plus cetuximab versus placebo plus cetuximab.

3.3. Therapeutic HPV vaccines

3.3.1. Mechanisms of action and immunologic rationale

Therapeutic HPV vaccines are intended to elicit robust T-cell–mediated immunity against the constitutively expressed E6 and E7 oncoproteins of HPV-positive tumors, which are absent from normal tissues. These viral proteins act as ideal immunologic targets because they are essential for maintaining the malignant phenotype and are specific to infected cells, reducing the risk of off-target toxicity (Garbuglia et al., 2020).

Following vaccination, genetic material (DNA/mRNA) is translated by host cells, while peptides or vector-expressed antigens are captured and processed by antigen-presenting cells (APCs). These cells present the processed antigens on both MHC class I and class II molecules, thereby activating cytotoxic $CD8^+$ T lymphocytes and helper $CD4^+$ T cells (Pishesha et al., 2022). This dual activation establishes a bridge between innate and adaptive immunity, potentially overcoming the immune ignorance often observed in the tumor microenvironment.

Once the antigen presentation phase is initiated, a cascade of immune events follows.

Specific T-cell clones directed against E6 and E7 are generated and expand, broadening the diversity of the T-cell receptor (TCR) repertoire. This process facilitates “epitope spreading”, an immunological phenomenon critical for counteracting tumor heterogeneity and preventing immune escape, whereby an immune response initially directed against a single epitope progressively extends to additional epitopes, either within the same antigen (intramolecular spreading) or across distinct antigens (intermolecular spreading) (Kidman et al., 2020).

This diversification toward novel epitopes is paralleled by the broadening of the TCR repertoire, (Brossart, 2020). This process may be particularly relevant in HPV-driven tumors, where epitope spreading is hypothesized to contribute to durable responses, although direct clinical evidence remains limited.

HPV-positive tumors often develop multiple mechanisms of immune escape, including T-cell exhaustion mediated by PD-1/PD-L1 interactions, recruitment of immunosuppressive cell populations such as myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs). To overcome these barriers, therapeutic HPV vaccines are frequently combined with ICIs, particularly PD-1/PD-L1 blockade, or with immunomodulatory agents such as IL-12 or TGF-β inhibitors. These synergistic combinations aim to 'prime' the immune system via vaccination and 'disinhibit' the effector response via PD-1/PD-L1 blockade, thereby restoring immune competence within the tumor milieu (Smalley Rumfield et al., 2020).

Several technological platforms have been developed for therapeutic HPV vaccination, each employing distinct strategies to deliver the E6 and E7 oncoproteins to the immune system and to elicit a strong, durable cytotoxic response. Despite differences in their construction and delivery, all share a common goal: to induce a broad and sustained T-cell–mediated immunity against HPV-transformed cells.

3.3.2. Vaccine Platforms and Mechanisms of Immune Activation

mRNA–LNP vaccines, such as BNT113 and other HPV mRNA–LNP constructs, represent one of the most innovative approaches.

In these formulations, the mRNA encoding HPV16 E6 and E7 is encapsulated in lipid nanoparticles and administered systemically. Once taken up by dendritic cells, the mRNA is translated into protein antigens, which are subsequently processed and presented through both MHC

class I and class II pathways. This strategy not only ensures efficient antigen expression but also exploits the intrinsic immunogenicity of mRNA and the adjuvant properties of lipid nanoparticles, which can activate innate immune sensors such as Toll-like receptors (TLR) and the STING pathway (Wang et al., 2024).

Peptide-based vaccines, including ISA101 and PDS0101, utilize synthetic long peptides derived from HPV16 E6 and E7. These peptides, administered with suitable adjuvants, are processed by antigen-presenting cells and presented to both $CD8^+$ and $CD4^+$ T lymphocytes. PDS0101, in particular, leverages the Versamune lipid-based delivery system, which facilitates antigen cross-presentation to MHC-I and promotes robust dendritic cell activation, leading to potent CD8 + T-cell priming and proliferation (Sousa et al., 2022).

DNA vaccines, exemplified by MEDI0457 (also known as INO-3112), consist of plasmids encoding E6/E7 antigens often in detoxified forms to prevent oncogenic risk together with immune-stimulatory cytokines such as IL-12. Delivered through in vivo electroporation, these plasmids facilitate direct transfection of host cells, which then express the encoded antigens and present them to APCs. This results in coordinated $CD8^+$ and $CD4^+$ T-cell activation, while IL-12 further promotes Th1 polarization and enhances the cytotoxic quality of the immune response (Aggarwal et al., 2019).

Finally, viral vector–based vaccines, such as PRGN-2009 and TG4001, employ replication-deficient adenoviruses or modified vaccinia Ankara (MVA) viruses engineered to carry E6/E7 transgenes. These viral vectors infect antigen-presenting cells and drive intracellular antigen expression, mimicking natural infection processes. Importantly, their abortive replication activates innate immune sensors via pattern-recognition receptors, eliciting strong adjuvant effects and generating robust T-cell priming and a broad, polyclonal immune response (Custers et al., 2021).

A key advantage of these vectors is their ability to induce potent cell-mediated immunity even in the absence of exogenous adjuvants. While their mechanisms differ ranging from nucleic acid–based expression systems to synthetic peptide delivery, the ultimate aim remains the same: to generate a durable cytotoxic T-cell response capable of recognizing and eradicating HPV-driven malignant cells.

Key characteristics of therapeutic HPV vaccine platforms are summarized in Table 2.

3.3.3. *Therapeutic HPV vaccines combined with PD-1/PD-L1 blockade: clinical evidence and translational rationale*

The most mature clinical evidence supporting therapeutic HPV vaccination in combination with ICI derives from studies evaluating ISA101, a therapeutic vaccine composed of synthetic long peptides (SLP) derived from HPV16 E6/E7, evaluated in combination with nivolumab at MD Anderson in a phase II, single-arm trial (Massarelli et al., 2019). Twenty-four patients with R/M HPV16-positive malignancies were enrolled, the vast majority (92%) with OPSCC, although non-oropharyngeal malignancies were also included and no site-specific efficacy analysis was performed. Notably 79% of patients were platinum-refractory (recurrence $\leq$6 months). The combination achieved an ORR of 33% (8/24), with a median duration of response of 10–11 months, a mPFS of 2.7 months, and a mOS of 17.5 months; an updated follow-up reported a median OS of 15.3 months and a 3-year OS of 12.5%. Toxicities were manageable, with few grade 3–4 events. Importantly, the trial incorporated a translational immune monitoring program: peripheral blood mononuclear cells were analyzed by IFN-γ ELISPOT using HPV16 E6/E7 peptide pools, demonstrating a statistically significant expansion of HPV16-specific T cells post-vaccination, more pronounced in responders. These findings confirmed the vaccine's immunogenicity and suggested that ISA101 may broaden the benefit of PD-1 blockade even in PD-L1–negative tumors (Sousa et al., 2022).

Another candidate, MEDI0457, is a DNA-based vaccine encoding HPV16/18 E6/E7 with IL-12 as an adjuvant, delivered via electroporation, evaluated with durvalumab in phase I/II multicenter studies. It should be noted that patients were enrolled across the broader HNSCC population, and the study was not restricted to OPSCC, although the majority of tumors originated in the oropharynx. The study included multiple cohorts (platinum-sensitive 42.9%, platinum-refractory R/M patients 25.7%, second-line R/M 31.4%). The combination showed an acceptable safety profile and induced robust HPV-specific T-cell responses with Th1 polarization, alongside signals of clinical activity (notably disease control in a proportion of patients). However, efficacy outcomes remain exploratory given the small and heterogeneous cohorts, and the trials were primarily designed for safety and immunogenicity endpoints (Aggarwal et al., 2023).

Recently, PDS0101 (Versamune-HPV16), a lipid-based peptide vaccine, has been evaluated in combination with pembrolizumab in the ongoing VERSATILE-002 phase II trial as first-line treatment for patients with R/M HPV16-positive HNSCC with CPS $\geq$ 1. Updated data reported a median OS of 30.0 months (95% CI: 23.9, NE) in the overall CPS $\geq$ 1 population. When stratified by PD-L1 expression, median OS was 29.5 months (95% CI: 15.3, NE) in the CPS 1–19 subgroup and reached 39.3 months (95% CI: 18.4, NE) in patients with CPS $\geq$ 20. Notably, outcomes appeared numerically enriched in the CPS $\geq$ 20 subgroup, although the small sample size precludes definitive conclusions (Weiss et al., 2025). However, definitive confirmation is awaited from the phase III VERSATILE-003 trial (2:1 randomization), which will provide the necessary randomized evidence to validate this synergistic approach.

Regarding BNT113, a liposomal mRNA vaccine encoding HPV16 E6/E7, is being investigated in combination with pembrolizumab in the ongoing phase II/III AHEAD-MERIT trial (NCT04534205), which includes a randomized comparison versus pembrolizumab monotherapy in the first-line setting for HPV16-positive R/M HNSCC (CPS $\geq$1).

Available clinical data currently derive from the non-randomized safety run-in cohort (n = 15), presented at ESMO 2024, which reported an unconfirmed ORR of 40% per blinded independent review, a median PFS of 3.9 months (BICR), and a median OS of 22.6 months (investigator assessment).

Although based on a limited early-phase cohort, these findings supported continued development of the program, and in 2026 the U.S. Food and Drug Administration granted BNT113 Fast Track designation

Table 2
Comparison of main platform systems: advantages, disadvantages.

Platform	Advantages	Disadvantages	Citations
Protein (subunit)	High safety, no risk of infection, suitable for immunocompromised, large-scale production	Lower immunogenicity, often requires adjuvants and multiple doses, critical antigen selection	(Li et al., 2021)
DNA	High stability, easy production, no infectious agent, low cost, long shelf life	Limited immunogenicity in humans, need for advanced delivery systems, few clinical approvals	(Lu et al., 2024)
RNA (mRNA)	Rapid development, high efficacy, no infectious risk, strong immune response, scalability	Instability, requires cold chain, limited long-term data, reactogenicity	(Sayour et al., 2024)
Viral vectors	Strong immune response (humoral and cellular), rapid development, possibility of specific targeting	Pre-existing immunity to vector, rare adverse events, complex production, biosafety risks	(Travieso et al., 2022)
Cell-based	Ability to present complex antigens, targeted activation of the immune system	Expensive and complex production, standardization challenges, limited clinical application	(Liu, 2019)

for unresectable or metastatic HPV16-positive HNSCC.

Toxicity was generally manageable; the most common adverse events were flu-like symptoms including pyrexia and chills, along with fatigue and nausea. Grade ≥ 3 treatment-related adverse events were reported in a minority of patients (approximately 13%), including anemia, pyrexia, and decreased appetite (Saba et al., 2024).

Across the available evidence, common themes emerge:

1) Clinical benefit appears more pronounced when vaccines are combined with PD-1/PD-L1 blockade, consistent with the mechanistic rationale of antigen priming plus checkpoint release (Saxena et al., 2021).
2) Current evidence is limited by the reliance on early-phase, single-arm trials with small, heterogeneous populations. Notably, in the post-ICI setting, responses have been more modest but not absent, suggesting that antigenic re-priming may rescue a fraction of resistant patients, especially within combinatorial regimens (Massarelli et al., 2019).

A comparative summary of additional therapeutic HPV vaccines and their main clinical outcomes is provided in the table below (Table 3).

Although therapeutic HPV vaccines in combination with ICI have shown promising activity, several challenges remain before their integration into routine practice.

A major obstacle is antigenic heterogeneity and HLA restriction, which is particularly relevant in the post-ICI setting. Most available trials have enrolled heavily pre-treated and PD-1–exposed patients, where tumors often develop immune escape through HLA class I loss of heterozygosity (LOH) and antigen processing defects (Stern, 2021). HLA LOH reduces the breadth of antigen presentation, limiting recognition by cytotoxic T cells and contributing to an immune-excluded or “cold” microenvironment; genomic analyses of HNSCC have shown that HLA LOH is common and associated with decreased lymphocyte infiltration, highlighting its relevance as a mechanism of immune evasion in this setting (Morris, 2024). In such cases, even a robust vaccine-induced T-cell expansion may fail to translate into clinical benefit if the tumor 'hides' its viral targets. Strategies under investigation include multi-epitope or multi-genotype vaccines and the addition of immunomodulatory adjuvants aimed at broadening the T-cell repertoire and overcoming immune escape mechanisms (Peng et al., 2025).

The issue of timing and treatment setting also deserves emphasis. While most studies to date have focused on R/M disease, evidence supporting the use of therapeutic vaccines in the adjuvant setting for OPSCC is extremely limited. Early intervention in minimal residual disease or oligometastatic burden remains a major unmet need, as vaccines may be more effective when the immunosuppressive burden of a large tumor mass is absent. (Sun and Colevas, 2025).

Finally, the question of scalability and standardization is paramount. For translation into real-world practice, platforms must be reproducible, reliable, and clinically compatible, overcoming technical hurdles such as electroporation devices, cold-chain requirements for mRNA formulations, and injection-site standardization (Gupta et al., 2023). Without such harmonization, the field risks generating heterogeneous datasets that are difficult to integrate into evidence-based guidelines.

3.4. *Emerging strategy in HPV-positive disease: ROR2-directed antibody–drug conjugates*

Receptor tyrosine kinase-like orphan receptor 2 (ROR2) is a non-canonical Wnt receptor that primarily mediates Wnt5a-driven, β-catenin–independent signaling (Castro and Lopez-Bergami, 2022). Beyond its physiological role in embryonic development, aberrant ROR2 expression has been implicated in multiple solid tumors, where it promotes tumor cell plasticity and aggressive behavior. Functionally, ROR2 activation has been associated with enhanced proliferation, migration, invasion, and anchorage-independent growth, largely through the induction of epithelial–mesenchymal transition (EMT) and extracellular matrix remodeling programs (Si et al., 2022). In the context of virally driven carcinogenesis, Avincsal et al. demonstrated that HPV16 E6/E7 oncoproteins upregulate ROR2 expression in HPV-positive HNSCC models, with significantly higher expression compared to HPV-negative counterparts. Mechanistically, this effect is likely mediated through E2F1 activation downstream of E6/E7-induced disruption of p53 and pRB pathways, thereby linking viral oncogenesis to a non-canonical Wnt-associated invasive phenotype. Functionally, ROR2 silencing reduced proliferation, impaired G1/S transition, and markedly decreased invasive migration, supporting its role as a driver of tumor aggressiveness in HPV-positive disease (Avincsal et al., 2021).

These biological insights provided a strong rationale for therapeutic targeting of ROR2. In this context, the antibody–drug conjugate ozuriftamab vedotin (BA3021), a ROR2-directed ADC carrying an MMAE payload, demonstrated robust preclinical antitumor activity across multiple solid tumor models, including head and neck cancer. The ADC showed selective cytotoxicity in ROR2-expressing cells and induced significant tumor growth inhibition and regression in xenograft models, whereas the unconjugated antibody lacked antitumor efficacy, supporting a payload-dependent mechanism of action. These findings established ROR2 as a druggable surface antigen and supported further clinical development (Chang et al., 2025).

More recent preliminary clinical evidence further strengthens the biological and therapeutic relevance of ROR2 in HPV-driven disease. In a Phase II study of heavily pretreated recurrent/metastatic SCCHN

Table 3
Comparison of vaccine platforms, delivery, study design, and outcomes in HPV+ R/M HNSCC.

Vaccine	Platform	Study Type	Patient Population	OS (months)	PFS (months)	ORR (%)	% Grade 3–4 and Type of Toxicity	Citations
ISA101 + nivolumab	Synthetic long peptide vaccine (subcutaneous)	Phase II, single-arm	24 pts; HPV16 + solid tumors (92% OPSCC); R/M setting; 79% platinum-refractory	17.5	2.7	33	8% (2/24): rash, hyperglycemia	(Sousa et al., 2022)
MEDI0457 + durvalumab	DNA vaccine + IL-12 (electroporation)	Phase Ib/IIa, single-arm	35 pts; HPV16/18 + HNSCC (83% OPSCC); R/M mixed-line cohort	29.2	3.5	27.6	14% (5/35): anemia, fatigue, hyponatremia, hypertension, hyperglycemia	(Aggarwal et al., 2023)
PDS0101 + pembrolizumab	HPV16 peptide vaccine (lipid-based platform)	Phase II, single-arm	53 pts, 1st line R/M CPS ≥ 1	30	6.3	35.8	19% TRAE grade 3–4 reported	(Weiss et al., 2025)
BNT113 + pembrolizumab	mRNA-LNP vaccine (intravenous)	Phase II/III (AHEAD-MERIT), randomized; safety run-in analysis	15 pts HPV16 + R/M HNSCC; CPS ≥ 1	22.6	3.9	40	13.3% Grade ≥ 3 TRAEs	(Saba et al., 2024)

patients, ozuriftamab vedotin achieved an objective response rate (ORR) of 36%, including complete and partial responses, alongside a disease control rate of 86% (Adkins et al., 2025). Notably, these responses were observed in a population previously exposed to and refractory to anti–PD-1 therapy, highlighting a potentially non-overlapping mechanism of action. Overall, these findings indicate promising yet still preliminary clinical activity, warranting further validation in larger studies.

3.5. Bispecific and bifunctional immunotherapies in HNSCC: emerging strategies to overcome PD-1 resistance

3.5.1. Petosemtamab (MCLA-158) and EGFR/LGR5-targeted bispecific antibodies

The EGFR/LGR5 pathway has emerged as a promising therapeutic target in HNSCC. Petosemtamab (MCLA-158) is a bispecific IgG1 antibody designed to simultaneously bind EGFR and leucine-rich repeat-containing G-protein coupled receptor 5 (LGR5), a cancer stem cell marker overexpressed in several epithelial tumors, including oropharyngeal and laryngeal squamous carcinomas (Herpers et al., 2022). This dual binding promotes tumor-selective EGFR internalization and degradation in LGR5-expressing cells, thereby minimizing on-target toxicities in normal epithelial tissues with low LGR5 expression. Furthermore, petosemtamab exerts antibody-dependent cellular cytotoxicity (ADCC) and may reprogram the immune microenvironment by favoring effector cell infiltration (Lundberg et al., 2025).

In contrast to HPV-positive tumors, HPV-negative HNSCC is characterized by enhanced EGFR signaling and epithelial plasticity, both of which are associated with immune resistance and poor responsiveness to PD-1 blockade (Sun and Colevas, 2025).

In the phase I/II study, petosemtamab monotherapy was evaluated in heavily pretreated patients with R/M HNSCC. In the expanded cohort (n = 42 evaluable), investigator-assessed ORR was 35.7%, with a median DoR of 6.0 months and median PFS of 5.0 months. Toxicity was manageable and mainly driven by infusion-related reactions (74% all-grade; 21% grade 3–4), mostly occurring at first infusion and generally resolving. Other common adverse events (all-grade/grade 3–4) included rash (33%/0%), hypotension (26%/6%), dyspnea (26%/4%), nausea (26%/1%), acneiform dermatitis (24%/1%), decreased magnesium (19%/5%), erythema (19%/0%), and diarrhea (19%/0%) (Cohen et al., 2023).

In the first-line setting, interim results from the ASCO 2024 update of the petosemtamab + pembrolizumab cohort reported an impressive ORR of 67% (13 confirmed and 3 unconfirmed responses among 24 evaluable patients) in PD-L1-positive recurrent/metastatic HNSCC, with early evidence of durable disease control and acceptable tolerability (Fayette et al., 2024). This high response rate in a PD-L1-positive population suggests a potent synergistic effect between EGFR degradation and PD-1 blockade. A phase III registrational study of petosemtamab plus pembrolizumab as first-line treatment for HNSCC is currently ongoing NCT06525220 and NCT06496178.

Mechanistically, petosemtamab represents a distinct class of bispecific antibody that selectively targets the cancer stem cell (CSC) compartment (Lundberg et al., 2025). Although EGFR-driven signaling is biologically more prominent in HPV-negative HNSCC, preliminary data suggest that petosemtamab retains activity regardless of HPV status, potentially due to the ubiquitous role of LGR5 + CSCs in driving tumor recurrence across both subtypes.

3.5.2. Ficerafusp alfa (BCA101) and TGF-β–targeted bispecific strategies

HPV-negative HNSCC demonstrate significantly higher transforming growth factor-beta (TGF-β) expression compared to HPV-positive tumors (Wang et al., 2017).

TGF-β plays a central role in tumor progression by promoting EMT and driving a 'desmoplastic' immune-excluded phenotype (Peng et al., 2022). Importantly, upregulation of TGF-β signaling has been identified as a key mechanism of resistance to anti–PD-1/PD-L1 therapy, contributing to the formation of an immunosuppressive tumor microenvironment rich in regulatory T cells and myeloid-derived suppressor cells (Yi et al., 2022).

Ficerafusp alfa (BCA101) is a bifunctional antibody construct designed to simultaneously inhibit EGFR and neutralize TGF-β signaling. In a phase I study enrolling patients with advanced solid tumors, including HNSCC, ficerafusp alfa demonstrated an acceptable safety profile as both monotherapy and in combination with pembrolizumab. Treatment-related adverse events were predominantly dermatologic and consistent with EGFR blockade, with acneiform dermatitis reported in 46% of patients receiving monotherapy and 73% in the combination cohort. Additional common events in the combination arm included fatigue (53%), pruritus (40%), epistaxis (40%), and maculopapular rash (40%). Only one dose-limiting toxicity was observed, the maximum tolerated dose was not reached, and no treatment-related deaths occurred (Hernando-Calvo et al., 2025).

In a 1/1b study, in first-line R/M HPV-negative HNSCC with PD-L1 CPS $\geq$ 1, ficerafusp alfa achieved an overall ORR of 54% (21/39), rising to a striking 64% in HPV-negative tumors with 21% complete responses. Notably, the consistency of responses across PD-L1 CPS subgroups (1–19 vs. $\geq$20) suggests that TGF-β blockade may overcome low PD-L1-mediated resistance. Responses were durable, with 72% lasting $\geq$ 6 months and 56% $\geq$ 12 months overall (60% $\geq$12 months in HPV-negative responders). mPFS was 7.4 months and 9.8 months in HPV-negative disease; mOS was not reached (>20 months) in HPV-negative patients. Median time to response was 1.4 months. Outcomes, including ORR, PFS and OS, were similar across CPS 1–19 versus CPS $\geq$ 20 (Chung et al., 2025).

The ongoing FORTIFI-HN01 trial (NCT06788990) is a phase 2/3 randomized study comparing ficerafusp alfa plus pembrolizumab versus pembrolizumab plus placebo as first-line therapy in patients with PD-L1–positive R/M HPV-negative HNSCC.

Mechanistically, ficerafusp alfa represents a biologically-tailored strategy for HPV-negative HNSCC, where TGF-β–driven immune exclusion acts as a major barrier to ICI efficacy. By simultaneously counteracting EGFR signaling and TGF-β–mediated stromal remodeling, the drug promotes T-cell infiltration into the tumor nests, potentially synergizing with PD-1 blockade.

3.5.3. Amivantamab and dual EGFR/MET targeting in Post-ICI HNSCC

Amivantamab is a fully human bispecific IgG1 monoclonal antibody targeting EGFR and MET, designed to inhibit ligand-dependent signaling and to induce ADCC. It is currently approved for the treatment of non–small cell lung cancer (NSCLC) harboring EGFR exon 20 insertion mutations after platinum-based chemotherapy, and is under active clinical investigation in other solid tumors, including R/M HNSCC (Chon et al., 2023).

Preclinical evidence supports amivantamab plus ICI in HNSCC. In humanized PDX models, amivantamab combined with pembrolizumab produced synergistic tumor growth inhibition versus either agent alone and reshaped the TME, increasing granzyme B–positive cytotoxic $CD8^+$ T cells and expanding central memory $CD8^+$ T cells. Mechanistically, pembrolizumab was found to induce adaptive EGFR/MET upregulation and glycolytic reprogramming, whereas amivantamab reversed these escape pathways, effectively 're-sensitizing' the tumor to immune-mediated attack (Lim et al., 2024).

The clinical activity of amivantamab in R/M HNSCC is currently being investigated in the ORIGAMI-4 study, a multi-arm, phase Ib/II clinical trial evaluating subcutaneous amivantamab both as monotherapy and in combination with standard-of-care therapeutic agents in patients with R/M HNSCC. This innovative trial design allows parallel assessment of single-agent activity and rational combination strategies in biologically and clinically distinct patient subsets.

Recently, Harrington and colleagues reported the first efficacy results from Cohort 1 of the ORIGAMI-4 trial, which evaluated subcutaneous amivantamab monotherapy in patients with R/M HNSCC who

had progressed after prior ICI therapy. This represents one of the first prospective evaluations of a dual EGFR–MET targeting strategy specifically in the post-ICI setting. In this heavily pretreated population, amivantamab demonstrated clinically meaningful antitumor activity, with an ORR of 45% (95% CI, 29%–62%). The mPFS was 6.8 months (95% CI, 4.2–9.0), indicating a degree of disease control that compares favorably with historical benchmarks for salvage therapies in this setting. At the time of data cutoff, OS data remained immature and were not yet available for formal analysis, though early signals are encouraging (Harrington et al., 2025).

Administration-related reactions were reported in only 7% of patients treated with subcutaneous amivantamab, with no events of grade $\geq$ 3 severity. This incidence is markedly lower than that historically observed with intravenously administered amivantamab, where infusion-related reactions are relatively common in 66–72% of patients.

Although these results are promising, they are derived from early-phase, non-randomized studies and should therefore be considered hypothesis-generating, requiring prospective validation.

Subcutaneous amivantamab plus pembrolizumab and carboplatin in R/M HNSCC is proceeding to first-line, phase 3 development.

A comparative overview of bispecific antibodies and their clinical activity is summarized in Table 4.

4. Conclusion

This review addressed three predefined questions.

First, HPV-positive and HPV-negative OPSCC represent biologically distinct diseases with partially divergent immunotherapeutic behavior. HPV-positive tumors, characterized by an inflamed and antigen-rich microenvironment, are consistently associated with improved outcomes under PD-1/PD-L1 blockade. However, HPV status remains primarily a prognostic rather than a predictive biomarker and is insufficient to guide treatment selection in clinical practice.

Second, therapeutic strategies following progression on ICIs appear to diverge according to tumor biology. In HPV-negative disease, accumulating translational and early clinical evidence supports EGFR-centered approaches, particularly in tumors characterized by immune exclusion, hypoxia, and activation of MET/HGF and TGF-β pathways. Conversely, in HPV-positive tumors, the presence of viral neoantigens provides a strong biological rationale for immunologically driven strategies, although effective options in the post-ICI setting remain less clearly defined.

Third, emerging immunotherapeutic approaches are progressively shifting the field toward a biologically informed framework. Therapeutic HPV vaccines, especially in combination with PD-1 blockade, represent a promising strategy in HPV-positive disease, whereas bispecific and bifunctional agents targeting EGFR, TGF-β, or MET pathways have shown encouraging early activity, particularly in HPV-negative tumors. Nevertheless, most of these data derive from early-phase, non-randomized studies and should be considered hypothesis-generating.

Taken together, these findings support a transition from a purely HPV-based classification toward a multidimensional, biomarker-driven model integrating tumor immune contexture and pathway activation. Prospective validation through biomarker-driven clinical trials will be essential to translate these insights into clinically actionable strategies.

5. Critical View

Beyond the findings summarized above, several limitations of the current evidence base should be considered.

A key finding emerging from the current evidence is the disconnect between biological rationale and clinical benefit in unselected populations. In addition, most available evidence derives from retrospective series or early-phase trials with limited sample sizes. These studies lack formal treatment-by-biomarker interaction analyses, thereby limiting the strength of causal inference. Furthermore, the distinction between prognostic and predictive value of HPV status remains unresolved, as the improved outcomes observed in HPV-positive disease may primarily reflect underlying tumor biology rather than true differential sensitivity to specific therapeutic strategies.

Importantly, much of the available clinical evidence is derived from anatomically heterogeneous HNSCC populations, often lacking OPSCC-specific stratification and prospective biomarker-driven design. This limitation has likely diluted treatment effects and hindered the identification of clinically actionable subgroups.

This issue is particularly relevant for emerging therapeutic strategies, many of which are still supported by early-phase or non-randomized clinical evidence. While PD-1–based therapy is supported by randomized phase III data and represents the established standard of care, vaccine-based combinations, ADCs, bispecific antibodies, and

Table 4
Comparative table of bispecific antibodies in HNSCC, with detailed AE rates by grade.

Antibody	Mechanism of Action	Study Phase	Number of patients	Setting (Line)	ORR (%)	mPFS (months)	mOS (months)	Safety Data: AE % (G1–2 / G3–4)	Citations
Petosemtamab	anti-EGFR/LGR5	Phase 1/2 dose-expansion, single-arm	43	$\geq$ 2 L R/M HNSCC; monotherapy; mixed anatomical sites (no HPV selection)	37.2% (investigator assessed)	Not formally reported (median DOR 6.0 months)	Not reported	Acneiform dermatitis: 49% (G1–2), 7% (G3); Asthenia: 49% (G1–2), 7% (G3); Rash: 44% (G1–2), 0% (G3–4); Infusion reactions: 38% (G1–2), 7% (G3)	(Van Herpen et al., 2025)
Ficerafusp alfa	anti-EGFR/TGF-β	Phase 1/1b	39	1 L, treatment-naïve unresectable R/M HNSCC, CPS $\geq$ 1	Overall: 54% (21/39) HPV–: 64% (18/28) CR rate HPV–: 21.4%	7.4 (overall); 9.8 (HPV–)	Not reported (>20 in HPV–)	Acneiform dermatitis: 73% (G1–2), 0% (G3–4); Fatigue: 53% (G1–2), 0% (G3–4); Pruritus: 40% (G1–2), 0% (G3–4); Serious TRAEs: 20% (G3) in combo	(Chung et al., 2025)
Amivantamab	anti-EGFR/cMET	Phase 1b/2 (OrigAMI-4)	38	$\geq$ 2 L R/M HNSCC; post anti-PD-(L)1 + platinum; Oropharynx required p16-negative	45%	6.8	Not reported	Rash: 60% (G1–2), 8% (G3); Infusion reactions: 20% (G1–2), 0% (G3–4); Fatigue, infections: mostly G1–2; manageable profile	(Harrington et al., 2025)

bifunctional agents require prospective validation before they can be integrated into routine treatment algorithms.

From a therapeutic standpoint, emerging approaches suggest a divergence toward subtype-specific strategies: vaccine-based combinations in HPV-positive disease and EGFR-centered or bifunctional approaches in HPV-negative tumors, particularly in the post–ICI setting. However, most data remain preliminary and derived from early-phase studies, underscoring the need for prospective validation.

5.1. Future directions

To translate current evidence into a clinically meaningful framework, future therapeutic development in R/M OPSCC can be prioritized across three levels of evidence maturity.

First, the most immediate priority is the prospective validation of rational combinations already entering randomized clinical development, including vaccine plus PD-1 blockade strategies in HPV-positive disease and EGFR-centered or bifunctional approaches in HPV-negative disease.

Second, biomarker co-development should become an integral component of these trials, with prospective assessment of pathway activation, immune contexture, hypoxia-related signatures, antigen-presentation competence, and resistance mechanisms.

Third, future treatment algorithms should move beyond HPV status as a binary classifier and incorporate multidimensional models integrating viral status, PD-L1 CPS, spatial immune architecture, EGFR/MET/HGF signaling, TGF-β–driven immune exclusion, and tumor-intrinsic stemness programs.

In the post-immunotherapy setting, HPV-negative OPSCC appears to be primarily driven by EGFR-dependent and immune-excluded phenotypes. Within this context, EGFR-centered strategies may represent the backbone of treatment, with further biological stratification based on dominant resistance pathways. Tumors characterized by MET/HGF activation may preferentially benefit from dual EGFR/MET targeting approaches, such as amivantamab. Similarly, TGF-β–driven immune exclusion may identify candidates for bifunctional EGFR/TGF-β inhibitors such as ficerafusp alfa. In addition, LGR5-expressing, stem-like tumor populations may represent a rational target for bispecific agents such as petosemtamab.

In contrast, HPV-positive OPSCC is characterized by the presence of viral neoantigens, making therapeutic vaccination strategies targeting E6 and E7 oncoproteins a biologically compelling approach.

In the immunotherapy-naïve setting, treatment selection may evolve beyond PD-L1 CPS toward a more integrated model incorporating tumor immune contexture, hypoxia-related signatures, and tissue architecture, which may better capture the functional state of the tumor microenvironment and refine patient selection.

While this framework requires prospective validation, it provides a conceptual basis for the transition toward pathway-driven and subtype-specific therapeutic strategies in OPSCC.

A critical challenge moving forward will be the translational validation of pathway-specific biomarkers to guide patient selection. In particular, it remains to be determined whether activation of MET/HGF, TGF-β signaling, or stemness-related markers such as LGR5 can reliably predict response to corresponding targeted or bifunctional therapies. Addressing this gap will require integrated translational efforts within prospective clinical trials, incorporating robust biomarker assessment alongside therapeutic intervention.

Author contributions

A.D.B. and R.G. contributed to the conceptualization and drafting of the manuscript. M.F. contributed to manuscript drafting. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

Patient consent

Not applicable, as no individual patient data were included.

Ethics statement

Ethical approval was not required, as the study was based on previously published data.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

Appendix 1. PubMed search strategy

The PubMed/MEDLINE search was conducted to identify studies evaluating immunotherapeutic strategies in oropharyngeal squamous cell carcinoma (OPSCC), with a focus on HPV-related differences and recurrent/metastatic disease. The search strategy was structured around three main conceptual domains: (1) disease entity, (2) HPV status, and (3) therapeutic approaches.

The following search string was used:

(1) Disease:
("oropharyngeal squamous cell carcinoma"[Title/Abstract] OR OPSCC[Title/Abstract] OR "head and neck squamous cell carcinoma"[Title/Abstract])
AND
(2) HPV-related terms:
(HPV[Title/Abstract] OR "human papillomavirus"[Title/Abstract] OR p16[Title/Abstract])
AND
(3) Therapeutic strategies:

("PD-1"[Title/Abstract] OR "PD-L1"[Title/Abstract] OR pembrolizumab[Title/Abstract] OR nivolumab[Title/Abstract] OR immunotherapy[Title/Abstract] OR "immune checkpoint inhibitor"[Title/Abstract]
OR EGFR[Title/Abstract] OR cetuximab[Title/Abstract]
OR bispecific[Title/Abstract] OR bifunctional[Title/Abstract]
OR "TGF-beta"[Title/Abstract] OR MET[Title/Abstract] OR HGF[Title/Abstract]
OR vaccine[Title/Abstract] OR "therapeutic vaccine"[Title/Abstract])

Data availability

All data analyzed during this study are publicly available through the referenced databases (PubMed/MEDLINE, EMBASE, and CENTRAL).

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