Novel immune-modulating drugs for advanced head and neck cancer

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Abstract
Background: Recently, two anti-PD-1 immune checkpoint inhibitors, pembrolizumab and nivolumab, have been approved by the US Food and Drug Administration for patients who fail on platinum-based chemotherapy. However, overall response and progression-free survival are still limited, and multiple novel agents are under development to fulfill this unmet clinical need.

Methods: Publications between 1992 and 2019 regarding the immunological/biological mechanisms and early phase clinical trial outcomes of immunomodulatory agents for head and neck cancer were described in this review article.

Results: Eleven immunomodulatory agents for advanced head and neck, including small molecules, antibodies, and therapeutic vaccines were described. Treatment responses were noted in nearly all 11 agents, as monotherapy or combination therapy.

Conclusions: Potentials of the novel immunomodulatory agents to improve treatment efficacy of head and neck cancer and to maintain tolerable safety profile have been disclosed.

KEYWORDS
head and neck cancer, immunotherapy

1 | INTRODUCTION

Recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) encompasses various subgroups of cancer, with different anatomical sites (eg, oral, oropharyngeal, hypopharyngeal, laryngeal), biological characters (eg, p16 positive or p16 negative), and epidemiological factors (eg, smoking and tobacco use). In the preimmunotherapy era, platinumbased regimens were considered effective first-line treatments.1 Combination of cetuximab with a platinum-based regimen later demonstrated increased clinical benefit.2 However, in the second-line setting, many treatment options have been evaluated, including methotrexate,3 taxanes,4 cetuximab,5 and afatinib.6 These monotherapy studies showed comparable overall survival (OS), ranging from 5 to 8 months. Owing to the lack of effective treatments, the prognosis beyond first-line systemic treatment in patients with R/M HNSCC remains dismal.

Given the initial success of immunotherapy in various cancer types, much effort has been made to develop the immunotherapy concept in R/M HNSCC. Two PD-1 immune checkpoint inhibitors (pembrolizumab and nivolumab) have been approved by the U.S. FDA for use in R/M HNSCC patients who fail on prior platinum-based chemotherapy.7-9 Immunotherapy has been shown to provide a durable response with less frequent grade III/IV adverse events (AEs) compared with chemotherapy. In the CHECKMATE-141 trial, median OS was 7.5 months, duration of response (DOR) was 9.7 months, and grade III/IV treatment-related AEs were recorded in 13% of patients. Similarly, in KEYNOTE-012,
median OS was 8 months, and grade III/IV treatment-related AEs occurred in 13% of patients. To further improve efficacy of immunotherapy in treating HNSCC, combinations of immune checkpoint inhibitors (ICIs) with chemotherapy or targeted therapy, as well as novel agents, are now under development. In this review, we will specifically focus on the current progress of novel immunotherapy agents in R/M HNSCC.

2 | SMALL MOLECULES

2.1 | Danvatirsen

Many studies have shown that janus kinases (JAKs) and their downstream effectors, signal transducer and activator of transcription (STAT) proteins, have important roles in maintaining multiple immune system functions as well as modulating the tumor microenvironment. Within the JAK/STAT pathway, phosphorylated STAT3 is the principal protein that leads to an immunosuppressive microenvironment and attenuates antitumor immunity.10,11

Danvatirsen (AZD9150) is an antisense oligonucleotide inhibiting STAT3 transcription and translation in tumor-infiltrating immune cells and stromal cells. A phase 1b/2 study of danvatirsen plus durvalumab has been initiated in patients with R/M HNSCC (ClinicalTrials.gov, NCT02499328). Three trial arms were included: danvatirsen plus durvalumab as second-line treatment, danvatirsen monotherapy as second-line treatment, and danvatirsen plus durvalumab as first-line treatment. With danvatirsen plus durvalumab as second-line treatment, median progression-free survival (PFS) was 2.9 months, and the OS rate at 6 months was 47%. The overall response rate (ORR) was 26%, with a complete response (CR) in 4 out of 38 patients, and a partial response (PR) in 6 patients. The median DOR was not reached (range, 5-70 weeks). Compared with other second-line treatments for R/M HNSCC, previous studies of ICI monotherapy (pembrolizumab, nivolumab, durvalumab) have shown median PFS durations of approximately 2 months, and ORRs ranging from 9% to 16%.7,8,13,14

In the danvatirsen plus durvalumab study, 43 patients experienced a treatment-emergent adverse event (TEAE), and 35 patients had a grade 3 or 4 TEAE. Anemia, abnormal liver function, and thrombocytopenia were among the most common severe TEAEs. Further study is ongoing to evaluate the advantages and safety of combining danvatirsen plus ICI therapy over ICIs alone.

2.2 | MK-1454

Stimulator of Interferon Genes (STING) is a transmembrane protein located in the endoplasmic reticulum. The STING pathway is activated after encountering cytosolic dsDNA, including viral or bacterial DNA, and as recently discovered, mammalian DNA. Activation of the STING pathway in tumor-infiltrating dendritic cells leads to interferon release and recruitment of cytotoxic T cells, which results in an enhanced antitumor effect.15,16

Previous studies have shown that intratumoral injection of STING agonist provokes the systemic immune response and induces metastatic tumor shrinkage. MK-1454, a STING agonist, has been evaluated in a phase 1 study as monotherapy or in combination with pembrolizumab in solid tumors and lymphoma (ClinicalTrials.gov, NCT03010176). Twenty patients were enrolled in the monotherapy group, with no responders and 4 of 20 patients showing stable disease (SD). Twenty-five patients were enrolled in the MK-1454/pembrolizumab combination group; there were no CRs, but 6 of 25 patients achieved a PR, and 6 had SD.17 Both injected tumors and other metastatic tumors showed regression in responders, with a median 83% reduction in tumor size. All responders had not received prior immunotherapy, and 3 of the 6 responders were HNSCC patients. 8.7% of patients in the monotherapy arm and 14.3% of patients receiving combination therapy experienced grade 3 or 4 AEs. Pyrexia, injection site pain, chills, and fatigue were among the most frequent toxicities.

2.3 | IPI-549

The phosphoinositide 3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway is frequently dysregulated in multiple cancer types, and elevation of PI3Kγ levels in tumor-associated macrophages (TAM) contributes to ICI resistance.18 IPI-549, a PI3Kγ inhibitor, exhibits the ability to initiate reprogramming of TAM to M1 macrophages and to increase tumor-infiltrating cytotoxic T cells. Through rebalancing the M1 to TAM ratio in the tumor microenvironment, IPI-549 has demonstrated its potential to overcome ICI resistance.19 A phase 1 study recruited patients with advanced solid tumors to receive either IPI-549 monotherapy or IPI-549 plus nivolumab combination therapy (ClinicalTrials.gov, NCT02637531). In the IPI-549 monotherapy arm, tumor volume reduction of 42% was noted in one patient with peritoneal mesothelioma, and the disease control rate (DCR) was 39%. In the ICI combination arm, a PR was noted in 2 of 31 patients (one with adenocortical carcinoma; one with gallbladder adenocarcinoma). TEAEs were recorded in 58% of patients, and grade III/IV TEAEs were noted in 23% of patients. There were no treatment-related deaths. The most frequent severe TEAEs were skin rash and elevated liver enzymes. Several dose expansion cohorts evaluating combination therapy are ongoing, including one HNSCC cohort.20

2.4 | Motolimod

Toll-like receptor 8 (TLR8) is an endosome-localized toll-like receptor (TLR) that recognizes foreign nucleic acids of
intracellular pathogens. The activation of different TLRs will lead to stimulation of different subsets of immune cells and production of different classes of cytokines, and hence a potential target for antitumor immunotherapy. Motolimod (VTX-2337), an TLR8 agonist, have been developed with the ability to enhance cytokine production (INF-γ, TNF-α, IL-12, etc.), monocyte and dendritic cell activation, NK-cell lytic activity and antibody-dependent cell-mediated cytotoxicity (ADCC) in preclinical studies.\textsuperscript{21} To further evaluate the safety and potential of regimen combining TLR8 agonist and anti-epidermal growth factor receptor (EGFR) antibody, a phase Ib trial recruits 13 R/M HNSCC patients to receive Motolimod and cetuximab combination therapy. Partial response was noted in 2 patients and SD was noted in 5 patients (ORR 15%, DCR 54%).\textsuperscript{22} Another phase II, randomized, placebo-controlled, double-blinded, multicenter trial compared EXTREME regimen in combination with Motolimod or placebo in R/M HNSCC patients.\textsuperscript{23} In the intent-to-treat analysis, no significant difference was noted in OS (HR 0.95; 1-sided 90% CI 0.00-1.22; \( P = .4 \)) or PFS (HR 0.99; 1-sided 90% CI 0.00-1.22; \( P = .47 \)). However, in the prespecified HPV-positive subgroup, a trend of prolongation in PFS (7.8 vs 5.9 months; HR 0.58; 1-sided 90% CI 0.00-0.90, \( P = .05 \)) and OS (15.2 vs 12.6 months; HR 0.41; 1-sided 90% CI, 0.00-0.77, \( P = .03 \)) was noted. Further studies are needed to evaluate the efficacy and optimal combination regimen of TLR8 agonist therapy.

### 2.5 IMO-2055

TLR9, another endosome-localized TLR also possesses the ability to induce pro-inflammatory cytokines and NK cell activation.\textsuperscript{24,25} A phase II study has been conducted to compare IMO-2055 plus cetuximab versus placebo plus cetuximab in second-line, cetuximab naive, R/M HNSCC patients. The ORR were 5.7% in both arms. The DCR was 37% in IMO-2055 arm and 43% in placebo arm (\( P = .56 \)). PFS was 1.5 months in IMO-2055 arm and 1.9 months in placebo arm (\( P = .79 \)). Other oncolgical indication or optimal combination adjustment may be needed for IMO-2055.\textsuperscript{26}

### 2.6 Antibodies

#### 2.6.1 FAP IL-2v

Fibroblast activation protein-\( \alpha \) (FAP-\( \alpha \)) is a transmembrane serine proteinase enriched in activated fibroblasts. This protein is specifically and abundantly expressed in pathologic conditions, including cancer, wounds, fibrosis, and inflammation, and is not expressed in normal tissue. FAP-\( \alpha \) is especially highly expressed in epithelial cancer-associated fibroblasts, including breast cancer, colon cancer, and head-and-neck cancer. Owing to its specific expression in tumor stromal fibroblasts, FAP-\( \alpha \) serves as a target of several developing anticancer therapies.\textsuperscript{27,28} FAP interleukin-2 variant (IL-2v) is a recombinant fusion antibody with high binding affinity to FAP-\( \alpha \), with its Fc portion linked to IL-2v. This IL-2v is a modified form of wild-type interleukin at the CD25 binding site, which results in decreased CD25 binding on inhibitory T regulatory cells. This modification of interleukin leads to expanded NK and CD8+ T cell populations without activation of T regulatory cells, resulting in enhanced antitumor efficacy compared to wild-type IL-2. FAP IL-2v recognizes tumor-associated fibroblasts and further concentrates IL-2v in tumor tissue, resulting in a vigorous immune response in the target lesion.\textsuperscript{29,30} A phase Ia/Ib study was initiated to evaluate FAP IL-2v efficacy in metastatic solid tumors. A long-standing response exceeding 6 months was noted in 1 patient with R/M HNSCC and another with penile squamous cell carcinoma. Another phase Ib study was initiated to evaluate the efficacy of combining FAP IL-2v with cetuximab in R/M HNSCC. Frequent AEs included fever, diarrhea, nausea, and abnormal liver function. An additional phase Ib/II trial of FAP IL-2v combined with apezolizumab is also now in progress.\textsuperscript{31}

#### 2.6.2 ASP1948

Neuropilin-1 (NRP1) is a transmembrane protein with receptor domains able to bind multiple growth factors, including tumor growth factor\( \beta \)1 (TG\( \beta \)-\( \beta \)1), vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), and fibroblast growth factor (FGF). NRPI is mainly expressed in regulatory T cells, contributing to immune inhibitory effects though maintaining regulatory T cell stability and function.\textsuperscript{32,33} ASP1948 is a high-affinity anti-NRP1 antibody, which binds to NRPI and blocks the ligand/receptor interaction to reverse the inhibitory effect of regulatory T cells. An ongoing phase I study was initiated to evaluate the safety profile and antitumor effect of ASP1948 monotherapy (ClinicalTrials.gov, NCT03565445). If the predefined threshold for efficacy is achieved, an expansion cohort of ASP1948 monotherapy in R/M HNSCC will be initiated.

#### 2.6.3 MK-7684

TIGIT (T-cell Immunoreceptor With Ig And ITIM Domain) is a transmembrane protein participating in immune modulatory function. TIGIT is exclusively expressed on the cell surface of regulatory T cells, effector T cells, and natural killer cells (NK cells). In the tumor microenvironment, TIGIT interacts with CD155 or CD122 and exerts an inhibitory effect on T cells and NK cells. MK-7684 is a humanized monoclonal antibody, which binds to TIGIT and blocks its interaction with CD155 or CD122.\textsuperscript{34} A phase I study with two arms
(MK-7684 monotherapy or MK-7684 in combination with pembrolizumab) was initiated in patients with metastatic solid cancers to evaluate dosage, safety, and efficacy (ClinicalTrials.gov, NCT02964013). In the MK-7684 monotherapy group, no patients achieved a CR, and 1 of 34 (3%) patients showed a PR. The DCR was 35% in the monotherapy arm. In the combination therapy arm, there were no CRs, while 8 of 43 (19%) patients achieved a PR. The DCR was 47% in the combination therapy arm. The most common side effects included pruritis, fatigue, nausea, poor appetite, and abnormal liver function. Rates of all-cause grade 3 or 4 AEs were 38% in the MK-7684 monotherapy arm and 43% in the MK-7684/pembrolizumab combination arm. Grade 3-4 TEAEs were observed in 6% and 11% of patients, respectively.35

### 2.6.4 MEDI6469

Tumor necrosis factor receptor superfamily, member 4 (OX-40) is among the most potent T-cell costimulatory receptors, and is expressed primarily on activated CD4 and CD8 T-cells. Antigen-presenting cells (APC) that coexpress OX-40L (OX-40 ligand) and B7-1 (ligand of CD28) interact with T-cells through the synergy of these 2 costimulatory receptors, and strongly increase T-cell proliferation.36 MEDI6469 is an immune-stimulating anti-OX40 antibody that induces T-cell proliferation and cytokine production, and decreases T-cell apoptosis. In a phase I dose-escalation study, patients with solid tumors refractory to standard treatment were enrolled to receive 3 dose levels of MEDI6469 (ClinicalTrials.gov, NCT01644968). There were no responses, but 6 of 30 patients achieved SD. However, regression of at least 1 metastatic lesion was noted in 12 patients.37 In another phase Ib trial, 17 patients with resectable stage III/IVA HNSCC were enrolled to receive neoadjuvant administration of MEDI6469 before surgery (ClinicalTrials.gov, NCT02274155). Pathology specimens were analyzed, and increased tumor-infiltrating CD8 T cells (CD39 + CD103 + CD8+) were noted in 4 patients, indicating evidence of immune response to the tumor. At a median follow-up of 20 months, 13 of 17 (76%) patients were free of disease, including all 4 patients showing an immune response. No grade III/IV TEAEs were noted.38

### 2.6.5 M7824

Transforming-growth factorβ (TGF-β) signaling abnormalities are involved in various pathological processes, including tumor growth and metastasis in late-stage cancer.39 TGF-β also induces an immune-suppressive tumor microenvironment by decreasing CD8 T cell and CD4 T effector cell proliferation while activating regulatory T cells.40 Elevated TGF-β levels are also associated with poorer clinical outcomes in the HNSCC patient population, and may be involved with the tumorigenesis process of human papillomavirus (HPV)-associated HNSCC.41,42 With this increased understanding of TGF-β signaling and tumorigenesis, M7824, a bifunctional fusion protein comprising an anti-PD1 antibody and TGF-β receptor II (TGF-β trap), was designed to concurrently block PD1 and TGF-β signaling.43 The efficacy and safety of M7824 were examined in HPV-associated cancers, including cervical cancer and HNSCC. An ORR of 45% was noted in 11 confirmed HPV-positive cases.44 A further dose-expansion cohort comprising stage III/IV HNSCC patients who failed first-line treatment received treatment with M7824 (ClinicalTrials.gov, NCT02517398). The ORR was 22% in the whole cohort, while the response rate reached 50% in HPV+ patients. Among the 7 responders, 6 continued to show a durable response. The 1-year OS rate was 51%. Sixty-nine percent of patients experienced TEAEs, and 33% of patients experienced grade III/IV TEAEs. The most common AEs were liver enzyme abnormalities, maculopapular rash, and hyperglycemia.45

### 2.7 Cabiralizumab

Macrophages are divided into 2 groups. The first group comprises the pro-inflammatory M1 macrophage that increases inflammatory, antimicrobial, and antineoplastic activity. The other group is the M2 macrophage that exhibits anti-inflammatory function and contributes to the pro-tumor microenvironment. TAMs are similar to M2 macrophages and can be classified as one subtype of M2 macrophage.46,47 Increased TAM infiltration is associated with unfavorable prognosis in pancreatic cancer, breast cancer, and head and neck cancers.48-51 Colony-stimulating factor 1 receptor (CSF-1R) is a tyrosine kinase receptor for CSF-1 and IL-34. The signaling pathway downstream of CSF-1R is crucial for the survival and differentiation of TAM.52,53 Cabiralizumab, a humanized monoclonal antibody targeting CSF-1R, blocks downstream pathways and decreases TAM infiltration and activation in the tumor microenvironment. A phase Ib trial evaluating the safety and efficacy of cabiralizumab plus nivolumab recruited several cohorts of patients with advanced solid cancers, including non-small cell lung cancer, HNSCC, and pancreatic cancer (ClinicalTrials.gov, NCT03336216). In the pancreatic cancer cohort, 3 of 31 (10%) heavily pretreated patients experienced a PR. The DCR at 6 months was 13%. Grade III-V TEAEs were noted in 43% of patients. Elevation of creatinine kinase (CK) and aspartate aminotransferase (AST) were among the most frequent severe AEs. These data showed the feasibility of combining cabiralizumab and anti-PD-1 therapy. Further efficacy data from the HNSCC cohort is pending.54
2.8 | Cetuximab/Immune therapy agents combination

Cetuximab is a chimeric antibody with its variable region from the murine anti-EGFR antibody and constant region from human IgG1. Cetuximab exhibits the antitumor effect though specifically binding to EGFR and blocking EGF-induced phosphorylation. The downregulation of EGFR signaling induces cell cycle arrest and tumor cell apoptosis. Moreover, preclinical and clinical data have revealed that comparing to other IgG subtypes, IgG1 is the most potent to induce antibody-dependent cell-mediated cytotoxicity (ADCC). Except cetuximab, other monoclonal antibodies including trastuzumab and rituximab also induce ADCC, which recruits NK cells to eliminate the antibody-coated tumor cells. Owing to the ability to induce ADCC, cetuximab is regarded as a potential candidate for immunotherapy combinations. In a phase II open-label, non-randomized trial, R/M HNSCC patients who were platinum refractory or ineligible were treated with pembrolizumab plus cetuximab. The ORR was 42.8%, and DCR was 71.4%. Median PFS was 4.3 months, and median DOR was 5.4 months. Another phase I/II study recruits 23 R/M HNSCC patients to receive recombinant IL-12 and cetuximab combination therapy, while no clinical response was noted within this trial (ClinicalTrials.gov, NCT01468896). Currently, a phase II trial with avelumab plus cetuximab combination therapy in advanced HNSCC, and another phase I trial with ex vivo expanded terminally differentiated NK cells (Fate-NK100) plus cetuximab combination therapy are ongoing (ClinicalTrials.gov, NCT03494322, NCT03319459). The potential and optimal regimen of cetuximab/immune therapy agents combination will be further elucidated through these proceeding trials.

2.9 | Vaccines

2.9.1 | MEDI0457

The incidence of high-risk HPV-related HNSCC has increased steadily in recent years. HPV-16 and HPV-18 account for the majority of HPV-related HNSCC. The constantly expressed viral oncoproteins E6 and E7 inhibit 2 principal tumor suppressor genes, p53 and pRb, leading to impaired cell cycle control and accelerated cancer cell proliferation. This virus-mediated carcinogenesis provides a unique target for vaccine development. MEDI0457 is a vaccine consisting of HPV-16 and HPV-18 E6/E7 expressing plasmids, and IL-12 expressing plasmids. This vaccine is injected intramuscularly, followed by electroporation with CELLECTRA, a constant current device that can enhance the transfection of target plasmids. By utilizing cell machinery, an antigen is produced to induce an E6/E7 specific immune response. IL-12, which is important for T-cell maturation and function, further enhances the efficacy of the vaccine. In a phase Ib/II pilot study that enrolled 21 patients with locally advanced, p16-positive HNSCC, MEDI0457 was administered perioperatively or after completion of concurrent chemoradiotherapy (ClinicalTrials.gov, NCT02163057). An increased tumor-infiltrating CD8 T-cell/regulatory T-cell ratio and the appearance of HPV-16-specific T-cells were noted after MEDI0457 administration. The DFS rate at 12 months was 89%. The most common AE was grade I/II injection site pain. No grade III/IV AEs were reported. Finally, in a current phase Ib/II study, the combination of durvalumab and MEDI0457 is being evaluated as second-line treatment in HPV-16- or HPV-18-associated R/M HNSCC. Safety, efficacy, and immunogenicity will be evaluated.

2.9.2 | ISA-101

ISA-101 is a HPV-16 vaccine that consists of HBV-E6 and E7 long peptides. These long peptides contain all potential cytotoxic-T lymphocyte epitopes and T-helper epitopes, and can be efficiently processed by dendritic cells to activate HPV-16-specific responses. The concept of utilizing HPV-16 E6/E7 synthetic long peptides for immunization and enhancing antineoplastic activity has been verified in vulvar intraepithelial neoplasia (VIN). A phase II study enrolled patients with HPV-16 positive, high-grade VIN to receive ISA-101 vaccination. At the 1-year follow-up, 15 of 19 patients had achieved a clinical response, of whom 9 achieved a CR. However, in advanced HPV-16 positive cervical cancer, the efficacy of ISA-101 monotherapy appeared to be limited. In a phase II ISA-101 monotherapy trial, 20 patients with HPV-16 positive advanced/recurrent gynecological carcinoma were enrolled. Although a vaccine-induced immune response was noted in the majority of patients, no clinical responses were observed, and 19 patients died of progressive disease. One explanation for the discrepancy between the 2 clinical trials is that the tumor microenvironment of late-stage cancer is highly immunosuppressive and significantly diminished the vaccine-activated response. Accordingly, the combination of ISA-101 with ICI is one feasible option to overcome this immune inhibition. In another phase II trial in 24 patients with advanced, incurable HPV-16 positive solid cancers, combination therapy with ISA-101 and nivolumab was tested (ClinicalTrials.gov, NCT02426892). Median PFS was 2.7 months, and median OS was 17.5 months. The ORR was 33%, and the median DOR was 10.3 months. 22 of 24 patients had advanced oropharyngeal cancer; among this group, the CR rate was 9%, the PR rate was 27%, and the DCR was 45%. Six patients were both cetuximab- and platinum-refractory; among these 6 patients, no CRs were observed; a PR was noted in 3 patients, and
| Name       | Category          | Target | Regimen/Patient population                                                                 | Efficacy                                                                 | Common AEs                                                                 | Current status                     |
|------------|-------------------|--------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------|------------------------------------|
| **Small molecules** |                   |        |                                                                                             |                                                                          |                                                                             |                                    |
| Danvatirsen | Antisense oligonucleotide | STAT3  | • Danvatirsen plus durvalumab <br> • 2nd line, PD-L1 ICI naïve HNSCC                      | • ORR: 26% (CR:7%, PR:16%) <br> • Median OS: NA <br> • Median PFS: 2.9 mo <br> • Median DOR: NR | • Anemia, dyspnea, asthenia, thrombocytopenia, elevated transaminase         | Phase I/II NCT02499328             |
| MK-1454    | Small molecule    | STING  | • Intratumoral MK-1454 monotherapy <br> • Intratumoral MK-1454 plus pembrolizumab <br> • Advanced/metastatic solid cancers or lymphoma | Monotherapy <br> • ORR: 0% <br> • Combined with pembrolizumab <br> • ORR: 24% (CR: 0%, PR:24%) <br> • PR: 3/6 patients had HNSCC | Monotherapy <br> • Grade III-V TEAE: 8% Combined with pembrolizumab <br> • Grade III-V TEAE: 14% <br> • Pyrexia, fatigue, infusion related reactions, nausea, diarrhea, pruritis | Phase I NCT03010176                |
| IPI-549    | Small molecule    | PI3Kγ  | • IPI-549 monotherapy <br> • IPI-549 plus nivolumab <br> • Advanced solid cancers        | Monotherapy <br> • ORR: 3% (CR: 0%, PR:3%) Combined with nivolumab <br> • ORR: 6% (CR: 0%, PR: 6%) | Combined with nivolumab <br> • Grade III-V TEAE: 23% <br> • Rash, pruritis, nausea, anemia, pyrexia, elevated liver enzymes | Phase I NCT02637531                |
| Motolimod  | Small molecule    | TLR8   | • Motolimod plus cetuximab <br> • Motolimod vs placebo plus EXTREME regimen              | Motolimod plus cetuximab <br> • ORR 15%, DCR 54% Motolimod vs placebo plus EXTREME regimen <br> • Median PFS: 6.1 vs 5.9 mo; HR 0.99, P = .47 <br> • Median OS: 13.5 vs 11.3 mo; HR 0.95, P = .4 Motolimod vs placebo plus EXTREME regimen, HPV+ <br> • Median PFS: 7.8 vs 5.9 mo; HR 0.58, P = .05 <br> • Median OS: 15.2 vs 12.6 mo; HR 0.41, P = .03 | Motolimod vs placebo plus EXTREME regimen <br> • Grade III-V AE: 39% in Motolimod arm, 40% in placebo arm <br> • Injection site reaction, dematitis acneform, anemia, vomiting, pneumonia, mortality | Phase I NCT01836029 Phase II NCT01836029. |

(Continues)
| Name         | Category    | Target | Regimen/Patient population                        | Efficacy                                                                 | Common AEs                                      | Current status |
|--------------|-------------|--------|--------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------|---------------|
| IMO-2055     | Small molecule | TLR9   | IMO-2055 vs placebo plus cetuximab               | ORR: 5.7% vs 5.7%                                                        | Rash, dematiitis acniform, dyspnea, hypokalemia | Phase II NCT01040832 |
| FAP IL-2v    | Antibody    | FAP-α  | FAP IL-2v monotherapy Metastatic solid cancers   | Durable response in 1 R/M HNSCC patient                                  | Pyrexia, asthenia, infusion related reactions, nausea, diarrhea, elevated transaminase | Phase I NCT02627274 |
| ASP1948      | Antibody    | NRP-1  | ASP1948 monotherapy Unresectable/metastatic solid cancers |                                                                                       |                                                 | Phase I NCT03565445 |
| MK-7684      | Antibody    | TIGIT  | MK-7684 Monotherapy MK-7684 plus pembrolizumab Metastatic solid cancers | Monotherapy                                                                 | Monotherapy                                                                                       | Phase I NCT02964013 |
| MEDI6469     | Antibody    | OX40   | Neoadjuvant MEDI6469 monotherapy Resectable stage III/IV HNSCC | 76% patients remained free of disease at median follow-up of 20 mo       | Grade III-V TEAE: 0%                                                                 | Phase I NCT02274155 |
| M7824        | Antibody    | TGF-β  | M7824 monotherapy 2+ line stage II/IV HNSCC      | ORR: 22% (CR: 0%, PR: 22%)                                                | Grade III-V TEAE: 33% Abnormal liver enzyme, maculopapular rash, and hyperglycemia | Phase I NCT02517398 |
| Cabiralizumab| Antibody    | CSF-1R | Cabiralizumab plus nivolumab Advanced solid cancers | Pancreatic cancer cohort ORR: 10% (CR: 0%, PR: 10%) | Grade III-V TEAE: 43% Periorbital edema, fatigue, rash, nausea, pruritis, elevated pancreatic enzyme, creatinine kinase, aminotransferase | Phase I NCT03336216 |
| Name | Category | Target | Regimen/Patient population | Efficacy | Common AEs | Current status |
|------|----------|--------|----------------------------|----------|------------|---------------|
| Cetuximab/Pembrolizumab | Antibody | EGFR/PD-1 | Cetuximab plus pembrolizumab; R/M HNSCC, platinum refractory/ ineligible | ORR: 42.8% (CR: 0%); Median PFS: 4.3 mo; Median DOR: 5.4 mo | Grade III-V TEAE: 50% | Phase II NCT03082534 |
| Cetuximab/Recombinant IL-12 | Antibody/ Recombinant protein | EGFR/ IL-12 receptor | Cetuximab plus recombinant IL-12; R/M HNSCC, cetuximab naïve | ORR: 0%; Median PFS: 4.6 mo; Median OS: 10.6 mo | Grade III-V AE: 53% | Phase I/II NCT01468896 |
| Cetuximab/Avelumab | Antibody | EGFR/PD-L1 | Cetuximab plus avelumab; R/M HNSCC | Results pending | Results pending | Phase II NCT03494322 |
| Cetuximab/Fate- NK100 | Antibody/NK cell | EGFR | Cetuximab plus Fate-NK100; Advanced colorectal cancer, HNSCC, or EGFR-positive solid cancer | Results pending | Results pending | Phase I NCT03319459 |

**Vaccine**

| Name | Category | Target | Regimen/Patient population | Efficacy | Common AEs | Current status |
|------|----------|--------|----------------------------|----------|------------|---------------|
| MEDI0457 | Vaccine | HPV E6/E7 | Perioperative/post-CCRT intramuscular MEDI0457 monotherapy; Locally advanced, p16+ HNSCC | 1-year DFS rate: 89% | Grade III-V TEAE: 0%; Injection site pain | Phase II NCT02163057 |
| ISA-101 | Vaccine | HPV E6/E7 | ISA-101 plus nivolumab; Advanced, incurable HPV-16+ solid cancers (92% oropharyngeal cancer) | ORR: 33% (CR: 8%, PR: 25%); Median PFS: 2.7 mo; Median OS: 17.5 mo; Median DOR: 10.3 mo | Grade III-V TEAE: 8%; Injection site reaction, fever, diarrhea, hepatotoxicity | Phase II NCT02426892 |

Abbreviations: AE, adverse event; CCRT, concurrent chemoradiotherapy; CR, complete response; CSF-1R, colony stimulating factor 1 receptor; DFS, disease-free survival; DOR, duration of response; FAP-α, fibroblast activation protein alpha; HNSCC, head-and-neck squamous cell carcinoma; HPV, human papillomavirus; ICI, immune checkpoint inhibitor; NA, not applicable; NR, not recorded; NRP1, neuropilin 1; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PI3Kγ, phosphoinositide 3-kinase; PR, partial response; R/M, recurrent/metastatic; STAT3, signal transducer and activator of transcription 3; STING, stimulator of interferon genes; TGF-β, transforming growth factor beta; TEAE, treatment-emergent adverse event; TIGIT, T cell immunoreceptor with Ig and ITIM domains.
1 patient had SD. The most common AEs included injection site reactions, fever, diarrhea, and hepatotoxicity. Two patients (8%) experienced grade III/IV elevated transaminase and amylase/lipase.67

3 | DISCUSSION

The field of immunotherapy within cancer treatment has progressed rapidly through exploration and increasing understanding of the interaction between the tumor microenvironment and the immune system. Recent progress in ICI development has positively impacted the management of R/M HNSCC. The efficacy and safety of ICIs in R/M HNSCC have been demonstrated in recent clinical trials. In R/M HNSCC patients who failed first-line treatment, current evidence suggests that nivolumab results in prolonged OS and a more durable response compared to chemotherapy. Results of pembrolizumab trials suggest similar benefits.7-9 ICI therapy is also associated with a reduction in severe AEs, being more tolerable than standard chemotherapy. Improved quality of life was also noted when patients received ICIs instead of chemotherapy. In spite of these appealing advantages, ICIs do have limitations. Trials of nivolumab and pembrolizumab both disclosed a tendency toward an improved OS compared to chemotherapy; however, the ORRs remained below 15%. Consequently, a low ORR poses a risk of early progression and mortality. Several combination therapies were proposed to improve the efficacy of ICI monotherapy, including ICI plus chemotherapy and dual ICI therapy (ClinicalTrials.gov, NCT02358031; NCT02823574; NCT02741570; NCT02551159).68 Novel agents and treatment strategies are required to improve immunotherapy efficacy in HNSCC treatment.

Recent research has more fully elucidated the key players in the tumor microenvironment and inspired new aspects of drug development. Multiple novel immunotherapy agents in the field of HNSCC are now undergoing clinical trials, and these agents can be classified into 3 major categories (Table 1): small molecules, antibodies, and vaccines. These novel agents directly target different molecular pathways and affect the activity of different cell components, including effector T cells (MK-9684, MEDI6469), regulatory T cells (danvatirsen, ASP1948), tumor infiltrating macrophages (cabiralizumab, IPI-549), stromal cells (MK-1454), NK cells and ADCC (Cetuximab, Motolimod, IMO-2055) and cytokine concentrations in the tumor microenvironment (FAP IL-2v, M7824). Vaccines (MEDI0457, ISA-101) utilizing the unique antigen HPV-16/18 E6/E7 protein to stimulate tumor-specific responses were also studied in HPV-16/18+ HNSCC patients. These novel agents induced modest antitumor activity as monotherapy, with an ORR ranging from 0% to 3%. However, when combining these novel agents with anti-PD1 therapy, there was a strong tendency toward improved antitumor activity, with ORRs ranging from 6% to 33%. Grade III-V TEAE rates were <20% in combination therapy with MK-1454, MK-7684, MEDI6469, ISA-101, and >20% in combination therapy with IPI-549, M7824, and cabiralizumab. These early phase data highlight the potential of combining immuno-oncology agents that have different targets and therefore may show synergistic antitumor activity. Whether combinations of these novel agents can provide improved clinical outcomes and tolerability compared to current anti-PD1/PD-L1 monotherapies remains to be confirmed.

In conclusion, cancer immunology and immunotherapy are rapidly evolving fields. To overcome the efficacy limitations of current ICIs, multiple agents were developed to target different molecular mechanisms. These agents have been shown to affect the balance between immune-stimulatory and immune-inhibitory signals in the tumor microenvironment. Whether these observed immune responses can be translated into improved clinical outcomes needs to be confirmed by further well-designed clinical trials. Given that some of the agents mentioned have shown impressive efficacy thus far, it is believed that the possibility to achieve greater response rates and more durable responses do exist, and that the development of novel immunotherapy agents may positively impact the care and outcomes of patients with HNSCC in the future.

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