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REVIEW ARTICLE

Targeted Therapy in Head and Neck Cancer: An Update on Current Clinical Developments in Epidermal Growth Factor Receptor-Targeted Therapy and Immunotherapies

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Abstract Most patients diagnosed with head and neck squamous cell carcinoma (HNSCC) will present with locally advanced disease, requiring multimodality therapy. Despite this curative approach, a significant subset of these patients will develop locoregional failure and/or distant metastases. Despite significant progress in the treatment and subsequent prognosis of locally advanced HNSCC, the prognosis of those patients with recurrent and/or metastatic (R/M) HNSCC is poor, with short-lived responses to palliative chemotherapy and few therapeutic agents available. The discovery of the integral role of epidermal growth factor receptor overexpression in the pathogenesis of HNSCC, coupled with emerging data on the role of tumor evasion of the immune system, has opened new pathways in the development of novel therapeutic agents for the treatment of R/M HNSCC. As a result, cetuximab, a monoclonal antibody targeting epidermal growth factor receptor, as well as pembrolizumab and nivolumab, monoclonal antibodies targeting programmed cell death 1 (PD-1), are now US Food and Drug Administration approved for the treatment of R/M HNSCC. This review will detail the data supporting the use of these agents, as well as clinical trials evaluating the efficacy of other novel and promising drugs.

Key Points

Despite the significant expansion of clinical trials of novel molecularly targeted agents, only a few drugs have been US FDA approved for the management of patients with recurrent and/or metastatic head and neck squamous cell carcinoma (R/M HNSCC).

The appreciation of the role of epidermal growth factor receptor (EGFR) signaling in HNSCC has led to the approval of the anti-EGFR antibody cetuximab for this indication.

The discovery of the integral role of the immune system in tumorigenesis has led to rapid and significant developments in the field of immunotherapy, as evidenced by the approval of two immunotherapeutic agents for R/M HNSCC in a 3-month period.

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1 Introduction

The advent of multimodality therapy has led to significant improvements in the prognosis of patients diagnosed with locally advanced (LA) head and neck squamous cell carcinoma (HNSCC). These therapeutic advances, coupled with the declining incidence of hypopharyngeal, laryngeal, and oral cavity squamous cell carcinomas (SCCs) [1], have led to declining numbers of patients afflicted with these malignancies, although there remain 550,000 cases and

300,000 deaths diagnosed each year worldwide [2]. Unfortunately, these advances have not had a substantial impact on the prognosis of patients with recurrent or metastatic (R/M) HNSCC. Sixty percent of patients presenting with LA-HNSCC are at risk of local failure, and up to 30% of patients are at risk of distant failure [3–5]. Thus, the development of novel therapeutic agents is needed to improve the prognosis of this subset of patients.

Systemic treatment/therapy has been the mainstay of therapy for patients presenting with R/M HNSCC. Historically, this has consisted of a platinum-based doublet regimen with either cisplatin or carboplatin and 5-flurouracil [6]. Vermorken et al. demonstrated the superiority of incorporating cetuximab, a monoclonal antibody (mAb) targeting epidermal growth factor receptor (EGFR), in combination with cisplatin/carboplatin and fluorouracil in patients with R/M HNSCC [7]. Recent data from the KEYNOTE-012 trial have demonstrated the efficacy of pembrolizumab, a mAb targeting programmed cell death 1 (PD-1), in heavily pre-treated patients with R/M HNSCC [8–10].

As a result of the successful incorporation of cetuximab into the treatment paradigm of R/M HNSCC as well as the presence of EGFR overexpression in approximately 90% of patients with HNSCC [11–15], mAbs and tyrosine kinase inhibitors (TKIs), the ErbB family of receptors, have been an area of considerable interest and pharmacologic development. Additionally, the successful incorporation of checkpoint inhibitors in various solid and hematologic malignancies has led to considerable interest in the implementation of immunotherapeutic agents in the repertoire of agents to be used in R/M HNSCC. This review focuses on the role of immunotherapy and ErbB receptor inhibition in the management of R/M HNSCC, as well as the emergence of additional novel therapeutics that hold promise in redefining the therapeutic landscape of this disease.

2 Role of ErbB Inhibitors in Head and Neck Squamous Cell Carcinoma

The ErbB family consists of four transmembrane receptors: EGFR/ErbB1/human epidermal growth factor receptor (HER)-1, ErbB2/HER-2/neu, ErbB3/HER-3, and ErbB4/HER-4 [11, 16, 17]. Binding of natural ligands [i.e., EGF and transforming growth factor-α] to EGFR, ErbB3, or EbB4 is the first step in ErbB signaling activation [11]. Ligand binding induces receptor homo- or heterodimerization with other ErbB family receptors, leading to the phosphorylation of intracellular tyrosine residues and a cascade of downstream effects [16, 17]. There are four primary signaling pathways implicated in downstream EGFR signaling: (1) phosphatidylinositol-3-kinase/v-akt murine thymoma viral oncogene homolog; (2) Ras/raf/mitogen-activated protein kinase; (3) phospholipase-C-γ/protein kinase C; and (4) signal transducers and activators of transcription pathways [11, 18]. These signaling pathways result in the transcription of genes involved in cellular proliferation, survival, angiogenesis, invasion, and metastasis [16–19]. Increased ErbB expression has been linked to poor outcomes in HNSCC, including poorer overall survival (OS), increased locoregional relapse, and treatment failure [20–22]. Biomarker analysis from a phase III trial demonstrated that high EGFR expression was associated with significantly shorter OS ($p = 0.0006$) and disease-free survival ($p = 0.0016$), and higher locoregional relapse rates ($p = 0.0031$) [21], and ErbB2 gene expression and ErbB3 protein expression have been linked to reduced treatment response and poor outcomes in laryngopharyngeal cancer [20, 22]. In patients with oral SCC, combined expression of EGFR, ErbB2, and ErbB3 was more predictive of decreased survival, with ErbB2 exhibiting the strongest correlation [11, 23].

Epidermal growth factor receptor overexpression has been linked to poor radiation therapy (RT) responses in glioblastoma multiforme, and SCC cell lines, and EGFR inhibition has subsequently been explored as a potential therapeutic adjunct to RT in HNSCC [24, 25]. Ionizing RT stimulates kinase activity via ErbB receptors, leading to downstream activation of intracellular proliferative pathways in human SCC cell lines [24–26]. Additionally, ionizing RT triggers ligand-independent, caveolin-driven nuclear translocation of EGFR and formation of a complex with DNA-dependent protein kinase, leading to the prevention of DNA repair after RT exposure. Cytoprotective pathways initiated via EGFR may also increase cell survival in response to RT [27]. In addition to the promotion of EGFR-dependent signaling cascades, ionizing RT may also permit tumor cells to bypass EGF-mediated growth inhibition [11]. Exposure to RT promotes entry of SCC cells into S and G_2/M phases after stimulation with EGF and ionizing RT, thereby markedly increasing SCC proliferation in an EGFR-dependent manner [25], suggesting a potential role that EGFR may play in the post-RT tumor repopulation [25]. EGFR overexpression has also been implicated in fostering cancer stem cell survival, including the expression of certain cancer stem cell genes and tumorsphere formation in HNSCC cell lines [11, 28].

Anti-EGFR agents are largely divided into two classes of drugs: mAbs and TKIs. Monoclonal antibodies act at the receptor's extracellular domain, whereas TKIs act on the cytosolic adenosine triphosphate-binding domain of EGFR to inhibit autophosphorylation [11, 28]. This section will explore EGFR inhibitors that have been US Food and Drug

Administration (FDA) approved for the treatment of HNSCC as well as those under clinical investigation (Table 1).

2.1 Anti-Epidermal Growth Factor Receptor Monoclonal Antibodies

2.1.1 Cetuximab

Cetuximab is an immunoglobulin (Ig)G1 human-murine antibody with high affinity to EGFR. Bonner et al. conducted a multinational phase III trial evaluating the use of cetuximab concurrent with RT for patients with LA-HNSCC (stages III–IVB). Median duration of locoregional control was the primary endpoint of the study, and was better with cetuximab-RT vs. RT alone (24.4 vs. 14.9 months; $p = 0.005$). Median OS was also improved with cetuximab-RT vs. RT alone (49 vs. 29.3 months; $p = 0.03$) [29]. A subsequent 5-year follow-up study demonstrated a superior OS rate in the patients receiving cetuximab-RT (45.6%) vs. those receiving RT alone (36.4%; $p = 0.018$) [30]. Of note, OS was significantly improved in patients who experienced grade $\geq$2 acneiform rash compared with patients who experienced a grade 1 rash or no rash at all [hazard ratio (HR) 0.49; 95% confidence interval (CI) 0.34–0.72; $p = 0.002$] [30]. These results led to the approval of cetuximab in combination with radiation therapy for LA-HNSCC.

Several studies demonstrated the efficacy of cetuximab in the R/M HNSCC setting. Eastern Cooperative Oncology Group (ECOG) 5397 was a proof-of-principle, multi-institutional, placebo-controlled study randomizing patients with R/M HNSCC to receive cisplatin [intravenous (IV) 100 mg/m^2 every 4 weeks] and cetuximab (400 mg/m^2 IV loading dose, then IV 250 mg/m^2 every 2 weeks) vs. cisplatin and placebo [31]. The cetuximab group demonstrated a significantly higher response rate than the cisplatin-alone group (26 vs. 10%, respectively; $p = 0.03$), and also demonstrated non-significant trends towards better median progression-free survival (PFS) and OS. Because of these compelling data, Vermorken et al. conducted an open-label multi-center study in patients who had progressed on two to six cycles of platinum therapy [32]. Patients received single-agent cetuximab (400 mg/m^2 IV loading dose, then IV 250 mg/m^2 weekly) for $\geq$6 weeks. One hundred and three patients were enrolled, and demonstrated a response rate of 13%, a disease control rate [complete response (CR)/partial response (PR)/stable disease (SD)] of 46%, and the median time to progression was 70 days.

The results from ECOG 5397 provided the rational for the Erbitux in First-line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME) trial, which confirmed the benefit of adding cetuximab to a platinum-containing combination regimen [7]. Four hundred and forty-two patients were randomly assigned to cisplatin (100 mg/m^2) or carboplatin (AUC 5) on day 1, followed by 5-fluorouracil (1000 mg/m^2/day for 4 days) every 3 weeks for a maximum of six cycles, or the same chemotherapy plus cetuximab (400 mg/m^2 IV loading dose, then IV 250 mg/m^2 weekly). Patients in the cetuximab arm continued to receive maintenance cetuximab until disease progression or unacceptable toxicity, and crossover was not allowed. Overall survival, the primary endpoint, was 10.1 months in the cetuximab group vs. 7.4 months in the chemotherapy-alone group (HR 0.80, 95% CI 0.64–0.99; $p = 0.04$). The addition of cetuximab to platinum-based combination chemotherapy also improved the median PFS to 5.6 months vs. 3.3 in the platinum doublet (HR 0.54; $p < 0.001$) and improved the response rate to 36 vs. 20% ($p < 0.001$). Patients receiving cetuximab did have an increased risk of developing adverse events (AEs), including a higher than grade 3 skin toxicity ($p < 0.001$), hypomagnesemia ($p = 0.05$), and sepsis ($p = 0.02$), but these were not associated with an adverse quality of life. The FDA and European Medicines Agency (EMA) approved the use of cetuximab with platinum-based combination chemotherapy on 7 November, 2011. To date, cetuximab is the only EGFR inhibitor that has conferred a survival advantage when combined with platinum-based combination chemotherapy in the first-line R/M setting [7]. Of note, given the lack of crossover, the benefit of sequential therapy has not been explored.

2.1.2 Panitumumab

Panitumumab is a fully human IgG2 mAb that, like cetuximab, has a high affinity for EGFR [33]. Given the human structure of panitumumab, it generates minimal infusion-related reactions. The SPECTRUM trial, a phase III multinational randomized study, enrolled 657 patients with R/M HNSCC and randomized them to either cisplatin (100 mg/m^2 on day 1) and 5-fluorouracil (1000 mg/m^2/day, days 1–4) every 3 weeks with or without panitumumab (9 mg/kg on day 1) until disease progression or for a maximum of six cycles. Despite patient crossover being prohibited, there was no significant difference in the primary endpoint, OS (11.1 vs. 9 months; $p = 0.14$). Panitumumab did result in a modest but significant prolongation of the median PFS by 1.2 months (5.8 vs. 4.6 months; $p = 0.004$). Additionally, grade 3 or higher toxicities were more frequent in the panitumumab group (diarrhea, ocular and skin toxicity, cardiac arrhythmias, and hypomagnesemia). More treatment-related deaths were associated with panitumumab (14; 4% of patients) vs. chemotherapy (8; 2% of patients). The PARTNER trial was

Table 1 US FDA-approved epidermal growth factor receptor (EGFR) inhibitors for the treatment of head and neck squamous cell carcinoma as well as those under clinical investigation

Study/Drug	Mechanism of action	Phase of development	Year	Number of patients	Response rate (%)	Median survival (months)
ECOG 5397/cisplatin ± cetuximab	Anti-EGFR IgG1 mAb	III	2005	117	26 vs. 10	PFS: 4.2 vs. 2.7 OS: 9.2 vs. 8
Cetuximab		II	2007	103	13	OS: 6 months
EXTREME/cisplatin or carboplatin + 5-FU ± cetuximab		III	2008	442	36 vs. 20	OS: 10.1 vs. 7.4 PFS: 5.6 vs. 3.3
SPECTRUM/cisplatin + 5-FU ± panitumumab	Anti-EGFR IgG2 mAb	III	2013	657	36 vs. 25	OS: 11.1 vs. 9 PFS: 5.8 vs. 4.6
PARTNER/docetaxel + cisplatin ± panitumumab		II	2013	103	44 vs. 37	OS: 12.9 vs. 13.8 PFS: 6.9 vs. 5.5
NCT00382031/best supportive care ± zalutumumab	Anti-EGFR IgG1 mAb	III	2011	286	6.3 vs. 1.1	OS: 6.7 vs. 5.2 PFS: 2.5 vs. 2.1
Sym004	Two recombinant anti-EGFR IgG1 mAbs	II	2013	26	40	PFS: 3.7
MEHD7945A vs. cetuximab	Anti-EGFR/HER-3 IgG1 mAb	II	2016	122	N/A	N/A
LUX Head and Neck 1/afatinib vs. methotrexate	TKI that inhibits EGFR, ErbB2/HER-2, and ErbB4/HER-4	III	2015	483	10 vs. 6	OS: 6.8 vs. 6 PFS: 2.6 vs. 1.7
Afatinib vs. cetuximab		II	2014	121	161./8.1 vs. 6.5/9.7	OS: 9 vs. 11.8 PFS: 3.3 vs. 3.8
Dacomitinib	TKI that inhibits EGFR, ErbB2/HER-2, and ErbB4/HER-4	II	2012	69	12.7	OS: 8.7 PFS: 3
Gefitinib	Reversible EGFR TKI	II	2014	100	14	OS: 10.6 TTP: 5.3
Gefitinib 250 and 500 mg vs. methotrexate		III	2009	486	2.7, 7.6, and 3.9	OS: 5.6, 6.0 and 6.7
NCT00088907/docetaxel ± gefitinib		III	2013	270	12.5 vs. 6.2	OS: 7.3 vs. 6 TTP: 3.5 vs. 2.1
Erlotinib	TKI that inhibits EGFR	II	2004	115	4.3	OS: 6 PFS: 2.4
Erlotinib + cisplatin		I/II	2007	51	21	OS: 7.9 PFS: 3.3
Erlotinib + cisplatin + docetaxel		II	2007	50	67	OS (at 19 months): 11 PFS (at 19 months): 6
Lapatinib in patients without (arm A) and with (arm B) prior EGFR TKI exposure	A reversible TKI that inhibits EGFR and ErbB2/HER-2	II	2012	45	0 vs. 0	OS: 9.6 vs. 5.2 PFS: 1.7 vs. 1.7
Docetaxel ± vandetanib	TKI that inhibits both EGFR and VEGFR-2	II	2013	29	13 vs. 7	OS: 6 vs. 6.7 PFS: 2.25 vs. 0.8

HER human epidermal growth factor receptor, *Ig* immunoglobulin, *mAb* monoclonal antibody, *N/A* not applicable, *OS* overall survival, *PFS* progression-free survival, *TKI* tyrosine kinase inhibitor, *TTP* time to progression, *5-FU* 5-fluorouracil

a phase II randomized trial that evaluated the role of panitumumab in combination with chemotherapy. Patients were randomized to either docetaxel/cisplatin plus panitumumab vs. docetaxel/cisplatin alone as first-line therapy for R/M HNSCC [34]. Preliminary results from this study demonstrated improved PFS and RR in the panitumumab group, but also with an increased frequency of grade 3/4 AEs (73 vs. 56%).

2.2 Tyrosine Kinase Inhibitors Targeting the ErbB Receptor Family

2.2.1 Afatinib

Afatinib is an irreversible TKI targeting EGFR, ErbB2/HER-2, and ErbB4/HER-4 [35, 36]. The LUX-Head and Neck 1 trial was a phase III, randomized multicenter study exploring the role of afatinib in patients with R/M HNSCC and refractory to platinum-based chemotherapy and/or cetuximab [37]. This open-label multinational study randomized patients in a 2:1 ratio to either afatinib (40 mg/day) or methotrexate (40 mg/m^2/week) and stratified them by ECOG performance status and previous anti-EGFR-targeted antibody therapy. The primary endpoint was PFS, and 483 patients were enrolled. After a median follow-up of 6.7 months, PFS was significantly longer in the afatinib group (2.6 months) vs. the methotrexate group (1.7 months) with a HR of 0.8 (95% CI, 0.65–0.8; $p = 0.03$). The overall response rate (ORR) amongst afatinib-treated patients was 10 vs. 6% in methotrexate patients, and the disease control rate (DCR) was 49% and 39%, respectively. Serious AEs occurred in 44 (14%) of afatinib-treated patients and 18 (11%) of methotrexate-treated patients. A subgroup analysis demonstrated that p16-negative patients with non-oropharyngeal carcinomas and who had not received a prior EGFR-targeted mAb derived the most benefit from afatinib therapy. A subsequent biomarker analysis of LUX-Head and Neck 1 demonstrated that those patients with phosphatase and tensin homolog (PTEN) high (2.9 vs. 1.4 months; HR 0.47; $p = 0.014$), HER-3-low (2.9 vs. 2.0 months; HR 0.47; $p = 0.014$), and EGFR amplified (2.8 vs. 2.2 months; HR 0.64; $p = 0.162$) patterns had derived greater benefit in PFS from afatinib therapy [38].

The efficacy of anti-EGFR TKI therapy in comparison to cetuximab therapy has also been explored. Seiwert et al. conducted an open-label randomized phase II trial that enrolled 124 patients and conducted a 1:1 randomization to either afatinib (50 mg/day) or cetuximab (250 mg/m^2/week) until disease progression or intolerable AEs (stage I) with the option to crossover (stage II) [39]. The primary endpoint was tumor shrinkage before crossover as assessed by independent review and independent central review. Of 121 patients that were treated, 68 crossed over to stage II. ORR in stage I was 16.1%/8.1% with afatinib, and 6.5%/9.7% with cetuximab (independent review/independent central review). Afatinib and cetuximab demonstrated comparable disease control (50 vs. 56.5%, respectively). Afatinib was associated with more frequent AEs, including rash/acne (18 vs. 8.3%), diarrhea (14.8 vs. 0%), and stomatitis/mucositis (11.5 vs. 0%), and led to 23% of patients discontinuing afatinib vs. 5% of patients on cetuximab. The authors concluded that, given these results, sequential EGFR/ErbB treatment with afatinib and cetuximab could provide sustained clinical benefit in patients after crossover, and found these results to be suggestive of a lack of cross resistance. Several studies are ongoing to explore additional roles for afatinib in the management of patients with HNSCC, including a phase II trial of afatinib in the neoadjuvant setting (NCT01538381 [EORTC NOCI-HNCG 90111-24111]) [40], to evaluate potential biomarkers and their role in determining response to afatinib (NCT0145674 [PREDICTOR]), and the role of afatinib in human papillomavirus (HPV)-negative LA-HNSCC as a component of induction chemotherapy (NCT01732640) [11].

2.2.2 Dacomitinib

Dacomitinib is an irreversible TKI that inhibits EGFR, ErbB2/HER-2, and ErbB4/HER-4 [11, 41]. An open-label, multicenter, single-arm phase II trial investigated the clinical activity of dacomitinib in R/M HNSCC [42]. Sixty-nine patients were enrolled, and received 45 mg of dacomitinib daily, in 21-day cycles. The primary endpoint was ORR. Among response evaluable patients, eight (12.7%, 95% CI 5.6–23.5) achieved a PR and 36 (57.1%) had stable disease, which lasted $\geq$24 weeks in nine patients (14.3%). The median PFS was 12.1 weeks and the median OS was 34.6 weeks. The most common grade 3 or higher treatment-related AEs were diarrhea (15.9%), acneiform dermatitis (8.7%), and fatigue (8.7%); these AEs led to at least one dose interruption in 28 (40.6%) patients and dose reductions in 26 (37.7%) patients, as well as permanent treatment discontinuation in eight (11.6%) patients. A phase I/II study aiming to identify biomarker modulations associated with dacomitinib treatment when given preoperatively for resectable oral cavity HNSCC is currently ongoing (NCT01116843).

2.2.3 Gefitinib

Gefitinib is a reversible EGFR TKI [43]. Patel et al. conducted an open-label single-arm trial of gefitinib in elderly patients (aged >65 years) with ECOG performance status of 3–4 with R/M HNSCC and otherwise not eligible for other systemic therapy [44]. One hundred patients received oral gefitinib at a daily dose of 250 mg. Primary endpoints

of the study included clinical response rate and DCR, and secondary endpoints included time to progression (TTP), OS, and toxicity evaluation. The study demonstrated a clinical response rate with gefitinib of 14% and a DCR of 45%. Of note, 55% experienced an improvement in their symptoms, and median TTP and survival were 5.3 and 10.6 months, respectively. Acneiform folliculitis was the most frequent toxicity observed (24%) followed by diarrhea (16%). Other phase III studies have demonstrated little activity of gefitinib in HNSCC, and there are therefore no further plans to develop gefitinib for patients with R/M HNSCC [11, 45, 46].

2.2.4 Erlotinib

Erlotinib is a reversible TKI targeting EGFR [47, 48]. Soulieres et al. conducted a phase II single-arm study in 115 patients with R/M HNSCC, regardless of HER-1/EGFR status [49]. Forty-seven percent of patients received erlotinib at the full dose (150 mg daily) throughout the entire study, and 46% of patients required a dose reduction and/or interruption. Five patients achieved a partial response, for an overall ORR of 4.3% (95% CI 1.4–9.9). Disease stabilization was maintained in 44 (38.3%) patients for a median duration of 16.1 weeks. Median PFS was 9.6 weeks (95% CI 8.1–12.1), and the median OS was 6 months (95% CI 4.8–7). Patients who experienced at least grade 2 skin rashes were found to have a significant difference in OS vs. those who did not ($p = 0.045$), similar to patients experiencing skin toxicity but improved efficacy on cetuximab. No difference was noted, however, on HER-1/EGFR expression status.

A phase I/II trial investigated the potential use of erlotinib in combination with cytotoxic chemotherapy in patients with R/M HNSCC. This single-arm study in treatment-naïve patients sought to determine the phase II dose and ORR of erlotinib in combination with cisplatin [50]. Fifty-one patients were enrolled and treated in three different dose-escalating cohorts of daily continuous oral erlotinib and IV cisplatin given every 21 days. The recommended phase II dose was then evaluated in a two-stage trial with a primary endpoint of ORR. The intention-to-treat response rate was 21%, with one complete and eight partial responses (95% CI 10–36), and disease stabilization was achieved in 21 patients (49%; 95% CI 33–65). Median PFS was 3.3 months (95% CI 2.7–4.8) and median OS was 7.9 (95% CI 5.6–9.5). The development of higher grade skin rashes during cycle 1 resulted in improved survival outcomes ($p = 0.034$). Another phase II study of 50 patients receiving erlotinib in combination with cisplatin and docetaxel for R/M HNSCC demonstrated a ORR of 67% and a DCR of 95%, with median PFS and OS of 6 and 11 months, respectively [51]. The use of erlotinib in LA-HNSCC as monotherapy and combined with either RT or bevacizumab, however, has demonstrated conflicting results [52–55].

2.2.5 Lapatinib

Lapatinib is a reversible EGFR and ErbB2/HER-2 TKI [56, 57] that has been US FDA approved for the treatment of R/M breast cancer. Although there have been data to suggest efficacy in patients with treatment-naïve LA-HNSCC [58], data in patients with R/M HNSCC are less promising. A phase II multi-institutional study in R/M HNSCC enrolled 45 patients into two cohorts: those with (Arm A) and without (Arm B) prior exposure to an EGFR inhibitor [59]. In an intent-to-treat analysis, no complete or partial responses were observed, although stable disease was observed in 41% of patients in Arm A (median duration, 50 days, range, 34–159) and 17% of patients in Arm B (median, 163 days, range, 135–195). Median OS was 288 days in Arm A (95% CI 62–374) and 155 days in Arm B (95% CI 75–242), and median PFS was 52 days in both arms. Although well tolerated, the authors concluded that lapatinib was inactive in patients who were both EGFR inhibitor naïve and refractory. At the time of this writing, there are currently no trials actively recruiting patients to further explore the role of lapatinib in patients with R/M HNSCC, although its use in combination with definitive chemoradiotherapy (CRT) is currently being explored in a phase II trial that is actively accruing patients (TRYHARD, NCT01711658).

2.2.6 Vandetanib

Vandetanib is a multi-targeted TKI that inhibits both EGFR and VEGFR-2. [60, 61] A randomized, open-label, multicenter phase II study enrolled 29 patients who had progressed on platinum-based chemotherapy and randomized patients to two arms, docetaxel (IV 75 mg/m^2 every 21 days) alone vs. docetaxel plus vandetanib (oral 100 mg daily) [62]. The primary objective was response rate and the secondary objectives were PFS, OS, DCR, and duration of response (DOR). PR was achieved in one patient in the docetaxel arm vs. two patients in the combination arm. The objective response rate (RR) was 1/14 (7%; 95% CI 0.2–33.8) patients in the docetaxel arm vs. 2/15 (13%; 95% CI 1.6–40.4) in the combined arm. Median PFS was 3.21 (95% CI 3.0–22.0) and 9 weeks (95% CI 5.86–18.1), and median OS was 26.8 (95% CI 17.7–100.7+) and 24.1 (95% CI 16.4–171.1+) weeks, in the docetaxel arm and combined arm, respectively. Given the minor and non-significant trend towards PFS in the combination arm, the authors concluded that the inclusion of vandetanib was not of clinical significance. Although there is one clinical trial currently recruiting patients to explore the use of

vandetanib in the prevention of head and neck cancer (NCT01414426), there are no active trials exploring its use in patients with R/M HNSCC.

3 Programmed Cell Death 1 Pathway

PD-1 is a cell surface receptor and member of the B7 receptor superfamily with an important role in the regulation of the immune response [63]. PD-1 receptor is a 288 amino acid, 50–55 kDa, type I transmembrane glycoprotein encoded by the *PDCD1* gene on chromosome 2q37.3 and is part of the Ig superfamily [63–66]. Programmed Death-1 knockout murine models have provided insight into the role of PD-1 in immune regulation. Programmed Death-1-deficient mice developed a delayed-onset organ-specific autoimmunity similar to lupus, characterized by glomerulonephritis, arthritis, and Ig deposition in affected tissues, suggesting that PD-1 might function as an inhibitor of lymphocyte responses at peripheral tissues [67, 68]. Furthermore, PD-1 is highly expressed by exhausted dysfunctional T cells in the context of chronic infections, and antibody-mediated blockade of PD-L1, one of the major PD-1 ligands, results in the restoration of T-cell function and enhances control of viral replication [69, 70]. These observations suggest that PD-1 may play a role in hampering immune-mediated tissue destruction in the setting of chronic antigenic stimulation.

The PD-1 receptor binds two ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC). PD-L1 is expressed constitutively on hematopoietic cells, including dendritic cells, macrophages, mast cells, B cells, and T cells, as well as non-hematopoietic cells, such as endothelial cells and numerous types of epithelial cells [68, 71]. Its broad distribution suggests that interactions between PD-1 and PD-L1 may play an important role in regulating effector T-cell responses in peripheral tissues, especially at inflammatory sites [68]. Data from studies in PD-L1 deficient mice demonstrate that PD-L1 expression on hematopoietic cells inhibits cytokine production in lymphoid tissues by T cells, and its expression on non-hematopoietic cells limits pathologic immune responses in peripheral tissues [72]. PD-L2 expression is largely restricted to immune cells, such as dendritic cells, macrophages, and mast cells, and further enhanced by inflammatory signals, including interferon (IFN)-γ, granulocyte-macrophage colony-stimulating factor, and interleukin (IL)-4 [73, 74]. The role of PD-L2 in immune function is less clear, although some data suggest that interactions between it and PD-1 may restrain effector T-cell function within lymphoid organs [68].

The end result of the interaction of the PD-1 receptor and its ligands appears to be regulation of the immune response via down-regulation of T-cell receptor (TCR) signals, leading to apoptosis of activated T lymphocytes [75–78]. Several cells of the immune system, including activated B and T lymphocytes, progenitor T cells, natural killer (NK) cells, and myeloid cells express PD-1, but the primary function of PD-1 is on effector/memory T lymphocytes, ultimately leading to the regulation of T-cell activation and apoptotic pathways [64, 79]. The PD-1 receptor is in close proximity to the TCR in activated T cells. SHP-2, a cytoplasmic SH2 domain-containing protein tyrosine phosphatase, is recruited to the cytoplasmic tail, interfering with the TCR signaling complex and blocking activation of the phosphatidylinositol-3-kinase pathway as well as activation of Akt. Phosphatidylinositol-3-kinase inhibition results in decreased levels of survival proteins, such as Bcl-xL, a transmembrane mitochondrial molecule essential to the intrinsic apoptotic pathway [64], and ultimately leading to immune tolerance.

The PD-1 pathway has been exploited in several disease types, including infectious diseases. The PD-1 pathway is a critical factor in harmonizing an effective antimicrobial immune response without significant immune-mediated damage to host tissues. Modifications to the PD-1 pathway have been implicated in an assortment of viral infections, including human immunodeficiency virus, hepatitis B, and hepatitis C [69, 80–82]. Exploitation of the PD-1 pathway is not limited to viral pathogens. *Helicobacter pylori* has been demonstrated to exploit the PD-1 pathway in the promotion of T-cell suppression through the regulation of effector/memory T cells [83]. Helminthes also use the PD-1 pathway by inducing macrophages to produce immune suppression [84]. The use of PD-1 inhibitors in the management of chronic infectious diseases is also an area of active and ongoing research.

Several hematologic and solid malignancies have been demonstrated to exploit a similar mechanism of immune evasion [85]. During a normal immune response, TCR activation leads to the upregulation of PD-1 on T-cell surfaces. However, this continuous antigenic exposure (such as in malignancy or chronic infection) may also lead to T-cell exhaustion, with subsequent immune evasion. In addition, PD-L1 expression on antigen-presenting cells facilitates T regulatory cell (Treg) proliferation and survival, and sustained expression of PD-1 inhibits NK cells [85]. Either of these cellular processes may ultimately lead to inhibition of anti-tumor immunity [82, 86], with subsequent impairment of both the innate and adaptive immune response. Tumor cells may adapt to attempts of the host immune system to neutralize it, by upregulating PD-L1 on its surface via induction by inflammatory cytokines, illustrating an example of adaptive immunity [85]. These varied mechanisms ultimately result in more efficient apoptosis of activated tumor-specific T cells and decreased efficacy of T-effector cell-mediated apoptosis of tumor cells.

4 Role of the Immune System in Head and Neck Cancer

The successful proliferation of HNSCC cells is contingent upon their ability to exploit various mechanisms to evade the immune system [87]. A reduction of T-cell-mediated recognition by tumor cells is executed by altering human leukocyte antigen (HLA) class I expression, and thereby altering TCR:HLA peptide antigen interactions [87]. Because complete loss of HLA may trigger NK cell activation, HNSCC cells may evade T-cell recognition through decreased expression and/or mutation of antigen presenting machinery (APM) components and attenuated HLA I expression, so as to simultaneously avoid T-cell recognition and NK-cell recognition [87]. Additionally, immune checkpoint receptors are exploited in the tumor microenvironment to promote tumor growth, and several receptors have been identified on dysfunctional and exhausted lymphocytes, including CTLA-4, lymphocyte activation gene 3, T-cell Ig mucin protein-3, as well as PD-1 [87–89].

HNSCCs also secrete various cytokines that lead to immune suppression [90]. These include: (1) transforming growth factor-β, which induces NK- and T-cell activation, and is a key cytokine in the differentiation of Tregs [91]; (2) IL-6, which signals via signal transducer and activator of transcription 3 to inhibit dendritic cell maturation and NK-cell, T-cell, neutrophil, and macrophage activation, and is also correlated with the recurrence and survival of HNSCC [92, 93]; (3) prostaglandin E2, a pro-survival pro-angiogenic molecule [94–96]; and (4) vascular endothelial growth factor, which is expressed in more than 90% of HNSCCs and thought to promote T-cell inactivation and dysfunction by increasing the ratio of immature to mature dendritic cells [87, 97, 98]. Such cytokines influence the actions of a subset of suppressor Tregs that prevent autoimmunity as well as promote cancer progression by causing anergy, apoptosis, and the cell-cycle arrest of activated T cells [87, 99]. Increased levels of Tregs have been isolated from the peripheral blood of patients with HNSCC, and are more potent amongst infiltrating T cells in the tumor, ultimately contributing to an immunosuppressed state [100–102]. Treg frequency has also been found to be increased in patients following treatment, suggesting that cytotoxic therapy increases Treg numbers [100].

Various cellular components of the tumor microenvironment play an integral role in the immune system's modulation of tumor growth. Myeloid-derived suppressor cells have been demonstrated to suppress activated T cells. Myeloid-derived suppressor cells secrete nitric oxide and other reactive oxygen species, which catalyze the nitration of the TCR, thereby inhibiting the TCR:HLA interaction, signaling, and subsequent activation [87, 103]. Tumor-associated macrophages are also found in the tumor microenvironment and can generate a potent antitumor response if they possess an 'M1' phenotype, which is characterized by the secretion of IFN-α as well as other type 1 cytokines [87]. Alternatively activated macrophages ('M2' phenotype), in turn, lead to a T-helper 2 response, with subsequent secretion of IL-4, IL-13, and other ILs that permit tumor growth [87]. Thus, tumor-associated macrophage-infiltrating tumors, which are closely associated with the M2 phenotype, also correlate with a worse clinical outcome, and have been demonstrated to secrete EGF, IL-6, and IL-10, as well as being associated with angiogenesis, local tumor progression, and metastasis [87, 104].

These cytokines and cellular components, in concert with HPV infection, facilitate the development of immune evasion and suppression in HNSCC [87]. Human papillomavirus interferes with many cellular signaling pathways, including IFN, which link the innate immune response to the adaptive immune response via the activation of immature dendritic cells and CD8+ T cells and the production of virus-specific antibodies [105, 106]. Interferon-α and IFN-β both have immunostimulatory properties, are secreted by virally infected cells, and execute their antiviral effects via messenger RNA inhibition, inhibition of viral protein expression, and NK-cell stimulation [106].

Human papillomavirus also interacts with antigen presentation to reduce adaptive immune response and suppress signal transducer and activator of transcription 1 signaling inhibition via IFN pathways, thereby leading to the downregulation of HLA class I APM [107, 108]. These observations suggest that an antiviral immune response is dependent on inflammatory signaling [87]. In normal settings, checkpoint receptors such as PD-1 and CTLA-4 limit an overzealous immune response that could potentially lead to auto-immunity [79, 109]. Patients with HPV-mediated HNSCCs have been found to have elevated PD-1 expression on CD8+ HPV plus tumor-infiltrating lymphocytes [110]. Paradoxically, patients with high numbers of PD-1 expressing T-cell infiltration have demonstrated superior 5-year OS (93.9%) vs. those with low PD-1 expressing T-cell infiltration. This is likely a reflection of a quantitatively greater overall antitumor immune response because proinflammatory conditions may also stimulate PD-1 expression [87, 110]. Recent analyses correlating the number of tumor-infiltrating lymphocytes in patients with HPV-positive oropharyngeal disease prognosis suggest that the quality and quantity of tumor-infiltrating lymphocytes determines the antitumor response [111, 112].

The immunotherapeutic intervention most likely to generate success against HPV-mediated HNSCCs is an immunoprevention strategy [87]. Although the effects of large-scale immunization for the prevention of cervical cancer on the prevention of HPV-positive HNSCC have yet

to be fully elucidated, there have been demonstrations of significantly reduced incidences of oral HPV infection in the vaccine arms of large-scale randomized trials [113]. Such promising interventions are limited to patients who have not yet been exposed to HPV. Thus, additional immunotherapeutic interventions must be developed and implemented to benefit patients after exposure to HPV. Immune checkpoint inhibition, therefore, holds significant promise in re-shaping the therapeutic landscape of R/M HNSCC. These pathways, which regulate the inhibitory pathways that prevent excessive inflammatory responses in addition to the development of auto-immunity, determine the duration and extent of immune response and have been the subject of considerable investigation in HNSCC [87]. Tumor immune evasion can occur by high tumor expression of PD-L1 and/or tumor immune infiltration by PD-1-positive T lymphocytes. Preliminary analyses indicate that PD-L1 is expressed in 50–60% of HNSCCs [87]. Additionally, data suggest that tumor infiltration by PD-1 positive Tregs may be more common for HPV-positive vs. HPV-negative HNSCC [87], which may potentially carry prognostic and therapeutic implications for the future use of immunotherapy in these populations.

This section will explore FDA-approved immunotherapy agents for the treatment of HNSCC as well as those under clinical investigation (Table 2).

4.1 Pembrolizumab

Pembrolizumab is a high-affinity, humanized, IgG4-κ mAb directed against the human cell surface receptor PD-1. Several clinical studies have demonstrated its efficacy in the treatment of a variety of malignancies, and it has previously been FDA and EMA approved for the treatment of melanoma, Hodgkin lymphoma, and non-small-cell lung cancer. Robust clinical data from the KEYNOTE-012 trial have demonstrated its efficacy in the management of R/M HNSCC. In an open-label, multicenter phase Ib trial of patients with R/M HNSCC whose tumors expressed PD-L1 ($\geq$1% by immunohistochemistry), patients received 10 mg/kg of pembrolizumab intravenously every 2 weeks [114]. Primary outcomes were safety in the per-protocol population and the proportion of patients with centrally reviewed overall response per Response Evaluation Criteria In Solid Tumors (Version 1.1). Of 104 patients screened between 7 June, 2013 and 3 October, 2013, 81 patients (78%) were PD-L1 positive. Of these patients, 60 patients with PD-L1-positive HNSCC were enrolled and treated: 23 (38%) were HPV positive and 37 (62%) were HPV negative. Furthermore, 10/60 (17%) patients experienced grade 3–4 drug-related AEs, the most common of which was transaminitis and hyponatremia, each occurring in 2/60 patients. There were 27/60 (45%) of patients who experienced a serious AE, but no drug-related deaths were reported. Additionally, 8/45 (18%) patients demonstrated an overall response by central imaging review (95% CI 8–32); the ORR was 4/16 (25%) in HPV-positive patients and 4/29 (14%) in HPV-negative patients [114].

An expansion cohort of KEYNOTE-012 enrolled 132 patients with R/M HNSCC, regardless of HPV status or PD-L1 tumor marker status. The ORR was 20% (95% CI 13–28) by investigator review and 18% (95% CI 12–26) by a central imaging vendor [115]. Median DOR was not reached (range, $\geq$2 to $\geq$11 months), and 6-month PFS and OS rates were 23 and 59%, respectively. There was a statistically significant increase in ORR observed in PD-L1-positive vs. PD-L1 negative patients (22 vs. 4%), suggesting that PD-L1 status may serve as a potential prognostic and therapeutic biomarker. At the American Society of Clinical Oncology Annual Meeting in June 2016, Mehra et al. presented a pooled analysis after a long-term follow-up of patients enrolled in KEYNOTE-012 [8]. One hundred and ninety-two patients with R/M HNSCC received pembrolizumab, either at 10 mg/kg every 2 weeks or 200 mg intravenously every 3 weeks for 24 months until disease progression, unacceptable safety, or investigator/patient decision. The primary endpoint was ORR (Response Evaluation Criteria In Solid Tumors, Version 1.1) per central imaging vendor review. Secondary endpoints included PFS, OS, and DOR. Of note, 61% of patients received two or more prior therapies for recurrent disease. Results were similar to those published in the initial cohort of KEYNOTE-012. The ORR was 17.7% (95% CI 12.6–23.9; seven CRs, 27 PRs). Median follow-up duration in responders was 12.5 months (range, 8.4–24.4 months). A median DOR had not yet been reached at the time of data cutoff, and amongst responders, 22 (76%) of patients had ongoing responses. The ORR was 21.9% (95% CI 12.5–34) in HPV-positive patients and 15.9% in HPV-negative patients, and the median OS was 8.5 months (95% CI 6.5–10.5). These results led to the FDA's accelerated approval for pembrolizumab for the treatment of patients with R/M HNSCC on 5 August, 2016. As a condition of the accelerated approval, Merck is required to conduct a multicenter randomized trial establishing the superiority of pembrolizumab over standard therapy to verify and describe the clinical benefit of pembrolizumab.

Additional studies will explore the role of pembrolizumab beyond R/M HNSCC. Uppaluri et al. presented a phase II trial of neoadjuvant and post-operative pembrolizumab in patients with locally advanced, surgically resectable, stage III/IV HPV-negative HNSCC (NCT02296684) at the American Society of Clinical Oncology Annual Meeting in 2016 [114]. This trial is actively accruing patients. Powell et al. are investigating the role of pembrolizumab concurrent with cisplatin and

Table 2 Immunotherapy agents that have been US FDA approved for the treatment of head and neck squamous cell carcinoma as well as those under clinical investigation

Study/drug	Mechanism of action	Phase of development	Year	Number of patients	Response rate (%)	Survival vs. control (months)
KEYNOTE-012/pembrolizumab	Anti PD-1 IgG4-κ mAb	FDA approved	2016	45	18	N/A
KEYNOTE-048/pembrolizumab				825	N/A	N/A
CheckMate-141/nivolumab	Anti PD-1 IgG4 mAb	FDA approved	2016	361	13.3	7.5 vs. 5.1 (control)
NCT02207530/durvalumab	Fc optimized anti PD-L1 mAb	II	2016	112	N/A	N/A
NCT02812524/ipilimumab	Anti CTLA-4 IgG1 mAb	I	2016	18	N/A	N/A
NCT01860430/ ipilimumab + cetuximab	Anti CTLA-4 IgG1 mAb + anti-EGFR IgG1 mAb	Ib	2016	18	N/A	N/A
KESTREL/durvalumab + ipilimumab		III	2016	628	N/A	N/A
Motolimod + cetuximab	TLR-8 agonist + anti-EGFR IgG1 mAb	Ib	2016	13	15	N/A

EGFR epidermal growth factor receptor, *Ig* immunoglobulin, *mAb* monoclonal antibody, *N/A* not applicable, *PD-1* programmed cell death 1, *TLR* Toll-like receptor

RT in a single-arm, multi-site, open-label trial of pembrolizumab in patients with stage III–VB HNSCC (NCT02586207). Treatment will consist of a loading dose of IV pembrolizumab 200 mg given 7 days prior to initiation of CRT and continued every 3 weeks during CRT and following completion of CRT for a total of eight doses. This trial is also currently accruing patients [31].

4.2 Nivolumab

Nivolumab is a fully human, IgG4 anti-PD-1 mAb that is FDA approved for the treatment of patients with melanoma, Hodgkin lymphoma, NSCLC, renal cell cancer, urothelial carcinoma, and now HNSCC. In Europe, the approval is for melanoma, NSCLC, or renal cell carcinoma. Ferris et al. recently published the results of an open-label phase III trial exploring the use of nivolumab in patients with R/M HNSCC [115]. Three hundred and sixty-one patients who had progressed within 6 months after platinum-based chemotherapy were randomized in a 2:1 ratio to receive nivolumab every 2 weeks or standard single-agent systemic therapy with methotrexate, docetaxel, or cetuximab. The primary endpoint was OS, and secondary endpoints included PFS, rate of objective response, safety, and patient-reported quality of life. The median OS was 7.5 months (95% CI 5.5–9.1) in the nivolumab group vs. 5.1 months (95% CI 4.0–6.0) in the standard therapy group (HR 0.70, $p = 0.01$). The estimates of the 1-year survival rate were approximately 19 percentage points higher with nivolumab than with standard therapy (36 vs. 16.6%), and the median PFS was 2 months in the nivolumab group vs. 2.3 months (95% CI 1.9–3.1) with standard therapy (HR for disease progression or death, 0.89; 95% CI 0.7–1.13; $p = 0.32$). The rate of PFS at 6 months was 19.7% with nivolumab vs. 9.9% with standard therapy. The response rate in the nivolumab group was also higher at 13.3 vs. 5.8% in the standard therapy group. Grade 3–4 treatment-related AEs were also less frequent in the nivolumab group (13.1%) vs. the standard therapy group (35.1%). Based on these results, the FDA approved nivolumab for the treatment of patients with R/M HNSCC with disease progression on or after platinum-based therapy on 10 November, 2016.

Several studies are currently underway exploring the role of nivolumab in concert with other agents for the management of R/M HNSCC. CheckMate 651 (NCT02741570) is an open-label, randomized, two-arm phase III study exploring the use of nivolumab in combination with ipilimumab compared with the standard of care (EXTREME study regimen). Primary outcome measures include OS and PFS, and secondary objectives include ORR, time to deterioration, and PD-L1 expression. It is actively enrolling patients. A phase II, double-blind randomized two-arm study of nivolumab in combination with ipilimumab vs. nivolumab in combination with placebo (CheckMate 714; NCT02823574) in patients with R/M HNSCC is also currently recruiting patients. Its primary objectives include ORR in a platinum refractory subgroup, with secondary objectives including ORR in a platinum-eligible subgroup, as well as PFS in both platinum- eligible

and platinum-refractory subgroups, and OS in platinum-eligible and platinum-refractory subgroups, and aims to enroll 315 patients.

4.3 Durvalumab

Durvalumab is an Fc optimized mAb that targets PD-L1. There are ongoing clinical trials exploring its utility in HNSCC. The KESTREL study (NCT02551159) is a phase III, randomized open-label study of first-line durvalumab ± tremelimumab vs. standard of care (EXTREME regimen) in R/M HNSCC [116]. Patients who have not received any prior systemic chemotherapy (unless part of multimodality treatment for locally advanced disease) will be stratified by PD-L1 status, smoking history, tumor location, and then HPV status and randomized in a 2:1 ratio to receive a flat dose of tremelimumab of 75 mg every 4 weeks (maximum of 4 doses) plus durvalumab 1500 mg every 4 weeks, single-agent durvalumab 1500 mg every 4 weeks, or the EXTREME regimen, all until progression of disease. A phase II study was unveiled at the American Society of Clinical Oncology Annual Meeting in 2015 (NCT02207530) exploring the role of durvalumab monotherapy in R/M HNSCC [117]. This phase II, open-label. single-arm multicenter study will enroll 112 patients with PD-L1-positive HNSCC who are immunotherapy naïve but have received at least one platinum-containing regimen for R/M disease. Patients will receive IV durvalumab at 10 mg/kg every 2 weeks for up to 12 months. Primary objectives are ORR, and secondary outcome measures will further assess disease control rate, DOR, PFS, and OS, as well as safety and tolerability and health-related quality of life. Neither study, however, is actively recruiting patients.

4.4 Ipilimumab

Ipilimumab is a fully human. IgG1 mAb that inhibits CTLA-4. It has been FDA approved for the treatment of patients with melanoma, and is under investigation for the management of patients with R/M HNSCC. A phase I open-label study plans to administer intra-tumoral ipilimumab to patients with HNSCC prior to surgical resection (NCT02812524). The primary objectives of the study will be to measure the time of delay to surgery. A phase Ib study (NCT01860430) will explore the use of ipilimumab in combination with cetuximab and intensity-modulated radiotherapy in patients with LA-HNSCC. Primary outcome measures will be to identify the starting dose of ipilimumab in combination with cetuximab and intensity-modulated radiotherapy, and secondary outcome measures will evaluate treatment response, PFS, tissue biomarkers, and dose-response modeling. This study anticipates recruiting 18 patients.

4.5 Motolimod (VTX-2337)

Motolimod is a small-molecule TLR-8 agonist that activates myeloid dendritic cells, monocytes, and NK cells. A phase Ib study in patients with HNSCC administered escalating doses of the agent in combination with cetuximab and demonstrated a response rate of 17%, as well as a disease control rate of 50% [5, 118, 119]. Because these data suggested synergistic antitumor activity with platinum and 5-fluorouracil, a randomized phase II study comparing the EXTREME regimen with or without motolimod was launched and is currently ongoing (NCT01836029).

5 Conclusions

Clinical trials have long been the mainstay of drug development and exploring novel therapeutics for all oncologic diseases. Despite numerous trials, few agents have shown promise in the management and treatment of head and neck cancer. With researchers establishing the role of the immune system in tumorigenesis, the field of immunotherapy has flourished and two immunotherapeutic agents have recently been FDA approved for R/M HNSCC in a 3-month period. In the 10 years prior to this development, only two agents (docetaxel and cetuximab) had received approval for the management of patients with R/M HNSCC. Despite the promise of ErbB receptor family inhibitors and the extensive evaluation of both mAbs and TKIs, there has been little success in translating this into meaningful clinical benefits for patients. Continued elucidation of immune dysfunction, coupled with additional insight into the increasing prevalence of HPV-positive HNSCC, may provide the needed impetus to accelerate the development of much needed novel therapeutic agents for head and neck cancer.

The future direction of the treatment of patients with HNSCC remains hopeful and exciting. As we appreciate the complex nature of cancer biology and tumor resistance, we continue to engage patients in clinical trials with the goals of improving outcomes. Immunotherapy drugs are exciting and novel approaches for the treatment of HNSCC. While they remain approved only in the metastatic second-line setting, future studies will certainly explore their role concurrently with chemotherapy or radiation therapy or the combination of the two. Induction therapy with immunotherapies will also be evaluated and may impact the treatment of patient with LA-HNSCC. We are only at the beginning of our understanding of the role of

immunotherapy in patients with HNSCC and will certainly see a larger landscape for its use.

Compliance with Ethical Standards

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