Abdul Qader *et. al.*, Babcock Univ. Med. J.2026 9(1):42-53
https://doi.org/10.38029/babcockuniv.med.j..v9i1.1154
eISSN: 2756-4657

REVIEW ARTICLE OPEN ACCESS

Redefining head and neck cancer treatment with targeted therapy: Current landscape and emerging directions

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Submitted: 5th May 2025
Accepted: 23rd September 2025
Published: 31st March 2026
ID: Orcid ID

Abstract

Background: This comprehensive review discusses the current role of targeted therapies in head and neck squamous cell carcinoma, with a focus on known resistance mechanisms, recent combination strategies, and the direction of personalised treatment.

Main Text: We performed a literature search between March and July 2025 across PubMed, Scopus, and Web of Science. The search focused on both MeSH terms and free-text keywords, including “Head and Neck Neoplasms,” “EGFR inhibition,” “Immune Checkpoint Inhibitors,” and “Combination Therapy.” Clinical trials, original research articles, and major reviews relevant to the scope of this review were included, with no restriction on publication year, resulting in a comprehensive synthesis of the available evidence.

Cetuximab remains the only epidermal growth factor receptor targeting drug formally approved for head and neck squamous cell carcinoma, though its benefits are limited to specific patient groups. Immunotherapies like pembrolizumab and nivolumab demonstrate meaningful survival benefits in recurrent and metastatic settings, and their application is expanding into earlier disease stages. Combination strategies, including EGFR and programmed cell death protein 1 blockade, have shown promising activity. Consequently, dual-target regimens and adaptive strategies are attracting increasing attention. Liquid biopsy and biomarker-guided treatment selection are under active investigation to refine the personalisation of therapy.

Conclusion: The management of head and neck squamous cell carcinoma is shifting toward more personalised and adaptive strategies that combine targeted therapies with immunomodulation. The integration of molecular profiling, real-time monitoring, and smarter trial designs will likely play a key role in improving the precision and durability of treatment responses.

Keywords: Head and Neck Neoplasms, Molecular Targeted Therapy, Receptor, Epidermal Growth Factor, Programmed Cell Death 1 Receptor, Drug Resistance, Neoplasm

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Plain English Summary
Head and neck squamous cell carcinoma (HNSCC) is a type of cancer that develops in the mouth, throat, and nearby areas. It is among the most common cancers worldwide and is most often seen with smoking, alcohol use, and infection with human papillomavirus (HPV). Although surgery, radiotherapy, and chemotherapy are the core therapies, relapse and side effects afflict most patients. The last few years have witnessed the introduction of new approaches such as targeted therapy and immunotherapy, which have offered hope. Targeted therapy blocks some of the molecules that support cancer growth, and immunotherapy stimulates the body's own immune system to attack the cancer. These treatments are already improving survival in some patients, but problems remain, including drug resistance, side effects, and affordability. This article reviews the latest studies on targeted and immunological therapies in head and neck cancer, highlights their current strengths and weaknesses, and discusses forthcoming approaches that may help patients and maximise quality of life.

Background
Head and neck squamous cell carcinoma (HNSCC) remains challenging due to molecular heterogeneity, late presentation, and treatment resistance. While cetuximab introduced targeted therapy, outcomes remain suboptimal. Immune checkpoint inhibitors and combination strategies are shifting treatment paradigms. Advances in molecular oncology have highlighted pathways such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR). While these approaches have broadened the treatment landscape, their success remains inconsistent due to resistance mechanisms and the absence of robust predictive biomarkers. This review provides an overview of targeted therapies in HNSCC, emphasising their mechanisms, limitations, and potential integration into future precision-based treatment strategies.

Head and neck squamous cell carcinoma (HNSCC) is a malignancy arising from the mucosal linings of the oral cavity, oropharynx, larynx, and hypopharynx (1). It is one of the most common cancers globally, and recent estimates say there are nearly 900,000 new cases each year, along with more than 400,000 deaths (2). Although surgery, radiotherapy, and chemotherapy remain the backbone of treatment, outcomes in advanced disease have improved only marginally, and many patients still relapse or develop resistance to standard therapies (3, 4). Importantly, epidemiological shifts have been observed, with a rising incidence of Human Papillomavirus (HPV)-positive oropharyngeal cancers, particularly among younger adults, which carry distinct biological behaviour and generally more favourable prognosis (5). Younger Human Papillomavirus–associated Oropharyngeal Cancer (HPV-OPC) patients also show different biomarker and behavioural profiles, including higher HPV16 positivity and earlier age at sexual debut, compared to older cases (6). Reduced-dose chemoradiotherapy in HPV-OPC can yield similar survival outcomes with less long-term toxicity, highlighting the therapeutic implications of these epidemiologic and biologic differences (7). Progress in the molecular characterisation of HNSCC has helped explain these divergent outcomes. Abnormal signalling pathways, oncogene activation, and immune evasion mechanisms are central to tumour progression (8). Certain alterations enable cancer cells to evade host immune surveillance (9). Key molecular targets have been identified, including epidermal growth factor receptor (EGFR), vascular endothelial growth factor receptor (VEGFR), and immune checkpoints such as programmed cell death protein 1 (PD-1) and programmed death ligand 1 (PD-L1), which are now being actively explored in clinical settings (10, 11, 12). Therapeutic strategies are beginning to incorporate these insights. Immunotherapy has shown particular promise, with neoadjuvant and adjuvant pembrolizumab achieving a one-year disease-free survival rate of 97% in resectable HNSCC (13). A 2024 study combining pembrolizumab with chemotherapy showed a 64.5% objective response rate and high organ preservation (14), and by 2025, the Food and Drug Administration (FDA) had approved pembrolizumab for locally advanced HNSCC (15). Nevertheless, resistance to EGFR-targeted therapies continues to be a challenge, driving investigations into rational drug combinations and immune-based strategies (16). In addition to biological complexity, real-world barriers also limit progress. High costs of novel immunotherapies and targeted agents can contribute to financial toxicity for patients, while access to biomarker testing remains inconsistent, particularly in low- and middle-income countries (17). These challenges highlight the need for strategies that are not only biologically effective but also feasible and sustainable across diverse healthcare settings. This review examines the primary molecular pathways involved in the development of HNSCC and highlights current

therapeutic agents that have either been approved or are currently in clinical trials. In addition, it addresses combination treatment approaches, emerging resistance patterns, and future directions for specific therapy guided by molecular profiling.

Main Text

Search Strategy

A comprehensive search was conducted in electronic databases, including PubMed, Scopus, and Web of Science, from March 2025 to July 2025. The following keywords and MeSH terms were used in various combinations: "Head and Neck Neoplasms"; "Molecular Targeted Therapy"; "Receptor, Epidermal Growth Factor"; "Programmed Cell Death 1 Receptor" and "Drug Resistance, Neoplasm". Articles were included if they were in English, peer-reviewed, and focused on pathogenesis, therapeutic targets, combination strategies, and future directions of HNSCC. We included peer-reviewed original research articles, clinical trials (phase I–III), and major reviews published in English that addressed targeted therapies, immunotherapy, or combination strategies in head and neck squamous cell carcinoma. Studies reporting molecular mechanisms, resistance pathways, or biomarker-driven treatment approaches were also considered. We excluded case reports, conference abstracts, editorials, letters, non-English publications, and studies unrelated to head and neck squamous cell carcinoma. Preclinical studies without clinical relevance were not included. No formal meta-analysis was performed due to heterogeneity in study design and reported outcomes. A basic quality narrative review approach was applied by restricting inclusion to peer-reviewed clinical trials, original research articles, and major reviews published in indexed journals, while excluding case reports, conference abstracts, and non-peer-reviewed material.

Molecular Pathogenesis of Head and Neck Cancer

HNSCC develops over time as cells accumulate a series of molecular and genetic disruptions that interfere with normal epithelial regulation. One of the most common early events is the mutation of the TP53 gene, which normally helps maintain genomic stability by controlling DNA repair and programmed cell death. TP53 inactivation, which occurs in the majority of HNSCC cases, allows damaged cells to survive and divide abnormally (18). In addition to this, alterations in genes such as CDKN2A and NOTCH1 have been found to be linked to the disease. CDKN2A encodes the p16 protein, and its inactivation removes an important checkpoint in the cell cycle. Meanwhile, NOTCH1 mutations show both tumour-suppressing and oncogenic roles, depending on tumour context (19, 20). A number of growth and survival pathways also become dysregulated. The EGFR signalling pathway is most commonly studied, as EGFR overexpression is present in the majority of HNSCC tumours (21). This promotes a series of downstream signalling pathways involved in cell growth, angiogenesis, and resistance to apoptosis. The phosphatidylinositol 3-kinase (PI3K)/AKT/ mechanistic target of rapamycin (mTOR) axis is also commonly activated through either mutation in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), amplification of growth factor receptors, or loss of phosphatase and tensin homolog (PTEN) (22). These changes give tumour cells a growth advantage and are often linked to resistance to conventional therapies. Additionally, oncogenic mutations in Harvey rat sarcoma viral oncogene homolog (HRAS) and other members of the rat sarcoma viral oncogene homolog (RAS) family contribute to the activation of the mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK) pathway, which further encourages proliferation and invasion (23, 24). Recently, pathways like Janus kinase (JAK)/STAT and wingless-related integration site (Wnt)/β-catenin are implicated in immune evasion and tumour spread, but their roles are still being studied (25, 26). Tumour heterogeneity is also a key factor in the biology of HNSCC. Variations at the genetic and epigenetic level and differences in the tumour microenvironment can occur not just between patients but also within a single tumour. This means that different regions of the same tumour might behave differently — a concept referred to as intra-tumoral heterogeneity — while inter-patient variability adds another layer of complexity. These differences affect how tumours respond to treatment and make it harder to design therapies that are effective across all tumour cell populations (27, 28). The complex molecular landscape of HNSCC drives tumour initiation and progression and influences treatment response and, therefore, makes it central to the development of more precise, targeted therapies. Key molecular pathways and their sites of therapeutic intervention are shown in Figure 1.

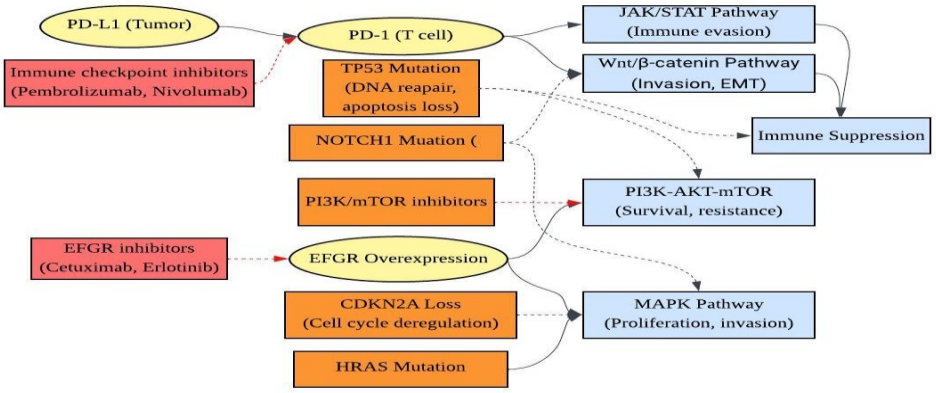

Figure 1- Molecular pathways and their sites of therapeutic intervention

Mutations in *TP53, NOTCH1, CDKN2A,* and *HRAS* activate EGFR-driven signalling, leading to proliferation, survival, invasion, and immune evasion. Key therapeutic inhibitors include EGFR inhibitors, PI3K/mTOR inhibitors, and immune checkpoint inhibitors. Solid arrows show activation; dotted grey arrows show indirect interactions; red arrows indicate drug-targeted inhibition.

Therapeutic Targets and Mechanism

EGFR remains the most widely studied target in HNSCC, with over 90% of tumours exhibiting overexpression (8). It is present in high amounts in most tumours and plays a key role in triggering pathways that help cancer grow and survive. It mainly targets the RAS/RAF/MEK/ERK and PI3K/AKT pathways (29). Treatments like cetuximab, erlotinib, and afatinib try to interrupt these signals (3). Kiss Z, et al. showed that survival improves when EGFR inhibitors are added to chemotherapy (30).

However, EGFR mutations, compensatory signalling, and tumour heterogeneity limit long-term efficacy. Some tumours adapt by using backup pathways or altering the receptor itself (16). For this reason, the researchers are exploring combination strategies that also block other molecules like MET, signal transducer and activator of transcription 3 (STAT3), or insulin-like growth factor 1 receptor (IGF1R), based on lab results that look promising (31, 32). Another significant pathway is the one driven by VEGFR, which helps tumours build blood vessels. VEGFR is often overproduced in head and neck tumours (33). Drugs like bevacizumab aim to block it, and early tests show some benefit. Still, Jain RK pointed out that blood vessels in tumours often resist these drugs by changing how they grow. That's why current thinking is shifting toward combining anti-angiogenic drugs with other therapies that boost immune response or fix the tumour environment (34). As for the PI3K/AKT/mTOR axis, it is frequently altered in these cancers. Mutations in PIK3CA or loss of PTEN can push this pathway into overdrive (35). Several drugs like buparlisib and everolimus are being looked at, especially for tumours that don't respond well to EGFR drugs (36, 37). Immunotherapy has also entered the picture. Drugs like pembrolizumab and nivolumab, which target PD-1 or PD-L1, have already changed how recurrent or metastatic HNSCC is treated (38). Wise-Draper TM, et al. showed that even when given before surgery, pembrolizumab could reduce recurrence risk significantly (13). Because of this, newer trials are looking at how early immunotherapy might help more patients. Finally, research into multi-targeted agents has gained traction. Lin et al. discussed how dual-action drugs that act on both EGFR and another member of the erythroblastic leukaemia viral oncogene homolog (ErbB) family, like human epidermal growth factor receptor 2 (HER2), might slow down resistance and produce stronger responses than single-target treatments (4).

Approved Targeted Therapies and Clinical Trial Highlights

Cetuximab is one of the earliest and most established targeted therapies in HNSCC, which is a monoclonal antibody that binds to EGFR. It is the only FDA-approved EGFR-targeted therapy for HNSCC. It is approved for use in combination with radiotherapy for locally advanced disease and with platinum-based chemotherapy in recurrent or metastatic settings (3). It acts by blocking ligand-induced EGFR activation and promoting antibody-dependent cellular cytotoxicity. Bonner et al.'s

study confirmed its efficacy in early trials, which demonstrated improved locoregional control and survival when combined with radiotherapy (11). Phase II trials have investigated combinations of cetuximab with immune checkpoint inhibitors. Cetuximab with pembrolizumab showed an objective response rate (ORR) of approximately 45% (39). Immune checkpoint inhibitors have changed the treatment landscape of HNSCC. Anti-PD-1 antibody Nivolumab was the first to be approved after the CheckMate-141 trial and showed significantly improved overall survival of 7.5 months vs. 5.1 months in patients with platinum-refractory recurrent or metastatic HNSCC (40). Similarly, pembrolizumab gained approval after the KEYNOTE-012 and KEYNOTE-040 trials and confirmed durable responses and survival advantages in the same population (4, 41). The KEYNOTE-048 trial established pembrolizumab as a first-line treatment option either as monotherapy or in combination with chemotherapy in patients with a combined positive score (CPS) of PD-L1 ≥20 (42). Pembrolizumab received FDA approval in 2025 for use in the neoadjuvant and adjuvant setting in resectable and PD-L1–positive locally advanced HNSCC after compelling data showed improved disease-free survival in such patients (15). Beyond EGFR and PD-1 pathways, anti-angiogenic therapies have also shown promise. Multi-kinase inhibitor Lenvatinib, targeting VEGFR1–4 among other pathways, has shown early efficacy in combination regimens. In phase I/II studies, lenvatinib paired with cetuximab achieved an ORR of 67% and its combination with pembrolizumab yielded an ORR of 46% and progression-free survival (PFS) of 4.7 months (42). Lenvatinib is not yet accepted for HNSCC despite these promising results and is still under evaluation. Targeting the PI3K/AKT/mTOR signalling axis has also attracted attention due to the high frequency of pathway alterations in HNSCC, including PIK3CA mutations and PTEN loss. Pan-PI3K inhibitor buparlisib showed modest results when combined with paclitaxel in early-phase trials (44). Alpelisib, which selectively targets the PI3Kα isoform, has been tested in combination with tipifarnib in patients harbouring PIK3CA mutations or HRAS overexpression, showing promising activity (45). Everolimus and temsirolimus, both mTOR inhibitors, have been studied in HNSCC trials, but the results were not satisfactory. Some studies showed limited benefit, mostly due to side effects or reduced efficacy when used alone (46, 47). Aside from cetuximab, a few other EGFR-targeted antibodies have had mixed outcomes. For example, panitumumab failed to demonstrate superiority over cisplatin when combined with radiotherapy (48, 49).

On the other hand, nimotuzumab, when combined with cisplatin and radiation, improved local control and extended survival over five years in some patients with locally advanced disease (50). Zalutumumab led to modest survival benefits for people with recurrent or metastatic disease (51). As for the small-molecule drugs, lapatinib, which targets both EGFR and HER2, helps stabilise the disease in about 20% of cases, but the responses weren't long-lasting (52). Afatinib and erlotinib, which target the broader ErbB family, continue to be explored in ongoing trials, with some indications of benefit (52, 53). Over time, the treatment of HNSCC has undergone a significant shift. EGFR-targeted drugs were initially the main focus, but now, more attention is going toward combinations that especially include immunotherapy. The recent FDA approval of pembrolizumab for perioperative use underscores the growing role of immunotherapy in the early stages of the treatment pathway. It shows that immunotherapy isn't just for late-stage or recurrent cases anymore. Continued efforts in biomarker-driven trials and novel agent development will be key in further improving outcomes for patients with HNSCC.

Combination Strategies and Resistance Mechanisms

Resistance to EGFR-targeted therapies like cetuximab is frequently driven by activation of the PI3K/AKT/mTOR pathway, which sustains cell survival and proliferation despite EGFR inhibition. Dual inhibition using cetuximab in combination with PI3K/mTOR inhibitors such as PKI-587 has shown reciprocal effects in preclinical HNSCC models, reversing resistance and enhancing apoptosis (54).

One known resistance mechanism involves the activation of MET/hepatocyte growth factor (HGF) signalling after EGFR inhibition. In this setting, MET can take over key survival functions, essentially bypassing EGFR blockade, a rationale that has prompted investigations into dual EGFR–MET inhibition (55). Similarly, human epidermal growth factor receptor 3 (HER3) becomes relevant in cetuximab-resistant tumours. When EGFR is blocked, HER3 can activate downstream PI3K/AKT pathways, assisting tumour growth, but this compensatory loop may be disrupted by agents like MEHD7945A, a bispecific antibody targeting both EGFR and HER3 (56). Together, these observations underscore the need for combination strategies that can intercept bypass signalling pathways,

potentially improving treatment durability in patients with resistant head and neck cancers. Table 1 summarises the combination strategies.

Table 1- Key Combination Strategies in HNSCC

Combination	Targets	Trial Phase	Key Outcome	Notes
Cetuximab + PD-1 inhibitors	EGFR + PD-1	Phase II	ORR ~45% (Pembrolizumab); overall survival (OS) 44% (Nivolumab combo)	Promising synergy in recurrent or metastatic (R/M) HNSCC
Cetuximab + VEGFR inhibitors	EGFR + VEGFR	Phase I/II	ORR 46% with lenvatinib + pembrolizumab	Early-stage evidence; trials ongoing
PI3K/mTOR inhibitors + EGFR agents	PI3K/AKT/mTOR + EGFR	Phase I/II	Synergistic apoptosis with buparlisib + cetuximab	Resistance reversal shown in mutation-enriched tumours
Dual HER3/EGFR targeting	EGFR + HER3	Preclinical	Inhibition of HER3-mediated resistance in vitro	Investigational agent (e.g., MEHD7945A)
Alpelisib + Tipifarnib	PI3Kα + HRAS	Phase I/II	Activity seen in HRAS/PIK3CA altered tumours	Molecular selection required
MET + EGFR blockade	MET + EGFR	Preclinical	MET bypasses EGFR; dual inhibition restores sensitivity	Rationale for combination in resistant models

Clinical practice implications

1. HPV-positive disease has a distinct prognosis and may warrant tailored treatment approaches (5, 57).
2. Biomarker testing (PD-L1, PIK3CA) is important but often inaccessible in low-resource settings (8, 20, 57).
3. EGFR inhibitors remain standard but resistance limits long-term benefit (3, 11, 16, 30).
4. Immunotherapy, especially pembrolizumab, is FDA-approved and increasingly used in advanced HNSCC (13, 14, 15, 52, 54, 55).
5. Combination regimens and perioperative immunotherapy are promising future strategies (10, 38, 56).
6. Cost and accessibility remain major real-world challenges (5, 9, 57).

Current Challenges and Limitations

Despite advances in targeted therapies and immunotherapies, significant challenges persist in treating HNSCC. One major limitation is the emergence of therapeutic resistance, frequently driven by compensatory activation of signalling pathways such as PI3K/AKT/mTOR, MET, and HER3, which can bypass EGFR blockade and reduce the long-term efficacy of monoclonal antibodies like cetuximab (8). HNSCC exhibits considerable interpatient and intratumoral heterogeneity with variations at the genetic, epigenetic, and microenvironmental levels. It complicates the identification of reliable therapeutic targets and reduces treatment predictability (58). Even though immune checkpoint inhibitors, such as pembrolizumab and nivolumab, show durable responses in a subset of patients, overall response rates remain modest, at ~15–20%. This is largely due to the presence of immune-evasive mechanisms like T-cell exhaustion and immunosuppressive cell infiltration (4). The toxicity profiles, high costs, and the absence of validated predictive biomarkers limit the proper use of these therapies in regular practice (57). Furthermore, concerns regarding long-term patient quality of life, including treatment-related fatigue, mucositis, and functional impairments, as well as the lack of comprehensive cost-effectiveness analyses, remain significant barriers to optimising treatment decisions. For example, while some studies suggest chemoradiotherapy can be cost-effective without compromising health-related quality of life in selected populations (59), others indicate that newer agents like nivolumab may not be cost-effective at current pricing despite survival benefits (60).

Future Directions

Future directions in HNSCC therapy are focused on personalising treatment through biomarker-driven approaches, matching molecular alterations with targeted agents, such as PIK3CA mutations with PI3K inhibitors or HRAS mutations with

tipifarnib (29). A major area of present research is the development of rational combination strategies that combine immune checkpoint inhibitors with targeted agents (e.g., anti-EGFR or anti-angiogenic drugs). The aim is to increase efficacy and overcome resistance mechanisms (10). Neoadjuvant and perioperative immunotherapy is coming up as an auspicious approach, with early studies showing improved disease-free survival when checkpoint inhibitors are administered pre- and post-surgery (13). There is increasing interest in targeting the tumour microenvironment, such as inhibiting myeloid-derived suppressor cells (MDSC) or modulating T-cell exhaustion, for increasing the responsiveness of “cold” tumours to immunotherapy (17). Non-invasive liquid biopsy, specifically circulating tumour DNA (ctDNA) and exosomes, is being investigated for monitoring treatment response and real-time detection of minimal residual disease (58). Clinical trials are currently underway investigating ctDNA as a biomarker for HPV-related oropharyngeal cancer, with viral-specific DNA fragments in plasma available as a very sensitive method of monitoring disease and detecting recurrence. (61, 62). These emerging directions promise to refine the management of HNSCC by improving precision and treatment durability and allowing earlier interventions. The future directions are summarised in Table 2.

Table 2- Future Directions in HNSCC Management

Research Focus	Description	Current Status/Notes
Biomarker-Driven Personalization	Matching mutations (e.g., PIK3CA, HRAS) to specific agents	Under investigation in multiple trials
Neoadjuvant Immunotherapy	Checkpoint blockade before surgery to reduce recurrence risk	FDA approved for perioperative pembrolizumab (2025)
Targeting Tumour Microenvironment	Inhibiting Myeloid-Derived Suppressor Cell (MDSCs), reversing T-cell exhaustion	Preclinical and early clinical studies
Liquid Biopsy Technologies	Monitoring ctDNA and exosomes for real-time response and recurrence	Still exploratory; not yet standard practice
Multi-Target Adaptive Therapies	Sequential or combined inhibition of resistance pathways	Rational strategy to combat heterogeneity and resistance

Conclusion

The management of HNSCC is increasingly transitioning to more individualised and precise strategies. Biomarker-directed treatment, wherein therapy is based on genetic abnormalities such as PIK3CA and or HRAS mutations, represents a critical advance. The introduction of perioperative immunotherapy, particularly PD-1 inhibitors, is changing practice by improving survival in earlier stages of disease. At the same time, combination regimens that bring together targeted agents and immunotherapies appear to be the most promising way to overcome resistance and tumour heterogeneity.

Therefore, the future of HNSCC treatment is likely to rely on simultaneous multiple targeting of multiple pathways, rather than a single one, and may depend on strategies that can adjust to changes in the tumour's biology and its interactions with the immune system over time. Looking ahead, adaptive trial designs and real-world evidence will be essential to accelerate the translation of novel therapies into clinical practice and ensure that treatment strategies remain relevant in diverse patient populations.

List of Abbreviations

AKT: Protein kinase B
CPS: Combined positive score
CtDNA: Circulating tumour DNA
DNA: Deoxyribonucleic acid
EGFR: Epidermal growth factor receptor
ErbB: Erythroblastic leukaemia viral oncogene homolog
ERK: Extracellular signal–regulated kinase
FDA: Food and Drug Administration
HGF: Hepatocyte growth factor
HER2: Human epidermal growth factor receptor 2
HER3: Human epidermal growth factor receptor 3
HNSCC: Head and neck squamous cell carcinoma
HPV: Human Papillomavirus
HPV-OPC: Human Papillomavirus–associated Oropharyngeal Cancer
HRAS: Harvey rat sarcoma viral oncogene homolog
IGF1R: Insulin-like growth factor 1 receptor
JAK: Janus kinase
MAPK: Mitogen-activated protein kinase
Mtor: Mechanistic target of rapamycin
MDSC: Myeloid-derived suppressor cell
MET: Mesenchymal-epithelial transition factor
ORR: Objective response rate
OS: Overall survival

PD-1: Programmed cell death protein 1
PD-L1: Programmed death ligand 1
PFS: Progression-free survival
PI3K: Phosphatidylinositol 3-kinase
PIK3CA: Phosphatidylinositol-4,5-Bisphosphate 3 -Kinase Catalytic Subunit Alpha
PTEN: Phosphatase and tensin homolog
R/M: Recurrent or metastatic
RAS: Rat sarcoma viral oncogene homolog
STAT3: Signal transducer and activator of transcription 3
VEGFR: Vascular endothelial growth factor receptor
Wnt: Wingless-related integration site

Declarations

Ethical approval and consent to participate-
Not applicable

Consent for publication
The authors gave consent for the publication of the work under the Creative Commons Attribution-Non-Commercial 4.0 license.

Availability of data and materials
The data and materials associated with this research will be made available by the corresponding author upon reasonable request.

Competing interests
The authors declare that they have no known competing interests regarding this paper or its content.

Funding
The authors have not received any financial support for writing this mini-review.

Author contributions
AQOAJ: Conceptualisation, Writing – original draft
RN: Data curation and Conceptualisation, Writing – editing
AL-RM: Data curation, Writing – original draft, Writing – review & editing
OM and AJY: Data curation, Writing – review & editing
All authors conceived, designed, and conducted the study; collected and analysed the relevant data, and developed the manuscript. All the authors are responsible for the intellectual content of the manuscript and have approved the final draft of the manuscript.

Acknowledgement
Not applicable.

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