Anti-EGFR Therapy: Strategies in Head and Neck Squamous Cell Carcinoma

Renato J. Oliveira-Silva¹, Ana-Carolina de Carvalho¹, Luciano de Souza Viana¹,², André L. Carvalho¹,* and Rui M. Reis¹,³,4,*

¹Molecular Oncology Research Center, ²Department of Medical Oncology, Barretos Cancer Hospital, Barretos, São Paulo, Brazil; ³Life and Health Sciences Research Institute (ICVS), Health Sciences School, University of Minho, Braga, Portugal; ⁴ICVS/3B’s-PT Government Associate Laboratory, Braga/Guimarães, Portugal

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Abstract: Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor that activates downstream signaling pathways, including the Ras-MEK-Erk and PI3K-AKT pathways, leading to cell proliferation, resistance to apoptosis, angiogenesis and the ability to metastasize. EGFR overexpression is a significant finding in cancer, particularly in head and neck cancer, where it is also associated with a poor prognosis. In recent years, several molecules have been designed to inhibit EGFR activation. Among the many available anti-EGFR drugs, only cetuximab was approved for the treatment of head and neck cancers. However, no predictive biomarkers of cetuximab response are currently known. In the present review, we provide an updated assessment of EGFR biology and its clinical impact in head and neck cancers. A special emphasis is placed on novel patents of EGFR-inhibitors that are anticipated to diversify the anti-EGFR therapies available to treat head and neck cancers. In particular, we outline a new class of irreversible multi-target inhibitors (e.g. afatinib, icotinib, CUDC-101), which may significantly contribute to new head and neck cancer therapies.

Keywords: Anti-EGFR patents, EGFR, EGFR overexpression, head and neck squamous cell carcinoma, tyrosine kinase inhibitors, targeted therapies.

1. INTRODUCTION

Head and neck cancer is the sixth most common cancer worldwide with a global incidence between 400,000 and 600,000 new cases per year and a mortality rate of 300,000 deaths annually [1-3]. It comprises a spectrum of malignancies that develop primarily within the oral cavity, pharynx, and larynx. Squamous cell carcinoma is the principal histologic subtype of this disease, accounting for more than 90% of all cases [4, 5]. The high incidence and mortality rate make these cancers a significant public health problem [6]. Head and neck squamous cell carcinoma (HNSCC) patients have a 50% five year survival rate, which is highly dependent on the stage at diagnosis [7]. Accurate assessment of clinical symptoms, physical examination and laboratory results are of paramount importance to guide diagnostic approaches, staging and choice of therapy [8].

The treatment plan depends upon patient and disease-related factors, such as the site of the primary tumor, the stage of the disease (early-stage vs. advanced-stage), feasibility of organ preservation, the ECOG performance status (Eastern Cooperative Oncology Group), significant comorbidities and the goal of therapy [8]. Patients harboring early stage disease (stage I and II) are potentially curable with single modality treatments (either surgery or radiation). Advanced disease patients (stage III and IV) require a multidisciplinary and multimodality approach with a combination of surgery, radio- and chemotherapy [8]. Despite recent advances in radio- and chemotherapy, survival rates of HNSCC patients remain poor. Local recurrences are frequent and 20-30% of cases will develop metastatic disease [9].

Extensive surgeries involving the resection of the primary tumor and cervical lymph nodes usually cause functional and aesthetic consequences, having a great impact on a patient’s quality of life [8]. The standard treatment for most patients is currently multimodal, and includes combined chemotherapy and radiotherapy. Moreover, the addition of induction chemotherapy (IC) remains an appropriate approach for advanced disease with a high risk of local or distant failure [8]. Platinum and taxane combinations are the backbone of several IC regimens for locally advanced head and neck cancers (LAHNSCC) and the TPF (docetaxel, cisplatin and fluorouracil) regimen is the most accepted induction regimen for LAHNSCC [10].

Tobacco and alcohol use are the most common risk factors for HNSCC and the human papillomavirus (HPV) has been recently established as a cause of oropharyngeal cancer [11, 12]. Tobacco use is the main risk factor for HNSCC.
carcinogenesis, with smokers having a 5 to 25 fold risk compared to non-smokers [13], due to the genotoxic effects of carcinogenic substances in tobacco [14]. Alcohol consumption is relevant for HNSCC development for its capacity to synergistically enhance the carcinogenic effects of tobacco [15]. Moreover, the acetaldehyde metabolite forms DNA adducts that interfere with synthesis and repair [16].

HPV is found in 23-35% of all HNSCC biopsies [17] and in 45-90% of oropharyngeal cancers [17-20]. HPV-16 is the most prevalent subtype, occurring in 87-90% of HPV-positive oropharyngeal cancers [21-23]. A recent comprehensive integrative genomic analysis of HNSCC and HPV status was performed by mapping RNA-Seq reads of 279 patients and it was observed that 12% (36/279) were HPV(+). Of 33 oropharyngeal tumours, 64% (21/33) were positive for HPV. The HPV(+) subset of oropharyngeal HNSCCs, exhibited a loss of TRAF3 (TNF Receptor-Associated Factor 3), activating mutation of PIK3CA, and amplification of E2F1 (E2F Transcription Factor 1) involving NF-kB, activation. In HPV(+) HNSCCs, the most prominent findings were subsets containing amplicons on 11q with CCND1, FADD, BIRC2 and YAP1 and mutually exclusive CASP8 and HRAS mutations. Importantly, these findings in HPV-associated cases may have the potential to be used as tools for treatment decisions [24].

Recently, molecular alterations underlying HNSCC tumorigenesis have been explored [24-29]. One of the pivotal molecules is the EGFR, which is overexpressed in more than 90% of HNSCCs [30, 31]. EGFR is upregulated not only in HNSCC but also in the vast majority of solid tumors, becoming, therefore, a major target for molecular therapies [32, 33].

Based on EGFR expression in HNSCC, cetuximab, a chimeric monoclonal antibody that binds with high affinity to the EGFR, has been used in the United States since 2006 as first-line treatment in combination with radiation therapy for LAHNSCC [34] or as a single agent for patients with metastatic disease and poor responses to platinum-based regimens [35]. In 2011, combinations of cetuximab with other agents were approved by the U.S. Food and Drug Administration for the first line of treatment of HNSCC. Cetuximab combination therapy with cisplatin or carboplatin and 5-fluorouracil was based on a multi-center clinical study involving 442 participants that, demonstrated an improvement in survival [36].

In the present review, we will perform an updated assessment of EGFR biology in HNSCC and its clinical impact, with a special emphasis on novel, multi-target EGFR-inhibitors, which may transform HNSCC therapy.

2. EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR)

The EGFR was discovered in the 1970s. Cohen and colleagues isolated a protein that caused precocious tooth eruption in neonatal mice, now known as EGF (epidermal growth factor) [37]. A few years later, the same research group identified a high level of radio-labeled EGF bound to the cytoplasmic membrane of A431 squamous carcinoma cell lines. This was the first evidence of a membrane receptor with affinity to EGF, the EGFR [38]. EGFR belongs to the ErbB receptor family (EGFR, ErbB2/Neu/Her2, ErbB3/Her3 and ErbB4/Her4), and the protein is composed of 1210 amino acids with four extracellular domains (ED), a transmembrane domain (TD) and an intracellular tyrosine kinase domain (TKD) (Fig. 1). Its carboxy-terminal tail contains several phosphorylation sites: one serine residue (Ser-1142), one threonine residue (Thr-654) and seven tyrosine residues (Try-845, 992, 1045, 1068, 1086, 1148, 1173) [39, 40]. EGFR can be activated by several specific ligands: (1) Amphiregulin, (2) Betacellulin, (3) Epiregulin, (4) Neuregulin, (5) Heparin-binding EGF, (6) Transforming growth factor alpha (TGF-α) and (7) EGF (Fig. 1). Under normal physiological conditions, all four ErbB receptors can form 10 possible dimer combinations including 4 homodimers and 6 heterodimers. Each combination has specific affinity for signaling in effective intracellular pathways [40, 41] (Fig. 1).

EGFR ligands cause a conformational change, resulting in domain II interaction and receptor dimerization (Fig. 1) [39]. In addition, EGFR phosphorylation sites can activate downstream protein kinases such as the Src kinase family, protein kinase C and protein kinase A. EGFR itself is also able to phosphorylate other protein residues and target downstream signaling such as the MAPK, STAT and PI3K/AKT pathways, which control cell survival, proliferation, migration, differentiation, and adhesion [42-45].

2.1. EGFR Deregulation in Tumors

Due to its significance in the regulation of multiple cellular mechanisms, EGFR homeostasis is key to normal function. Inasmuch, EGFR activity and regulation is tightly controlled by a plethora of mechanisms including copy number variation, single nucleotide polymorphism (SNP), alternative splicing, phosphorylation, ligand availability, dimerization partner availability, trafficking and degradation [46]. In the pathogenesis of cancer, EGFR/EGFR is deregulated at several levels, namely: autocrine/paracrine factors; gene amplification; gene mutations, and protein nuclear translocation. All of these alterations lead to overexpression or constitutive activation of related signaling pathways (Fig. 1).

2.1.1. Autocrine/Paracrine Factors

EGFR-mediated neoplastic transformation may be effected by autocrine/paracrine mechanisms of overexpression of both EGFR and its ligands, providing multiple advantages to tumors through the promotion of cell proliferation, survival, angiogenesis, invasion and metastasis. Most studies that have analyzed EGFR protein in HNSCC patients, used immunohistochemistry (IHC) methodologies on paraffin-embedded tumor samples, and described EGFR overexpression in 43 to 100% of cases (Table 1). These discrepancies between EGFR overexpression rates might be the result of the type of antibodies or fixative used, differences in IHC technique, and storage time of samples. Nevertheless, the biological role of EGFR overexpression in HNSCC is unquestionably significant. Interestingly, a recent meta-analysis evaluated EGFR expression as a prognostic factor in HNSCC [47]. This meta-analysis included 37 studies and found that overall, EGFR overexpression was associated with reduced overall survival (OS) hazard ratio (HR) of 1.694, 95% confidence interval (CI): 1.432–2.004) [47].
A majority of carcinomas express EGF-like growth factors that, contribute to increased signaling mediated by EGFR activation [45, 48]. A decade ago, the co-expression of EGFR and its ligands in the tumor microenvironment was hypothesized to have an important role in carcinogenesis and progression in patients with HNSCC [49]. Recently, The Cancer Genome Atlas (TCGA) offered a comprehensive and extensive landscape of somatic genomic alterations in HNSCC patients, including mRNA expression levels of the ErbB family ligands (supplementary Table 1). In total, HRG, NRG4 and NGR1 mRNA levels, were upregulated in 15, 7 and 6% of cases, respectively, while EGF, AREG and EREG mRNA levels were upregulated in 4% of cases [24].

The TNF gene family, although it typically has low mRNA expression levels (2%) [24], is implicated with autocrine neoplastic transformation and increased proliferation in HNSCC cell lines [50]. In the clinical setting, patients with upregulated TNF mRNA expression had an overall survival estimate of 12.98 months compared to patients with normal TNF expression (21.85 months) (supplementary Table 1). Amphiregulin (AREG) overexpression is associated with an increased risk of developing breast cancer [51], lung, colorectal, ovarian and prostate carcinomas [52]. AREG overexpression was detected in 4% (12/279) of HNSCC patients and associated with a mean overall survival of 28.29 months compared to 21.75 months for patients with normal expression (supplementary Table 1). Heparin binding-EGF (HB-EGF) is an EGF mainly produced by monocytes and macrophages. Some studies have associated HB-EGF expression with the development of malignant phenotypes including a metastatic mechanism that displays aggressive tumor behavior [53, 54]. HB-EGF is upregulated in human breast carcinomas, ovarian, gastric, melanoma and glioblastoma tumor cell lines [55-57]. In HNSCC, HB-EGF expression is altered in 4% (11/279) of cases (supplementary Table 1).

2.1.2. EGFR Amplification

Gene amplification of the EGFR has been observed in distinct tumors, including gliomas, colorectal, esophageal, breast and pancreatic cancers [58-64]. Several studies have detected increased EGFR copy number in HNSCC patients ranging from 7.8 to 58% (Table 1). The most comprehensive study was performed by the TCGA and reported a frequency of 11% of EGFR gene amplification, which induced EGFR overexpression, therefore demonstrating its pathogenic effect [24]. In addition, the authors showed EGFR gene amplification was associated with worse patient outcomes, with overall survival of 17.15 months in EGFR amplified cases versus 26.41 months in patients without gene amplification [24].

2.1.3. EGFR Mutation

The majority of the EGFR somatic mutations identified in tumors are concentrated in the extracellular and intracellular tyrosine kinase domains, clustered in specific areas, which assumes the role of mutational hot spots. Initial studies in lung cancer showed the importance of mutations involving exons 18, 19, 20 and 21, which encode a portion of
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The EGFR tyrosine kinases domains [65]. These mutations predict patient responses to anti-EGFR drugs, such as erlotinib and gefitinib, and are assessed on a routine basis [65].

In HNSCC, the data available is more limited. Despite a disparity of published research, a low frequency of EGFR somatic mutations has also been reported in these tumors (Table 1). Nagalakshmi et al., using SSCP followed by sequencing, observed a mutation frequency of 81.4% in cases. In contrast, other studies and more recently, the TCGA consortium, showed that EGFR mutations are rare events, present in less than 10% of cases (Table 1, Supplementary Table 2) [24, 66, 67]. The lack of EGFR somatic mutations in available HNSCC cell lines reinforce the absence of this event in HNSCC tumorigenic process [68].

One mutation in HNSCC that has gained particular attention is the EGFRvIII, which is located in the extracellular domain [69]. The EGFRvIII is described by an in-frame deletion of 267 amino acids in the extracellular domain, resulting in the loss of exons 2 to 7. The instability in the extracellular domain of EGFRvIII results in significant functional changes in the EGFR and acquires constitutive tyrosine kinase activity [70]. This mutation was first detected in glioblastomas, and later studies reported its presence and importance in HNSCC (Table 1). The first studies used immunohistochemistry and reverse transcription-PCR, and

<table>
<thead>
<tr>
<th>Author</th>
<th>Date</th>
<th>Expression % (N)</th>
<th>Methods</th>
<th>Amplification % (N)</th>
<th>Methods</th>
<th>TK Domain Mutations % (N)</th>
<th>Methods</th>
<th>Other Mutations (EGFRvIII) % (N)</th>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chung et al.</td>
<td>2006</td>
<td>-</td>
<td>-</td>
<td>58% (49/86)</td>
<td>FISH</td>
<td>-</td>
<td>-</td>
<td>42% (14/33)/ 21% (7/33)</td>
<td>IHC/RT-PCR</td>
</tr>
<tr>
<td>Sok. J.C. et al.</td>
<td>2006</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>Payne, C. et al.</td>
<td>2006</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8% (2/24)</td>
<td>HRMAA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sheik Ali. et al.</td>
<td>2008</td>
<td>32% (21/65)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>0% (0/91)</td>
<td>Sanger</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Al-Swiahb et al.</td>
<td>2010</td>
<td>83.63% (195/220)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hong A. et al.</td>
<td>2010</td>
<td>87% (216/249)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>Numico G. et al.</td>
<td>2010</td>
<td>35% (43/122)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Young R.J. et al.</td>
<td>2011</td>
<td>87% (81/93)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>20% (41/204)</td>
<td>FISH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nakata Y. et al.</td>
<td>2011</td>
<td>82% (73/99)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>36% (32/89)</td>
<td>FISH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pectasides E. et al.</td>
<td>2011</td>
<td>50% (32/64)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>17% (11/64)</td>
<td>FISH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chau. N.G. et al.</td>
<td>2011</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>42% (22/53)</td>
<td>RT-PCR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Huang S.F. et al.</td>
<td>2012</td>
<td>46.88% (75/160)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sweeney. L. et al.</td>
<td>2012</td>
<td>56% (28/50)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Smilek. P. et al.</td>
<td>2012</td>
<td>-</td>
<td>-</td>
<td>20.7% (6/29)</td>
<td>RT-PCR</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Maiti G. P. et al.</td>
<td>2013</td>
<td>84% (37/44)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>26.4% (47/178)</td>
<td>DPCR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rossle M. et al.</td>
<td>2013</td>
<td>100% (119)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>7.8% (9/115)</td>
<td>FISH</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chang J. Y. et al.</td>
<td>2013</td>
<td>63.9% (69/108)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gröbe A. et al.</td>
<td>2014</td>
<td>95% (196/206)</td>
<td>IHC</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Nagalakshmi K. et al.</td>
<td>2014</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>81.39% (104/129)</td>
<td>SSCP/ Sanger</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Melchers. L.J. et al.</td>
<td>2014</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>8% (42/531)/ 0% (0/97)</td>
<td>IHC/RT-PCR</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TCGA</td>
<td>2015</td>
<td>47% (17/279)</td>
<td>RNA Seq.</td>
<td>11% (31/279)</td>
<td>DNA Seq.</td>
<td>4.65% (13/279)</td>
<td>DNA seq.</td>
<td>0.35% (1/279)</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Khattri. A. et al.</td>
<td>2015</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.38% (2/540)</td>
<td>RT-PCR</td>
</tr>
</tbody>
</table>

IHC: Immunohistochemistry; FISH: Fluorescence in situ hybridization; DPCR: differential polymerase chain reaction; RT-PCR: Reverse transcription polymerase chain reaction; HRMAA: High-resolution melting amplicon analysis; SSCP: single-strand chain polymorph; RNA Seq: RNA Sequencing.
Table 2. Anti-EGFR Agents and Multi-Target Action. Recent Clinical Trials for HNSCC

<table>
<thead>
<tr>
<th>Anti-EGFR Agent</th>
<th>Manufacturer</th>
<th>Target</th>
<th>Patent Number</th>
<th>Phase</th>
<th>Clinical Trial Number</th>
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<tbody>
<tr>
<td><strong>Monoclonal Antibodies</strong></td>
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<tr>
<td>Cetuximab</td>
<td>Bristol-Myers Squibb</td>
<td>EGFR</td>
<td>US20040170632 A1</td>
<td>Approval</td>
<td>n.a</td>
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<tr>
<td>Panitumumab</td>
<td>Amgen Oncology</td>
<td>EGFR</td>
<td>WO2013181572 A2</td>
<td>Approval</td>
<td>n.a</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>CIMYM Bioscience</td>
<td>EGFR</td>
<td>--</td>
<td>II and III</td>
<td>NCT01425736, NCT00910117, NCT00702481</td>
</tr>
<tr>
<td>Zalutumumab</td>
<td>Genmab</td>
<td>EGFR</td>
<td>--</td>
<td>III</td>
<td>NCT00496652</td>
</tr>
<tr>
<td>MEHD7945A</td>
<td>Roche</td>
<td>EGFR, HER3</td>
<td>US20130259867 A1</td>
<td>I and II</td>
<td>NCT01577173</td>
</tr>
<tr>
<td>RO5083945</td>
<td>Roche</td>
<td>EGFR</td>
<td>--</td>
<td>I</td>
<td>NCT01046266</td>
</tr>
<tr>
<td>Sym004</td>
<td>Merck KGaA</td>
<td>EGFR</td>
<td>US7887805 B2</td>
<td>II</td>
<td>NCT01417936</td>
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<tr>
<td><strong>Reversible Tyrosine Kinase Inhibitors</strong></td>
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<tr>
<td>Erlotinib</td>
<td>Osi Pharms Inc.</td>
<td>EGFR</td>
<td>RE41065</td>
<td>III</td>
<td>NCT00442455</td>
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<tr>
<td>Lapatinib</td>
<td>GlaxoSmithKline Inc.</td>
<td>EGFR, HER2 and HER4</td>
<td>US8513262 B2</td>
<td>II, II</td>
<td>NCT01417936</td>
</tr>
<tr>
<td><strong>Irreversible Tyrosine Kinase Inhibitors</strong></td>
<td></td>
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<tr>
<td>Afatinib</td>
<td>Boehringer Ingelheim, Inc.</td>
<td>EGFR, EGFR&lt;sub&gt;L858R, E746_A750, L858R/T790M&lt;/sub&gt; and HER2</td>
<td>WO2013052157A1</td>
<td>II, II, III</td>
<td>NCT01538381, NCT01721525, NCT01345682</td>
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<tr>
<td>AST-1306</td>
<td>Alist Pharmaceuticals Inc.</td>
<td>EGFR, EGFR&lt;sup&gt;T790M/L858R&lt;/sup&gt; HER2 and HER4</td>
<td>US 20080300248 A1</td>
<td>II</td>
<td>ChiCTR-ONC-10000893</td>
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<tr>
<td>AZD9291</td>
<td>AstraZeneca, Inc.</td>
<td>EGFR&lt;sup&gt;WT, L858R/T790M&lt;/sup&gt;</td>
<td>WO 2013014448</td>
<td>n.a</td>
<td>n.a</td>
</tr>
<tr>
<td>CNX-2006</td>
<td>Clovis Oncology, Inc.</td>
<td>EGFR&lt;sub&gt;L858R, L858R/T790M&lt;/sub&gt;</td>
<td>WO2013014448</td>
<td>n.a</td>
<td>n.a</td>
</tr>
<tr>
<td>CO-1686</td>
<td>Clovis Oncology, Inc.</td>
<td>EGFR&lt;sup&gt;WT, L858R/T790M&lt;/sup&gt;</td>
<td>-</td>
<td>-</td>
<td>n.a</td>
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<tr>
<td>CUDC-101</td>
<td>Curis, Inc.</td>
<td>EGFR, HER2 and HDAC</td>
<td>US7547781 B2</td>
<td>I</td>
<td>NCT01384799</td>
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<tr>
<td>Dacomitinib</td>
<td>Pfizer Inc.</td>
<td>EGFR, HER2 and HER4</td>
<td>CN 103288758 A</td>
<td>II</td>
<td>NCT01737008</td>
</tr>
<tr>
<td>Icotinib</td>
<td>Zhejiang Beta Pharma Inc.</td>
<td>EGFR, EGFR&lt;sub&gt;L858R, L858R/Q, T790M&lt;/sub&gt;</td>
<td>US20110182882 A1</td>
<td>II</td>
<td>NCT02328261</td>
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<td>Pelitinib</td>
<td>Wyeth Inc.</td>
<td>EGFR, HER2, Src, MEK/ERK, Raf, c-Met, CDK4</td>
<td>CN 103275002 A</td>
<td>I</td>
<td>NCT00098501</td>
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<td><strong>Other Inhibition Approaches</strong></td>
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<tr>
<td>EGFR Antisense</td>
<td></td>
<td>EGFR</td>
<td>-</td>
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n.a: not available.

detected EGFRvIII in approximately 40% of cases. In vitro studies were also performed, suggesting a biological role in HNSCC tumorigenesis and (cetuximab) therapy response [71]. The presence of EGFRvIII in HNSCC was also reported by other authors in frequencies varying from 8-42% (Table 1). However, more recent studies (including the TCGA consortium) performed using more accurate methodologies do not confirm these findings and report an absence or very low frequency of EGFRvIII in HNSCC (Table 1) [72-74].

2.1.4. Protein Nuclear Translocation

The first discovery of nuclear translocation was observed in hepatocyte regeneration studies in the last decade [75]. Additionally, EGFR internalization and nuclear translocation has been demonstrated in different healthy tissue types such as the uterus of pregnant mice and mouse embryos [76]. The classic EGFR translocation mechanism occurs in proteins containing nuclear localization sequences (NLS) that interact with importin α/β protein, which mediates interactions with...
the nuclear pore complex (NPC) [77]. Subsequently, EGFR nuclear localization is correlated with increased cellular proliferation, supporting the role of EGFR as a transcription factor of cyclin D1 genes [78] that mediate synthesis of proliferating cell nuclear antigen (PCNA), which is a DNA polymerase delta cofactor [79]. Over the last decade, several studies have suggested that, nuclear expression of EGFR may be an important molecular determinant of resistance to cetuximab therapy [80]. Specifically, EGFR nuclear translocation was evaluated in a cetuximab-resistant cell line that demonstrated increased nuclear localization of EGFR, mediated by the Yes and Lyn proteins which belong to Src family kinase family [81]. Furthermore, a non-invasive methodology to monitor the response to EGFR-inhibitor treatment has been tested in mice with HNSCC xenografts using [64] Cucetuximab-F(ab')2, an EGFR-directed PET tracer [82] or (111) In-cetuximab-F(ab')(2) [83]. An experimental approach observed that EGFR nuclear translocation is associated with DNA-PKcs in DNA repair after exposure to cisplatin or ionizing radiation (IR), and is required for the repair of DNA damage [84]. The role of EGFR traffic has been associated with HNSCC resistance to multimodal therapy. The use of radiolabeled EGFR-inhibitors may be an efficient tool to monitor clinical response [85].

3. EGFR INHIBITORS

Due to the central role of EGFR in several tumors, the scientific community and pharmaceutical companies designed agents that could specifically inhibit EGFR. Two major strategies were developed: monoclonal antibodies (mAbs) and small molecule tyrosine kinase inhibitors (TKIs).

3.1. Monoclonal Antibodies

Cetuximab (Erbitux®, Bristol-Myers Squibb; New York, NY.) is a chimeric human-murine monoclonal antibody that binds competitively to EGFR. Cetuximab is 152 kDa, made up of four polypeptide chains: two heavy (lambda) chains (449 amino acids) and two light (kappa) chains (214 amino acids). Both chains contain one and two consensus sequences for N-linked glycosylation [86]. Cetuximab prevents stimulation by EGF and TNF-α endogenous ligands, disrupting intracellular signaling [87]. Blocking this receptor reduces proliferation, metastasis, angiogenesis and increases apoptosis levels [88]. In February 12, 2004, the Food and Drug Administration (FDA) approved cetuximab in combination with irinotecan, for the treatment of metastatic colorectal carcinoma in patients refractory to irinotecan-based chemotherapy [89]. In 2006, cetuximab was approved by the FDA [90] for the treatment of LAHNSC and is so far the only anti-EGFR agent for its treatment in combination with radiation and chemotherapy, or as a monotherapy for recurrent, metastatic HNSCC that is unresponsive to platinum-based chemotherapy [36].

In the Phase III EXTREME trial, patients with recurrent or metastatic HNSCC were treated with a chemo/cetuximab combination had prolonged overall survival rates compared with patients treated with chemotherapy alone (median 10.1 versus 7.4 months, HR for death 0.80, 95% CI 0.64 to 0.99) [91]. However, in Eastern Cooperative Oncology Group Study phase III, patients with metastatic or recurrent HNSCC were randomized to cisplatin plus placebo or cisplatin plus cetuximab. Progression-free survival (PFS) and overall survival (OS) were not significantly improved [92].

Panitumimab (Vectibix®, Amgen, Thousand Oaks, CA, USA) is anti-EGFR monoclonal antibody that has been evaluated as an adjuvant therapy to traditional chemotherapy (cisplatin and 5-fluorouracil) in HNSCC patients. However, a Phase III study (SPECTRUM trial) did not show improvement in OS in patients with recurrent or metastatic HNSCC, but did show an improvement in PFS and had an acceptable toxicity profile [93]. Another study demonstrated that among patients with a positive HPV status, as assessed by p16 immunohistochemistry, showed increased PFS after treatment with cisplatin and fluorouracil plus panitumumab. Therefore, the authors suggested that p16 status might be important considerations in future trials with HNSCC patients [93].

Currently, clinical trials are using the combination of panitumumab in combination with other chemotherapeutic agents. At present, the benefit of combined panitumumab and paclitaxel therapy as a first-line treatment is being conducted in HNSCC patients (NCT01264328).

Nimotuzumab (TheraCIM, CIMYM Bioscience, Ontario, Canada) is another type of humanized chimeric monoclonal antibody. It binds to different epitopes in domain III of the extracellular region of EGFR. Several Phase I, II and III trials have been conducted in patients with HNSCC (NCT01425736, NCT00910117 and NCT00702481). A recent phase II pharmacodynamic trial of nimotuzumab was conducted in 10 unresectable HNSCC patients and demonstrated positive results, and also there was no evidence of skin rashes during 8 weeks of treatment [94]. An advanced approach is being carried to evaluate the association of nimotuzumab in combination with DCF (docetaxel, cisplatin and 5-fluorouracil) in recurrent or metastatic HNSCC (NCT01425736) [95]. An ongoing Phase II trial (NCT00702481) intends to define the response and toxicities associated with the addition of nimotuzumab to chemoradiation based on cisplatin for LAHNSC. Additionally, Nixontumab plus radiotherapy combination therapy was conducted in 106 advanced HNSCC patients, and showed a significant survival improvement for nimotuzumab treated patients [96].

Zalutumumab (Genmab; Copenhagen, Denmark) is an anti-EGFR mAb entirely humanized with high-affinity to EGFR. Twenty eight patients with metastatic/recurrent HNSCC were treated with zalutumumab and showed a response rate of only 7.1% and the most frequently adverse effects (AEs) reported in Phase I/II studies were infusion-related reactions, rash/acne, and dyspnea [97]. Furthermore, 286 HNSCC patients resistant to platinum-based chemotherapy showed a significant improvement in PPS (p = 0.0012) when treated with zalutumumab, and a trend in improved OS (6.7 months vs. 5.2 months in zalutumab vs. control groups, respectively; HR, 0.77; 95% CI, 0.57-1.05; P = 0.0648) [98]. Zalutumumab has also failed to show increased loco-regional control and 3-year disease specific or overall survival in another randomized phase III study (NCT00496652). This study was conducted by the Danish Head and Neck Cancer
Consortium (DAHANCA) and aimed to evaluate if concurrent treatment with zalutumumab during RT improved outcomes in patients with HNSCC.

MEHD7945A (Roche, Genentech, South San Francisco, CA), is a mAb against EGFR and HER3 that inhibits the binding of specific ligands dependent on EGFR- and HER3-mediated downstream signaling [99]. This monoclonal antibody has modulated radiation responses in lung and head and HNSCC. Preclinical studies have demonstrated that MEHD7945A in combination with radiation is more cytotoxic in comparison to individual anti-EGFR or anti-HER3 antibodies using xenograft models. The dual EGFR/HER3 targeting action of MEHD7945A merits further investigation and clinical trial evaluation [100].

RO5083945 (Roche, Genentech, South San Francisco, CA) is a glyco-engineered anti-EGFR IgG1 mAb with a high affinity for all CγRIIIa variants. An antibody-dependent cellular cytotoxicity assay (ADCC) showed increased activity of RO5083945 compared to cetuximab and panitumumab. Preclinical approaches provided steps for the clinical trial recruitment. The pharmacodynamics investigation has been conducted in patients with KRAS mutated tumors in an open label multicenter in patients with operable HNSCC (Data not published; NCT01046266).

Sym004 (MerckKGaA) is a novel combination between 992 and 1024 antibodies, directed against different non-overlapping epitopes in the extracellular domain of EGFR, with a superior anticancer efficacy compared with existing mAbs. Additionally, the antibody mixture showed a potent inhibition of cell growth, efficient inhibition of ligand binding and also the internalization and degradation of EGFR [101]. More recently, the efficacy and tolerability of Sym004, was investigated in recurrent and/or metastatic HNSCC patients (NCT01417936). The results showed moderate anti-tumor activity of Sym004 in patients (reduced disease progression at 6 months in 12% of patients). In addition, the safety profile of the Sym004 was comparable to other anti-EGFR mAbs [102]. For this reason, Sym004 represents a promise in treatment of HNSCC patients, mainly those that are cetuximab-refractory.

3.2. Tyrosine Kinase Inhibitors -TKIs

TKIs are small molecules that can bind directly into the adenosine triphosphate (ATP) of the tyrosine kinase domain (TKD), thus inhibiting the intracellular signaling pathways [103]. Currently, there are a variety of multi-targeted small molecule tyrosine kinase inhibitors under investigation in Phase II and III trials in different HNSCC therapeutic settings with the potential to significantly modify the approach to anti-EGFR therapy for HNSCC.

The first TKI approved by the FDA was gefitinib (Iressa®, AstraZeneca, Inc.) for use in non-small-cell lung cancer (NSCLC) [104]. A Phase II study showed a tolerable cytotoxic action rate and a response to neoadjuvant treatment in 18% of 22 HNSCC patients [105]. Furthermore, the response rate (RR) was 10.6%, median OS was 8.1 months, and 1-year OS rate was 29.2% in HNSCC patients (n = 52) with metastatic or recurrent disease and tolerable levels of AEs were reported [106].

Erlotinib (Genentech; South San Francisco, CA), also known as Tarceva®, is a TKI FDA-approved as a first-line treatment for NSCLC for patients with exon 19 deletions or exon 21 (L858R) EGFR mutations [107]. A Phase II study conducted recently with 21 HNSCC patients, showed an increase of 63% in overall survival and few adverse events, after treatment with erlotinib, cisplatin and radiotherapy [108]. In recent years, these clinical studies have supported use of erlotinib with other chemotherapeutic agents by displaying an improvement in overall survival and acceptable levels of toxicity [109-111]. The effect of erlotinib mono-therapy in combination with radiotherapy has been proposed as a Phase I/II trial (NCT00442455). So far, there is no published data on cytotoxicity and clinical effects of this combination. Everolimus, an inhibitor of mammalian target of rapamycin (mTOR), was combined with erlotinib in a clinical trial of patients with metastatic platinum-resistant HNSCC. This approach was based on the frequent activation of the mTOR pathway in HNSCC. Unfortunately, the trial showed little benefit, with a modest influence on immunosuppression and tumor growth [112]. Currently, a Phase II clinical trial is being conducted to evaluate the effect of docetaxel and cisplatin combination with or without erlotinib, and is currently recruiting participants (NCT01064479).

Lapatinib (GlaxoSmithKline Inc.) also known as Tykerb® is a reversible TKI with high affinity for the EGFR and HER2 receptor. Recently, this chemotherapy received FDA approval in combination with letrozole for patients with estrogen receptor and HER2, and in combination with capecitabine (Xeloda®) for patients with advanced breast cancer [113]. Few studies have evaluated lapatinib alone or in combination, which may be explained by the low rate of HER2 receptor expression in HNSCC tumors [114]. However, there is evidence that the use of lapatinib prolongs tumor stabilization of salivary glands tumors at approximately 6 months (36% - 62 patients) [115] and that combination with chemoradiotherapy increased the 6 month complete response rate post-chemoradiotherapy [116]. Currently, there is one Phase II trial (NCT00901492) using the combination of lapatinib with capecitabine. Study objective include the evaluation of OS, PFS response rate, toxicity and quality of life. The THY-HARD (NCT01711658) Phase II trial is recruiting HNSCC patients and evaluating the additive effects of radiotherapy plus cisplatin with or without lapatinib. Although lapatinib was initially considered a promising drug to treat HNSCC, a study testing adjuvant lapatinib in high-risk HNSCC after surgery was terminated early by the sponsor when outcomes between the placebo and lapatinib arms were not observed to be different (data not published; NCT00424255).

4. RECENT PATENTS (NEW GENERATION OF TKIs)

A variety of TKIs have been developed in recent years, and many of them tested in pre-clinical studies that show promising results against various tumor types. However, use is not approved for clinical use yet. Our review draws attention to promising chemotherapeutic agents in the treatment of HNSCC.

CUDC-101 (Curis, Inc.) 7-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yl)-N-hydroxyheptanamide is a recently discovered reversible TKI that has multiple molecu-
lar targets (EGFR, HER2 and HDAC). A preclinical trial demonstrated increased anti-proliferative activity of CUDC-101 in HNSCC cell lines, when compared to exposure with erlotinib, lapatinib or vorinostat combination [117]. Recently, a Phase I trial, was conducted in twenty-five patients with advanced solid tumors who received incremental doses of CUDC-101. Preliminary evidence of antitumor activity was demonstrated with good tolerance levels [118]. Additionally, a Phase I trial was conducted in HNSCC to investigate the safety and pharmacokinetics of CUDC-101 in combination with cisplatin and radiation (data not published) (NCT01384799).

Icotinib (Zhejiang Beta Pharma Inc.)[1,4,7,10] tetraoxacyclodeceno[2,3-g]quinazolin-4-amine, \( N-(3\text{-ethynlyphenyl})-7,8,10,11,13,14\text{-hexahydro targets wild type and mutated EGFR variants (L858R, L861Q, T790M). The in vitro approach showed an increased anti-proliferative effect in A431 cell lines, while in vivo studies, an antitumor effect was observed in nude mice of human tumor-derived xenografts [119]. Icotinib clinical trials, conducted in patients with advanced NSCLC, showed positive clinical antitumor activities and acceptable toxicity in monotherapy or in combination [120, 121]. Although there are several clinical trials in other solid tumors such as NSCLC, esophageal and pancreatic cancers, there is only one Phase II clinical trial that is active but not recruiting patients with advanced nasopharyngeal carcinoma to evaluate the icotinib efficacy as a monotherapy (NCT02328261).

Irreversible TKIs covalently bind to a phosphorylation-specific site in the intramembrane portion of their target, blocking the phosphorylation and subsequent activation of intracellular pathways. This class of molecules is known as the second-generation irreversible tyrosine kinase inhibitor and some irreversible TKIs are in advanced stages of clinical and preclinical testing approaches.

Afatinib (Gilotrif®, Boehringer Ingelheim, Inc.)((E)-N-[4-(3-chloro-4-fluorophenyl)-7-(3S)-oxolan-3-yl]oxyquinazolin-6-yl]-4-(dimethylamino)but-2-enamide (Fig. 2B), also known as Allitinib,® is a potent anti-EGFR with irreversible action. In addition, it has an affinity for other EGFR family member proteins (HER2 and HER4) and exhibits significant antineoplastic activity in vitro and in vivo [125]. A recent clinical trial conducted in patients with solid tumors showed a preliminary anti-tumor effect and stable disease for \( \geq 6 \) months in 7 patients (ChiCTR-ONC-10000893). Despite these promising results, AST1306 has not been tested in head and neck cancer patients.

PF-00299804 (Dacomitinib®, Pfizer Inc.) (E)-N-(4-(3-chloro-4-fluorophenylamino)-7-methoxyquinazolin-6-yl)-4-(piperidin-1-yl)but-2-enamide (Fig. 2C) is an irreversible pan-Her inhibitor with cytotoxicity activity in tumor xenograft models that express HER family members, and efficient inhibition in double EGFR (L858R/T790M) mutation [126]. Recently, a phase II trial showed positive results in metastatic HNSCC, in which 57% of patients (36/69) maintained stable disease and treatment had acceptable toxicity levels (NCT01737008) [127].

EKB-569 (Wyeth Inc.), (E)-N-(4-(3-chloro-4-fluorophenylamino)-3-cyano-7-ethoxyquinolin-6-yl)-4-(dimethylamino)but-2-enamide (Fig. 2D), also known as Pelitinib,® is an irreversible EGFR inhibitor that has shown potential anti-neoplastic effects in solid tumors [128]. Recently, a Phase I trial was conducted to determine the dosing for acceptable toxicity levels and induced therapy responses of EKB-559 [129]. Pre-clinical studies, using squamous cell carcinoma suggest that EKB-569 increases sensitivity to radiotherapy [130]. At present, no clinical trial has been conducted in HNSCC patients.

CWNX-2006, (Clovis Oncology, Inc.) N-[3-[2-[4-[[1-[2-fluoroethyl]azetidin-3-yl]amino]-2-methoxyanilino]-5-(trifluoro methyl)pyrroimidin-4-yl]amino]phenyl]prop-2-enamide (Fig. 2E) is an irreversible EGFR inhibitor that inhibits activating mutations of EGFR with high affinity as well as cells harboring the T790M mutation [131]. Although, in initial stages few studies have been conducted with CWNX-2006 in HNSCC models, we believe that clinical trials will soon follow due to its EGFR inhibitory potential.

AZD9291, (AstraZeneca, Inc.) N-[2-[2-(dimethylamino)ethyl-methylamino]-4-methoxy-5-[4-(1-methylindol-3-yl)-pyrimidine-2-yl]amino]phenyl]prop-2-enamide is a potent irreversible mutant-selective EGFR inhibitor also known as Osimertinib (Fig. 2F). Initially clinical trials with this inhibitor demonstrated a clinical benefit in lung cancer patients with a L858R/T790M EGFR mutation [132]. In November 2015, AZD9291 (Tagrisso™) was approved by the FDA for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC that was resistant to first-generation EGFR TKI therapy [133]. However, our search for this review did not any clinical and preclinical approaches in head and neck cancer. Due to its potent EGFR wild-type inhibi-
tory action [134], AZD9291 may be a promising candidate in head neck cancer therapy.

CO-1686 (Clovis Oncology, Inc.) 2-propenamide, N-[3-[[2-[4-(4-acetylpiperazin-1-yl)-2-methoxyanilino]-5-(trifluoromethyl)pyrimidin-4-yl]amino]phenyl]prop-2-enamide, also known as Rociletinib®, (Fig. 2G) is an irreversible inhibitor of EGFRwt and mutant-selective EGFR. The TIGER, I, II and III trials are recruiting patients with EGFR-mutated, advanced NSCLC after failure of at least one previous EGFR-directed TKI. The most recent clinical studies conducted in NSCLC patients treated with CO-1686 showed a positive tumor response and sustained disease control [135]. Although, CO-1686 has been demonstrating promising results in preclinical models, no clinical trial has been conducted in HNSCC.

Finally, EGFR antisense (EGFR AS) has been used in experimental models to evaluate its ability to inhibit the proliferation of HNSCC cell lines [136]. This approach consists of innoculating EGFR antisense that binds to specific mRNAs to interfere with the endogenous expression of EGFR. EGFR antisense results in a dysfunctional, mature protein, thereby reducing the activity of the ligand-binding domain and the kinase domain [136]. In nude mice xenografts, intratumoral plasmids that were injected with antisense EGFR sequences showed reduced tumor volumes when compared with the control group [137]. Subsequently, intratresional injections of EGFR liposomal antisense gene therapy in normal mice showed tolerable toxicity levels [138]. Based on the results, 17 patients with LAHNSCC were treated with intratumoral EGFR AS injections and a favorable clinical response was observed in (5/17) of patients (29%) [139].

5. PREDICTIVE BIOMARKERS TO ANTI-EGFR THERAPY IN HNSCC

Currently, the only anti-EGFR drug approved for HNSCC is cetuximab/panitumumab. A focus of great interest has been on the identification of predictive biomarkers of clinical response to these drugs [140, 141]. Despite this rationale, a large body of evidence has showed that alteration of EGFR (protein overexpression, gene amplification) were not associated with patient response [141]. Intracellular pathways regulators, particularly, activating mutations of K\textit{RAS} oncogene, were associated with mAbs response [142]. The oncogene K\textit{RAS}, drives signal transduction downstream of transmembrane receptor tyrosine kinases, especially the EGFR receptor. However, K\textit{RAS} mutations result in incessant activation of the intracellular RAS/MAPK/PI3K pathways, resulting in increased cell proliferation and survival, neoplastic transformation, cell migration and metastasis [143]. Hot-spot K\textit{RAS} activating mutations are recognized as strong predictors of resistance to EGFR-mAbs (cetuximab or panitumumab) in metastatic colorectal cancer (MCC) [142, 144, 145]. In the last few decades, some \textit{in vitro} findings have associated the low response rate to mAbs with an overexpression of the PI3K/AKT/mTOR pathway [146]. A seminal retrospective study of MCC showed that K\textit{RAS}, B\textit{RAF}, N\textit{RAS}, and P\textit{IK3CA} exon 20 mutations were significantly associated with a low cetuximab response rate [147].

In HNSCC, no predictive molecular marker of response to anti-EGFR agents is known. K\textit{RAS} mutations are very rare (< 1%), while EGFR mutations represent less than 5% of HNSCCs [24]. Thus, the mutational status of E\textit{GFR} and K\textit{RAS} genes are not useful tools for predicting response to mAbs, due to low frequencies [148]. In HNSCC, other alterations may be associated with patient response, such as ligand levels, which have been associated to a few response rates for EGFR therapies. \textit{In vitro} approaches in HNSCC cell lines, showed that the detection of values > or = 20pmol/L of amphiregulin are associated with increased efficiency of cetuximab and gefitinib, when compared to cell lines that have low amphiregulin expression [149]. These \textit{in vitro} findings were observed in 47 patients with HNSCC in which high expression of amphiregulin demonstrated significantly shortened OS (HR: 2.2, p = 0.002) and PFS (HR 2.2, p = 0.019), compared with patients with low expression scores [150]. Other ligands such as HRG, have shown that signifi-
cantly increased levels of expression in HNSCC patients is preferably associated with HER3 activation and defines a biologically distinct subset of patients, with a positive correlation with cetuximab/cisplatin response [151].

TGF-α overexpression, was implicated in cetuximab resistance in cell lines [152]. Interestingly, the whole expression profile of xenograft models using cetuximab-resistant colorectal cancer cell lines showed that phosphorylated MET was detected in resistant cell lines. The authors associate the increase in MET phosphorylation levels with TGF-α overexpression [152]. Regarding HNSCC, TGF-β overexpression is related to de novo and acquired resistance to EGFR-targeted mAbs, and supply a rationale for TGF-β combination therapies [153].

Another hypothesis suggests that, EGFR nuclear translocation is mediated by the Src kinase family and overexpression of HER ligands (EGF, ARG, HB-EGF) leads to a cetuximab-resistant phenotype [79]. In HNSCC, EGFR nuclear translocation is associated with cetuximab/radiation therapeutic response. In this study, HNSCC cell lines treated with this combination showed elevated levels of nuclear EGFR and consequently a resistance phenotype, while Dasatinib therapy combination can inhibit EGFR translocation and restore cetuximab sensitivity [154].

5. CURRENT & FUTURE DEVELOPMENTS

EGFR inhibitors represent a class of chemotherapeutic agents with promising results in monotherapy or in combination with other anticancer agents. HNSCC tumors frequently exhibit very high expression of EGFR and anti-EGFR, and Cetuximab is the only targeted therapy approved for HNSCC treatment. However, a subgroup of HNSCC patients demonstrate a response to cetuximab monotherapy, although the underlying mechanisms of this response remain ill-defined and there is no biomarker to predict responders.

The studies reported in this review reveal the potential of the newest generation of tyrosine kinase inhibitors, which are mainly being designed for the effective inhibition of the EGFR and other tyrosine kinase receptors simultaneously. Moreover, the development of multi-targeted therapies and irreversible anti-EGFR inhibitors reveals new perspectives in clinical trials and future treatment regimens. Third-generation EGFR inhibitors, include afatinib, and is currently being tested in HNSCC patients. The multi-modality treatment adopted in HNSCC frequently impacts quality of life due to extensive surgeries and toxicities related to intensive chemo-radiation approaches. Targeted therapies are becoming increasingly adopted for the treatment of various tumor types due to their ability to adopt efficient and selective mechanisms of action, which limits cytotoxicity when compared to conventional chemotherapeutic agents. Thus, the evaluation of new generation tyrosine kinase inhibitors in clinical trials, which includes HNSCC patients, and the search for molecular markers that predict sensitivity to these drugs, are of great importance to successfully improve the treatment of these patients.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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