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HER2 and HER3 as Therapeutic Targets in Head and Neck Cancer

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Abstract

Work over the past several decades has identified that aberrations in the ErbB signaling pathways are key drivers of oncogenesis; and, concurrent efforts to discover targetable vulnerabilities to counter this aberrant oncogenic signaling offer tremendous promise in treating a host of human cancers. These efforts have been centered primarily on EGFR (also known as HER1), leading to the discovery of the first targeted therapies approved for head and neck cancer. More recently, HER2 and HER3 signaling pathways have been identified as highly dysregulated in head and neck cancer. This review highlights the HER2 and HER3 signaling pathways and clinical efforts to target these receptors and their aberrant signaling to treat head and neck squamous cell carcinomas and other head and neck malignancies, including salivary gland carcinomas. This includes the use of small molecule inhibitors and blocking antibodies, both as single agents or as part of multimodal precision targeted and immunotherapies.

Keywords

ErbB; EGFR; HER2; HER3; Head and Neck Cancer; Precision Therapy; Cancer Immunotherapy; Tyrosine Kinase Inhibitors; Signal Transduction

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a highly lethal cancer that affects over 60,000 people in the US annually and has been traditionally associated with tobacco

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and ethanol exposure as well as Human Papilloma Virus (HPV) infection. The majority of patients with HNSCC initially present with locally advanced disease; and, despite aggressive, combined-modality treatment, a significant proportion of patients will develop recurrent or metastatic disease that is no longer amenable to curative therapy [1]. Currently, treatment options include platinum-based doublets, EGFR inhibition, and immunotherapy, but outcomes are generally poor, and most patients succumb to disease within a year of diagnosed recurrent/metastatic (r/m) HNSCC. However, insights gleaned from ongoing work to define dominant oncogenic signaling pathways in HNSCC – namely, the ErbB oncogene family – offers promise for the development of new and more efficacious multimodal, precision therapies [2].

Initially identified in carcinogen-induced rat brain tumor models and as the oncogene *neu* in mouse embryonic fibroblasts [3, 4], the ErbB family of oncogenes consists of four related tyrosine kinase receptors: HER1 (EGFR, ErbB1), HER2 (Neu, ErbB2), HER3 (ErbB3), and HER4 (ErbB4)[5]. They are now known to play a major role in the pathogenesis of many types of cancers, such as lung, breast, colorectal, thyroid, melanoma and head and neck. The ErbB receptors are characterized by their defining feature: they are type 1 single membrane-spanning tyrosine kinase (RTK), which dimerize to initiate a host of signaling cascades which, ultimately, converge to promote cell growth, migration, and differentiation, and if persistently activated, can lead to cancer (Fig. 1). As an example, amplification and overexpression of HER2 is now recognized as an oncogenic driver in many human malignancies [6] and has been the focus of tremendous preclinical and clinical research, converging upon the development of a host of targeted therapeutics, some of which are now standard of care as discussed below. Similarly, EGFR (epidermal growth factor receptor, Erb1) is overexpressed, mutated or aberrantly activated by excess expression of its ligands, including EGF, transforming growth factor-alpha (TGF-α), amphiregulin, heparin-binding EGFR, and betacellulin, in some of the most prevalent human cancers [7]. Remarkably, ErbB family members represent the first growth factor receptors that were successfully targeted with blocking monoclonal antibodies (mAbs) in the clinic. Indeed, cetuximab (targeting EGFR) and trastuzumab and pertuzumab (targeting HER2) have been approved for the treatment of many solid malignancies. The FDA initially approved cetuximab, a humanized IgG1 monoclonal antibody against the EGFR extracellular domain, for metastatic colorectal cancer in 2004, thereby initiating the era of immunotherapies for solid tumors [8, 9]. Subsequently, it was demonstrated in seminal clinical studies that cetuximab prolonged the median overall survival and reduced disease progression in advanced HNSCC patients when delivered in combination with radio- and chemotherapies [10, 11]. Based on these findings, cetuximab in combination with standard chemotherapy gained FDA approval in 2006 for use together with radiation or as a single agent in HNSCC patients that failed to respond to platinum-based therapy and for recurrent or metastatic disease [11]. However, the overall increased response of adding cetuximab to radiation and/or chemotherapy is ~10–20% [10, 11], much lower than initially expected considering the high level of EGFR expression in HNSCC. The mechanism of resistance to cetuximab and emerging opportunities for targeting EGFR in HNSCC has been extensively reviewed (see Chapter 1). More recently, HER2 and HER3 signaling pathways have been identified as highly dysregulated in HNSCC, which will be the focus of this Chapter.

HER2 and HER3 Signaling

HER2 (ErbB2) is 185-kDa and an orphan receptor without an endogenous ligand-binding domain, but it is recognized as the preferred and most catalytically potent binding partner for other EGFR family members – a status conferred both by its overexpression and rapid cell membrane recycling imbue [12–15]. Another characteristic feature of HER2 is that, unlike other ErbB family members, it does not cycle between active and inactive conformations but rather is constitutively in the activated state, which relates to its inability to bind ligand [16, 17]. Clinically, HER2-targeted therapies are best-known for their role in treating breast cancers and are now a bedrock of standard oncologic therapy for breast cancers featuring aberrant HER2 expression signaling [18, 19]. Trastuzumab, the first HER2 targeting monoclonal antibody and developed in 1990, blocks HER2 signaling via several mechanisms – by promoting receptor internalization and degradation, inhibiting dimerization, blocking downstream PI3K-AKT signaling, and through antibody-dependent cellular cytotoxicity (ADCC) [20].

HER3 (ErbB3), lacks intrinsic tyrosine kinase activity, hence often referred to as pseudokinase [21]. HER3 is an obligate dimerization partner and serves as a central enabler for other kinases, principally other ErbB family members [5, 22, 23]. Additionally, and particularly with respect to its role in cancer signaling, HER3 serves as a scaffolding protein that enables the maximal induction of the phosphoinositide 3 kinase (PI3K)/ PI3K protein kinase B (AKT)/mTOR pathway. Specifically, HER3 harbors a cluster of 6 C-terminal tyrosine-containing motifs that, when phosphorylated, represent a consensus PI3K/p85 binding site [24–27]. Accordingly, by forming heterodimers with HER3, the upstream kinase-active oncodrivers (HER2 or others) can couple efficiently with and signal through the PI3K/AKT/mTOR pathway [28, 29] (Fig. 1). Therefore, it is reasonable to expect that a loss of HER3 activity may block cancer progression in diverse systems driven by divergent RTKs. In this regard, preclinical and clinical studies have implicated HER3 as a potential resistance pathway to other targeted therapies [30], particularly ErbB family-targeted therapies; and, overexpression of HER3 is known to correlate with poor prognosis for some cancers, including breast [31], gastric [32] and head and neck cancer [28], discussed in more detail below. Indeed, HER3 is now appreciated to confer therapeutic resistance to several targeted oncologic therapies: namely, monoclonal antibodies and tyrosine kinase inhibitors that target HER2 [30, 33–35] and EGFR [36, 37], as well as small molecule inhibitors of downstream targets such as PI3K/AKT [38, 39], BRAF [40], and MEK [41]. By virtue of its direct cancer promoting signaling via PI3K/AKT/mTOR in addition to its role as a resistance pathway from other therapies, HER3 is increasingly appreciated as an attractive therapeutic target. Moreover, HER3 has recently been shown to be expressed exclusively within epithelial cells and not immune cells in HNSCC, raising the possibility of effective next-generation, multimodal precision therapies with targeted HER3 blockade plus immunotherapy [28].

Apart from HER3 as described above, the ErbB RTKs can become activated with ligand binding to the extracellular domain, which subsequently leads to conformational changes that promote homo- and heterodimerization. With respect to HER3, it has been shown to bind neuregulin-1 and neuregulin-1 and to be a promiscuous dimerization partner [33, 36].

Dimerization then leads to reciprocal allosteric activation and C-terminal phosphorylation of tyrosine residues [2]. Once phosphorylated, tyrosine residues can bind and recruit PTB-binding proteins and SH2 domains, ultimately converging upon downstream activation. Interestingly, HER2:HER3 heterodimers can be formed in a ligand-dependent or ligand-independent fashion [29]. However, the heterodimers that result consequent to ligand-depended vs -independent binding are structurally and functionally distinct as elucidated by the study of two different HER2-binding antibodies, trastuzumab and pertuzumab. While pertuzumab disrupts only ligand-dependent HER2:HER3 heterodimer signaling, trastuzumab disrupts only ligand-independent HER2:HER3 signaling [42]. This insight, and a large body of published studies into the nuances of ErbB signaling have led to combination strategies with dual ErbB inhibition, yielding clinical benefit in both the preclinical and clinical settings [43, 44].

Anti-HER2 and anti-HER3 therapies in clinical practice

To date, an array of antibody, antibody-drug conjugate and small molecule inhibitors of HER2 and HER3 signaling have been under study in early-stage clinical trials of HNSCC. A summary of currently available agents is available in Table 1. Additional preclinical and early-stage clinical trials utilizing anti-HER2 and -HER3 therapies in combination with other targeted treatments (e.g., anti-VEGF, pan receptor tyrosine kinase inhibitors) have been reported and are beyond the scope of this focused review.

Anti-HER2 antibodies

Trastuzumab is and FDA approved for the treatment of HER2+ breast and metastatic gastric cancers. In head and neck cancers – encompassing both mucosal and salivary tumors - 4 phase II clinical trials have been published demonstrating promising results in HER2+ disease. This agent was studied in the first-line setting in metastatic or recurrent HNSCC in combination with chemotherapy [45]. Of 61 patients treated, PFS was 19.8% (95% CI, 10.6–30.9) and OS was 44% (95% CI, 31.6–56.2) at one year. Of note, they found a statistically significant difference in these parameters for patients with <10% compared to >10% EGFR expression. PFS was 6.7 vs. 3.1 months (p=0.003) and OS was 16.1 vs. 7.4 months (p=0.005). The study by Haddad et al. was meant to evaluate patients with HER2 overexpressing advance salivary gland tumors but was stopped early as it was found that most of the screened tumors were not overexpressing HER2. Ultimately of the 14 patients enrolled, median PFS was 4.2 month [46].

In addition to HNSCC, trastuzumab in combination with docetaxel for patients with HER2-positive salivary ductal carcinoma was studied in a single institution, open label, single-arm phase II trial that enrolled 57 patients [47]. Patients exhibited a response rate of 70.2% (95% CI, 56.6–81.6) with median PFS 8.9 months (95% CI, 7.8–9.9 months) and overall survival 39.7 months (95% CI, not achieved). Trastuzumab has also been studied in combination with pertuzumab by Kurzrock et al. In this study of stage III/IV HER2-positive salivary gland cancers, 15 patients were found to have an objective response rate of 60% (95% CI, 32–84%) with 8.6-month PFS and OS of 20.4 months [48].

Anti-HER2 therapy in the standard of care for salivary tumors

Current standard of care guidelines by multi-disciplinary consensus from the National Comprehensive Caner Network (NCCN) recommend testing for HER2 expression in the setting of recurrent, unresectable, or metastatic salivary tumors. In this setting, HER2 expression is assessed as part of a biomarker panel that includes androgen receptor (AR), neurotrophic tyrosine receptor kinase (NTRK), Harvey rat sarcoma viral oncogene homolog (HRAS), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) and tumor mutational burden (TMB) prior to initiating treatment. This recommendation is based on accumulated high-quality evidence from preclinical and clinical studies demonstrating the efficacy, and safety of agents that target each of these biomarkers. Approved systemic therapy regimens include Trastuzumab [49], Ado-trastuzumab emtansine (TDM-1) [50], Trastuzumab/pertuzumab [48], docetaxel/trastuzumab [47], Fam-trastuzumab deruxtecan-nxki (T-DXd) [51], with or without Pembrolizumab [52]. These anti-HER2 agents are appropriate for clinical use in this setting due to moderate effectiveness, mild toxicity, average quality of evidence and relatively consistent clinical trial outcomes, despite the high financial cost. All regimens are given in conjunction with radiotherapy when the extent of disease makes locoregional therapy feasible (NCCN guidelines). Conversely, for resectable disease, complete surgical clearance remains the standard of care due to superior clinical outcomes. In the setting of distant HER2+ salivary gland metastases, anti-HER2 treatment alone should be given only in the case of appropriate performance status and is preferred in the context of a clinical trial (NCCN guidelines). At this time, routine testing for neither HER3 expression, nor HER2 expression in other head and neck cancer subtypes is recommended but is often conducted as part of clinical trial enrollment.

Anti-HER3 antibodies

A phase Ib evaluating the addition of duligotuzumab, an antibody with activity against EGFR and HER3, to chemotherapy in first-line treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma revealed a promising response rate of 67% [53]. This agent was further studied in MEHGAN, which compared it to cetuximab in the recurrent or metastatic squamous cell carcinoma population following progression on chemotherapy [54]. This study found no significant improvement with duligotuzumab, with an OS of 7.2 vs. 8.7 months for cetuximab, with a HR of 1.15 (90% CI, 0.81–1.63). Additionally, the anti-HER3 monoclonal antibody, LJM716, was studied in Phase I trial including 21 patients with advanced HNSCC [55]. Of these, one had an extended period of stable disease greater than forty weeks. The maximum tolerated dose was not reached, and 40mg/kg weekly was determined to be the dose for further studies. Grade 3 diarrhea and hypokalemia was experienced by one patient during the dose expansion period. Patritumab, another HER3-targeting antibody, was studied in untreated recurrent and/or metastatic HNSCC [56]. Patients were assigned to receive this treatment or placebo, in combination with cetuximab and up to six cycles of platinum therapy. There was no statistically significant improvement in PFS or OS, with the trend favoring the placebo group in OS.

Most promisingly, the activity of the HER3 antibody CDX-3379 was investigated in the neoadjuvant setting in a window of opportunity trial in patients with untreated head and neck

squamous cell carcinoma who were surgical candidates [57]. A total of 12 patients were treated with two doses of CDX-3379. Among them, 83% of patients showed a reduction in phosphorylation of HER3 upon treatment and tumors decreased in size in 42% of patients. These findings have led to a completed phase II clinical trial evaluation of this treatment in combination with cetuximab in advanced head and neck squamous cell carcinoma with cetuximab-refractory disease, finding a 6.7% overall response rate in genomically unselected patients [57].

HER2 and HER3 Antibody-drug conjugates

The efficacy of Ado-trastuzumab emtansine (T-DM1) in salivary gland carcinomas with HER2 amplification was reported as a subset of the NCI-MATCH trial (EAY131) [50]. Three patients with salivary gland tumors were included and two of these patients showed a partial response to T-DM. Response appeared to correlate with higher gene copy numbers. An abstract presented at ASCO 2019 by Li et al. supported this high response rate, where they demonstrated an objective response in nine of ten patients with *HER2* amplified salivary ductal carcinoma [58]. Median PFS was not reached at the time of reporting. Of note, a case report has demonstrated efficacy of T-DM1 in the treatment of metastatic salivary gland carcinoma with brain metastases [59].

Trastuzumab deruxtecan (T-DXd) has been approved for treatment of both HER2+ breast and gastric cancer and has shown promising activity in additional HER2+ solid tumors in first in human (FIH) and drug-drug interaction (DDI) trials [58]. In a 17-patient pooled analysis of the HER2- positive salivary gland carcinoma patients from these studies, Bando et al. has demonstrated a 47% response rate with a PFS of 14.1 months.

Although the development of the anti-HER3 mAb patritumab was discontinued due to limited activity in a Phase III trial, Daiichi has recently reported that the antibody–drug conjugates (ADC) patritumab deruxtecan (HER3-DXd; U3-1402) showed encouraging response rates in Phase I/II trials, including in EGFR mutated and TKI-resistant lung cancer [60–62]. These recent positive results support the druggability of HER3 using ADC anti-HER3 antibodies in lung cancer, which is now being extended to HNSCC.

Small molecule inhibitors

Lapatinib was studied in a phase II trial evaluating its efficacy in recurrent or metastatic squamous cell carcinoma of the head and neck [63]. Patients were separated into two arms based on those without or with exposure to an EGFR inhibitor. Response rate and progression free survival were used as primary endpoints for these groups, respectively. The first group failed to have any complete or partial responses, and stable disease was seen in 41% of patients in arm A and 17% in arm B. Median PFS was 52 days for both, and median OS was 288 (95% CI, 62–374) and 155 (95% CI, 75–242) days, respectively. They performed correlative analysis in tumors that revealed that EGFR was not inhibited, leading to the conclusion that lapatinib as monotherapy is ineffective in recurrent or metastatic head and neck squamous cell carcinoma. Lapatinib was further studied in combination with chemoradiation in patients with locally advanced head and neck squamous cell carcinoma [64]. This combination showed a numerical improvement compared to chemoradiation with

placebo, particularly in p16-negative patients, with a median PFS of >20.4 vs. 10.9 months. A similar study by del Campo et al. in patients treated with either lapatinib (71 patients) or placebo (36 patients) before chemoradiotherapy, found an objective response rate of 70% cs. 53% which was not statistically significant [65]. Of note, for patients that received four weeks or greater lapatinib therapy, the ORR prior to definitive treatment was 17% vs. 0%. Notably, all of these patients overexpressed EGFR, with 50% having HER2 expression by IHC.

Afatinib was first explored in a phase II window of opportunity trial to assess its potential role as a neoadjuvant agent [66]. Patients were assigned 5:1 to receive afatinib for 14 days prior to surgery or no neoadjuvant treatment. Patients who received the neoadjuvant afatinib had a 70% (95% CI, 47–87%) partial metabolic FDG-PET response. Assessed objectively by RECIST v1.1, the response rate was 22% (95% CI 8–44%). Afatinib therapy was then evaluated in a phase III platinum-progressed recurrent and metastatic head and neck squamous cell carcinoma in the LUX-H&N1 study [66]. Patients were assigned to receive either afatinib or methotrexate. PFS favored afatinib at 2.6 months (95% CI, 2.0–2.7) compared to 1.7 months (95% CI, 1.5–2.4). This was statistically significant with a HR of 0.80 (95% CI, 0.65–0.98). A subsequent biomarker analysis of this patient population showed that afatinib was likely to be more effective in patients with p16-negative, *EGFR*-amplified, HER3-low, or PTEN-high tumors [67]. A similar study in primarily Asian populations, LUX-Head and Neck 3, found a similar improvement in PFS with afatinib but no significant improvement in OS compared to methotrexate [68]. The LUX-Head and Neck 2 study assessed the role of afatinib in adjuvant treatment following definitive therapy in locally advanced head and neck squamous cell carcinoma [69]. This study, along with the similar LUX-Head and Neck 4, were stopped early due to signals of lack of efficacy with increased toxicity from afatinib. Afatinib was combined with pembrolizumab in a phase II trial [70]. The ORR was 41.4% with a PFS of 4.1 months and OS of 8.9 months. Of note, the combination led to upregulation of genes associated with the immune response through enhanced antigen presentation.

Dacomitinib, an irreversible inhibitor of EGFR/HER1, HER2 and HER4 is currently FDA approved for treatment of metastatic non-small cell lung cancer (NSCLC) and was studied in a phase II trial in patients with recurrent and/or metastatic head and neck squamous cell carcinoma following progression on platinum therapy [71]. Patients receiving dacomitinib demonstrated a response rate of 20.8% and OS of 6.6 months (95% CI, 5.4–10.3). Notably, patients with alterations in the PI3K pathway and high cytokine expression were noted to have a significantly shorter median OS, at 6.1 vs. 12.5 months (p=0.005).

Conclusion

While EGFR, HER2, and HER3 are widely expressed and known to initiate and drive pro-tumorigenic signaling in HNSCC, overall rates of response to singly-targeted therapies remain low. These tempered clinical responses to ErbB-directed therapies can be in part explained by redundancy and overlap across oncogenic signaling pathways. Cetuximab, for example, a monoclonal antibody which targets EGFR and is approved in HNSCC, has proven to be of significant but, ultimately, limited benefit monotherapeutically secondary to

the numerous and well-characterized mechanisms of both primary and secondary resistance (described in chapter 1). It may be the case that while targeted blockade of EGFR controls the RAS-ERK signaling pathway, it may not concurrently regulate PI3K/mTOR signaling pathway that is also responsible for driving oncogenesis in established tumors. Indeed, emerging preclinical and clinical data suggest that the same may be true of targeting HER2 and HER3 in HNSCC: just as the signaling pathways that support oncogenesis are multifaceted and overlapping, so must our therapeutic strategy be multimodal. Optimal outcomes may necessitate combination strategies as has been demonstrated in the literature [72–74]

In addition, there is now a growing appreciation of the dynamic interplay between aberrant cancer signaling and the immune-suppressive cancer microenvironment. Specifically, it has been recently demonstrated that ErbB oncogenic signaling pathways may polarize towards immunosuppression, which provides a premise for employing combination precision immuno-oncology therapeutic strategies. Early results from such combination IO approaches demonstrates improved response rates both preclinically with HER3 plus PD-1 [28] and clinically with cetuximab plus PD-1 [75]. Ultimately, we can envision that the mechanism of action underlying successful combination therapies targeting HER2 and HER3 in HNSCC will entail both tumor growth inhibition by concurrent disruption of aberrant downstream signaling pathways – both the RAS-MEK-ERK and PI3K-AKT-mTOR cascades – in addition to a reversal towards immune-permissive tumor microenvironment, thereby increasing the response to anti-PD-1 treatment [28].

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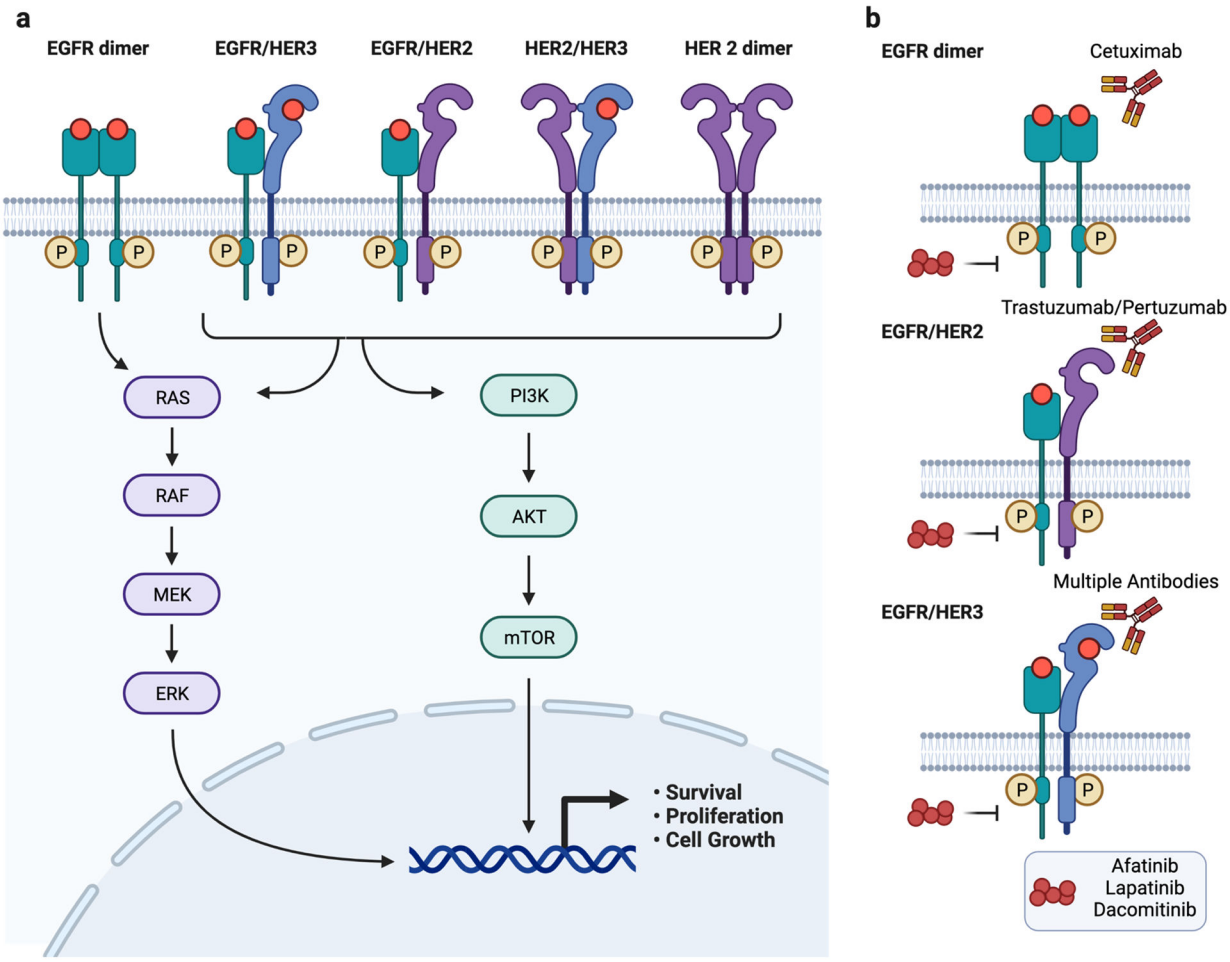

Figure 1. EGFR, HER2 and HER3 Signaling in Head and Neck Cancer.

(a) Cartoon overview highlighting the dominant signaling pathways known to play a role in HNC; HER3 has ligand dependent and independent activity (see text for details). (b) EGFR, HER2 and HER3 therapeutic targets (antibodies and small molecule inhibitors) with FDA-approval or under current clinical evaluation are depicted (see text for details). Created with the BioRender online platform (BioRender.com)

Table 1:
Recently Completed and Ongoing Clinical Trials Targeting HER2 and HER3 in HNC.

HNSCC = head and neck squamous cell carcinoma, R/M = recurrent / metastatic, LA = locally advanced, WoO = window of opportunity, FIH = first in human

Class	Study	Agent	Target	Phase	Population
Antibody	Gillison[45]	Trastuzumab	HER2	II	R/M HNSCC
	Haddad[46]	Trastuzumab	HER2	II	LA- or R/M salivary gland carcinoma overexpressing HER2
	Takahashi[47]	Trastuzumab	HER2	II	HER2-positive LA- or R/M salivary ductal carcinoma
	Kurzrock[48]	Trastuzumab / Pertuzumab	HER2	II	HER2 amplified/overexpressing stage III/IV salivary gland cancers
	Jimeno[52]	Duligotuzumab	EGFR(HER1), HER3	Ib	R/M HNSCC
	MEHGAN (Fayette)[53]	Duligotuzumab	EGFR(HER1), HER3	II	R/M HNSCC post-chemotherapy
	Duvvuri[56]	CDX-3379	HER3	WoO	Operable HNSCC
	Forster[55]	Patritumab	HER3	II	Untreated R/M HNSCC
Antibody-drug conjugate	Jhaveri[49]	T-DM1	HER2	II	*HER2* amplified with CN>7 and no prior *HER2*-targeting antibodies
	Li[57]	T-DM1	HER2	II	*HER2* amplified salivary gland cancers
	Bando[50]	T-DXd	HER2	FIH/I	*HER2*-positive persistent or recurrent salivary ductal carcinoma
Small molecule	Harrington[63]	Lapatinib	EGFR(HER1), HER2	II	LA-HNSCC
	de Souza[62]	Lapatinib	EGFR(HER1), HER2	II	R/M HNSCC without (A) or with (B) prior EGFR inhibition
	del Campo[64]	Lapatinib	EGFR(HER1), HER2	II	LA-HNSCC
	Machiels[65]	Afatinib	EGFR(HER1), HER2	II	Treatment-naive surgical candidates with HNSCC
	LUX-H&N[65,67]	Afatinib	EGFR(HER1), HER2	III	R/M HNSCC post-platinum
	Kim[70]	Dacomitinib	EGFR (HER1), HER2, HER4	II	R/M HNSCC post-platinum