

Head and neck cancer: the role of anti-EGFR agents in the era of immunotherapy

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Abstract: Head and neck cancers (HNC) represent the seventh most frequent cancer worldwide, with squamous cell carcinomas as the most frequent histologic subtype. Standard treatment for early stage diseases is represented by single modality surgery or radiotherapy, whereas in the locally advanced and recurrent or metastatic settings a more aggressive multi-modal approach is needed with locoregional intervention and/or systemic therapies. Epidermal Growth Factor Receptor (EGFR) plays an important role in HNC biology and has been studied extensively in preclinical and clinical settings. In this scenario, anti-EGFR targeted agent cetuximab, introduced in clinical practice a decade ago, represents the only approved targeted therapy to date, while the development of immune-checkpoint inhibitors has recently changed the available treatment options. In this review, we focus on the current role of anti-EGFR therapies in HNCs, underlying available clinical data and mechanisms of resistance, and highlight future perspectives regarding their role in the era of immunotherapy.

Keywords: cetuximab, EGFR, HNC, HNSCC, immunotherapy

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Introduction

Head and neck cancer (HNC) is the seventh most frequent cancer worldwide.¹ HNC arises from oral cavity, pharynx, larynx, sinuses, nasal cavity, and salivary gland, and HNC squamous cell carcinoma (HNSCC) is the major histologic subtype (>90%). Alcohol and tobacco abuse are the two most important risk factors for HNSCC. Human papillomavirus (HPV) infection also plays a role in the development of certain HNCs, particularly those in the oropharynx.² HPV-positive and -negative cancers represent two distinct biologic entities, but these differences have not yet been translated into a different treatment approach in the clinic.³

Unfortunately, the majority of HNSCC patients are diagnosed at later stages. Standard therapies used for treatment of HNSCC achieve only a 40–50% 5-year survival rate in advanced stages.⁴

Early stage disease (stages I and II) is treated with single modality surgery or radiotherapy (RT) with 5-year survival rates of approximately of 90% and 70%, respectively.

In locally advanced (LA) disease, a more aggressive multimodality treatment combining locoregional intervention and systemic treatment using chemotherapy (CT) and/or anti-Epidermal Growth Factor Receptor (EGFR) targeted therapy is required.⁵ The anti-EGFR monoclonal antibody cetuximab (Cx) was introduced into clinical practice about a decade ago when available treatments for HNSCC were still very limited; to date, however, it remains the only targeted therapy approved for this cancer type.

Approximately 12% of HNSCC cases are diagnosed at the metastatic stage. Furthermore, 10–20% of patients treated for early stage HNSCC disease are expected to experience

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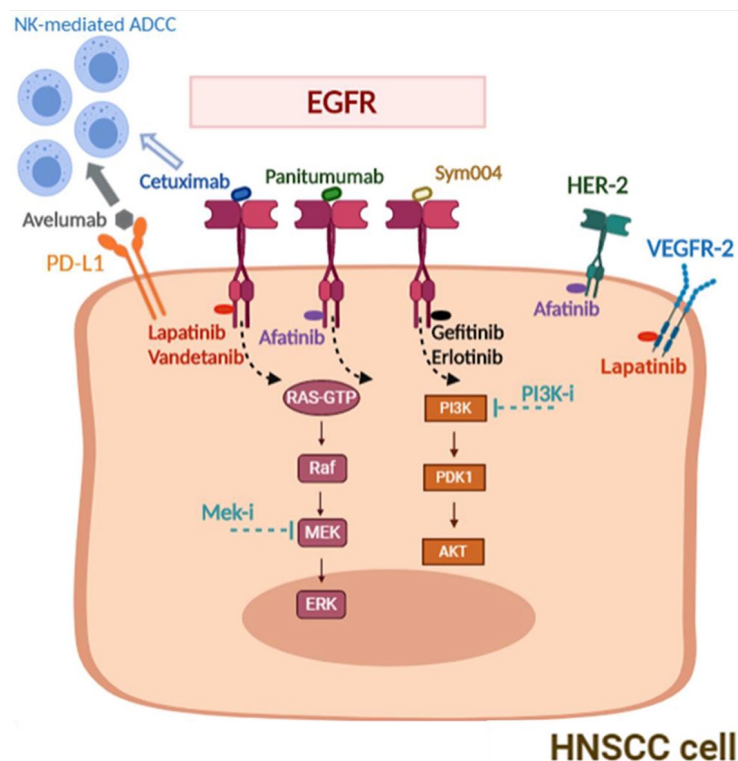


Figure 1. EGFR pathway and targets for combination strategies in HNSCC. EGFR, epidermal growth factor receptor; HNSCC, head and neck cancer squamous cell carcinoma.

recurrence during follow up. Prognosis of recurrent or metastatic (R/M) HNSCC is poor, with a median overall survival (mOS) of 1 year.⁵ In this setting, medical treatment usually consists of doublet platinum-based CT (EXTREME regimen).⁶

More recently, development of immune-checkpoint inhibitors (ICIs) has greatly changed the treatment of HNSCC. The anti-PD-1 (programmed death 1) antibodies Nivolumab and Pembrolizumab showed survival improvements in platinum-treated patients with R/M disease,^{7,8} leading to approval of these two drugs by the United States Food and Drug Administration (FDA) in 2016. Finally, given the results of KEYNOTE-048 trial, Pembrolizumab is a candidate to replace, or be associated with, CT in a large portion of patients in front-line treatment.⁹

In the present article, we review the biological rationale and clinical development of anti-EGFR in the treatment of HNCs, and highlight future perspectives for use of anti-EGFR in the era of immunotherapy.

EGFR in HNSCC: pathogenetic and predictive role

EGFR pathway

EGFR is a transmembrane protein receptor that belongs to the ErbB family of receptor tyrosine kinases (RTKs) (Figure 1). Four different ErbB receptors have been characterized, EGFR (or ErbB 1 or Her-1), Her-2, Her-3, and Her-4, which exert critical physiological functions in epithelial normal cells. EGFR can be activated by soluble ligands (e.g., EGF or transforming growth factor alpha, TGF- α) or by homodimerization or heterodimerization with other HER family receptors (especially ErbB 2); EGFR activation results in stimulation of a proliferative and pro-survival intracellular signaling, through the mitogen-activated protein kinase (MAPKs) cascade, PI3K/AKT/mTOR and JAK/STAT pathway.^{10,11}

EGFR in HNSCC carcinogenesis

EGFR is overexpressed in 80–90% of HNSCCs, playing a key role in carcinogenesis and tumor evolution. In fact, EGFR expression is higher in HNC patients' normal mucosa than in healthy

people, and EGFR expression gradually increases according to histological malignant transformation, from hyperplasia to invasive carcinoma.^{12–14}

Predictive role of EGFR alterations

Playing a fundamental role in its carcinogenesis, EGFR is an extensively studied biomarker in HNSCC. Although EGFR overexpression and aberrant EGFR gene copy number (GCN) have commonly been associated with poorer prognosis and disease specific survival in HNSCC,^{15,16} recent reports suggest a controversial prognostic role of EGFR expression in HNSCC, evaluated according different cytogenetic/molecular markers: protein expression levels, protein activation, GCN, polymorphisms, mutation, EGFRvIII expression, and EGFR ligand expression.¹⁷

Up to now, results are still conflicting in terms of predictive value of EGFR expression in HNSCC for standard treatments, including RT alone or combined with surgery, CT, and anti-EGFR drugs. Alterations of EGFR, including EGFR mutation frequency and EGFR protein expression/phosphorylation, were not associated with disease free survival (DFS).¹⁸ HNSCC with high EGFR expression had poor outcome with RT alone, while no difference was found when using RT+Cx.¹⁹

Also, discordant results were obtained by investigating the association between EGFR GCN and clinical outcome after primary CT: in some studies, it was a negative prognostic factor, being significantly associated with shorter progression-free survival (PFS) and OS,^{15,16} but this was not confirmed by other studies.²⁰

Moreover, an inverse correlation between HPV positivity and EGFR expression has been reported in HPV-positive oropharyngeal squamous cell carcinoma (OSCC).²¹ This should be taken into account, considering that about 5–20% of HNSCC are HPV positive, with a significantly higher percentage in OSCC (range 40–90%).²² Also, HPV-positive patients are less likely to experience recurrence or disease progression than HPV-negative patients, independent of treatment.²³

Biomarkers for anti-EGFR therapy

From the past 10 years, numerous randomized trials have been conducted with the aim to identify patients who can mostly benefit from

anti-EGFR therapy [ClinicalTrials.gov identifier: NCT02999087].^{4–6}

In a retrospective analysis on 37 R/M HNSCC patients treated with Cx+CT, high tumor expression of EGFR ligands epiregulin (EREG) and amphiregulin (AREG), correlated with OS and PFS.²⁴

We still lack validated molecular features that can predict clinical outcome to anti-EGFR therapy in HNSCC; however, an important and valid clinical predictive factor is represented by onset of skin toxicity under EGFR treatment. A meta-analysis by Klinghammer *et al.* showed a positive trend in PFS and OS from the addition of Cx to CT in patients who had experienced a Grade 1 skin rash compared with patients with Grade 0 skin rash.²⁵ A recently published study confirmed a correlation between Grade 3 skin toxicity emerged within 90 days from starting Cx therapy and benefit in OS in R/M HNSCC.²⁶

Generally, targeted therapy holds great promise to improve patients' outcome while limiting toxicity as compared with CT. Thus, identifying predictive biomarkers for anti-EGFR treatment is an important challenge to guide HNSCC patients' selection.

Anti-EGFR drugs in treatment of HNSCC

Two different anti-EGFR therapeutic strategies have been developed (Figure 1): the first is to target the extracellular domain of the receptor with monoclonal antibodies as Cx and Panitumumab,²⁷ and the second is to target the intracellular domain of the receptor with low-molecular-weight tyrosine kinase inhibitors (TKIs) such as Gefitinib, Erlotinib or Afatinib.²⁸

Cx is a chimeric mouse-human monoclonal IgG1 antibody that binds EGFR at its extracellular domain and blocks EGF-induced autophosphorylation of EGFR.¹¹ It has preclinical activity *in vitro* and *in vivo* both as a single agent and in combination with cytotoxic compounds and RT in different human cancer models, including HNC.^{29–31} Anti-EGFR antibody competes with EGFR ligands, resulting in internalization and degradation of the antibody-receptor complex and leading to the death of tumor cells also through the indirect mechanism of NK-dependent antibody mediated cytotoxicity [antibody dependent cell-mediated cytotoxicity (ADCC)].^{32,33} It

also induces the dimerization and downregulation of EGFR, perturbs cell cycle progression,³¹ and inhibits tumor-induced angiogenesis.³⁴ Beyond Cx, other anti-EGFR antibodies have been developed in HNSCC.³⁵ Zalutumumab is a human monoclonal antibody against EGFR that has shown activity in preclinical models by blocking the EGFR signaling pathway and, as Cx, by stimulating ADCC.³⁶ Panitumumab is a fully human anti-EGFR monoclonal antibody that effectively inhibits EGFR signaling similarly to Cx. It diverges from Cx due to its IgG2-based structure, which does not allow an enhanced NK-dependent ADCC activity.³⁷ The other class of drugs is represented by TKIs, which inhibit EGFR signaling through preventing the intracellular phosphorylation cascade.³⁸ First-generation TKI, gefitinib and erlotinib, are anilinoquinazolines that bind reversibly to the K745 site in the ATP binding pocket,³⁹ with anti-tumor activity *in vitro* mediated by inhibition of AKT and MAPK.⁴⁰ Also, erlotinib is able to radio-sensitize HPV-negative HNSCC cells by inhibiting DNA double-strand-break (DSB) repair *via* MAPK and PARP1,⁴¹ and inducing arrest of the cells in the G2 cell cycle phase.⁴² Afatinib is a second-generation pan-EGFR-TKI that irreversibly binds to EGFR1, HER2, and HER4,⁴³ performing a sustained receptor inhibition compared with first-generation TKI inhibitors. Macha *et al.* demonstrated that afatinib is more potent than erlotinib in EGFR inhibition in HNSCC *in vitro* models, and is able to inhibit the expression of cancer stem cells (CSCs) markers, including CD44 and Oct3/4, and CSCs growth. Of interest, they showed also that afatinib significantly radiosensitizes preclinical model of HNSCC through eradication of CSCs.⁴⁴ These results encourage clinical testing of afatinib in the setting of heterogeneous HNSCC.⁴⁵

Anti-EGFR antibodies

Cetuximab

Cx remains to date the only targeted drug approved for the treatment of LA and R/M HNSCC (Table 1).

Exclusive treatment with concomitant RT. In a pivotal randomized study reported by Bonner *et al.*, 424 patients with LA-HNSCC were randomized to RT alone or combined with Cx (RT-Cx).⁴⁶ The mOS was 49 months after combined therapy compared with 29 months after RT alone

($p=0.03$). The 5-year OS (46 *versus* 36%) and 3-year loco-regional control (47 *versus* 34%) were prolonged with the use of Cx in all clinical subgroups.⁴⁶ Interestingly, Cx-induced skin rash (grade 2 or above) and p16-positivity predicted better outcomes in terms of OS (HR 0.38 *versus* 0.93, respectively).⁴⁷

Based on these data, RT-Cx is incorporated in guidelines as an alternative to standard chemoradiation (CRT) in this setting for patients considered unfit for cisplatin, even given the lack of a direct comparison with standard concurrent CRT with cisplatin in a phase III randomized clinical trial and toxicity profile. A randomized phase II trial evaluating CRT *versus* RT-Cx was stopped prematurely for slow accrual, resulting in being underpowered for efficacy outcomes. However, a higher rate of acute toxicity (severe cutaneous toxicity and need for nutritional support) was found for RT-Cx, with 11% of toxic death and 13% of discontinuation rate of RT *versus* 0% of CRT group ($p=0.05$).⁴⁸

In a meta-analysis of 15 trials (3 of which were perspective), including 1088 patients, conducted by Petrelli *et al.*, CRT was associated with better PFS (RR 0.68, $p=0.02$) and OS (RR 0.66, $p=0.02$) at 2 years compared with RT-Cx in treatment of LA-HNSCC.⁴⁹ Conversely, a meta-analysis of 31 studies by Huang *et al.*, revealed no significant difference in 3 years OS and PFS ($p>0.05$), and confirmed a better outcome in HPV + and primary OSCC patients.⁵⁰

Because CRT and RT-Cx were demonstrated as superior to RT alone for LA-HNSCC, a randomized trial was performed to determine whether adding Cx to CRT could enhance its effects – the RTOG 0522 study. The intensification regimen did not result in improved OS; in the EGFR high subgroup, increased toxicity (grade 3–4 mucositis 43.2% *versus* 33.3%, $p=0.002$) and higher discontinuation rate of RT (26.9% *versus* 15.1%) were detected.⁵¹

Recently, two randomized phase III trials, RTOG 1016 and De-ESCALaTE, investigated the substitution of cisplatin with Cx in patients with advanced HPV + OSCC. Historically, it has been considered a more chemo- and radiosensitive disease, but, since it arises in younger patients without classical risk factors for HNSCC, the long-term impact on quality of life of traditional therapeutic interventions led to investigation of

Table 1. Summary of clinical data investigating anti-EGFR therapy in HNSCC.

Drug	Study	Phase	Treatment	Setting	Results
Cetuximab	EXTREME	III	Cisplatin and 5-FU ± cetuximab (PFEx)	R/M	OS (10.1 <i>versus</i> 7.4) and PFS (5.6 <i>versus</i> 3.3) for triplet arm
	RTOG 1016	III	RT plus cetuximab or cisplatin in HPV + oropharyngeal cancer	LA	Outcomes at 5 years of treatment: cetuximab + RT inferiority in terms of OS (78% <i>versus</i> 85%), PFS (67% <i>versus</i> 78%), locoregional failure (17% <i>versus</i> 10%), distant metastasis (12% <i>versus</i> 9%)
	De-ESCALaTE	III	RT plus cetuximab or cisplatin in HPV + oropharyngeal cancer	LA	ORR at 12 weeks: 44.4%, PFS 6.2 months, OS 14.0 months. TPEx regimen is effective and might be substitute for PFEx
	GORTEC	II	Cetuximab, docetaxel and cisplatin combination (TPEx)	R/M	ORR at 12 weeks: 44.4%, PFS 6.2 months, OS 14.0 months. TPEx regimen is effective and might be substitute for PFEx
Panitumumab	PRISM	II	Panitumumab in monotherapy	R/M	Limited activity in previously treated patients
	SPECTRUM	III	Cisplatin and 5-FU ± panitumumab	R/M	No improvement in OS (11 <i>versus</i> 9 months)
Afatinib	LUX- Head & Neck 1	III	Afatinib <i>versus</i> Metotrexate	R/M	Afatinib improved PFS (2.6 <i>versus</i> 1.7) with a manageable safety profile
	LUX- Head & Neck 2	III	Afatinib <i>versus</i> placebo	Adjuvant after CRT	Afatinib after CRT did not improve DFS <i>versus</i> placebo
	LUX- Head & Neck 3	III	Afatinib <i>versus</i> Metotrexate	R/M	Result are consistent with Trial 1
Gefitinib	IMEX	III	Gefitinib <i>versus</i> Methotrexate	R/M	No OS improvement compared with methotrexate

CRT, chemoradiation; EGFR, epidermal growth factor receptor; 5-FU, 5-fluorouracil; HNSCC, head and neck cancer squamous cell carcinoma; HPV, human papillomavirus; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/M, recurrent or metastatic; RT, radiotherapy.

chemo-sparing regimens. However, both trials showed that substitution of cisplatin with Cx had no significant impact on toxicity and did not improve survival: no difference in OS was found in RTOG study (HR 1.45, $p=0.5056$)⁵² and worse OS (97.5% *versus* 89.4%, $p=0.0012$) in De-ESCALaTE trial in Cx group.⁵³ Collectively, these data indicate that cisplatin should be used as first-choice radiosensitizer in all eligible patients with HPV + OPC. A study comparing CRT and RT-Cx in overall HNSCC population is currently ongoing and will provide further results (ARTSCAN III).

In an induction setting, the addition of Cx to CT appears to improve overall response rate

(ORR), especially with taxane-based treatment, but it is still not a standard of care for higher toxicity in the absence of survival benefit.⁵⁴ Sequential RT-Cx after induction CT appears, at the moment, to be the most promising and feasible option as part of an organ preservation strategy.⁵⁵

Adjuvant treatment. To date, no evidence supports the use of Cx, awaiting the result of the phase III study ACCRA-HN comparing RT-Cx plus Cisplatin-5FU and RT-Cx.

Metastatic setting. Approval of Cx in the metastatic setting was based on the EXTREME trial. A total of 442 patients with R/M HNSCC were

randomized to cisplatin/carboplatin and 5-fluorouracil (5-FU) with or without Cx for six cycles, followed by maintenance Cx. No crossover was allowed. On triplet arms, both mOS (10.1 *versus* 7.4 months, $p=0.04$) and PFS (5.6 *versus* 3.3, $p<0.01$) were improved, with an increase of 16% in ORR in the arm with Cx. These data led to the introduction of the EXTREME protocol in clinical practice for the treatment of HNCs in the forefront of recurrent or metastatic setting.

Although no differences in quality of life outcomes were reported, more sepsis and skin reactions were observed in the experimental arm. EGFR expression was not predictive of treatment benefit.⁵⁶ Several attempts have been made to replace 5-FU in the EXTREME scheme. In the GORTEC phase II study, the combination named TPEx (docetaxel, cisplatin and weekly Cx for four cycles followed by Cx maintenance) obtained an ORR at 12 weeks of 44.4% with a manageable safety profile; median PFS and OS were 6.2 and 14.0 months, respectively.⁵⁷ Preclinical evidence suggested a mechanism for the synergistic activity of Cx with taxanes, represented by prevention of taxane-induced EGFR phosphorylation and regulation of EGFR downstream pathways.⁵⁸ Several clinical studies have investigated combinations without platinum.⁵⁹ A combination of weekly paclitaxel and Cx proved feasible and safe as first-line treatment of patients unfit for cisplatin, with an ORR of 54%, and PFS of 4.2 months in a phase II single-arm Spanish study.⁶⁰ A phase II study called CACTUS is investigating the combination of Cx and nab-paclitaxel in R/M HNSCC. The efficacy of Cx and docetaxel combination was evaluated also in platinum-pretreated patients obtaining in a single arm study a disease control rate (DCR) of 51% and mPFS of 3.1 months, independently from a previous response to platinum.⁶¹

Panitumumab

Two clinical studies investigated the use of Panitumumab as a single agent in pretreated HNSCC. An open-label, single-arm, multicenter trial published in 2015 studied panitumumab monotherapy at the dose of 9 mg/kg Q3W (PRISM trial). Only mild activity of panitumumab in this setting was shown with an ORR of 4%, mPFS of 1.4 months.⁶² Another study investigated the safety and efficacy of a 2-week schedule of panitumumab at 6 mg/kg in the same setting, obtaining similar moderate activity, with an ORR of 6%, a mPFS of 2.6 months, and a

mOS of 9.7 months.⁶³ Moreover, the efficacy of Panitumumab in first line R/M HNSCC was assessed by a phase III SPECTRUM trial, evaluating cisplatin and 5-FU with or without the anti-EGFR antibody panitumumab. The benefit seen in EXTREME with anti-EGFR Cx was not reproduced: primary endpoint of improvement in OS was not reached, even if ORR (36% *versus* 25%, $p=0.0065$) and mPFS (5.8 *versus* 4.6 months, $p=0.0036$) were significantly improved with panitumumab. In subgroup analysis, OS was improved only in p16-negative patients ($p=0.0115$).⁵⁶ Different features of panitumumab may be responsible for these differences: lower ADCC-inducing ability, lack of maintenance treatment, and the 3-week schedule. Also, the prevalence of p16-positive tumors in the SPECTRUM trial was higher, maybe due to geographic differences (EXTREME trials enrolled only European patients).

Sym004

Sym004 is a synergistic antibody combination containing two recombinant mAbs, futuximab and modotuximab, which bind to different, non-overlapping epitopes of EGFR, different from the epitopes of Cx and panitumumab. In contrast to single anti-EGFR antibodies, Sym004 induces rapid and highly efficient degradation of EGFR.⁶⁴ Preclinical studies have shown that the combination of Sym004 and radiation resulted in significant tumor regrowth delay and superior anti-tumor effects compared with treatment with Sym004 or radiation alone in lung and HNC.⁶⁵ In a proof of concept trial, clinical activity of Sym004 was investigated in 26 patients, including 23 progressing on previous anti EGFR treatment. Even if no objective responses were observed, 50% of patients had stable disease (SD) as best response, with a mPFS and mOS of 82 and 156 days, respectively. This trial revealed modest anti-tumor activity of Sym004 in an extensively pretreated advanced HNSCC population, and, interestingly, paired biopsies showed a significant down-regulation of EGFR in both skin and tumors following exposure to Sym004, supporting the activity of Sym004 in this setting.⁶⁶

EGFR tyrosine kinase inhibitors

Afatinib

The LUX-Head & Neck 1 trial tested Afatinib in European patients with R/M HNSCC whose

disease progressed after first-line platinum regimens *versus* methotrexate. Afatinib improved the primary endpoint of PFS by 0.9 months (mPFS = 2.6 *versus* 1.7 months, $p=0.030$), with a DCR of 49.1% *versus* 38.5% of CT, but OS was not significantly different. Prespecified tumor biomarkers analysis identified subgroups of patients achieving increased benefit from target therapy: p16-negative, EGFR-amplified, HER3-low, PTEN-high.⁶⁷ Similar data were obtained by the more recent LUX-Head & Neck 3 trial, with the same design in Asian population.⁶⁸ The accrual of trial LUX-Head & Neck 2 trial, comparing Afatinib and placebo after CRT in primary unresected HNSCC patients, was halted due to futility of interim pre-planned analysis.⁶⁹

Lapatinib

Lapatinib is a reversible dual EGFR and HER2-TKI that has been tested in HNSCC. In a phase II trial on pretreated R/M HNSCC patients, no objective responses were observed with lapatinib, regardless of prior EGFR treatment.⁷⁰ In L/A unresected HNSCC, Lapatinib combined with cisplatin-based CRT was well tolerated, with increases in ORR at 6 months post-CRT (53% *versus* 36%), and better PFS benefit in p16-negative disease (>20.4 months *versus* 10.9),⁷¹ but these data were not confirmed by a phase III randomized trial.⁷²

Gefitinib and erlotinib

In refractory metastatic HNC patients, gefitinib and erlotinib showed some benefit in ORR, and mOS ranged from 0% to 15% and 5.9–8.1 months, respectively.^{73,74} However, gefitinib did not obtain OS benefit *versus* methotrexate in a phase III trial, also having higher hemorrhagic toxicity events.⁷⁵ In LA-HNSCC, addition of erlotinib to CRT did not improve PFS and primary endpoint of CR (CR 52 *versus* 40%, $p=0.08$).⁷⁶ In a first-line setting, adjunction of erlotinib to cisplatin and docetaxel as first-line regiment followed by erlotinib maintenance improved PFS from 4.4 to 6.1 months ($p=0.026$), RR (56 *versus* 44%) and OS from 13.7 to 17.0 months ($p=0.07$) in a randomized phase II trial.⁷⁷ The onset of skin rash was associated with clinical benefit to both agents,⁷⁸ in the absence of other known molecular predictors of response. A recent meta-analysis provides pooled estimates of the effectiveness and safety of gefitinib-based therapy in patients with advanced HNSCC in comparison with standard

regimens. As underlined by the authors, disappointingly, benefits from gefitinib-containing regimens are still negative.⁷⁹

Vandetanib

Vandetanib is an oral anti-cancer agent that selectively targets vascular endothelial growth factor receptor (VEGFR), EGFR, and rearranged during transfection (RET) tyrosine kinases. Preclinical evidence supports its potential role and clinical activity in HNSCC.^{80–83} In a phase II randomized trial, R/M HNSCC patients received docetaxel alone or with vandetanib: some trends in clinical benefit were observed, but they did not have enough clinical power to continue accrual.⁸⁴

Resistance to anti-EGFR in HNSCC

Resistance to targeted therapy can either be primary, meaning that patient do not respond to targeted treatment, or secondary, patients respond to treatment but will eventually develop resistance (Table 2).

Resistance to anti-EGFR targeted therapy may be due to: (1) intrinsic activation of EGFR, (2) activation of an EGFR downstream component, or (3) of another TK receptor such as hepatocyte growth factor (HGF) receptor (MET) (Figure 1).⁹⁰

- (1) Among the first genetic alterations of the EGFR that have been identified, the type-III mutated variant (EGFRvIII), and the EGFR_{K521} variant correlates with therapeutic resistance to Cx in preclinical models and in clinical trials. Mechanistically, EGFRvIII is characterized by an in-frame deletion from exons 2 through 7 in the extracellular domain, which inhibits EGFR ligands from binding and leads to constitutive activation of its TK domain, while the EGFR_{K521} variant is characterized by a frequent single nucleotide polymorphism in the extracellular domain that reduces affinity for Cx.^{85,86} A genetic profiling of HNSCC samples with EGFR activation revealed that EGFR ligands were highly expressed in a Cx resistant subset, suggesting an autocrine sustained EGFR hyperactivity.⁸⁸
- (2) Alternatively, the function of a target gene can be bypassed by activating downstream molecules. Comprehensive genomic analysis of HNSCC revealed

Table 2. Resistance to EGFR inhibition in HNSCC.

Signalling pathway	Mechanism	Reference
EGFR family	EGFRvIII	Wheeler <i>et al.</i> ⁸⁵
	EGFR _{K521} variant	Braig <i>et al.</i> ⁸⁶
	HER2 activation	Novoplansky <i>et al.</i> ⁸⁷
PIK3CA pathway	Ligand overexpression	Boeckx <i>et al.</i> ⁸⁸
	PIK3CA mutation	Kyungsuk <i>et al.</i> ⁸⁹
RAS	PTEN loss of expression	Da Costa <i>et al.</i> ⁹⁰
	KRAS mutation	Eze <i>et al.</i> ⁹¹
MET	HRAS mutation	Puram <i>et al.</i> ⁹²
	Expression and activation	Boeckx <i>et al.</i> ⁸⁸

EGFR, epidermal growth factor receptor; HNSCC, head and neck cancer squamous cell carcinoma.

frequent alterations in the PI3K pathway, e.g., mutations in PIK3CA, which is the third most commonly mutated gene in HNSCC. Compensatory activation of PI3K downstream pathway is demonstrated by higher PI3K pathway gene expression and efficacy of PI3K inhibitors in Cx-resistant HNC cells.⁸⁹ In a clinical setting, the addition of PX-866, a PI3K inhibitor, to Cx did not show any significant clinical benefit in R/M HNSCC in a randomized phase II study, but other novel combinations are still under evaluation, such as combinations of Cx with Buparlisib, a pan-PI3K inhibitor [ClinicalTrials.gov identifier: NCT01816984], or with Alpelisib, an α -specific PI3K inhibitor [ClinicalTrials.gov identifier: NCT01602315], and/or with temsirolimus [ClinicalTrials.gov identifier: NCT01256385].

PTEN is a negative regulator of the PI3K pathway, and PTEN loss is detected in about 30% of cases.⁹⁰ Loss of PTEN expression in tumor samples correlates with longer PFS on Cx therapy, while patients with PTEN high-expressing tumors had improved PFS.⁹¹

In colorectal cancer, as an example, KRAS mutations are associated with intrinsic resistance to Cx or panitumumab.¹¹ In HNSCC, the majority of Cx-naïve tumors do not carry RAS mutations, with the exception of 4.3% with HRAS mutations, especially in patients with extensive tobacco exposure,⁹² while almost half of patients develop acquired RAS mutations as a resistance mechanism to EGFR inhibition.⁹¹

- (3) MET expression has been associated with resistance to Cx in a preclinical HNSCC model and in a retrospective study.^{93,94} Novoplansky *et al.* reported clinical evidence of MET activation by ligand-dependent (mediated by HGF produced by stromal cells) or ligand-independent (MET amplification and activating mutations).^{87,95} The activation of HER2 signaling has been also associated with Cx resistance, suggesting a potential role for afatinib in this setting.⁸⁸

Perspectives: role of anti-EGFR drugs in the era of immunotherapy

ICIs in HNSCC

Recently, the introduction of ICIs has changed the standard of care in oncology. ICIs, such as anti-PD-1/PD-L1 (programmed death-ligand 1), are currently approved in various cancer types, including HNSCC.⁹⁶ In cancers, tumor cells induce immunosuppression through the interaction of PD-L1 expressed on their surface with PD-1 expressed by T-cells, preventing attack from the immune system.⁹⁷ In particular, last year, two anti-PD-1 antibodies, nivolumab and pembrolizumab, were approved in Europe and Italy for treatment of relapsed metastatic HNSCC; nivolumab is used after progression to platinum CT independently from PD-L1 expression, whereas pembrolizumab is approved in the same setting for PD-L1-positive HNSCC, and also in first line as monotherapy or in combination with platinum-based CT in PD-L1 positive HNSCC. The approval of these drugs has been incredibly fast, based on positive results of three phase III trials – the Checkmate-141 trial for nivolumab, and the Keynote-040 and Keynote-048 trials for pembrolizumab.⁹⁸ Nivolumab showed improved OS and quality of life in relapsed HNSCC patients,^{99,100} compared with standard of care, according to investigators'

choice, especially in the absence of previous exposure to anti-EGFR Cx: nivolumab improved the mOS in patients not pre-treated with Cx by 3.3 months, while the benefit was only 2 months in patients with prior Cx exposure. Similarly, pembrolizumab showed a statistically significant increased OS in recurrent platinum-refractory HNSCC and also in PD-L1 positive HNSCC patients in first-line⁸: pembrolizumab alone improved OS compared with CT plus Cx (14.9 *versus* 10.7 months, HR: 0.61, in tumors with PD-L1 expression $\geq 20\%$; 12.3 *versus* 10.3 months, HR: 0.78, in tumors with PD-L1 $\geq 1\%$) and was non-inferior in the total population (11.6 *versus* 10.7, HR: 0.85), while pembrolizumab plus CT was even better in the same settings (OS of 14.7 *versus* 11 months, HR: 0.6, in tumors with PD-L1 $\geq 20\%$; 13.6 *versus* 10.4 months, HR: 0.65, in tumors with PD-L1 $\geq 1\%$; 13 *versus* 10.7, HR: 0.77 in the total population).⁹ Biologically, it is known that combination of immunotherapy with CT is synergistic due to the ability of CT to induce DNA damage and increase innate immunity pathway activation in other cancer types,^{101–103} and we speculate this may explain the benefit of combination of pembrolizumab with platinum also in this setting. However, we still do not know if the combination of Cx plus immunotherapy plus/minus CT may represent a future promising treatment strategy.

Combination of Cx with ICIs

The biological rationale for combining Cx and immunotherapy is still not completely known, but there are multiple hypotheses on the high relevance of the immunologic activity of Cx, based on its peculiar effect of promoting a more permissive anti-tumor immune reaction through NK activation.¹⁰⁴ Clinical and preclinical studies have shown that immunoglobulin G1 monoclonal antibodies, such as Cx, have the highest capability for stimulating ADCC as compared with other isotypes. Cx stimulates ADCC by binding its constant region, Fc, with a natural killer (NK) cell receptor, resulting in NK cell activation.¹⁰⁴ Active NK cells can carry out their own lytic activity on tumor cells, which causes the release of tumor antigens, resulting in the activation of cytotoxic T cells by the presentation of antigens by macrophages and dendritic cells. In this manner, the crosstalk between immune cells and the continuous release of antigens lead to the activation of both innate and adaptive immune systems.

Thus, Cx can potentially augment the activity of PD-1/PD-L1 inhibition by synergistically and fully mobilizing the adaptive and innate immune systems against tumor cells (Table 3). Specifically, combination of Cx plus anti-PD-L1 avelumab is object of study in ongoing prospective trials in various cancer types, like lung cancer,¹⁰⁵ CRC¹⁰⁶ and HNSCC [ClinicalTrials.gov identifier: NCT03494322] order to evaluate if using two ADCC-inducing mAbs can synergize in terms of beneficial immune effect.^{107,108} Also the anti-PD-1 pembrolizumab [ClinicalTrials.gov identifier: NCT03082534] in combination with Cx is being evaluated in phase II clinical trials.¹⁰⁷

Other combination strategies under clinical investigations in HNSCC includes combination of Cx with DNA damaging agents, like RT-Cx [ClinicalTrials.gov identifier: NCT02999087, NCT02707588] and PARP inhibitors,^{109,110} palbociclib (Table 3).

Conclusion

Squamous cell carcinoma represents the main histologic type of HNSCC with alcohol, tobacco, and HPV as well defined risk factors. Nowadays, the prognosis is still poor, especially in the R/M disease, with a mOS of 1 year. In this scenario, the role of the EGFR pathway in HNSCC has been established as the most feasible and effective molecular signal to target, with Cx playing a remarkable role. In this review, we have analyzed the current role of anti-EGFR drugs in the treatment of HNSCC, discussing available data on efficacy and safety results from clinical trials, and on novel prognostic and predictive factors and mechanisms of resistance. We strongly believe that more attention is needed on the mechanisms of intrinsic and acquired resistance, regarding the role of the “beyond-Cx” EGFR inhibition and the “beyond-EGFR targeting” effects of Cx. Clinical trials evaluating the combination of Cx with immunotherapy or other targeted agents are ongoing in order to identify potential novel therapeutic strategies. In particular, given the ascending role of ICIs in the clinical scenario of HNSCC and the biological rationale for combining Cx and immunotherapy, we foresee that these combinations may be of great interest. Moreover, despite the relative low incidence of HNSCC compared with other malignancies, the majority of HNC patients’ tumor lesions are easily accessible and tissue sample affordable, thus making HNSCC the perfect candidate for translational biomarker

Table 3. Summary of ongoing clinical trials of combinations including anti-EGFR therapy in HNSCC.

Combination	Study name	Phase	Treatment arms	Setting	Results
Cetuximab + Avelumab	REACH	II	Avelumab-cetuximab-radiotherapy <i>versus</i> standard of care (RT plus cetuximab or cisplatin)	LA	Ongoing
Cetuximab + RT	PembroRad	II	Pembrolizumab <i>versus</i> Cetuximab combined with RT	LA	Ongoing
Cetuximab + Olaparib + RT	[ClinicalTrials.gov identifier: NCT01758731]	I	Cetuximab + olaparib + RT	LA, heavy smokers	Safe profile for MTD of olaparib of 50 mg/die
Durvalumab + Cetuximab + RT	DUCRO-HN	I/II	Durvalumab, Cetuximab and RT followed by adjuvant Durvalumab (6 months)	LA	Ongoing
Cetuximab + afatinib	[ClinicalTrials.gov identifier: NCT02979977]	II	Cetuximab + afatinib	R/M	Ongoing
Monalizumab + cetuximab + anti-PD-L1	[ClinicalTrials.gov identifier: NCT02643550]	I/II	Monalizumab (anti-NKG2A) + cetuximab + anti-PD-L1	R/M	Ongoing
Avelumab, cetuximab and Palbociclib	[ClinicalTrials.gov identifier: NCT03498378]	I	Avelumab, Cetuximab, and Palbociclib	R/M	Ongoing

EGFR, epidermal growth factor receptor; HNSCC, head and neck cancer squamous cell carcinoma; LA, locally advanced; MTD, maximum tolerable dose; PD-L1, programmed death-ligand 1; RT, radiotherapy.

research. Hopefully, these studies will help in building a biomarker-driven approach for novel combinations, including Cx, in the real-world scenario of HNSCC patients.

Conflict of interest statement

FC: Advisory Boards: Roche, Amgen, Merck, Pfizer, Sanofi, Bayer, Servier, BMS, Cellgene, Lilly; Institutional Research Grants: Bayer, Roche, Merck, Amgen, AstraZeneca, Ipsen. FM: Advisory Boards: MSD, Lilly; Institutional Research Grants: AstraZeneca.

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