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Review

The challenge of blocking a wider family members of EGFR against head and neck squamous cell carcinomas

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SUMMARY

Head and neck squamous cell carcinoma (HNSCC) represent 95% of head and neck cancer with an incidence of over half a million people globally. The prognosis for patients with recurrent or metastatic HNSCC is generally poor with low 5-year survival rates despite treatment advances over the past few decades. Consequently, it is essential to search for new biomarkers and effective therapy options to optimize HNSCC treatment. Epidermal growth factor receptor (EGFR) is overexpressed in approximately 90% of tumours. EGFR has become one of most common targets for new therapies being investigated in HNSCC. In this way, multiple therapies targeting EGFR in HNSCC have been tested but response rates are still low especially in the recurrent or metastatic setting. This has been attributed to mechanisms of resistance to EGFR-targeted therapies. Afatinib, an oral small molecule ErbB Family Blocker that irreversibly binds to ErbB1 (EGFR), ErbB2 (HER2) and ErbB4 (HER4), is being investigated in HNSCC treatment with encouraging phase II results and several ongoing phase III trials. Results of these trials will help to understand the place of afatinib in the HNSCC treatment armamentarium.

Introduction

Head and neck squamous cell carcinoma (HNSCC), the sixth most common cancer globally, affects 600,000 new patients each year and is associated with high morbidity [1]. The most common sites for HNSCC are the pharynx/larynx, tongue and mouth [2]. Despite new advances in therapy, overall long-term survival remains low and approximately 40–50% of patients with advanced disease die within 5 years [3–7].

HNSCC is categorised into three general stages: early-stage (stage I/II), locally-regionally advanced (stage III/IV) and recurrent/metastatic disease [8]. More than two-thirds of patients present with locoregionally advanced disease, and over the last three decades, multimodal therapy with surgery, radiation therapy and pharmacotherapy has been the standard treatment for these patients [3,8]. Cisplatin-based chemoradiation is the standard of care for the definitive and adjuvant treatment of locoregionally advanced disease [8]. However, these therapies are often aggressive [9] and carry considerable side effects. Many patients (10–30%) with locoregionally advanced HNSCC develop metastasis [10], most commonly in the lungs [11]. Indeed, more than 50% of patients who die from HNSCC have experienced a failure of locoregional control of the tumour as it begins to invade surrounding tissues and eventually metastasises [9]. Approximately 90% of those patients with metastases also have locoregional failure. As such, locoregional control – that is, prevention of tumour growth – is essential in order to improve patient prognosis [9].

Treatment options for recurrent/metastatic HNSCC patients are limited, and palliative platinum-based chemotherapy is the standard of care [8] in conjunction with best supportive care. The choice of a systemic regimen depends on the patientś prior treatment and whether the patient has previously received systemic therapy for metastatic or incurable locoregional disease. High number of chemotherapeutic agents are used, [8] including platinum compounds (cisplatin, carboplatin) [12], taxanes (docetaxel, paclitaxel) [13]; methotrexate [13,14] and 5-fluorouracil [15]. Platinum-based combination regimens do appear to have improved the objective response rate compared with single-agent chemotherapy in these patients, although no improvement in overall survival has been demonstrated. For those patients who do not respond or progress during palliative treatment there is no effective alternative chemotherapy [8].

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HNSCC genetic profile, biomarkers and targets for new drugs

Molecular research on HNSCC is focused on identifying the genetic profile of primary tumours with the highest probability of metastasis. However, similar aberrations were identified in both primary tumours and lymph-node metastases: 3q (90%), 8q (65%), 1q (50%), 5p (43%), 2q (41%) and 11q (41%) and deletions 3p (57%), 1p (5%), 4p (48%), 13q (48%), 11q (41%) and 10q (37%) (Table 1). Unfortunately, no combination of chromosomal aberrations was associated with metastatic progression in HNSCC [16].

Multiple biomarkers have been described in HNSCC based on protein expression level [4]. Bcl-2 expression is related to outcome following chemoradiation in HNSCC [17]. Interestingly, Ki-67 expression was associated with radiosensitivity in glottic cancer, while in laryngeal HNSCC, Ki-67 expression has been shown to correlate with advanced stage and neoplasm progression [18,19].

Genome-wide sequencing and copy number analysis have clarified commonly mutated genes in HNSCC [20–22]. Some have higher therapeutic potential, such as epidermal growth factor receptor (*EGFR*), fibroblast growth factor receptor (*FGFR*), hepatocyte growth factor receptor (*c-MET*), cyclin D1 (*CCND1*) or phosphoinositide 3-kinase (PI3K) [23]. EGFR overexpression has been observed in approximately 90% of HNSCC tumours [24], and this overexpression is associated with poor prognosis and resistance to chemotherapy and radiation therapy [7,25]. Mechanisms that may contribute to the increased levels of EGFR observed include dysregulated p53 [26] and EGFR amplification [27]. Otherwise, EGFR expression analysis by immunohistochemistry has not been applied in clinical practice. Therefore, presence of mutations and detection of polymorphisms in *EGFR* is more extended [28].

FGFR synthesises for a transmembrane tyrosine kinase receptor and triggers signalling pathways including MAPK, PI3K, p38, JNK or STAT [23]. In lung squamous cell carcinoma which has similar molecular characteristics to HNSCC, amplification of variant 1 of *FGFR* (*FGFR1*) and *c-MYC* confers susceptibility to FGFR inhibitors [29]. Some studies concerning HNSCC showed decreased cell proliferation and invasion using inhibitors of FGFR1 [30,31].

Hepatocyte growth factor receptor (c-MET) is a tyrosine kinase receptor associated in cancer with high migration, invasion and angiogenesis ratios [32]. Gene amplification and mutation on *c-MET* is infrequent [33]; however, c-MET is overexpressed in around 80% of HNSCCs [34]. Furthermore, mutations on *c-MET* were associated with lower development of distant metastasis in patients treated with chemoradiotherapy [35].

Cyclin D1 encoded by *CCND1* is present in multiple neoplasms. It has been reported that *CCND1* amplification and overexpression are associated with poor prognosis, cisplatin resistance, EGFR-inhibitor resistance [36,37] and nodal metastasis [38].

Lui et al. showed that mutations on a catalytic subunit of *PI3K* (*PI3KCA*) sensitise tumours to an mTOR/PI3K inhibitor, and thus may serve as predictive biomarkers for treatment selection [39].

New discoveries involving tumour suppressor genes appear to provide an opportunity for target therapies. *TP53* is the most commonly mutated gene and is amplified in 5% of HNSCC cases [20,21]. The primary mutations of *TP53* are missense mutations or nonsense mutations that create a stop codon resulting in a truncated protein and leading to a loss of function [40]. In HNSCC, only *TP53* nonsense mutations that produced a truncated protein were statistically significant as prognostic factors [41]. Other *TP53* mutations were not associated with poor outcome [42].

In HNSCC, *NOTCH1* is considered to be a tumour suppressor gene because of the lack of mutational hotspots and the high proportion of nonsense mutations [20,21]. Mutations on *NOTCH1* appeared in 43% of Chinese HNSCC population and correlated with lymph-node metastasis and poor outcome [43]. Moreover, downstream Notch effectors were overexpressed in 32% of patients with HNSCC [44]. All this indicates the potential therapeutic target of Notch pathway in a subset of HNSCC.

There are other biomarkers based on viral aetiology. This is the case of human papillomavirus (HPV) and Epstein–Barr virus (EBV). The presence of HPV is a prognostic biomarker associated with better outcome in locally advanced oropharyngeal cancers, with a 40–80% reduction in death after treatment [45–48]. It has been reported that HPV infection indirectly produces an increase of $p16^{INK4A}$ expression [49–51]; as a result, $p16^{INK4A}$ is considered a surrogate marker for HPV in oropharyngeal cancers [52–55]. HPV-negative tumours bear more *EGFR* alterations [56] and overexpression of total and phosphorylated EGFR protein [57]. Thus, new anti-EGFR treatments could be of interest in the management of HPV-negative tumours.

DNA fragments from EBV detected by real-time quantitative PCR in cell-free plasma are considered a prognostic biomarker for nasopharyngeal carcinoma. High levels of EBV DNA were associated with advanced disease stage and poor outcome [58–60]. Furthermore, high levels of EBV DNA are a poor prognostic biomaker after radiotherapy, chemoradiotherapy and chemotherapy followed by radiotherapy with or without concurrent chemotherapy [61,62].

Table 1
Genetic aberrations of HNSCC (adapted from Patmore et al. [16]).

Location	Gain/deletion	Percent PT
3q26-27	Gain	78
3p25-pter	Deletion	52
5q34-qter	Deletion	52
1p34.2-pter	Deletion	43
5p15.1-pter	Gain	43
11q13.3-13.5	Gain	39
11q23.3	Deletion	39
12p12.3-13.1	Gain	39
2q31	Gain	39
3q24	Gain	39
8q21.3	Gain	39
8q23	Gain	39
18p11.31-pter	Gain	35
3p14p1-3	Deletion	35
6q12	Gain	35
10q26.1-qter	Deletion	30
13q31	Deletion	30
4p16	Deletion	30
8p22	Deletion	30
1q31	Gain	26
7q31.1-3	Gain	26
12q22	Gain	22
1q21.2	Gain	22
19p13.3-pter	Deletion	17
4q26	Gain	17
4q34	Deletion	17
6q22	Gain	17
5q13	Deletion	13
9p24	Deletion	13
13q22	Gain	9

PT = primary tumour.

Targeted treatments in HNSCC

With the identification of common genetic aberrations and altered signalling pathways in HNSCC, treatment of the disease is evolving with the development of new drugs designed to target crucial receptors and signalling pathways involved in carcinogenesis. The role of EGFR (ErbB1/HER1) and its associated pathways, such as the MAPK pathway (Fig. 1), have been extensively studied in HNSCC. EGFR belongs to the ErbB family of receptor tyrosine kinases, which also includes ErbB2 (HER2 or Neu), ErbB3 (HER3) and ErbB4 (HER4) [5,6]. In general, EGFR-targeted therapies

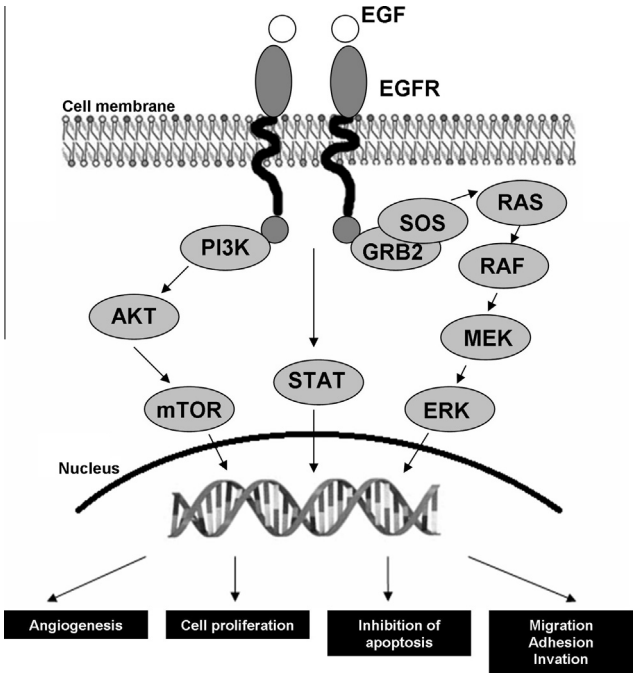

Fig. 1. EGFR signalling pathways. Epidermal growth factor receptor and ErbB family downstream signalling pathways potentially involved in squamous cell carcinomas of the head and neck. Downstream pathways activated by dimerisation and activation of the EGFR.

have been shown to inhibit cellular proliferation, survival, invasion and angiogenesis as well as acting synergistically with chemoradiation therapies [7]. It is postulated that EGFR-targeted agents may achieve this synergistic effect by upregulating cyclin-dependent kinase inhibitors such as p27, resulting in the arrest of the cell cycle in the G_1 phase [63]. EGFR is a 170 kd transmembrane glycoprotein that includes an extracellular ligand-binding domain, transmembrane domain and a tyrosine kinase active site within its intracellular domain [64]. Consequently, there are 2 potential sites for EGFR inhibitors to target. This discovery led to the development of monoclonal antibodies to target the EGFR extracellular ligand-binding domain and tyrosine kinase inhibitors which target the EGFR tyrosine kinase intracellular domain.

Monoclonal antibody inhibitors to treat HNSCC

EGFR-targeted monoclonal antibody therapies have also been investigated for treatment of patients with locoregionally advanced disease. Cetuximab (Erbitux, Merck; Darmstadt, Germany) is now approved for use in combination with radiotherapy in patients with unresectable, locoregionally advanced HNSCC. This approval was based on the phase III study by Bonner et al. in which significant improvement in overall survival was observed for cetuximab plus radiotherapy versus radiotherapy alone [65]. However, one of the main criticisms of the Bonner et al. study was that the standard of care, cisplatin-based chemoradiotherapy, was not included as a comparator arm. Consequently, it is difficult to determine whether cetuximab in combination with radiotherapy is superior in terms of efficacy. Recently, a study in locoregionally advanced HNSCC has concluded that platinum-based chemoradiotherapy is superior to cetuximab, used alone or in combination with chemotherapy [66].

In patients with recurrent/metastatic HNSCC, the use of cetuximab, alone and in combination with platinum-based therapy, has been encouraging, leading to improved outcomes in this patient group [67–69] including in the first-line setting [70,71]. Indeed, as a result of clinical data, cetuximab is currently approved for use (i) in Europe and the United States as a monotherapy in platinum-refractory recurrent disease [68,72,73]; and (ii) in the US combination with platinum (carboplatin or cisplatin) and 5-fluorouracil, as first-line therapy in recurrent/metastatic disease [8,68,71,72].

In HNSCC, several other treatments based on monoclonal antibodies have reached phase III of development, including panitumumab (Vectibix, Amgen; Thousand Oaks, CA, USA), nimotuzumab (YM Biosciences; Ontario, Canada) and zalutumumab (HuMax-EGFr, Genmab, Copenhagen, Denmark) [7]. Panitumumab is a fully human anti-EGFR monoclonal antibody that has recently been shown to extend progression-free survival (but not overall survival) when combined with cisplatin/5-fluouracil in unselected patients with recurrent or metastatic HNSCC (SPECTRUM trial) [74]. In addition, zalutumumab, also a fully human monoclonal antibody, has been shown to significantly improve progression-free survival (but not overall survival) versus best supportive care [75].

Tyrosine kinase inhibitors to treat HNSCC

Tyrosine kinases represent an excellent target for the development of cancer drugs, and consequently, multiple tyrosine kinase inhibitors have now been identified for potential use in HNSCC (Table 2). All the tyrosine kinase inhibitors that are being investigated in HNSCC target EGFR, including gefitinib (Iressa, AstraZeneca; Wilmington, DE) and erlotinib (Tarceva, Genentech; South San Francisco, CA) (Table 2), with some agents also now targeting multiple ErbB family members, including lapatinib (Tykerb, GlaxoSmithKline; Research Triangle Park, NC, USA), afatinib (GIOTRIF/GILOTRIF, Boehringer Ingelheim, Germany) and dacomitinib (Pfizer, Sandwich, Kent, UK). In addition to the newer agents, dacomitinib and afatinib bind to the EGFR tyrosine kinase irreversibly rather than reversibly, as is the case with gefitinib, erlotinib and lapatinib.

Investigation of erlotinib and gefitinib in recurrent or metastatic HNSCC has yielded somewhat disappointing results, with overall response rates of 1.4–10.6% [76–78]. Furthermore, a phase III trial has compared weekly intravenous methotrexate with gefitinib in a heavily pre-treated population [79]. Gefitinib almost doubled the objective response rate versus methotrexate (7.6% versus 3.9%), although no improvement in overall survival was observed [79]. These data are encouraging since objective responses to second-line cytotoxic chemotherapy after failure of first-line chemotherapy are unusual. Furthermore, there is no evidence that second-line treatment prolongs survival. These data suggest that targeted therapies may be a valuable addition to the treatment options in this setting.

Lapatinib has been investigated in a phase II trial in combination with chemoradiation versus chemoradiation alone in locoregionally advanced HNSCC. The study showed an overall response

Table 2
EGFR inhibitors for the treatment of head and neck squamous cell carcinoma.

Agent	Mechanism/target/binding
Panitumumab	Fully human anti-EGFR mAb
Nimotuzumab	Humanised anti-EGFR mAb
Zalutumumab	Fully human anti-EGFR mAb
Gefitinib	Reversible/small-molecule EGFR TKI
Erlotinib	Reversible/small-molecule EGFR TKI
Lapatinib	Reversible/small-molecule EGFR/ErbB2 TKI
Dacomitinib (PF-00299804)	Irreversible/small-molecule pan-HER TKI
Afatinib (BIBW 2992)	Irreversible/small-molecule ErbB family inhibitor

EGFR = epidermal growth factor receptor, TKI = tyrosine kinase inhibitor. mAb = monoclonal antibody.

rate of 53% in the lapatinib arm versus 36% in the placebo arm 6 months after completion of chemoradiotherapy [80]. However, no significant activity of lapatinib has been demonstrated in patients with recurrent or metastatic HNSCC [81].

The irreversible tyrosine kinase inhibitor of EGFR, dacomitinib, has been recently evaluated in a phase II trial in platinum-refractory patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck [82]. The study performed with 48 patients showed stable disease in 31 patients (65%) and disease progression in 6 patients (13%), while 10 patients (20.8%) presented partial response. The median progression-free survival was 3.9 months and overall survival was 6.6 months. These findings may be verified with phase III clinical trials in order to compare dacomitinib with other chemotherapies.

Resistance to EGFR-targeted therapies

A crucial handicap for the newly available EGFR-targeted therapies, including both monoclonal antibodies and tyrosine kinase inhibitors, is resistance [83]. One of the main mechanisms of resistance in HNSCC is the mutant type-III variant of EGFR (EGFRvIII) [83,84]. This variant is characterised by an in-frame deletion of exons 2 through 7 in the extracellular domain of EGFR (Fig. 2A). This avoids the binding of ligands and consequently the activation of the EGFR [83], and thereby it is associated with resistance to EGFR monoclonal antibodies. The prevalence of EGFRvIII in HNSCC is rather controversial. It has been reported that mutation EGFRvIII was found in over 42% of 33 HNSCC tumors in conjunction with wild-type EGFR [84]. In contrast, another study conducted with 638 HNSCC samples showed that mutation is very rare in HNSCC, as only 2 samples (0.31%) were positive for EGFRvIII [85].

Many EGFR mutations have been related to HNSCC [86–92] (Fig. 2B). Some of them have also been involved in resistance to EGFR targeted therapies in HNSCC [93–95] (Fig. 2B). The resistance to EGFR therapies could be different depending on the location of the mutation. For instance, Kobayashi et al. showed that mutation T790M, located in the catalytic region of the ATP-binding pocket, will thus reduce the binding interaction with anti-EGFR tyrosine kinase inhibitors [96].

Multiple other mechanisms of resistance to EGFR monoclonal antibodies and tyrosine kinase inhibitors have been postulated based on preclinical and clinical data [83,97]. In summary, the mechanisms studied include reactivation of proangiogenic factors, dysregulation of EGFR internalisation/degradation, oncogenic shift, epithelial to mesenchymal shift, constitutive activation of EGFR effector molecules and downstream signalling pathways and increased expression of ErbB family growth factors [83,97].

Afatinib as novel effective treatment against HNSCC

Afatinib (BIBW 2992) is an orally administered small molecule that irreversibly blocks ErbB family receptors including EGFR, ErbB2 and ErbB4 [5,6]. It is a new-generation ATP-competitive anilinoquinazoline derivative that carries a reactive acrylamide group [6] (Fig. 3) designed to bind covalently to active ErbB receptor family members including $EGFR^{wt}$, and mutant forms like $EGFR^{L858R}$, $EGFR^{L858R/T790M}$ (Fig. 2B) as well as HER2. When tested in vitro, the IC_{50} values of afatinib to inhibit $EGFR^{wt}$, $EGFR^{L858R}$, $EGFR^{L858R/T790M}$ and HER2 were: 0.5 nM, 0.4 nM, 10 nM and 14 nM, respectively [5]. Since afatinib binds irreversibly to ErbB family receptors, the ATP binding site is permanently blocked and downstream signalling cascades remain inhibited.

In vitro studies have demonstrated that afatinib significantly decreased the proliferation rate in a human hypopharyngeal HNSCC cell line (FaDu) [98,99]. In addition, a dose-dependent antiproliferative effect was observed with irreversible blockade of

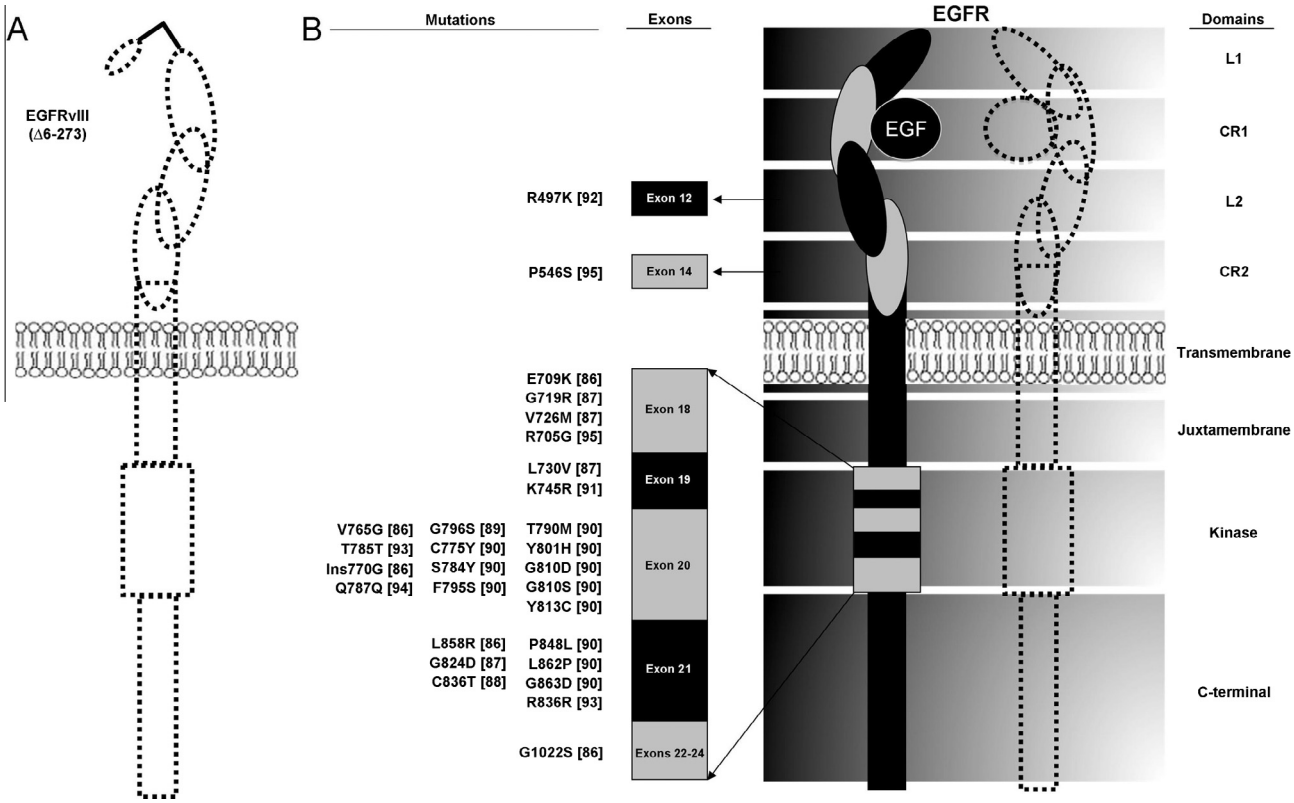

Fig. 2. Diagram of EGFR mutations. (A) Mutant type-III variant of EGFR (EGFRvIII). (B) EGFR domains and mutations involved in HNSCC. L1: Large EGF-binding domain 1; CR1: Cysteine-rich domain 1; L2: Large EGF-binding domain 2; CR2: Cysteine-rich domain 2. Citation number in [square brackets].

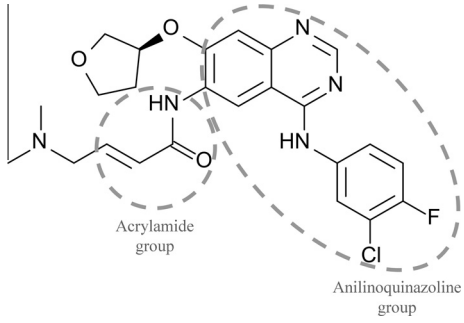

Fig. 3. Afatinib 2D molecular structure. IUPAC nomenclature: N-[4-[(3-Chloro-4-fluorophenyl)amino]-7-[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4(dimethylamino)-2-butenamid.

FaDu cells in the G_0/G_1 phase of the cell cycle [98,99]. Furthermore, incubation with afatinib for 3 days slightly increased cell radiosensitivity in vitro ($p = 0.006$) [99]. In vivo models generated with FaDu cells showed an antiproliferative effect after daily oral administration of afatinib and a significant prolongation of tumour growth delay ($p < 0.0001$) [98,99]. Afatinib has been evaluated in phase I clinical trials where anti-tumour activity was observed in patients with solid tumours [100,101].

Afatinib in clinical trials

As part of the LUX clinical trial programme, afatinib is, or has been, assessed in HNSCC in multiple clinical trials. A phase II trial in which afatinib treatment was compared to cetuximab as a monotherapy in 124 patients with platinum-refractory metastatic/recurrent HNSCC has recently been completed and reported [102,103]. In stage 1, the objective response rate was 16.1% and 6.5% by investigator review ($p = 0.09$) and median progression-free survival was 16 weeks and 15 weeks ($p = 0.93$) for afatinib and cetuximab, respectively [102]. In stage 2, when patients crossed over to the other treatment arm, the disease control rates were 33% (afatinib as second treatment) and 19% (cetuximab as second treatment) [103].

A 19-country phase III trial known as LUX-Head&Neck1 (NCT01345682) has recently been presented in ESMO [104]. The study compared oral treatment with afatinib (322 patients) to intravenous methotrexate (161 patients) with metastatic/recurrent HNSCC patients who have progressed after platinum-based therapy. Afatinib improved progression-free survival (PFS) versus methotrexate treatment (median 1.7 months) statistically significant ($p = 0.03$). Furthermore, secondary endpoints such as disease control rate were higher with afatinib versus methotrexate (49.1% versus 38.5%; $p = 0.035$) and overall response rate (ORR) was 10.2% versus 5.6% ($p = 0.10$). Tumour shrinkage from baseline was observed in 34.8% of afatinib-treated patients compared with 22.4% of methotrexate-treated patients. However, afatinib did not cause a statistically significant improvement in overall survival (OS) in comparison with methotrexate [104].

Other randomised trials assessing afatinib in the treatment of head and neck cancer are ongoing. One clinical trial with a design resembling that of LUX-Head&Neck1, called LUX-Head&Neck3 (NCT01856478), has also recently been initiated. Another phase III trial, LUX-Head&Neck2 (NCT01345669), is a double-blind trial in which afatinib is compared to placebo as adjuvant therapy after chemoradiotherapy in 300 patients with unresected locoregional HNSCC. A fourth trial, which is double-blind and placebo-controlled, is investigating afatinib as a maintenance therapy after post-operative radiochemotherapy, and results are expected in 2016 (NCT01523587).

Discussion and conclusion

Treatments based on the inhibition of aberrant EGFR receptor function have for a time been at the forefront of personalised therapy for various neoplasms including breast, colon, lung, pancreatic and stomach cancer. Multiple targeted drugs and monoclonal antibodies such as cetuximab, panitumumab or trastuzumab are now approved for several uses by health authorities worldwide.

Anti-EGFR drugs have been established as a novel and effective tool to manage HNSCC. Thus, in the era of genomics, the medical community now requires effective biomarkers to predict response to these treatments. Overexpression of EGFR is related to resistance to these drugs [24,25], EGFR overexpression determined by immunohistochemistry is not applied for diagnostic use due to a lack of sensitivity and specificity on available antibodies. Therefore, mutations on *EGFR* have been more accepted in routine clinical practice [28]. With the exception of EGFRvIII, this has recently reported to be very rare finding in HNSCC [85].

Recently, some researchers have defended the notion that HPV is a cause for some carcinomas. While the presence of HPV has been demonstrated in a subset of patients with oropharyngeal cancer [45,105], the role of HPV in other cases of HNSCC has not yet been clearly demonstrated [106,107]. In addition, the methodology that should be used to determine HPV is disputed [23]. Subsequently, p16 (*CDKN2A*) appeared as a surrogate biomarker for HPV status [51] and p16 was validated in a retrospective study (RTOG 0129) [45]. Moreover, p16 was used in the SPECTRUM and EXTREME trials' analyses as a biomarker for HPV [74,108]. However, the cutoff point used in the assignment of positive cases of p16 immunostaining was >10% in the SPECTRUM study versus >70% in the EXTREME study; in addition, p16 determination by immunohistochemistry is still controversial [23]. Furthermore, both studies lacked a representative p16-positive sample size in each treatment arm [74,108]. Accordingly, HPV predictive power of anti-EGFR therapy response is unclear. In the SPECTRUM trial, p16-positive patients presented longer OS, although p16-negative patients improved overall and in terms of PFS after addition of panitumumab [74]. In the EXTREME trial, as in the SPECTRUM trial, p16 and HPV were prognostic markers in HNSCC, but the efficacy of chemotherapy plus cetuximab over chemotherapy alone was independent of p16 or HPV status [108]. Consequently, to elucidate the power of HPV or its surrogate marker p16 to act as biomarkers requires a thorough study.

Moreover, other anti-EGFR therapies based on tyrosine kinase inhibitors have been designed to bind covalently and irreversibly to their targets. Covalent binding is thought to offer greater effectiveness through longer binding time [109]. This is the case of afatinib and dacomitinib. Phase II trials with dacomitinib involving platinum-failed patients with recurrent-metastatic HNSCC showed promising results. Nevertheless, 80% statistical power to obtain $\leqslant$5% of ORR resulted in 78% of stable disease or progression compared to 20.8% presenting partial response [82]. Therefore, these results may be validated in future phase III clinical trials to compare the efficacy of dacomitinib with other chemotherapies.

Afatinib is being investigated for several different types of cancer. Indeed, afatinib is now approved in many countries for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with *EGFR* mutation [110,111]. In HNSCC, afatinib has demonstrated anti-proliferative activity in preclinical studies and encouraging phase II clinical data versus cetuximab. Further evaluation of afatinib in HNSCC as part of a phase III trial has showed not only a significant improvement in PFS but also in tumour shrinkage, higher response rate and increased disease control rate versus methotrexate [104]. Other ongoing trials are eagerly awaited. The results of these trials will help us to understand the place of afatinib in the HNSCC treatment armamentarium.

Conflict of interest statement

None declared.

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