HER2 as a Therapeutic Target in Head and Neck Squamous Cell Carcinoma

Netanya I. Pollock1 and Jennifer R. Grandis1,2

Abstract

The majority of patients with head and neck squamous cell carcinoma (HNSCC) present with advanced-stage disease. The current standard of care is surgery followed by adjuvant radiotherapy with or without chemotherapy or chemoradiation alone. The addition of cetuximab for the treatment of patients with locally advanced or recurrent/metastatic HNSCC has improved overall survival and locoregional control; however, responses are often modest, and treatment resistance is common. A variety of therapeutic strategies are being explored to overcome cetuximab resistance by blocking candidate proteins implicated in resistance mechanisms such as HER2. Several HER2 inhibitors are in clinical development for HNSCC, and HER2-targeted therapy has been approved for several cancers. This review focuses on the biology of HER2, its role in cancer development, and the rationale for clinical investigation of HER2 targeting in HNSCC.

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the seventh most common cancer worldwide by incidence, with an estimated 600,000 new cases reported each year worldwide, two thirds of which occur in industrialized nations (1). The 5-year survival rate of patients with HNSCC is approximately 40% to 60% (2), with a high rate of tumor recurrence likely due to the advanced stage (stages III and IV) at diagnosis in many cases. Locoregional disease recurrence is common, and distant metastatic disease arises in 20% to 30% of patients (3).

The standard of care for advanced HNSCC is surgical resection followed by adjuvant radiotherapy or chemoradiation as a primary treatment approach. However, treatment strategies that target the biologic mechanisms of HNSCC tumorigenesis have been, and continue to be, investigated. Currently, cetuximab, an mAb to EGFR, is the only FDA-approved molecular targeting agent for the treatment of primary or recurrent/metastatic HNSCC. Overexpression of EGFR has been found in approximately 90% of cases of HNSCC and is a predictor of poor prognosis (4–6). However, responses to cetuximab as a single agent do not exceed 13% for patients with recurrent/metastatic disease, are typically short lived, and are not correlated with EGFR expression levels in the primary tumor (7). Many studies have proposed several mechanisms for resistance, the most common of which involves overactivation of other ErbB family receptors, including HER2 (8).

HER2, commonly referred to as ErbB2, c-erbB2, or HER2/neu, is a 185-kDa receptor tyrosine kinase and a member of the ErbB family of proteins (9). The ErbB family consists of four closely related receptors: EGFR (ErbB1/HER1), ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4; ref. 10). There is some homology among the family members; each is a membrane-spanning tyrosine kinase that exists as an inactive monomer. Upon ligand binding, the receptors homodimerize or heterodimerize with other members of the ErbB protein family, which triggers autophosphorylation of their intracellular tyrosine kinase domains and initiates a signaling cascade (11). The ErbB proteins are expressed in most epithelial cell layers and play a key role in cell differentiation during development (12).

ErbB2 was originally identified as the oncogene neu in mouse embryonic fibroblasts (NIH3T3 cells; ref. 13). HER2 has since been found to be amplified and overexpressed in a number of human cancers (12), contributing to tumor development, cell-cycle progression, and cellular motility and growth. Consequently, HER2 is an active focus of drug development and cancer research. To date, 20 articles have been reported in the peer-reviewed literature assessing HER2 expression in HNSCC tumors (14–33). Six articles have evaluated HER2 targeting in HNSCC preclinical models, and two trials have been completed and reported using HER2 inhibitors for this malignancy (18, 34–40). In this review, we evaluate the preclinical and clinical data implicating HER2 as a therapeutic target in HNSCC.

HER2 in Cancer

HER2 signaling pathway

Unlike the other family members, HER2 lacks a ligand-binding domain, characterizing it as an orphan receptor. The absence of a ligand likely contributes to its role as a powerful signal amplifier for the other ErbB family receptors (41). Evidence suggests that HER2 is the preferred dimerization partner among all members of the protein family, perhaps due to frequent recycling of the HER2 receptor heterodimers to the cell surface as well as the ability of HER2 to decrease the rate of ligand dissociation (42–44).
The downstream signaling effects of the HER2 receptor are complex due to the differential effects of the various HER2-containing heterodimers. For example, EGFR/HER2 heterodimers preferentially stimulate the MAPK pathway, whereas the HER2/HER3 heterodimers activate both the MAPK and the PI3K/v-akt murine thymoma viral oncogene homolog (AKT) pathway (ref. 45; Fig. 1). There are at least 10 known EGF-related peptides with varying degrees of affinity for the different heterodimers (11). These peptides do not directly bind to HER2 but instead promote the receptor's heterodimerization and cross-phosphorylation (11). EGFR/HER2 heterodimers are most commonly formed in response to stimulation with EGF, whereas formation of HER2/HER3 is driven by neuregulins (44). Even when overexpressed, HER2 maintains its dependence on other members of the HER family, namely HER3, for HER2-mediated tumorigenesis (46).

Variations in detection techniques and interpretation methods of HER2 overexpression have contributed to inconsistent reporting of overexpression of HER2 in many types of cancer, including HNSCC. The American Society of Clinical Oncology (ASCO) publishes guidelines for assessing HER2 status in breast carcinomas via IHC and FISH (47). Although distinct HER2 testing protocols have also been established in gastric cancer, none exist for HNSCC (48). Consequently, pathologists apply the IHC/FISH

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**Figure 1.** HER2 Signaling. Human epidermal growth factor receptors, EGFR (HER1), HER2, HER3, and HER4, are receptor tyrosine kinases that play a role in cell growth, survival, and differentiation. Each receptor is composed of an extracellular ligand-binding domain, transmembrane domain, and tyrosine kinase domain. Upon ligand binding, the receptors are activated by auto- and cross-phosphorylation. There are no known ligands for HER2, which does not need to be bound to a ligand to be activated. HER2 is the preferential dimerization partner among all family members. Dimerization and subsequent phosphorylation lead to activation of downstream targets, including the PI3K/AKT and RAF/MEK/MAPK pathways. Activation of these pathways enhances survival, proliferation, and cell-cycle progression. AKT, v-akt murine thymomaviral oncogene homolog 1; P, phosphorylation; RAF, v-raf-1 murine leukemia viral oncogene homolog; RAS, rat sarcoma viral oncogene homolog.
scoring techniques for breast cancers to HNSCC, a biologically different carcinoma. Reports of HER2 overexpression range from 0% to 47% in HNSCC (15, 20, 25). In laryngeal cancer, positive HER2 staining has been reported in 68% of cases (24). Azemar and colleagues found significantly elevated levels of HER2 in 26 of 45 primary HNSCC samples (49). We assessed 426 HNSCC tumors in The Cancer Genome Atlas (TCGA) database and found 18 cases (4%) with mRNA upregulation; however, only 8 of those 18 also harbored HER2 gene amplification. In a separate analysis of 213 HNSCC tumors in The Cancer Proteome Atlas (TCPA), low levels of activated (phosphorylated HER2) or total HER2 expression were detected (Fig. 2A).

Although HER2 mRNA levels correlated with HER2 protein expression, no correlation was observed with levels of phosphorylated HER2 (Fig. 2B). The protein levels of TCGA tumors were determined by reverse phase protein array (RPPA), a high throughput technique that reports HER2 scoring intensity on a continuum. Assadi and colleagues compared RPPA results with IHC and found a correlation of 0.86 (50). Comparing protein detection techniques with those for DNA or RNA is not as simple. Levels of RNA in TCGA tumors were determined by RNAseq processing, a profiling method that is subject to sample bias. Moreover, there remains a gap between mRNA and protein levels because of various degrees of regulation.

Figure 2.
Landscape of HER2 expression in HNSCC tumors (TCGA database, provisional). A, pH2 and HER2 expression z-scores were obtained from the TCPA database for HNSCC tumors (n = 213). pH2 expression levels were plotted as a function of frequency in R version 3.0.2. B, pH2 levels do not correlate with HER2 mRNA expression. HER2 levels do correlate with HER2 mRNA expression. RPPA data were obtained from the TCPA database for HNSCC tumors. Protein levels and mRNA expression were compared using a Pearson correlation in R version 3.0.2. C and D, RPPA expression for (C) HER2 and (D) pH2 correlates with RPPA expression for EGFR. E, RPPA expression for pH2 correlates with RPPA expression for HER2. RPPA data for pH2, HER2, and EGFR were obtained from the TCPA database for HNSCC tumors. Protein levels were compared using a Pearson correlation in R version 3.0.2.
Elevated HER2 overexpression has been reportedly associated with worse prognosis, increased recurrence, and decreased overall survival (OS) in HNSCC (26, 51). Cavalot and colleagues found that frequency of HER2 overexpression was significantly higher in patients with more aggressive disease occurring in conjunction with metastatic lymph nodes (15). In addition, the 5-year OS and the 5-year disease-free survival (DFS) probability were significantly lower for HER2-positive patients compared with HER2-negative individuals (15). Wei and colleagues found that in two laryngeal tumors, HER2 staining was higher in the metastases (2+ and 3+), whereas staining was lower in the corresponding primary tumors (17). However, other studies have shown that HER2 is not an independent prognostic factor (22, 29). Our analysis found that among the 213 tumors in the TCGA cohort, neither mRNA upregulation of HER2 nor increased expression of total or phosphorylated HER2 protein was an independent predictor of OS (data not shown). However, the small sample size limits the conclusiveness of this analysis.

HER2 has been found to be coexpressed with EGFR in HNSCC tumors (33). Among the 213 HNSCC tumors in the TCPA, expression of both HER2 and activated HER2 (pHER2) correlated with EGFR expression (Fig. 2C and D). As expected, expression of pHER2 correlated with total HER2 expression (Fig. 2E). These findings suggest that HER2 coexpression may contribute to the negative prognostic impact of EGFR because coexpression/activation has been reported to be associated with resistance to therapeutic agents (35, 52). Wheeler and colleagues generated cetuximab-resistant non–small cell lung cancer (NSCLC) and HNSCC cell lines and found that the cetuximab-resistant cell lines expressed higher levels of phosphorylated receptor tyrosine kinases, including HER2, than the parental cell lines (52). In addition, among all of the cetuximab-resistant cell lines, EGFR had increased coimmunoprecipitation with HER2 and HER3 when compared with the parental cell lines. Treating these cells with increasing concentrations of cetuximab had no effect on the autophosphorylation of EGFR or the activity of HER2. However, this resistance was overcome with several tyrosine kinase inhibitors (TKI), including erlotinib, gefitinib, and the pan-HER irreversible inhibitor canertinib (CI-1033). We previously reported that treatment with a dual EGFR-HER2 kinase inhibitor overcame acquired resistance of HNSCC tumors to cetuximab in xenograft tumor models (35). Together, these findings validate the active investigation of HER2 as a molecular target for HNSCC therapy.

**HER2 Inhibitors**

**Monoclonal antibodies: preclinical and clinical studies**

A number of strategies are used to inhibit HER2, including mAbs. Trastuzumab is a humanized mAb that binds domain IV of the extracellular domain of the HER2 receptor, preventing activation of its intracellular tyrosine kinase (53, 54). Trastuzumab has several possible mechanisms of action, including prevention of HER2 receptor dimerization, increased endocytosis of the receptor, and inhibition of the generation of a constitutively active truncated intracellular HER2 molecule (53, 55). A phase II trial evaluated trastuzumab in combination with paclitaxel and cisplatin (56). The addition of trastuzumab did not significantly improve patient response rate to the chemotherapy treatments.

Pertuzumab is a humanized mAb to the HER2 receptor that binds domain II of the extracellular domain and inhibits heterodimerization of HER2 with other members of the HER family (57). Because blocking the formation of heterodimers, particularly HER2/HER3, has had promising effects in the treatment of breast cancer (58, 59), pertuzumab was studied in combination with gefitinib, an EGFR inhibitor, in HNSCC cell lines (60). The cell lines that harbored high levels of phosphorylated HER2 and HER3 were more resistant to gefitinib, and a similar trend was observed for cell lines with amplified EGFR. However, combination treatments of gefitinib and pertuzumab overcame resistance (60). Currently, there are no reports of pertuzumab in HNSCC preclinical models or patients.

**Tyrosine kinase inhibitors: preclinical studies**

Small-molecule TKIs that bind to the ATP binding site of the HER molecule are also effective therapeutic agents. Lapatinib, a reversible dual TKI of both EGFR and HER2, is FDA approved for the treatment of HER2-positive breast cancer (61). By preventing phosphorylation and subsequent activation of the PI3K/AKT and MAPK/ERK pathways, lapatinib results in an increase in apoptosis and decrease in cellular proliferation and growth. Just like other small-molecule TKIs, lapatinib is administered orally and well tolerated by patients (61). An ex vivo study evaluating the combined effect of lapatinib and cisplatin in 72 different patient-derived HNSCC samples found that lapatinib provided an additive effect by limiting colony formation (38). However, there were significant differences in the response of individual tumors to lapatinib treatment, evident by the wide range of IC50 concentrations (38). Another study evaluating the combined effect of lapatinib with either cisplatin or paclitaxel found additive effects both in vivo and in vitro (40). Lapatinib reduced proliferation of HNSCC cells, but no correlation was found between expression levels of EGFR or HER2 and the antiproliferative effects (40). In vivo xenograft studies in mice bearing YCU-H891 HNSCC cells demonstrated that lapatinib alone induced apoptosis and displayed antitumor activity (40). Although lapatinib alone did not inhibit angiogenesis, inhibition of angiogenesis was observed when lapatinib was combined with paclitaxel. In addition, the combination of cisplatin or paclitaxel with lapatinib resulted in enhanced antitumor activity primarily by increasing apoptosis (40).

The irreversible ErbB family blocker afatinib (Gilotrif) binds to the tyrosine kinase domains of EGFR, HER2, and HER4 (62). The FDA recently approved afatinib for the treatment of patients with NSCLC harboring EGFR mutations. Owing to its irreversible activity and multireceptor binding, afatinib is also being investigated for treatment of patients with other ErbB-driven cancers, including HNSCC (63). To date, a few studies have reported on the use of afatinib in preclinical HNSCC models. In one study, mice inoculated with FaDu cells, which are cells derived from a hypopharyngeal cancer, received varying doses of afatinib; at every dose, afatinib significantly decreased tumor volume size when compared with the control (63).

Dacomitinib, another irreversible pan-HER kinase inhibitor, is an experimental drug under investigation in NSCLC, gastric cancer, glioma, and HNSCC. It has shown preclinical efficacy alone and in combination with ionizing radiotherapy in HNSCC cell lines and mice models (64). HNSCC cell lines, UT-SCC-8 and UT-SCC-42a, showed sensitivity to dacomitinib, with IC50s of 25 nmol/L, with combination treatment of dacomitinib and ionizing radiation further reducing cell...
viable. Although dacomitinib was effective in inhibiting EGFR phosphorylation, reduction of HER2 phosphorylation was not evaluated (64).

Clinical trials of HER2 TKIs in HNSCC

Ongoing trials of anti-HER agents in clinical development in HNSCC are summarized in Tables 1 and 2. IC50 values for these agents are listed in Table 3. Because of the current palliative nature of treatment associated with recurrent and/or metastatic HNSCC, Tables 1 and 2 delineate the trials as either curative or palliative, with *curative* meaning therapy for nonrecurrent/nonmetastatic HNSCC. Nonrecurrent/nonmetastatic HNSCC

Completed clinical trials for patients with nonrecurrent/nonmetastatic HNSCC include investigations of lapatinib therapy. In a randomized phase II placebo-controlled trial, patients with previously untreated locally advanced HNSCC received either lapatinib or placebo for 2 to 6 weeks, followed by chemoradiation (34). The response rate before chemoradiation was 17% (n = 4), 7% with HER2 overexpression and amplification in 4% among 24 patients receiving lapatinib and 0% among all 16 patients receiving the placebo. Despite a clinical response, the patients who received lapatinib monotherapy did not have a significant increase in apoptosis compared with placebo.

Table 1. Trials of anti-HER family agents for nonrecurrent/nonmetastatic HNSCC (curative therapy)

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Phase</th>
<th>Study regimens</th>
<th>Estimated accrual; study population</th>
<th>Primary endpoint</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01783587</td>
<td>I</td>
<td>Afatinib plus CRT or afatinib plus RT</td>
<td>N = 38, intermediate- and high-risk HNSCC</td>
<td>DLT</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01737008</td>
<td>I</td>
<td>Dacomitinib plus CRT or RT</td>
<td>N = 34; LA HNSCC</td>
<td>MTD</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01752640</td>
<td>I/II</td>
<td>Afatinib plus carboplatin and paclitaxel</td>
<td>N = 71; primary unresected patients with LA, HPV-negative, stage III or IV a/b HNSCC</td>
<td>MTD, objective tumor response</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01824823</td>
<td>II</td>
<td>Afatinib or placebo</td>
<td>N = 108; patients with LA, stage III or IV HNSCC</td>
<td>DFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01538381</td>
<td>II</td>
<td>Afatinib or observation</td>
<td>N = 30; newly diagnosed HNSCC</td>
<td>Reduction of tumor</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01415674</td>
<td>II</td>
<td>Afatinib</td>
<td>N = 60; untreated nonmetastatic HNSCC</td>
<td>Potential predictive biomarkers of afatinib activity</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT00490061</td>
<td>II</td>
<td>Lapatinib plus RT</td>
<td>N = 60; stage III/IV HNSCC who cannot tolerate concurrent CRT</td>
<td>TTP</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>NCT00387127</td>
<td>II</td>
<td>Lapatinib plus CRT or placebo plus CRT</td>
<td>N = 67; stage III, IV a/b HNSCC</td>
<td>Complete response rate</td>
<td>Active, not recruiting</td>
</tr>
<tr>
<td>NCT01472478</td>
<td>III</td>
<td>Afatinib or placebo</td>
<td>N = 315; resected, CRT-treated HNSCC with macroscopically complete resection of disease</td>
<td>DFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT02131155 (LUX-Head &amp; Neck 4)</td>
<td>III</td>
<td>Afatinib or placebo</td>
<td>N = 150; primary unresected, stage III, IV a/b LA HNSCC without evidence of disease after CRT</td>
<td>DFS</td>
<td>Recruiting</td>
</tr>
<tr>
<td>NCT01345669 (LUX-Head &amp; Neck 2)</td>
<td>III</td>
<td>Afatinib or placebo</td>
<td>N = 669; primary unresected, stage III, IV a/b LA HNSCC without evidence of disease after CRT</td>
<td>DFS</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

NOTE: Descriptions for ongoing (recruiting; active, not recruiting; or not yet recruiting) phase I/II clinical trials of anti-HER2 family agents for HNSCC as of September 2014 (as per listings on ClinicalTrials.gov).

Abbreviations: CRT, chemoradiation; DLT, dose-limiting toxicity; HPV, human papillomavirus; LA, locally advanced; RT, radiotherapy; TTP, time to progression.
those who received placebo. All of the lapatinib responders had EGFR overexpression, and 50% had HER2 expression. Although no other biologic characteristics predicted response to lapatinib therapy, the small sample size warrants future investigation (34).

Another phase II trial did not show the same success of lapatinib as a monotherapy (36). Patients were separated based on their treatment history with an EGFR inhibitor. Patients with no prior treatment with an EGFR inhibitor (EGFR-naïve) had a 6-month progression-free survival (PFS) rate of 7%, and the median PFS was 52 days. The EGFR-naïve group’s median OS and 6-month OS rate were 288 days and 52%, respectively. At the time of analysis, all patients in this group progressed. Similarly, all patients in the previously EGFR inhibitor–treated group had died. The 6-month median PFS was 52 days, and the PFS rate was 6%. The median OS was 155 days, and the 6-month OS rate was 39%. Most HNSCC tumors expressed both EGFR and HER2, and posttreatment biopsies showed a significant decrease in pHER2 levels. Samples were analyzed for the presence of HER2-activating mutations, but only one was found to contain a mutation, which did not produce a phenotype. Although lapatinib was well tolerated by all patients, it appeared to be largely inactive as a monotherapy in both EGFR-naïve and EGFR-refractory patients. A phase III (NCT00424255) trial did not show improvement when lapatinib was added to radiotherapy or cisplatin therapy in the postoperative setting in patients with HNSCC at high risk for recurrence. Patients with resected stage II to stage IVA HNSCC were randomized to receive chemotherapy/radiotherapy with either placebo or lapatinib before, during, and following concurrent chemoradiotherapy. There was no significant difference in DFS between treatment arms.

Although lapatinib has not demonstrated clear efficacy in HNSCC, it still remains in active clinical development for patients with nonrecurrent/nonmetastatic HNSCC. Two actively accruing clinical trials are designed to evaluate lapatinib plus radiotherapy or chemoradiation (Table 1). In a recently completed phase III trial, examining lapatinib with concurrent chemoradiation followed by maintenance monotherapy for high-risk patients with resected HNSCC (NCT00424255), addition of lapatinib to chemoradiation failed to prolong DFS (65). HER2 mutations are rare in HNSCC (2% of TCGA) and have not been evaluated as a predictive biomarker to select patients with HNSCC likely to benefit from anti-HER2 therapy. Attempts to correlate levels of EGFR, phosphorylated EGFR (pEGFR), and HER2 with clinical benefit from lapatinib as a monotherapeutic agent have not been informative to date.

Although there are no completed clinical trials, afatinib and dacomitinib are undergoing active investigation for therapy in nonrecurrent/nonmetastatic HNSCC. Table 1 describes the several ongoing trials investigating these agents alone or in combination with radiotherapy or chemoradiation.

### Recurrent/metastatic HNSCC

Among completed clinical trials, afatinib was compared with cetuximab in a recently published phase II study of patients with recurrent/metastatic HNSCC (NCT00514943; ref. 66). The disease control rate by investigator review was 50% for the afatinib-receiving cohort and 56.5% for the cetuximab-receiving cohort (P = 0.48), with similar rates observed by independent central review. Centrally reviewed median PFS was 13.0 weeks for afatinib and 15.0 weeks for the cetuximab group (P = 0.71). Preliminary report of another completed phase III trial (NCT01345682 LUX-Head & Neck 1) suggested that afatinib improved PFS as well as patient-reported outcomes. Patients with recurrent/metastatic HNSCC who progressed on or after platinum-based therapy were randomized to receive afatinib or methotrexate (MTX). Afatinib significantly improved PFS (median, 2.6 months), disease control rate (49.1%), and objective response rate (10.2%) compared with methotrexate (median, 1.7 months, 38.5%, 5.6%). Afatinib did not significantly improve OS (median, 6.8 months) compared with methotrexate (median, 6.2 months). Table 2 shows results from the phase III trials in which afatinib is being compared with methotrexate for patients with recurrent/metastatic HNSCC (NCT01345682/LUX-Head & Neck 1; NCT01856478/LUX-Head & Neck 3; Table 2).
Conclusions

The presence of activating HER2 mutations or HER2 overexpression, primarily due to gene amplification, has been associated with reproducible and robust responses to HER2 targeting therapy in most malignancies, including breast, lung, and gastric cancer. HER2 mutations and HER2 gene amplifications are rare in HNSCC. EGFR is a validated prognostic and therapeutic target for treatment of HNSCC, and the mAb cetuximab is the only FDA-approved molecular targeting agent in HNSCC. EGFR is frequently overexpressed in HNSCC tumors, resulting in constitutive downstream signaling activity. EGFR can heterodimerize with HER2, and preclinical evidence suggests that cotargeting of EGFR and HER2 may augment cetuximab responses and mitigate therapeutic resistance. The majority of agents under active clinical investigation in HNSCC dually target EGFR and HER2. Because a specific molecular inhibitor strategy is unlikely to be effective in all cases, the identification of biomarkers that will predict clinical responses to ErbB family blockers in HNSCC is of paramount importance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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