[Frontiers in Bioscience, Landmark, 18, 520-542, January 1, 2013]

Molecular markers of response and resistance to EGFR inhibitors in head and neck cancers

Carol Box[1], Miriam Zimmermann[1], Suzanne Eccles[1,2]

[1]Tumour Biology and Metastasis Team, Division of Cancer Therapeutics, McElwain Laboratories, The Institute of Cancer Research, Cotswold Road, Belmont, Sutton, Surrey, SM2 5NG, UK, [2]Cancer Research UK Cancer Therapeutics Unit

TABLE OF CONTENTS

1. ABSTRACT

Receptor tyrosine kinases (RTK) are key targets for novel cancer therapeutics since they activate multiple oncogenic signalling pathways. Also, they are inherently 'druggable' due to their small ATP-dependent kinase domains (inhibitable by small molecules) and cell surface location which renders them accessible to monoclonal antibody-based therapies. The epidermal growth factor receptor (EGFR) is overexpressed in the majority of SCCHN cases and this review focuses primarily on the progress made in targeting the EGFR for the therapy of SCCHN by both small molecules and antibody-based therapies. We then discuss the overlapping and distinct molecular markers of response, innate or acquired resistance to each modality, and how these may be overcome. We also consider other RTKs overexpressed in this disease that may impact on responses and/or provide additional targets for combination therapy.

2. INTRODUCTION

2.1. Characteristics of squamous cell carcinoma of the head and neck (SCCHN)

SCCHN is the 6th commonest cancer with more than 500,000 new patients diagnosed per year worldwide (1). It is generally an aggressive disease associated with significant morbidity and a high mortality rate (approximately 50% at 5 years (2)) due to spread to regional lymph nodes, development of distant metastases, lack of effective treatments and therapy-resistant recurrences. The majority of epithelial head and neck cancers are squamous cell carcinomas (SCCs) which encompass tumours arising in the oral cavity (including the lips, mouth and tongue), pharynx (naso-, oro- and hypopharynx), larynx and paranasal sinuses (3).

The most important independent risk factors for SCCHN are tobacco and alcohol consumption as well as

human papillomavirus (HPV) 16/18/33 infections with the degree of risk varying between tumour sites (4). The rising incidence of HPV-related cancers has changed the epidemiology and demographics of SCCHN with an increase in the proportion of oropharyngeal tumours occurring in a younger patient population of higher socioeconomic status (5). It is now well established that HPV-positive patients respond better to current standard treatment regimens than HPV-negative patients and consequently have a much better prognosis. Stimulation of the host immune response together with expression of the HPV oncogenes E6 and E7 changes the molecular landscape of SCCHN, *e.g.* by elevation of the tumour suppressor $p16^{INK4A}$ (6), thus also influencing response to molecularly targeted therapies.

2.1.1. The SCCHN microenvironment

Increasing attention is being paid to the microenvironment of cancers with the recognition that interactions with the host can significantly influence their biological behaviour and responses to therapy (7-8). The bulky nature of most advanced SCCHN is a major contributory factor to treatment failure. First, the delivery of drugs is limited due to poor vascularisation resulting in suboptimal and heterogeneous drug concentrations (9). Secondly, these inefficiencies in the tumour blood supply lead to hypoxic regions (10-11) which are strongly associated with insensitivity to both chemo- and radiotherapy (12). Cellular responses to hypoxia are mediated primarily via the transcriptional complex HIF-1 (hypoxia inducible factor 1) which consists of heterodimers of the hypoxia-responsive HIF-1alpha and constitutively expressed HIF-1beta. HIF-1 binds to hypoxia response elements (HREs) in DNA and leads to the transcription of target genes which regulate processes such as metabolism, survival, angiogenesis, migration and invasion; all of which can contribute to tumour progression (13). Thus, adaptation of tumour cells to the hypoxic microenvironment promotes progression via multiple mechanisms. Therapeutic agents targeting pathways upregulated in hypoxia could therefore be useful in the treatment of (particularly advanced) SCCHN and it has become increasingly apparent that treating a tumour 'holistically' - addressing both underlying genetic drivers and epigenetic/microenvironmental factors - holds the most promise for future success.

2.2. Receptor tyrosine kinase (RTK) therapeutic targets in SCCHN

RTKs have emerged as prominent targets for novel therapeutics due to both their position at the head of multiple cell signalling cascades and to the frequency of their overexpression and/or hyperactivation in most tumours. Undoubtedly the most widely studied growth factor receptor in SCCHN is the epidermal growth factor receptor (EGFR) whose overexpression in the majority of SCCHN cases was first described over 25 years ago (14). Nevertheless, given the so far disappointing results of most clinical trials with single agent EGFR inhibitors (particularly small molecules (15)), we will also consider other RTKs overexpressed in this disease that may impact on responses and/or provide additional targets for combination therapy.

Of these, vascular endothelial growth factor receptor (VEGFR) is the most established therapeutic target with a variety of tyrosine kinase inhibitors (TKIs) and an inhibitory VEGF antibody (bevacizumab) approved as drugs for cancer treatment. VEGFRs are expressed on the surface of vascular and lymphatic endothelial cells (and also on some tumour cells) where they regulate angiogenesis, a key requirement of malignant progression (16). Overexpression of VEGFRs and their ligands has been well documented in SCCHN and linked to lymph node metastasis (17) and poor prognosis (18). In particular, the hypoxic nature of advanced SCCHN yields high levels of VEGF-A via HIF transcriptional activity (16). Bevacizumab has not been evaluated as a monotherapy in SCCHN, but its ability to enhance the effects of chemotherapy/chemoradiation has been tested in clinical trials (19-20) (see Table 1 and http://www.clinicaltrials.gov). Several pan-VEGFR kinase inhibitors such as semaxanib, sorafenib and sunitinib also inhibit various other kinases including PDGFR, KIT and RAF and these have been tested in SCCHN both as single agents and in combinatorial approaches (16). Most recent results indicate that although well tolerated, these inhibitors show limited activity in SCCHN (21-23). The future for VEGFR as a therapeutic target in SCCHN may lie with a new generation of inhibitors, *e.g.* SKLB1206, BMS-690514 and XL647, which co-target the EGFR and are currently in early stages of development and yet to be tested clinically in SCCHN (Table 1).

The insulin-like growth factor-1 receptor (IGF-1R) is frequently overexpressed in SCCHN and is associated with the development of second primary tumours (24). It activates RAS-MAPK and PI3K-AKT signalling pathways to drive tumour growth and cell survival and is therefore another potential therapeutic target in SCCHN (25-26). The anti-IGF-1R antibody cixutumumab caused tumour regression in SCCHN xenografts (25), however in the recently published results of a phase II clinical trial, a second antibody, figitumumab, showed no benefit in unselected patients progressing after *cis*-platinum (27). Targeting IGF-1R may nevertheless prove useful in combination with other targeted therapies due to its role in resistance to both cytotoxic drugs and targeted agents, as discussed later.

Signalling from the receptor tyrosine kinase MET (hepatocyte growth factor receptor) leads to increased cell proliferation, motility, invasion and metastasis (28). It is frequently upregulated and/or mutated in SCCHN, a cancer with a propensity for local invasion and metastasis (29). Several molecules targeting MET are in early stage clinical trials. Of note is the success of the kinase inhibitor cabozantinib (XL184) in the treatment of both soft tissue and bone metastases in castration-resistant prostate cancer (30). A striking therapeutic response was also observed in a subset of non-small cell lung cancer (NSCLC) patients (carrying an EML4–ALK fusion) to the MET-ALK kinase inhibitor crizotinib (31). Studies of MET inhibitors in SCCHN are not as advanced, but with molecules such as crizotinib showing promise in preclinical studies (32) and the ability of MET to transactivate other relevant RTK signalling pathways (29), clinical studies in SCCHN may be merited (Also see article by Goetsch *et al.*).

Table 1. Therapies used to target receptor tyrosine kinases (RTKs) in SCCHN

Target	Expression & prognosis	Drug(s)	Class of inhibitor	Additional target(s)	Associated therapy	Status	Ref. or trial no.
EPH	EPHA2 associated with angiogenesis & survival (41)	dasatinib (Sprycel®, BMS-354825)	thiazole carboxamide	SFKs, ABL, KIT, PDGFR	none	ph II	(171)
	EPHB4 < survival & invasion *in vitro* & *in vivo* (39)	NVP-BHG712	pyrazolo pyrimidine	none	none	preclinical	(172)
FGFR	*FGFR1* amplification (173); *FGFR3b* activating mutation (174); *FGF19* amplification (175)	FP-1039	FGFR1-Fc fusion protein (ligand trap)	none	none	preclinical	(34)
		RO4383596	pyrimido pyrimidone	VEGFR2, PDGFR	none	preclinical	
		AZ12908010	unavailable	undisclosed	none	preclinical	
		ponatinib (AP24534)	imidazopyridazine	BCR-ABL	none	preclinical	(175)
IGF-1R	receptor & ligand overexpression (176-177)	cixutumumab (IMC-A12)	humanized IgG1	none	none	preclinical	(25)
		figitumumab (CP751,871)	fully human IgG2	none	none	ph II	(27)
MET	mutation, copy number increase, receptor & ligand overexpression (32, 54)	SU11274	pyrrole indolinone	none	none	preclinical	(32)
					cisplatin/erlotinib	preclinical	
		foretinib (XL880; GSK1363089)	quinoline	VEGFR2	none	ph II	*00725764
		crizotinib (PF-2341066)	aminopyridine	ALK	none	preclinical	(32, 178)
PDGFR	ligand overexpression (37)	imatinib (Gleevec®, STI571)	aminopyrimidine	BCR-ABL, KIT	docetaxel	ph II	*0058877
					carboplatin	preclinical	(179)
		dasatinib	*see above*				
VEGFR (and VEGF)	overexpression; ligand overproduction correlating with lymph node metastases & reduced survival [(16) and references within]	bevacizumab (Avastin®)	humanized IgG to VEGF	none	CXR	ph II	(19-20)
					CX	ph III	*00588770
		cediranib (AZD2171)	quinazoline	PDGFR, KIT	none	ph II	*00458978
		motesanib (AMG706)	nicotinamide	PDGFR, KIT	RX	preclinical	(180)
		semaxanib (SU5416)	indolin-2-one	FLT3, FGFR1, PDGFRβ	none	ph II	(21)
					paclitaxel	ph I	(181)
		sorafenib (BAY 43-9006, Nexavar®)	bi-aryl urea	RAF1, B-RAF, PDGFRβ, KIT	none	ph II	(23, 182)
		sunitinib (Sutent®, SU11248)	indolinone	FLT3, CSF-1R, RET, PDGFRβ, KIT	none	ph II	(22, 183-184)

*****Numbers refer to NCT trial numbers - see NIH website (http://www.clinicaltrials.gov) Abbreviations**:** L: lung, ph: clinical trial phase, Ref: reference, CX: chemotherapy, RX: radiotherapy, CXR: chemoradiotherapy

Mutations in *FGFR* (fibroblast growth factor receptor) genes are common in cancer (33) and have been reported in SCCHN. Alternatively, hyperactivated FGFR signalling is linked to receptor and ligand co-overexpression (34). Several approaches to inhibiting FGFR activity are in clinical development: (kinase inhibitors, antibodies and a ligand-trap fusion protein) and some of these have shown preclinical activity in SCCHN cell lines (34). The most advanced stage clinical trials have been with broad spectrum FGFR/VEGFR/PDGFR kinase inhibitors, *e.g.* ponatinib and dovitinib, whilst more FGFR-selective inhibitors, such as AZD4547 (AstraZeneca), BGJ398 (Novartis) and LY2874455 (Eli Lilley), are in earlier stages of development. All await clinical testing in SCCHN.

Similar to FGFR, many of the kinase inhibitors targeting PDGFR (platelet-derived growth factor receptor) co-target additional RTKs, particularly BCR-ABL and KIT, with the most notable examples being dasatinib and imatinib, piloted in the treatment of chronic myeloid leukaemia (35-36). There are few reports describing PDGFR expression in SCCHN. Although high levels of PDGF have been found in patients' sera, this did not correlate with clinicopathological stage (37). As such, it seems that the future of PDGFR in the therapy of SCCHN remains as a co-target of pan-RTK inhibitors until or unless more evidence of its function in this disease setting emerges.

Additional emerging targets for the therapy of SCCHN are the Eph receptors. Ephs comprise the largest family of RTKs and are unique in binding only membrane-bound ligands, the ephrins (38). Ephs and ephrins participate in bidirectional signalling contributing to a

variety of physiological processes and their expression in several types of cancer, including SCCHN, is well documented. For example, high levels of EphB4 in SCCHN correlate with higher stage and lymph node metastasis (39). EphA2 expression has been linked with early stages of SCCHN development (40) and with angiogenesis and survival (41). A chemical proteomics screen of a large panel of SCCHN cell lines led to the identification of EphA2 as critical for proliferation and survival and siRNA validated its potential as novel therapeutic target (42). Therapeutic strategies for inhibiting Eph signalling include targeting the kinase domain with either established drugs, such as dasatinib (or novel, more selective compounds) or targeting the ephrin binding site. Although disruption of protein-protein interactions is challenging, it may be more successful for Eph than for other molecules due to unique features of the ephrin binding pocket that enable high affinity binding of small molecules (43).

2.2.1. The EGFR family in SCCHN: validation as targets

The epidermal growth factor receptor (ERBB1/HER-1) is the archetypal member of the ERBB family of transmembrane RTKs which also includes ERBB2 (Neu/HER-2), ERBB3 (HER-3) and ERBB4 (HER-4). They are generally activated (except for the orphan receptor ERBB2) by binding one or more ligands such as epidermal growth factor (EGF), transforming growth factor-alpha (TGF-alpha), amphiregulin (AR) or heregulin (HRG) (44). In cancers including SCCHN, one or more ligands are often overexpressed (45) either by host cells or tumour cells themselves (autocrine signalling). Ligand binding leads to homo- or hetero-dimerisation of the receptors, frequently with the preferred partner ERBB2, and activation of the intrinsic kinase domain. Phosphorylation of C-terminal tyrosine residues enables interactions with multiple cytoplasmic proteins generating an enormous diversity in downstream signalling regulating cell behaviour (44). Unusually the kinase domain of ERBB3 is only weakly catalytically active; however once transactivated ERBB3 can directly bind to and activate PI3K and, via AKT , controls many biological processes critical for tumorigenesis. These include protein translation, cell survival, nutrient sensing, metabolic regulation, and cell cycle control (46). Hypoxia or cellular stress (*e.g.* induced by cytotoxic therapies) can also activate the PI3K pathway via HIF and/or the mammalian target of rapamycin (mTOR) (47).

EGFR is overexpressed in 90% of SCCHN and has been linked to malignant progression, resistance to radiotherapy and poor prognosis (48-49). Several groups have also reported increased EGFR expression in histologically-normal neighbouring tissue (50-51), suggesting a possible 'field effect' due to the initiating oncogenic driver(s). Overexpression of EGFR in SCCHN is frequently (10-30% cases) caused by *EGFR* gene copy number increases, either amplification at the 7p11 locus or polysomy (52-53). *EGFR* mutations in SCCHN are relatively rare with the exception of the constitutively active, ligand-independent EGFRvIII variant which has an in-frame deletion of exons 2–7 yielding a functional receptor with a truncated extracellular domain. Reports of EGFRvIII frequency in SCCHN vary widely with incidences ranging from 0 to 40% (52, 54) with similarly conflicting reports as to its impact on patient survival. It is clear, however, that EGFRvIII plays a significant role in resistance to anti-EGFR therapeutic antibodies (see below).

Whilst ERBB2 is also overexpressed in approximately 6% of SCCHN, its importance in this malignancy is uncertain with recent reports both of an association with poor prognosis (55) and of no relationship with outcome (56). Similarly, ERBB3 can be overexpressed in SCCHN (57) and has been found to correlate with reduced survival (58). There have been conflicting reports of ERBB4 expression in SCCHN (59) and its role is still under evaluation (60). Recently however high ERBB4 expressing SCC1 cells were found to proliferate rapidly *in vitro* and *in vivo* and were inhibited by a combination of cetuximab and an anti-ERBB4 antibody suggesting that ERBB4 may have value as a therapeutic target in SCCHN (61).

ERBB receptors are particularly implicated in cell motility and invasion (*e.g.* via activation of PLCgamma and/or the non-receptor kinase SRC (62-64)). Matrix metalloproteinase (MMP)-9 levels can be increased via JNK-1, which is often overexpressed in SCCHN, and EGFR activation has been correlated with MMP-9 expression and increased invasion in clinical cancers (59). EGFR can also mediate SCCHN invasion via the activation of STAT3, possibly via SRC (65-66). In addition, ERBB2 reportedly greatly promotes cell invasion via the activation of extracellular regulated kinase (ERK) (67). EGFR has been targeted by several agents such as gefitinib and erlotinib (TKIs) , cetuximab (monoclonal antibody), and lapatinib (dual EGFR/ERBB2 TKI) in SCCHN (15, 48) and we will now discuss progress and problems encountered to date.

3. FIRST GENERATION TYROSINE KINASE INHIBITORS (TKIs) OF EGFR

3.1. TKIs as SCCHN therapies

The first class of small molecules to successfully target EGFR are the quinazolines, exemplified by erlotinib and gefitinib, which compete with ATP binding to the kinase domain, resulting in reduced receptor autophosphorylation and signal transduction, cell-cycle arrest and inhibition of cell proliferation (24, 68-71) (Table 2). Although these agents have similar mechanisms of action, they differ in pharmacological properties. Since gefitinib accumulates in tumour tissue, but has lower plasma concentrations than erlotinib, it has been claimed that it can achieve target inhibition while causing less skin toxicity (72). There has been controversy over the optimal dose of gefitinib to be used in SCCHN. Single-arm Phase II studies suggested that 500 mg was more efficacious than 250 mg (the dose generally used in NSCLC) (73), and it is clear that experience in NSCLC (and determinants of sensitivity and resistance (see Section 3.2)) may not translate to SCCHN.

In most cases, responses to single agents in SCCHN have been limited and/or short-lived (15, 74),

Table 2. EGFR TKI used in SCCHN therapy

Drug	Alternative name(s)	Developed by	Chemical class	Target(s)	Associated therapy	Status	Ref.
erlotinib	OSI-774, Tarceva®	OSI, Genentech, Roche	anilinoquinazoline	EGFR	none	ph II	(185)
					cisplatin	ph I/II	(186)
					bevacizumab	ph I/II	(76)
					Bevacizumab + CXR	ph II	(77)
gefitinib	ZD1839, Iressa®	AstraZeneca	anilinoquinazoline	EGFR	none	ph III	(87)
					CX	ph III	(187) *00088907
					CXR	ph II	(85-86)
					PF2341066	preclinical	(188)
					vorinostat	preclinical	(189)
lapatinib	Tykerb®, Tyverb®, GW-572016	GlaxoSmithKline	anilinoquinazoline	EGFR, ERBB2	none	ph II	(80)
					CXR	ph II & ph III	(79) *00424255
vandetanib	Zactima®, Caprelsa®, ZD6474	AstraZeneca	anilinoquinazoline	EGFR, VEGFR2, RET	CXR	preclinical, ph I & ph II	(134, 190) *00720083
NVP-AEE788	none	Novartis	pyrrolopyrimidine	EGFR, ERBB2, VEGFR1	none	preclinical	(129)
afatinib	Tomtovok®, Tovok®, BIBW2992	Boehringer Ingelheim	anilinoquinazoline	EGFR, ERBB2	none	ph II	(191)
canertinib	CI-1033	Pfizer	anilinoquinazoline	EGFR, ERBB2, B4	none	ph II (L)	(125)
dacomitinib	PF-00299804	Pfizer	quinazoline	EGFR, ERBB2, B4	none	preclinical (L) & ph II	(124, 192) *1449201
icotinib	Conmana®, BPI-2009H	Beta Pharma	quinazoline	EGFR	none	preclinical (L)	(193)
neratinib	HKI-272	Pfizer	anilinoquinazoline	EGFR, ERBB2, B4	none	preclinical (B)	(194)
CUDC-101	none	Curis	quinazoline	EGFR, ERBB2, HDAC	none	preclinical & ph I	(195-197)
					CXR	ph I	*01384799
SKLB1206	none	Sichuan University	purine	EGFR, ERBB2, B4 VEGFR2	none	preclinical	(126)
BMS-690514	none	Bristol Myers Squibb	pyrrolotriazine	EGFR, ERBB2, VEGFR	none	preclinical (B, C, L, G)	(198)
XL647	EXEL-7647	Exelixis	quinazoline	EGFR, ERBB2, VEGFR2, 3, EPHB4	none	preclinical/ clinical (L)	(128)
					none	ph II (L)	(127)

*****Numbers refer to NCT trial numbers - see NIH website (http://www.clinicaltrials.gov) CX: chemotherapy, RX: radiotherapy, CXR: chemoradiotherapy

hence combination therapies are being actively pursued (75). These include erlotinib, gefitinib or lapatinib in combination with radio- and/or chemotherapy or other targeted agents such as bevacizumab (Table 2). However, in some cases any benefit in efficacy is counterbalanced by treatment-related toxicities. A phase I/II study of erlotinib and bevacizumab in patients with recurrent or metastatic SCCHN assessed the MTD, toxicity and effects on disease progression. The response rate was 15% with four complete responses, which were consistent with the degree of pharmacodynamic changes in receptor phosphorylation observed. Although considered well-tolerated, three of the 46 patients experienced severe bleeding events (76). More recently, synchronous erlotinib, bevacizumab and concurrent chemoradiotherapy were trialled prospectively in locally-advanced SCCHN. The regime was tolerated and efficacy compared favourably with historical controls, except for an increased risk of osteoradionecrosis. DCE-MRI was found to be useful in providing an early indication of response (77).

Lapatinib has been tested as a single agent and in combination with chemotherapeutic agents in SCCHN. In a panel of SCCHN cell lines, surprisingly, sensitivity to lapatinib did not correlate with expression levels of EGFR or ERBB2. Anti-tumour activity was observed in a xenograft model, which was enhanced by combination with paclitaxel, where there was evidence of increased apoptosis and anti-angiogenic effects (78). Clinically, lapatinib was tested as a short (2-6 weeks) treatment before chemo-radiotherapy in a Phase II trial of therapy-naïve patients with locally advanced SCCHN. Decreased cell proliferation (Ki67 staining) was seen, but no apoptosis. 17% of patients achieved an objective response and, of these, all had EGFR overexpression and 50% expressed ERBB2 (79). In a Phase II study, however, lapatinib - although well-tolerated - gave no benefit in recurrent/metastatic SCCHN regardless of

whether patients had received prior treatment with an EGFR TKI (80) (Table 2).

3.1.1. Molecular indicators of response to TKIs

The limited success of EGFR TKIs in treating SCCHN is in stark contrast to their use in NSCLC where significant increases in survival have been achieved (81). The reason for this is linked to the identification of a subset of NSCLC patients with EGFR-activating mutations who are particularly responsive to EGFR antagonists (such as gefitinib and erlotinib) and have an improved outcome (reviewed in (82)). These gain-of-function somatic mutations/in-frame deletions (in exons 18-21) modify the ATP binding pocket of EGFR and enable better access, not only of ATP, but also the competitive TKI, resulting in increased sensitivity(53). It has also been suggested that such patients have a better prognosis overall, somewhat confounding interpretation of the efficacy of EGFR TKIs (83). However, these sensitising mutations are rare in SCCHN (detection rates 0 to 8%) depending somewhat on ethnicity and tumour sub-anatomical site: slightly higher mutation rates were found in Asians (84) or in tongue or tonsilar cancers (85). Where mutations have been detected, no correlation with response has been seen (85). Clearly, EGFR sensitising mutations are not a useful biomarker for response to EGFR TKIs in SCCHN.

EGFR gene copy number, as determined by FISH (fluorescence *in situ* hybridisation) has also been proposed as a biomarker of response to TKI therapy in SCCHN. Reports are somewhat conflicting with Cohen *et al.* (86) concluding that high copy number associates with reduced survival but does not indicate response to EGFR TKIs whilst, in a larger phase III study, Stewart and colleagues observed an increased gefitinib response rate (14%) in EGFR FISH-positive compared with FISH-negative patients (5%) (87). Similarly, EGFR overexpression, possibly due to increased gene copy number, has been found to correlate with increased sensitivity to gefitinib in SCCHN cell lines (29) although this is yet to be confirmed in patients. Further exploration of EGFR's potential as a response biomarker is enabled by the wide availability of phospho-specific antibodies. Such reagents have recently been utilised to demonstrate an association between high levels of phospho-Y1068 EGFR and reduced progression-free survival (88). Stransky and colleagues carried out whole exome sequencing of 74 SCCHN tumour-normal tissue pairs and identified mutations in *NOTCH1*, *IRF6* and *TP63* genes, required for squamous differentiation, providing new insights into SCCHN biology which are likely to impact upon response to therapy (89). Alternative candidate biomarkers of response to EGFR TKIs in SCCHN are still being sought. In parallel studies efforts are focussed on trying to understand why so many EGFR-positive patients fail to respond to EGFR TKIs and to uncover mechanisms and biomarkers of resistance.

3.2. Resistance to TKIs: markers and mechanisms

Several different molecular mechanisms of innate and acquired resistance have been described in different tumour types including SCCHN (Figure 1).

3.2.1. EGFR-mediated

The discovery of EGFR 'sensitising' mutations hugely improved the TKI response rate in NSCLC, however around 30% of mutant NSCLCs either did not respond and the majority eventually acquired resistance to TKIs (81). This soon led to the discovery of the *EGFR* T790M 'gatekeeper' mutation, located in the receptor's ATP-binding pocket, accounting for approximately 50% of therapy-resistant NSCLC relapses ((90) and references within). The gatekeeper mutation has also been found in patients prior to gefitinib/erlotinib therapy and so may also contribute to primary resistance (reviewed in (82)).

The subcellular localisation of EGFR modulates its signalling and could be a determinant of response/resistance to TKIs. For example, in gefitinib-resistant breast cancer cell lines EGFR was localised to plasma membrane lipid rafts and disruption of the rafts with lovastatin overcame this resistance (91). An additive effect of lovastatin and an EGFR TKI (AG1478) in growth inhibition of SCC9 and SCC25 cells has previously been reported (92) suggesting that this mechanism may also be relevant to SCCHN. EGFR can also reside within the nucleus where it functions as a transcriptional co-activator and SCCHN patients with high levels of nuclear EGFR have a poor prognosis (93). In NSCLC, nuclear EGFR was found to upregulate transcription of the drug efflux pump BCRP (breast cancer resistance protein/ABCG2) thereby causing gefitinib resistance (94). Morris and colleagues analysed the genes of EGFR/PI3K pathway components and discovered that there was a frequent loss of *PTPRS*, encoding an EGFR-inactivating phosphatase, in oral cancers. Furthermore, knockdown of PTPRS reduced sensitivity to erlotinib in SCCHN or lung cancer cell lines (95) suggesting that PTPRS has potential as a predictive biomarker of resistance to EGFR TKIs.

3.2.2. Receptor switching

One potential mechanism of resistance is persistently active signalling mediated via other EGFR family members such as ERBB2 or ERBB3. ERBB2 is overexpressed in a significant proportion of SCCHN, but the FDA-approved therapeutic mAb trastuzumab has not been extensively tested clinically in this disease. Preclinical studies suggest that trastuzumab can potentiate the effects of gefitinib or cetuximab (96) and may be worth further investigation. However dual EGFR-ERBB2 targeting can be achieved by lapatinib (see Section 3.1). High levels of phosphorylated ERBB2 and total ERBB3 were associated with resistance to gefitinib in SCCHN cell lines and co-treatment of gefitinib-resistant cells with pertuzumab, an anti-ERBB2 antibody, yielded significant growth inhibition (97). The ability of ERBB3 to activate the PI3K-AKT pathway is key to its role in resistance to both EGFR and ERBB2 TKIs. A recent report describes an antibody to ERBB3, MM121, which blocks its ligand-dependent phosphorylation and re-enabled gefitinib- or cetuximab-mediated growth inhibition of xenografts that were previously resistant (98).

Alternatively, a kinase switch mechanism involving EGFR transactivation by RTKs such as insulin-

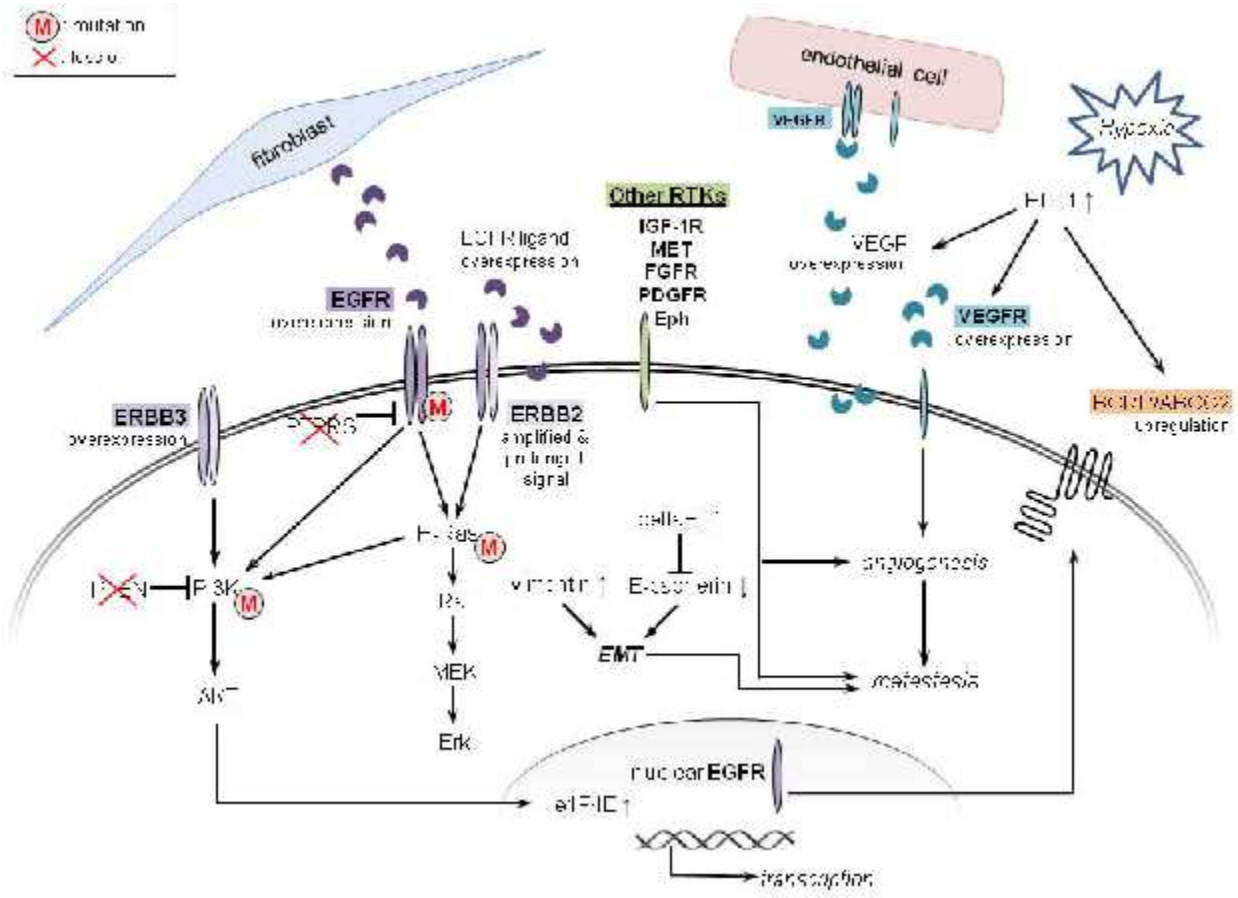

Figure 1. Potential mechanisms of resistance to EGFR inhibitors in SCCHN. Mechanisms of resistance to targeted therapies include overexpression of EGFR (and/or its ligands) or nuclear localisation which renders it inaccessible to mAbs and leads to transcriptional upregulation of drug efflux pumps linked to TKI resistance. Activation of alternative RTKs (such as ERBB2 MET or IGF-1R) or downstream signalling pathways can bypass the need for EGFR activity. EMT has been linked to resistance to TKIs via factors such as deltaEF1. Hypoxia, common in SCCHN, is also linked to enhanced resistance, angiogenesis and metastasis.

like growth factor-1 receptor (IGF-1R) or c-MET can overcome EGFR dependence. Amplification of *MET* can promote signalling in gefitinib-resistant lung cancer cells via ERBB3-dependent activation of PI3K (99). Similarly, increased *MET* copy number was found in 13% SCCHN tumours (32) and MET expression was found to correlate with sensitivity to gefitinib *in vitro* (29). Signalling via IGF-1R was upregulated in gefitinib-resistant SCCHN cell lines (100-101) and treatment with an IGF-1R TKI (AEW541 or PQ401) re-sensitised cells to gefitinib. This provides a rationale for using IGF-1R inhibitors to overcome resistance to EGFR TKIs in SCCHN patients but has yet to be tested clinically.

3.3.3. Non-receptor-mediated

Resistance may be due to signalling pathways being 'short-circuited' by mutations in downstream signalling molecules, rendering upstream RTK activation redundant. Resistance to EGFR inhibitors due to K-RAS mutation is well documented in colorectal carcinoma (102-103) and also in NSCLC (104-105). However, K-RAS mutations are rare and H-RAS mutations more common in SCCHN [18-22%; (106-107)] and the latter therefore more likely to play a role.

Alterations in the PI3K-AKT signalling pathway downstream of EGFR have also been implicated in resistance to EGFR TKIs. A variety of mechanisms including mutations in *PIK3CA* (causing constitutive activation of the PI3K p110alpha catalytic subunit) and loss/inactivation of the phosphatase PTEN, a negative regulator of PI3K activity, have been found in multiple tumour types (*e.g.* lung and breast) resulting in EGFR-independence and resistance to inhibitors such as gefitinib or erlotinib (108-109). *PIK3CA* mutations are present in approximately 8% of SCCHNs (60) whilst PTEN mutations are seldom detected (89). Both of these mechanisms may also be responsible for escape from lapatinib-mediated inhibition of ERBB2 in breast cancer (110) and may account for some inevitable cases of resistance when the drug is used in SCCHN. Expression of the translation-initiation factor e1F4E, downstream of PI3K and AKT, was found to be a critical determinant of acquired resistance to erlotinib in an SCCHN cell line and has been suggested as a surrogate biomarker of pathway activation (111).

Epithelial-mesenchymal transition (EMT) plays a role in cancer progression and may be important in the development of resistance. Characterised by loss of E-cadherin (and thus reduced cell-cell adhesion) and an increase in vimentin expression, there have been several reports linking EMT with intrinsic resistance to EGFR TKIs. Examples of potential mediators include cortactin, a cytoskeletal protein, and deltaEF1 (delta-crystallin enhancer binding factor 1, an E-cadherin repressor), which have been independently associated with resistance to gefitinib (112) and erlotinib (113), respectively, in SCCHN. Sequist *et al*. reported that EMT was concurrent with acquired resistance to erlotinib in 2/37 NSCLC tumours with no other known resistance mechanisms, suggesting that EMT, by itself, may be a cause of acquired resistance. By contrast, Maseki *et al*. reported emergence of EMT in an SCCHN cell line that acquired resistance to gefitinib and concluded that altered ubiquitin-mediated degradation of EGFR, rather than EMT *per se*, was the mechanism of resistance (114). Thus, further investigations are required to clarify the causal and directional relationship between EMT and resistance. Expression of the adhesion molecule EMP-1 (epithelial membrane protein-1) was found to associate with both intrinsic and acquired resistance to gefitinib in NSCLC patients (115). The authors postulated that EMP-1-integrin signalling circumvented the requirement for EGFR in these patients; however there have been no subsequent descriptions of this resistance mechanism and a report of downregulation of EMP-1 transcription in SCCHN (116) suggests that this is not likely to be a useful biomarker of EGFR TKI resistance in this context.

Clearly there are many potential routes for a tumour to become resistant to EGFR TKIs and the underlying molecular mechanisms identified in certain tumour types, such as NSCLCs, are not necessarily applicable to SCCHN. It should also be noted that, following a break from therapy, *EGFR* T790M TKI-resistant NSCLCs may become re-sensitised to the TKI concurrent with apparent loss of the T790M mutation (90) indicating that acquired resistance mechanisms may be transient and dependent upon continued drug exposure to maintain selective pressure (117). This also highlights the potential need for repeated tumour biopsies during therapy and that efforts should be focussed on finding biomarkers which are either detectable in blood or are non-invasive, such as magnetic resonance imaging modalities (118). Using multiplex bead-based assays, Byers and colleagues analysed the serum of 32 SCCHN patients for expression of 38 cytokine and angiogenic factors (CAFs). They identified an 8-protein signature (including VEGF and interleukins-4 and -8) that associated with shorter time to progression and which has the potential to predict (particularly HPV-negative) patients with a higher risk of recurrence (119). This demonstrates the potential of blood biomarkers for patient stratification and could easily be extended to look for biomarkers of therapeutic response/resistance especially as this approach would enable longitudinal studies of biomarker expression without the need for repeated biopsy of solid tumours.

4. NEXT GENERATION INHIBITORS OF ERBB SIGNALLING

4.1. Irreversible EGFR family TKIs

Potential advantages of irreversible TKIs over first generation reversible inhibitors are that blockade of signalling may be longer-lived, many have higher affinity and also inhibit more than one EGFR family member (120). The irreversible dual EGFR/ERBB2 TKI afatinib (BIBW 2992) has shown activity against cetuximab-resistant cells (121) and clinical efficacy in some advanced NSCLC trials, extending time before tumour progression (122). However, no benefit in overall survival was seen in the LUX-Lung1 trial of advanced, metastatic NSCLC patients who had failed erlotinib and/or gefitinib plus chemotherapy (123). Afatinib is currently being trialled in SCCHN. Dacomitinib (PF-00299804) is an irreversible pan EGFR/ERB inhibitor active in EGFR vIII mutant and EGFR TKI-resistant cell lines and xenografts. A recent phase II trial of first-line treatment in recurrent and/or metastatic SCCHN achieved its primary endpoint with an 11% partial response rate and 63% stable disease with a manageable toxicity profile (124). Canertinib (CI-1033) is an orally active irreversible pan-ERBB TKI designed to inhibit a unique cysteine residue in this receptor family, effectively suppressing signalling via all homo- and heterodimers (125). It not only inhibits downstream signalling, but invokes receptor ubiquitination, endocytosis and thus downregulation of RTK expression. It has shown activity in multiple human tumour xenografts, but is not being pursued in NSCLC and has not yet been trialled in SCCHN. Similarly, neratinib (HKI-271) is active against ERBB2 as well as EGFR L858R, T790M and vIII mutations and exon 19 deletions. However, in Phase II trials in NSCLC, toxicity limited the dose that could be administered and results were disappointing (120) (Table 2).

4.2. Multi-targeted inhibitors

SKLB1206 is a novel, orally available reversible inhibitor of EGFR that is not only potent against the wild-type receptor, but also activating and T790M mutants. It further inhibits ERBB2, ERBB4 and VEGFR2 and has shown efficacy in multiple xenograft tumour models with anti-angiogenic effects *in vitro* and in a zebra fish embryo assay (126). Similarly, XL-647 is an oral TKI which targets EGFR, ERBB2, VEGFR and EphB4. In a small Phase II trial of NSCLC patients who had relapsed on gefitinib or erlotinib, however, there was only a 3% response rate, and those with a T790M mutation had a significantly worse progression-free survival (127). Interestingly, however, EGFR mutant NSCLC treated as first-line with XL647 and which then relapsed, retained a degree of sensitivity to erlotinib. This intriguing finding suggests that agents with apparently similar modes of binding to the EGFR kinase domain may select for different mechanisms of resistance (128). Another agent that can inhibit both EGFR and VEGFR2 is NVP-AEE788. This agent was active in orthotopic SCCHN xenografts and potentiated the effects of paclitaxel, revealing decreased microvessel density and increased apoptosis (129). Vandetanib targets primarily VEGFR2, EGFR and RET. VEGFR2 is expressed on some tumour cells and thus represents a direct and indirect (via

angiogenesis) therapeutic target in cancer. Vandetanib has shown activity in SCCHN cell lines (130) and also restored their sensitivity to cisplatin and radiation *in vitro* and *in vivo* (131). Several Phase I and II trials are underway in SCCHN (Table 2). Signalling pathways downstream of RTK have also been targeted in SCCHN, for example using inhibitors of SRC family kinases (dasatinib, saracatinib) and RAF/MEK (sorafenib, sunitinib) (70).

4.3. HSP90 inhibitors

Heat shock protein (HSP) molecular chaperone inhibitors are of increasing clinical interest as 'multi-targeted' therapeutic agents. HSP90 is responsible for the correct folding, subcellular localisation and activation of multiple 'client' proteins, and it has been suggested that aberrant oncoproteins are particularly dependent on chaperones for their function (132). Chaperones are frequently upregulated in cancer (including SCCHN) (133) and especially so under conditions of microenvironmental cellular stress, such as hypoxia and nutrient deprivation (associated with aberrant tumour angiogenesis) or cytotoxic therapy. RTKs and many downstream kinases such as AKT, RAF and CDKs are key HSP90 client proteins, and others such as VEGFR2, VEGFR3, SRC, FAK, HIF-1alpha and MMPs play a key role in angiogenesis and invasion in SCCHN (133-134). Hence HSP90 inhibitors can simultaneously target multiple tumour and host oncogenic pathways and support networks. Preclinical studies have shown that chaperone inhibitors such as 17-AAG or NVP-AUY922 can have single agent activity in common solid tumours (135) and also potentiate the effects of radiotherapy in SCCHN (136). Second generation inhibitors with better pharmacological characteristics are now entering clinical trial in many solid cancers, and results are awaited with interest.

5. THERAPEUTIC ANTIBODIES TO THE EGFR

5.1. Cetuximab: an anti-EGFR monoclonal antibody (mAb) approved for therapy in SCCHN

Cetuximab (C225, Erbitux®) is an IgG1 mouse-human chimaeric mAb that targets the extracellular domain of EGFR, blocking ligand binding and enhancing receptor internalisation and degradation (137-138). An added benefit of many mAbs is their potential ability to induce antibody-dependent cellular cytotoxicity (ADCC) (139), but a disadvantage is that they may be less active in the presence of receptors that are ligand-independent or where there are mutated downstream signalling elements (such as *KRAS*) which can short-circuit the need for receptor activation. So far, of all the EGFR inhibitors tested, cetuximab is the only one with current FDA approval for SCCHN therapy. It has yielded objective clinical benefit as monotherapy in both metastatic and locally advanced SCCHN (68, 140). Several trials have established efficacy in SCCHN patients with platinum-refractory disease, although response rates are only of the order of around 10-13% in pre-treated patients (141). Cetuximab also improves responses when combined with radiotherapy (142) or chemotherapy, with an acceptable toxicity profile. In the EXTREME trial, cetuximab gave significantly improved survival, response rates, disease and symptom control compared with platinum-5-FU alone (140, 143) (Table 3).

5.2. Additional EGFR therapeutic antibodies and new applications in SCCHN

Panitumumab (ABX-EGF, Vectibix®) is a fully humanised anti-EGFR IgG2 mAb with similar direct effects to cetuximab (but less ADCC activity) which has yielded improved progression-free survival and/or overall survival in combination 1st-line palliative treatment with chemotherapy (144). The second generation fully human IgG1 zalutumumab (developed using phage display technology) reportedly binds EGFR domain III and locks the receptor in an inactive conformation, preventing dimerisation. It also mediates ADCC effectively and has the advantage of being weakly immunogenic. Zalutumumab has shown activity in Phase II-III trials (145-146) and was fast-tracked by the FDA for use in SCCHN patients who have failed standard therapies, but further trials are currently suspended. Nimotuzumab (h-R3) is a humanised mouse mAb that has been mainly trialled in oesophageal SCCs (alone or in combination with cytoreductive therapies), but is also in development for SCCHN (48). While both cetuximab and nimotuzumab reportedly inhibit both ligand-stimulated and -independent EGFR signalling, the effects vary with receptor density and antibody concentration. These properties may explain the reportedly differential clinical effects of the two mAbs (with fewer severe side-effects reported for nimotuzumab (147)). Nimotuzumab also gave a survival advantage in combination with radiotherapy or chemoradiotherapy in chemo-naive EGFR-overexpressing SCCHN (148). Necitumumab is another fully human IgG1 EGFR domain III-specific antibody in preclinical development which has shown good PK properties and some activity in Phase I trials (149); Phase II trials in NSCLC in combination with chemotherapy are ongoing (Table 3).

In spite of the fact that EGFR is overexpressed in the majority of SCCHN, the unique specificity of mAbs and the added benefit (with appropriate isotypes) of host-mediated ADCC, many trials were considered to be underpowered and failed to reach their primary endpoint (141). MAbs have also been used in combination with TKIs and other agents, but cetuximab combined with the HDAC inhibitor bortezomib and radiotherapy gave unexpected early tumour progression associated with EGFR stabilization, increased pro-survival signalling and cytokine induction (150).

In addition to the therapeutic deployment of mAbs (alone or in conjunction with chemo/radiotherapy) there has been extensive development of various engineered fragments and derivatives. Bispecific antibodies (bsAb), simultaneously targeting two oncoproteins, are proposed to increase specificity for cancer cells and limit the potential for 'receptor switching'. This hypothesis was proven with a bsAb combining the variable regions of necitumumab and cixutumumab which simultaneously inhibited EGFR and IGF-1R signalling *in vitro* and showed efficacy in xenograft models (151-152). Further examples include MEH7945A (targeting EGFR+ERBB3), now in

Table 3. EGFR therapeutic antibodies used in SCCHN

Drug	Developed by	Molecule type	Targets(s)	Associated therapy(s)	Status	Ref.
cetuximab (Erbitux®, IMC-C225)	Merck; ImClone; Bristol Myers Squibb	human-mouse chimeric IgG1	EGFR	none	FDA-approved for recurrent/metastatic SCCHN after platinum failure	(199)
				RX	FDA-approved for locally advanced SCCHN	(142, 200)
				CX	ph III	(201-202)
				CXR	ph II & ph III	(203-204)
				bevacizumab	ph II	(205) *00409565
				sorafenib	ph Ib/II	*00815295
				bortezomib & RX	ph I	(150)
				cilengitide & CX	ph I /II	(206)
				RAD001	preclinical	(207)
				R763	preclinical	(208)
				dasatinib	preclinical & ph II	(164) *01488318
matuzumab (EMD 72000)	Merck Serono; Takeda	humanized mouse IgG1	EGFR	none	ph I	(209)
necitumumab (IMC-11F8)	Bristol Myers Squibb, Eli Lilly	fully human IgG1	EGFR	CX	ph III (L)	(210)
nimotuzumab (h-R3, BIOMAb EGFR, THERACIM)	CIM, Cuba; YM Biosciences	humanized mouse IgG1	EGFR	RX	ph II	(211)
				CXR/RX	ph IIb	(148)
panitumumab (ABX-EGF, Vectibix®)	Amgen	fully human IgG2	EGFR	none	preclinical & ph II	(156) *00446446
				CX	ph III	(212) *00460265
				RX	ph III	*00820248
zalutumumab (HuMax-EGFr)	Genmab	fully human IgG1	EGFR	none	ph III	(145)
				RX	ph III	*00496652
				CXR	ph I/II ongoing	*00401401
DT-IgG	Emory University	recombinant human IgG	EGFR+ VEGFR	none	preclinical	(154, 214)
CONAN-1	Utrecht University	biparatropic nanobody	EGFR	none	preclinical	(155)
MEHD7945a	Genentech	IgG	EGFR+ ERBB3	none	preclinical	(153, 215)
XGFR series	Roche	bispecific human IgG1	EGFR+ IGF1R	none	preclinical (L)	(151)

*Numbers refer to NCT trial numbers - see NIH website (http://www.clinicaltrials.gov) CX: chemotherapy, L: lung, RX: radiotherapy, CXR: chemoradiotherapy

SCCHN clinical trials (153) and DT-IgG targeting EGFR and VEGF (154). Also, the ability of mAbs recognising different epitopes within EGFR itself has been exploited using phage display technology to generate high affinity biparatopic nanobodies. One example combines the specificity of cetuximab (which binds domain III) and matuzumab (recognising a region outside the ligand binding site which inhibits dimerisation) to generate CONAN-1, a potent receptor antagonist with *in vivo* therapeutic activity (155). A second approach involves replacing one Fab arm of the mAb with an immune effector arm that binds to a receptor such as CD3 and recruits T-cells to the tumour cells, but so far this has not been applied to EGFR mAbs (Table 3).

Finally, mAbs can be exploited for the targeted delivery of cytotoxic payloads, most notably radioisotopes, as exemplified by ^{90}Y labelled panitumumab in SCCHN xenografts (156). Also, an ^{188}Re-labelled anti-E6 specific antibody has been used to target HPV-16 expressing SCCHN cells, opening up the possibility of novel therapies for these increasingly prevalent cancers (157).

5.3. Markers of response or resistance to monoclonal antibodies

Surprisingly perhaps, immunohistochemically determined expression levels of EGFR do not serve as generic predictive biomarkers of response to cetuximab (71), although some studies could be complicated by the fact that certain tumours (*e.g.* colon cancer) have high levels of downstream mutations. Copy number (assessed by FISH) showed a significant association with response to cetuximab and panitumumab in colon cancer (158), but not in SCCHN (159). The EGFRvIII mutation was found in 22/53 (42%) SCCHN tumours and was associated with better disease control in recurrent/metastatic disease irrespective of treatment (-/+ erlotinib) (54). However, when it was transfected into SCCHN cells, EGFRvIII

decreased responses to cetuximab. The antibody is still able to bind to the mutant receptor, although internalisation is delayed (160). In cells in which acquired resistance to cetuximab was induced *in vitro*, a novel EGFR mutation was identified (S492R) and this was subsequently found in 2/10 patients who became refractory to treatment. Interestingly, the cells retained sensitivity to panitumumab, suggesting that some forms of resistance may be overcome by switching to a mAb with a different epitope specificity (161). Upregulation of EGFR/HER ligands are also linked to resistance: tumour biopsies showing high expression of AR were less likely to respond to cetuximab-docetaxel treatment (162) and increased expression of HB-EGF due to downregulation of miR-212 was identified in SCCHN cells with acquired resistance (163).

EGFR internalisation followed by ubiquitin-mediated degradation (164) or nuclear distribution (165) has been linked to certain cases of cetuximab resistance. In addition, to the lack of accessibility of antibodies to these locations, nuclear EGFR regulates genes involved in G1/S transition. EGFR nuclear translocation has been linked to the activity of SRC family kinases and inhibitors such as dasatinib have been reported to increase membrane expression of EGFR and restore sensitivity to cetuximab (165). Interestingly, although nuclear EGFR is also associated with resistance to gefitinib, the underlying molecular mechanism may be different. In this case AKT phosphorylation of EGFR Ser229 (promoting nuclear localisation and transcriptional upregulation of efflux pumps) was implicated, with beneficial effects seen with pharmacological AKT inhibitors or siRNA (94).

The presence of alternative RTK (such as ERBBs, MET, IGF-1R) could also minimise the dependence of tumour cells on EGFR signalling. In patient-derived xenografts, activation of MET was identified as a key cause of primary resistance (166). Yonesaka identified a new mechanism of resistance in patients who became refractory to cetuximab mediated by amplification of ERBB2 or increased levels of the ERBB2/B3 ligand HRG (167). In addition to its role in resistance to EGFR TKIs, IGF-1R may also be involved in resistance to cetuximab as co-treatment of SCCHN xenografts with cetuximab and cixutumumab (IGF-1R antibody) produced an additive effect (25). Barnes *et al.* showed functional EGFR-IGF-1R heterodimerisation and reciprocal re-sensitisation of cixutumumab-resistant SCCHN cell lines by cetuximab (and the mTOR inhibitor rapamycin) has subsequently been demonstrated (168). The combination of cetuximab and an IGF-1R inhibitor will be tested clinically in two phase II trials (NCT01427205 and NCT00957853). Several mechanisms of resistance apply to both pharmacological inhibitors and mAbs: for example cells with mutations in *KRAS*, *BRAF*, *HRAS* and *NRAS* genes, activated SRC or PI3K pathways, and those with mesenchymal characteristics generally fail to respond well to either modality.

In experimental models, xenograft tumours that escaped anti-EGFR antibody therapy became refractory to further treatment and exhibited significantly enhanced growth associated with high levels of VEGF. Since inhibiting EGFR downregulates VEGF production, these data suggest that escape from angiogenic inhibition can contribute to anti-EGFR antibody resistance. This hypothesis was substantiated by the fact that cells transfected with the *VEGF* gene were more resistant than parental cells (169). Clearly, a serum or tissue 'signature' of response to EGFR inhibition would be extremely valuable. Argiris *et al.* analysed the serum from patients with stage III-IVB SCCHN who had received cytotoxic combination therapy plus cetuximab by Luminex® technology pre- and post-treatment and 14 analytes showed interesting changes. Of these VEGF and IL-6 (angiogenic cytokines) were associated with tumour response as measured by PET and PFS (170).

6. SUMMARY AND PERSPECTIVES

Given the prevalence of EGFR overexpression in SCCHN and the availability of highly active and specific inhibitors, clinical trial results of monotherapy with drugs or antibodies have been disappointing. This is due to the complex signalling networks in cancer cells (allowing escape from suppression of a single receptor) and the emergence of multiple mechanisms of acquired resistance. Definitive biomarkers of sensitivity and resistance have been slow to emerge, and often do not translate between different types of cancer, thus the population of SCCHN patients likely to benefit from these therapies is still unclear. Several candidate determinants of resistance have been identified, leading to rational combinations of therapies and some incremental increases in response. Also, we are now (to a degree) able to exclude some patients who are unlikely to respond. Nevertheless, it is likely that the next breakthroughs will come from advances in high-throughput DNA analysis technologies which will enable unbiased evaluation of large numbers of genes in large patient populations to further our understanding of this malignancy and its response to therapy.

7. ACKNOWLEDGEMENTS

CB and MZ were supported by grants from the Oracle Cancer Trust. SE is supported by The Institute of Cancer Research and Cancer Research UK grant number C309/A8274. We acknowledge NHS funding to the NIHR Biomedical Research Centre.

8. REFERENCES

1. J Ferlay, HR Shin, F Bray, D Forman, C Mathers, DM Parkin: Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, 127(12), 2893-917 (2010)

2. ME Prince, LE Ailles: Cancer stem cells in head and neck squamous cell cancer. *J Clin Oncol*, 26(17), 2871-5 (2008)

3. A Argiris, MV Karamouzis, D Raben, RL Ferris: Head and neck cancer. *Lancet*, 371(9625), 1695-709 (2008)

4. EM Smith, LM Rubenstein, TH Haugen, M Pawlita, LP Turek: Complex etiology underlies risk and survival in

head and neck cancer human papillomavirus, tobacco, and alcohol: a case for multifactor disease. *J Oncol*, 2012, 571862 (2012)

5. KK Ang, EM Sturgis: Human papillomavirus as a marker of the natural history and response to therapy of head and neck squamous cell carcinoma. *Semin Radiat Oncol*, 22(2), 128-42 (2012)

6. CS Kong, B Narasimhan, H Cao, S Kwok, JP Erickson, A Koong, N Pourmand, QT Le: The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas. *Int J Radiat Oncol Biol Phys*, 74(2), 553-61 (2009)

7. C Box, SJ Rogers, M Mendiola, SA Eccles: Tumour-microenvironmental interactions: paths to progression and targets for treatment. *Semin Cancer Biol*, 20(3), 128-38 (2010)

8. M Allen, JL Jones: Jekyll and Hyde: the role of the microenvironment on the progression of cancer. *J Pathol*, 223(2), 162-76 (2011)

9. S Patiar, AL Harris: Role of hypoxia-inducible factor-1alpha as a cancer therapy target. *Endocr Relat Cancer*, 13 Suppl 1, S61-75 (2006)

10. DM Aebersold, P Burri, KT Beer, J Laissue, V Djonov, RH Greiner, GL Semenza: Expression of hypoxia-inducible factor-1alpha: a novel predictive and prognostic parameter in the radiotherapy of oropharyngeal cancer. *Cancer Res*, 61(7), 2911-6 (2001)

11. P Stadler, A Becker, HJ Feldmann, G Hansgen, J Dunst, F Wurschmidt, M Molls: Influence of the hypoxic subvolume on the survival of patients with head and neck cancer. *Int J Radiat Oncol Biol Phys*, 44(4), 749-54 (1999)

12. K Toustrup, BS Sorensen, J Alsner, J Overgaard: Hypoxia gene expression signatures as prognostic and predictive markers in head and neck radiotherapy. *Semin Radiat Oncol*, 22(2), 119-27 (2012)

13. GL Semenza: Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. *Trends Pharmacol Sci*, 33(4), 207-14 (2012)

14. B Ozanne, CS Richards, F Hendler, D Burns, B Gusterson: Over-expression of the EGF receptor is a hallmark of squamous cell carcinomas. *J Pathol*, 149(1), 9-14 (1986)

15. S Zhang, J Chen, H Jiang, H Ma, B Yang: Anti-epidermal growth factor receptor therapy for advanced head and neck squamous cell carcinoma: a meta-analysis. *Eur J Clin Pharmacol*, 68(5), 561-9 (2012)

16. A Christopoulos, SM Ahn, JD Klein, S Kim: Biology of vascular endothelial growth factor and its receptors in head and neck cancer: beyond angiogenesis. *Head Neck*, 33(8), 1220-9 (2011)

17. P O-charoenrat, P Rhys-Evans, SA Eccles: Expression of vascular endothelial growth factor family members in head and neck squamous cell carcinoma correlates with lymph node metastasis. *Cancer*, 92(3), 556-68 (2001)

18. PA Kyzas, IW Cunha, JP Ioannidis: Prognostic significance of vascular endothelial growth factor immunohistochemical expression in head and neck squamous cell carcinoma: a meta-analysis. *Clin Cancer Res*, 11(4), 1434-40 (2005)

19. MG Fury, NY Lee, E Sherman, D Lisa, K Kelly, B Lipson, D Carlson, H Stambuk, S Haque, R Shen, D Kraus, J Shah, DG Pfister: A phase 2 study of bevacizumab with cisplatin plus intensity-modulated radiation therapy for stage III/IVB head and neck squamous cell cancer. *Cancer* (2012)

20. JK Salama, DJ Haraf, KM Stenson, EA Blair, ME Witt, R Williams, R Kunnavakkam, EE Cohen, T Seiwert, EE Vokes: A randomized phase II study of 5-fluorouracil, hydroxyurea, and twice-daily radiotherapy compared with bevacizumab plus 5-fluorouracil, hydroxyurea, and twice-daily radiotherapy for intermediate-stage and T4N0-1 head and neck cancers. *Ann Oncol*, 22(10), 2304-9 (2011)

21. MG Fury, A Zahalsky, R Wong, E Venkatraman, E Lis, L Hann, T Aliff, W Gerald, M Fleisher, DG Pfister: A Phase II study of SU5416 in patients with advanced or recurrent head and neck cancers. *Invest New Drugs*, 25(2), 165-72 (2007)

22. JP Machiels, S Henry, S Zanetta, MC Kaminsky, N Michoux, D Rommel, S Schmitz, E Bompas, AF Dillies, S Faivre, A Moxhon, T Duprez, J Guigay: Phase II study of sunitinib in recurrent or metastatic squamous cell carcinoma of the head and neck: GORTEC 2006-01. *J Clin Oncol*, 28(1), 21-8 (2010)

23. SK Williamson, J Moon, CH Huang, PP Guaglianone, M LeBlanc, GT Wolf, SG Urba: Phase II evaluation of sorafenib in advanced and metastatic squamous cell carcinoma of the head and neck: Southwest Oncology Group Study S0420. *J Clin Oncol*, 28(20), 3330-5 (2010)

24. LA Elferink, VA Resto: Receptor-tyrosine-kinase-targeted therapies for head and neck cancer. *J Signal Transduct*, 2011, 982879 (2011)

25. CJ Barnes, K Ohshiro, SK Rayala, AK El-Naggar, R Kumar: Insulin-like growth factor receptor as a therapeutic target in head and neck cancer. *Clin Cancer Res*, 13(14), 4291-9 (2007)

26. RE Friedrich, C Hagel, S Bartel-Friedrich: Insulin-like growth factor-1 receptor (IGF-1R) in primary and metastatic undifferentiated carcinoma of the head and neck: a possible target of immunotherapy. *Anticancer Res*, 30(5), 1641-3 (2010)

27. S Schmitz, MC Kaminsky-Forrett, S Henry, S Zanetta, L Geoffrois, E Bompas, A Moxhon, L Mignion, J Guigay, L Knoops, M Hamoir, JP Machiels: Phase II study of figitumumab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: clinical activity and molecular response (GORTEC 2008-02). *Ann Oncol*, doi: 10.1093/annonc/mdr574 (2012)

28. E Gherardi, W Birchmeier, C Birchmeier, G Vande Woude: Targeting MET in cancer: rationale and progress. *Nat Rev Cancer*, 12(2), 89-103 (2012)

29. SJ Rogers, C Box, P Chambers, Y Barbachano, CM Nutting, P Rhys-Evans, P Workman, KJ Harrington, SA Eccles: Determinants of response to epidermal growth factor receptor tyrosine kinase inhibition in squamous cell carcinoma of the head and neck. *J Pathol*, 218(1), 122-30 (2009)

30. M Hussain, MR Smith, C Sweeney, PG Corn, A Elfiky, MS Gordon, NB Haas, AL Harzstark, R Kurzrock, P Lara, C Lin, A Sella, EJ Small, AI Spira, UN Vaishampayan, NJ Vogelzang, CM Scheffold, D Ballinger, F Schimmoller, DC Smith,: Cabozantinib (XL184) in metastatic castration-resistant prostate cancer (mCRPC): Results from a phase II randomized discontinuation trial. In: *J Clin Oncol, 2011 ASCO Annual Meeting Proceedings*, 29(Supplement 15), American Society of Clinical Oncology (2011) abstract nr 4516 (2011)

31. EL Kwak, YJ Bang, DR Camidge, AT Shaw, B Solomon, RG Maki, SH Ou, BJ Dezube, PA Janne, DB Costa, M Varella-Garcia, WH Kim, TJ Lynch, P Fidias, H Stubbs, JA Engelman, LV Sequist, W Tan, L Gandhi, M Mino-Kenudson, GC Wei, SM Shreeve, MJ Ratain, J Settleman, JG Christensen, DA Haber, K Wilner, R Salgia, GI Shapiro, JW Clark, AJ Iafrate: Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med*, 363(18), 1693-703 (2010)

32. TY Seiwert, R Jagadeeswaran, L Faoro, V Janamanchi, V Nallasura, M El Dinali, S Yala, R Kanteti, EE Cohen, MW Lingen, L Martin, S Krishnaswamy, A Klein-Szanto, JG Christensen, EE Vokes, R Salgia: The MET receptor tyrosine kinase is a potential novel therapeutic target for head and neck squamous cell carcinoma. *Cancer Res*, 69(7), 3021-31 (2009)

33. AN Brooks, E Kilgour, PD Smith: Molecular pathways: fibroblast growth factor signaling: a new therapeutic opportunity in cancer. *Clin Cancer Res*, 18(7), 1855-62 (2012)

34. ME Marshall, TK Hinz, SA Kono, KR Singleton, B Bichon, KE Ware, L Marek, BA Frederick, D Raben, LE Heasley: Fibroblast growth factor receptors are components of autocrine signaling networks in head and neck squamous cell carcinoma cells. *Clin Cancer Res*, 17(15), 5016-25 (2011)

35. A Gnoni, I Marech, N Silvestris, A Vacca, V Lorusso: Dasatinib: an anti-tumour agent via Src inhibition. *Curr Drug Targets*, 12(4), 563-78 (2011)

36. F Stegmeier, M Warmuth, WR Sellers, M Dorsch: Targeted cancer therapies in the twenty-first century: lessons from imatinib. *Clin Pharmacol Ther*, 87(5), 543-52 (2010)

37. B Bran, G Bran, K Hormann, F Riedel: The platelet-derived growth factor receptor as a target for vascular endothelial growth factor-mediated anti-angiogenetic therapy in head and neck cancer. *Int J Oncol*, 34(1), 255-61 (2009)

38. EB Pasquale: Eph receptors and ephrins in cancer: bidirectional signalling and beyond. *Nat Rev Cancer*, 10(3), 165-80 (2010)

39. R Masood, SR Kumar, UK Sinha, DL Crowe, V Krasnoperov, RK Reddy, S Zozulya, J Singh, G Xia, D Broek, AH Schonthal, PS Gill: EphB4 provides survival advantage to squamous cell carcinoma of the head and neck. *Int J Cancer*, 119(6), 1236-48 (2006)

40. RS Rivera, M Gunduz, H Nagatsuka, E Gunduz, B Cengiz, K Fukushima, LB Beder, D Pehlivan, N Yamanaka, K Shimizu, N Nagai: Involvement of EphA2 in head and neck squamous cell carcinoma: mRNA expression, loss of heterozygosity and immunohistochemical studies. *Oncol Rep*, 19(5), 1079-84 (2008)

41. Z Shao, WF Zhang, XM Chen, ZJ Shang: Expression of EphA2 and VEGF in squamous cell carcinoma of the tongue: correlation with the angiogenesis and clinical outcome. *Oral Oncol*, 44(12), 1110-7 (2008)

42. Z Wu, JB Doondeea, AM Gholami, MC Janning, S Lemeer, K Kramer, SA Eccles, SM Gollin, R Grenman, A Walch, SM Feller, B Kuster: Quantitative chemical proteomics reveals new potential drug targets in head and neck cancer. *Mol Cell Proteomics*, 10(12), M111 011635 (2011)

43. R Noberini, I Lamberto, EB Pasquale: Targeting Eph receptors with peptides and small molecules: progress and challenges. *Semin Cell Dev Biol*, 23(1), 51-7 (2012)

44. R Avraham, Y Yarden: Feedback regulation of EGFR signalling: decision making by early and delayed loops. *Nat Rev Mol Cell Biol*, 12(2), 104-17 (2011)

45. P O-Charoenrat, P Rhys-Evans, S Eccles: Characterization of ten newly-derived human head and neck squamous carcinoma cell lines with special reference to c-erbB proto-oncogene expression. *Anticancer Res*, 21(3B), 1953-63 (2001)

46. MR Campbell, D Amin, MM Moasser: HER3 comes of age: new insights into its functions and role in signaling, tumor biology, and cancer therapy. *Clin Cancer Res*, 16(5), 1373-83 (2010)

47. KR Legate, E Montanez, O Kudlacek, R Fassler: ILK, PINCH and parvin: the tIPP of integrin signalling. *Nat Rev Mol Cell Biol*, 7(1), 20-31 (2006)

48. M Agulnik: New approaches to EGFR inhibition for locally advanced or metastatic squamous cell carcinoma of the head and neck (SCCHN). *Med Oncol*, doi: 10.1007/s12032-012-0159-2 (2012)

49. L Vecchione, B Jacobs, N Normanno, F Ciardiello, S Tejpar: EGFR-targeted therapy. *Exp Cell Res*, 317(19), 2765-71 (2011)

50. W Bergler, H Bier, U Ganzer: The expression of epidermal growth factor receptors in the oral mucosa of patients with oral cancer. *Arch Otorhinolaryngol*, 246(3), 121-5 (1989)

51. J Rubin Grandis, MF Melhem, EL Barnes, DJ Tweardy: Quantitative immunohistochemical analysis of transforming growth factor-alpha and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer*, 78(6), 1284-92 (1996)

52. CR Leemans, BJ Braakhuis, RH Brakenhoff: The molecular biology of head and neck cancer. *Nat Rev Cancer*, 11(1), 9-22 (2011)

53. V Ratushny, I Astsaturov, BA Burtness, EA Golemis, JS Silverman: Targeting EGFR resistance networks in head and neck cancer. *Cell Signal*, 21(8), 1255-68 (2009)

54. NG Chau, B Perez-Ordonez, K Zhang, NA Pham, J Ho, T Zhang, O Ludkovski, L Wang, EX Chen, MS Tsao, S Kamel-Reid, LL Siu: The association between EGFR variant III, HPV, p16, c-MET, EGFR gene copy number and response to EGFR inhibitors in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *Head Neck Oncol*, 3, 11 (2011)

55. K Brunner, CA Fischer, O Driemel, A Hartmann, G Brockhoff, S Schwarz: EGFR (HER) family protein expression and cytogenetics in 219 squamous cell carcinomas of the upper respiratory tract: ERBB2 overexpression independent prediction of poor prognosis. *Anal Quant Cytol Histol*, 32(2), 78-89 (2010)

56. R Del Sordo, F Angiero, G Bellezza, A Cavaliere, MG Mameli, M Stefani, E Dessy, A Sidoni: HER family receptors expression in squamous cell carcinoma of the tongue: study of the possible prognostic and biological significance. *J Oral Pathol Med*, 39(1), 79-86 (2010)

57. G Sithanandam, LM Anderson: The ERBB3 receptor in cancer and cancer gene therapy. *Cancer Gene Ther*, 15(7), 413-48 (2008)

58. M Takikita, R Xie, JY Chung, H Cho, K Ylaya, SM Hong, CA Moskaluk, SM Hewitt: Membranous expression of Her3 is associated with a decreased survival in head and neck squamous cell carcinoma. *J Transl Med*, 9, 126 (2011)

59. P O-charoenrat, PH Rhys-Evans, H Modjtahedi, SA Eccles: The role of c-erbB receptors and ligands in head and neck squamous cell carcinoma. *Oral Oncol*, 38(7), 627-40 (2002)

60. LF Chen, EE Cohen, JR. Grandis: New strategies in head and neck cancer: understanding resistance to epidermal growth factor receptor inhibitors. *Clin Cancer Res*, 16(9), 2489-95 (2010)

61. I Barnea, S Haif, R Keshet, V Karaush, S Lev-Ari, A Khafif, A Shtabsky, Y Yarden, A Vexler, RB. Yosef: Targeting ErbB-1 and ErbB-4 in irradiated head and neck cancer: Results of in vitro and in vivo studies. *Head Neck*, doi: 10.1002/hed.22967 (2012)

62. JC Peak, NP Jones, S Hobbs, M Katan, SA Eccles: Phospholipase C gamma 1 regulates the Rap GEF1-Rap1 signalling axis in the control of human prostate carcinoma cell adhesion. *Oncogene*, 27(20), 2823-32 (2008)

63. H Nozawa, G Howell, S Suzuki, Q Zhang, Y Qi, J Klein-Seetharaman, A Wells, JR Grandis,SM Thomas: Combined inhibition of PLC{gamma}-1 and c-Src abrogates epidermal growth factor receptor-mediated head and neck squamous cell carcinoma invasion. *Clin Cancer Res*, 14(13), 4336-44 (2008)

64. SM Thomas, FM Coppelli, A Wells, WE Gooding, J Song, J Kassis, SD Drenning, JR Grandis: Epidermal growth factor receptor-stimulated activation of phospholipase Cgamma-1 promotes invasion of head and neck squamous cell carcinoma. *Cancer Res*, 63(17), 5629-35 (2003)

65. Q Zhang, SM Thomas, S Xi, TE Smithgall, JM Siegfried, J Kamens, WE Gooding, JR Grandis: SRC family kinases mediate epidermal growth factor receptor ligand cleavage, proliferation, and invasion of head and neck cancer cells. *Cancer Res*, 64(17), 6166-73 (2004)

66. S Xi, Q Zhang, KF Dyer, EC Lerner, TE Smithgall, WE Gooding, J Kamens, JR Grandis: Src kinases mediate STAT growth pathways in squamous cell carcinoma of the head and neck. *J Biol Chem*, 278(34), 31574-83 (2003)

67. KS Spencer, D Graus-Porta, J Leng, NE Hynes, RL Klemke: ErbB2 is necessary for induction of carcinoma cell invasion by ErbB family receptor tyrosine kinases. *J Cell Biol*, 148(2), 385-97 (2000)

68. C Cripps, E Winquist, MC Devries, D Stys-Norman, R Gilbert: Epidermal growth factor receptor targeted therapy in stages III and IV head and neck cancer. *Curr Oncol*, 17(3), 37-48 (2010)

69. NS Dhomen, J Mariadason, N Tebbutt, AMScott: Therapeutic targeting of the epidermal growth factor receptor in human cancer. *Crit Rev Oncog*, 17(1), 31-50 (2012)

70. C Fung, JR Grandis: Emerging drugs to treat squamous cell carcinomas of the head and neck. *Expert Opin Emerg Drugs*, 15(3), 355-73 (2010)

71. ME Sharafinski, RL Ferris, S Ferrone, JR Grandis: Epidermal growth factor receptor targeted therapy of

squamous cell carcinoma of the head and neck. *Head Neck*, 32(10), 1412-21 (2010)

72. Y Rukazenkov, G Speake, G Marshall, J Anderton, BR Davies, RW Wilkinson, DM Hickinson, A Swaisland: Epidermal growth factor receptor tyrosine kinase inhibitors: similar but different? *Anticancer Drugs*, 20(10), 856-66 (2009)

73. EE Cohen, MA Kane, MA List, BE Brockstein, B Mehrotra, D Huo, AM Mauer, C Pierce, A Dekker, EE Vokes: Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res*, 11(23), 8418-24 (2005)

74. DL Wheeler, EF Dunn, PM Harari: Understanding resistance to EGFR inhibitors-impact on future treatment strategies. *Nat Rev Clin Oncol*, 7(9), 493-507 (2010)

75. A Cassell, JR Grandis: Investigational EGFR-targeted therapy in head and neck squamous cell carcinoma. *Expert Opin Investig Drugs*, 19(6), 709-22 (2010)

76. EE Cohen, DW Davis, TG Karrison, TY Seiwert, SJ Wong, S Nattam, MF Kozloff, JI Clark, DH Yan, W Liu, C Pierce, JE Dancey, K Stenson, E Blair, A Dekker, EE Vokes: Erlotinib and bevacizumab in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck: a phase I/II study. *Lancet Oncol*, 10(3), 247-57 (2009)

77. DS Yoo, JP Kirkpatrick, O Craciunescu, G Broadwater, BL Peterson, MD Carroll, R Clough, JR MacFall, J Hoang, RL Scher, RM Esclamado, FR Dunphy, NE Ready, DM Brizel: Prospective trial of synchronous bevacizumab, erlotinib, and concurrent chemoradiation in locally advanced head and neck cancer. *Clin Cancer Res*, 18(5), 1404-14 (2012)

78. N Kondo, M Tsukuda, Y Ishiguro, M Kimura, K Fujita, A Sakakibara, H Takahashi, G Toth, H Matsuda: Antitumor effects of lapatinib (GW572016), a dual inhibitor of EGFR and HER-2, in combination with cisplatin or paclitaxel on head and neck squamous cell carcinoma. *Oncol Rep*, 23(4), 957-63 (2010)

79. JM Del Campo, R Hitt, P Sebastian, C Carracedo, D Lokanatha, J Bourhis, S Temam, D Cupissol, D De Raucourt, N Maroudias, CM Nutting, N Compton, D Midwinter, L Downie, N Biswas-Baldwin, I El-Hariry, KJ Harrington: Effects of lapatinib monotherapy: results of a randomised phase II study in therapy-naive patients with locally advanced squamous cell carcinoma of the head and neck. *Br J Cancer*, 105(5), 618-27 (2011)

80. JA de Souza, DW Davis, Y Zhang, A Khattri, TY Seiwert, S Aktolga, S Wong, MF Kozloff, S Nattam, MW Lingen, R Kunnavakkam, KM Stenson, EA Blair, J Bozeman, JE Dancey, EE Vokes, EE Cohen: A Phase II Study of Lapatinib in Recurrent/Metastatic Squamous Cell Carcinoma of the Head and Neck. *Clin Cancer Res*, 18(8), 2336-43 (2012)

81. D Jackman, W Pao, GJ Riely, JA Engelman, MG Kris, PA Janne, T Lynch, BE Johnson, VA Miller: Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. *J Clin Oncol*, 28(2), 357-60 (2010)

82. G Giaccone, Y Wang: Strategies for overcoming resistance to EGFR family tyrosine kinase inhibitors. *Cancer Treat Rev*, 37(6), 456-64 (2011)

83. SW Han, TY Kim, PG Hwang, S Jeong, J Kim, IS Choi, DY Oh, JH Kim, DW Kim, DH Chung, SA Im, YT Kim, JS Lee, DS Heo, YJ Bang, NK Kim: Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol*, 23(11), 2493-501 (2005)

84. J Loeffler-Ragg, M Witsch-Baumgartner, A Tzankov, W Hilbe, I Schwentner, GM Sprinzl, G Utermann, H Zwierzina: Low incidence of mutations in EGFR kinase domain in Caucasian patients with head and neck squamous cell carcinoma. *Eur J Cancer*, 42(1), 109-11 (2006)

85. EH Tan, C Goh, WT Lim, KC Soo, ML Khoo, T Tan, DS Tan, MK Ang, QS Ng, PH Tan, A Lim, J Hwang, YH Teng, TH Lim, SH Tan, N Baskaran, KM Hui: Gefitinib, cisplatin, and concurrent radiotherapy for locally advanced head and neck cancer: EGFR FISH, protein expression, and mutational status are not predictive biomarkers. *Ann Oncol*, 23(4), 1010-6 (2012)

86. EE Cohen, DJ Haraf, R Kunnavakkam, KM Stenson, EA Blair, B. Brockstein, EP Lester, JK Salama, A Dekker, R Williams, ME Witt, TA Grushko, JJ Dignam, MW Lingen, OI Olopade, EE Vokes: Epidermal growth factor receptor inhibitor gefitinib added to chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol*, 28(20), 3336-43 (2010)

87. JS Stewart, EE Cohen, L Licitra, CM Van Herpen, C Khorprasert, D Soulieres, P Vodvarka, D Rischin, AM Garin, FR Hirsch, M Varella-Garcia, S Ghiorghiu, L Hargreaves, A Armour, G Speake, A Swaisland, EE Vokes: Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol*, 27(11), 1864-71 (2009)

88. S Wheeler, DR Siwak, R Chai, C LaValle, RR Seethala, L Wang, K Cieply, C Sherer, C Joy, GB Mills, A Argiris, JM Siegfried, JR Grandis, AM Egloff: Tumor epidermal growth factor receptor and EGFR PY1068 are independent prognostic indicators for head and neck squamous cell carcinoma. *Clin Cancer Res*, 18(8), 2278-89 (2012)

89. N Stransky, AM Egloff, AD Tward, AD Kostic, K Cibulskis, A Sivachenko, GV Kryukov, MS Lawrence, C Sougnez, A McKenna, E Shefler, AH Ramos, P Stojanov, SL Carter, D Voet, ML Cortes, D Auclair, MF Berger, G Saksena, C Guiducci, RC Onofrio, M Parkin, M Romkes, JL Weissfeld, RR Seethala, L Wang, C Rangel-Escareno, JC Fernandez-Lopez, A Hidalgo-Miranda, J Melendez-Zajgla, W Winckler, K Ardlie, SB Gabriel, M Meyerson, ES Lander, G Getz, TR Golub, LA Garraway, JR Grandis: The mutational landscape of head and neck squamous cell carcinoma. *Science*, 333(6046), 1157-60 (2011)

90. LV Sequist, BA Waltman, D Dias-Santagata, S Digumarthy, AB Turke, P Fidias, K Bergethon, AT Shaw, S Gettinger, AK Cosper, S Akhavanfard, RS Heist, J Temel, JG Christensen, JC Wain, TJ Lynch, K Vernovsky, EJ Mark, M Lanuti, AJ Iafrate, M Mino-Kenudson, JA Engelman: Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med*, 3(75), 75ra26 (2011)

91. ME Irwin, KL Mueller, N Bohin, Y Ge, JL Boerner: Lipid raft localization of EGFR alters the response of cancer cells to the EGFR tyrosine kinase inhibitor gefitinib. *J Cell Physiol*, 226(9), 2316-28 (2011)

92. AJ Mantha, KE McFee, N Niknejad, G Goss, IA Lorimer, J Dimitroulakos: Epidermal growth factor receptor-targeted therapy potentiates lovastatin-induced apoptosis in head and neck squamous cell carcinoma cells. *J Cancer Res Clin Oncol*, 129(11), 631-41 (2003)

93. TM Brand, M Iida, C Li, DL Wheeler: The nuclear epidermal growth factor receptor signaling network and its role in cancer. *Discov Med*, 12(66), 419-32 (2011)

94. WC Huang, YJ Chen, LY Li, YL Wei, SC Hsu, SL Tsai, PC Chiu, WP Huang, YN Wang, CH Chen, WC Chang, AJ Chen, CH Tsai, MC Hung: Nuclear translocation of epidermal growth factor receptor by Akt-dependent phosphorylation enhances breast cancer-resistant protein expression in gefitinib-resistant cells. *J Biol Chem*, 286(23), 20558-68 (2011)

95. LG Morris, BS Taylor, TG Bivona, Y Gong, S Eng, CW Brennan, A Kaufman, ER Kastenhuber, VE Banuchi, B Singh, A Heguy, A Viale, IK Mellinghoff, J Huse, I Ganly, TA Chan: Genomic dissection of the epidermal growth factor receptor (EGFR)/PI3K pathway reveals frequent deletion of the EGFR phosphatase PTPRS in head and neck cancers. *Proc Natl Acad Sci U S A*, 108(47), 19024-9 (2011)

96. N Kondo, M Tsukuda, A Sakakibara, H Takahashi, H Hyakusoku, M Komatsu, T Niho, K Nakazaki, G Toth: Combined molecular targeted drug therapy for EGFR and HER-2 in head and neck squamous cell carcinoma cell lines. *Int J Oncol*, 40(6), 1805-12 (2012)

97. K Erjala, M Sundvall, TT Junttila, N Zhang, M Savisalo, P Mali, J Kulmala, J Pulkkinen, R Grenman, K Elenius: Signaling via ErbB2 and ErbB3 associates with resistance and epidermal growth factor receptor (EGFR) amplification with sensitivity to EGFR inhibitor gefitinib in head and neck squamous cell carcinoma cells. *Clin Cancer Res*, 12(13), 4103-11 (2006)

98. B Schoeberl, AC Faber, D Li, MC Liang, K Crosby, M Onsum, O Burenkova, E Pace, Z Walton, L Nie, A Fulgham, Y Song, UB Nielsen, JA Engelman, KK Wong: An ErbB3 antibody, MM-121, is active in cancers with ligand-dependent activation. *Cancer Res*, 70(6), 2485-94 (2010)

99. JA Engelman, K Zejnullahu, T Mitsudomi, Y Song, C Hyland, JO Park, N Lindeman, CM Gale, X Zhao, J Christensen, T Kosaka, AJ Holmes, AM Rogers, F Cappuzzo, T Mok, C Lee, BE Johnson, LC Cantley, PA Janne: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science*, 316(5827), 1039-43 (2007)

100. M Guix, AC Faber, SE Wang, MG Olivares, Y Song, S Qu, C Rinehart, B Seidel, D Yee, CL Arteaga, JA Engelman: Acquired resistance to EGFR tyrosine kinase inhibitors in cancer cells is mediated by loss of IGF-binding proteins. *J Clin Invest*, 118(7), 2609-19 (2008)

101. MJ Jameson, AD Beckler, LE Taniguchi, A Allak, LB Vanwagner, NG Lee, WC Thomsen, MA Hubbard, CY Thomas: Activation of the insulin-like growth factor-1 receptor induces resistance to epidermal growth factor receptor antagonism in head and neck squamous carcinoma cells. *Mol Cancer Ther*, 10(11), 2124-34 (2011)

102. F Di Fiore, F Blanchard, F Charbonnier, F Le Pessot, A Lamy, MP Galais, L Bastit, A Killian, R Sesboue, JJ Tuech, AM Queuniet, B Paillot, JC Sabourin, F Michot, P Michel, T Frebourg: Clinical relevance of KRAS mutation detection in metastatic colorectal cancer treated by Cetuximab plus chemotherapy. *Br J Cancer*, 96(8), 1166-9 (2007)

103. A Lievre, JB Bachet, D Le Corre, V Boige, B Landi, JF Emile, JF Cote, G Tomasic, C Penna, M Ducreux, P Rougier, . Penault-Llorca, P Laurent-Puig: KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res*, 66(8), 3992-5 (2006)

104. DA Eberhard, BE Johnson, LC Amler, AD Goddard, SL Heldens, RS Herbst, WL Ince, PA Janne, T Januario, DH Johnson, P Klein, VA Miller, MA Ostland, DA Ramies, D Sebisanovic, JA Stinson, YR Zhang, S Seshagiri, KJ Hillan: Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. *J Clin Oncol*, 23(25), 5900-9 (2005)

105. H Linardou, IJ Dahabreh, D Kanaloupiti, F Siannis, D Bafaloukos, P Kosmidis, CA Papadimitriou, S Murray: Assessment of somatic k-RAS mutations as a mechanism associated with resistance to EGFR-targeted agents: a systematic review and meta-analysis of studies in advanced non-small-cell lung cancer and metastatic colorectal cancer. *Lancet Oncol*, 9(10), 962-72 (2008)

106. JA Anderson, JC Irish, CM McLachlin, BY Ngan: H-ras oncogene mutation and human papillomavirus infection in oral carcinomas. *Arch Otolaryngol Head Neck Surg*, 120(7), 755-60 (1994)

107. AK Murugan, NT Hong, TT Cuc, NC Hung, AK Munirajan, MA Ikeda, N Tsuchida: Detection of two novel mutations and relatively high incidence of H-RAS

mutations in Vietnamese oral cancer. *Oral Oncol*, 45(10), e161-6 (2009)

108. R Bianco, I Shin, CA Ritter, FM Yakes, A Basso, N Rosen, J Tsurutani, PA Dennis, GB Mills, CL Arteaga: Loss of PTEN/MMAC1/TEP in EGF receptor-expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors. *Oncogene*, 22(18), 2812-22 (2003)

109. ML Sos, M Koker, BA Weir, S Heynck, R Rabinovsky, T Zander, JM Seeger, J Weiss, F Fischer, P Frommolt, K Michel, M Peifer, C Mermel, L Girard, M Peyton, AF Gazdar, JD Minna, LA Garraway, H Kashkar, W Pao, M Meyerson, RK Thomas: PTEN loss contributes to erlotinib resistance in EGFR-mutant lung cancer by activation of Akt and EGFR. *Cancer Res*, 69(8), 3256-61 (2009)

110. JT Garrett, CL Arteaga: Resistance to HER2-directed antibodies and tyrosine kinase inhibitors: mechanisms and clinical implications. *Cancer Biol Ther*, 11(9), 793-800 (2011)

111. P Zindy, Y Berge, B Allal, T Filleron, S Pierredon, A Cammas, S Beck, L Mhamdi, L Fan, G Favre, JP Delord, H Roche, F Dalenc, M Lacroix-Triki, S Vagner: Formation of the eIF4F translation-initiation complex determines sensitivity to anticancer drugs targeting the EGFR and HER2 receptors. *Cancer Res*, 71(12), 4068-73 (2011)

112. P Timpson, AS Wilson, GM Lehrbach, RL Sutherland, EA Musgrove, RJ Daly: Aberrant expression of cortactin in head and neck squamous cell carcinoma cells is associated with enhanced cell proliferation and resistance to the epidermal growth factor receptor inhibitor gefitinib. *Cancer Res*, 67(19), 9304-14 (2007)

113. Y Haddad, W Choi, DJ McConkey: Delta-crystallin enhancer binding factor 1 controls the epithelial to mesenchymal transition phenotype and resistance to the epidermal growth factor receptor inhibitor erlotinib in human head and neck squamous cell carcinoma lines. *Clin Cancer Res*, 15(2), 532-42 (2009)

114. S Maseki, K Ijichi, H Tanaka, M Fujii, Y Hasegawa, T Ogawa, S Murakami, E Kondo, H Nakanishi: Acquisition of EMT phenotype in the gefitinib-resistant cells of a head and neck squamous cell carcinoma cell line through Akt/GSK-3beta/snail signalling pathway. *Br J Cancer*, 106(6), 1196-204 (2012)

115. A Jain, CA Tindell, I Laux, JB Hunter, J Curran, A Galkin, DE Afar, N Aronson, S Shak, RB Natale, DB Agus: Epithelial membrane protein-1 is a biomarker of gefitinib resistance. *Proc Natl Acad Sci U S A*, 102(33), 11858-63 (2005)

116. LJ Kornberg, D Villaret, M Popp, L Lui, R McLaren, H Brown, D Cohen, J Yun, M McFadden: Gene expression profiling in squamous cell carcinoma of the oral cavity shows abnormalities in several signaling pathways. *Laryngoscope*, 115(4), 690-8 (2005)

117. P Workman, PA Clarke: Resisting targeted therapy: fifty ways to leave your EGFR. *Cancer Cell*, 19(4), 437-40 (2011)

118. HC Thoeny, BD Ross: Predicting and monitoring cancer treatment response with diffusion-weighted MRI. *J Magn Reson Imaging*, 32(1), 2-16 (2010)

119. LA Byers, FC Holsinger, MS Kies, WN William, AK El-Naggar, JJ Lee, J Hu, A Lopez, HT Tran, S Yan, Z Du, KK Ang, BS Glisson, MG Raso, II Wistuba, JN Myers, WK Hong, V Papadimitrakopoulou, SM Lippman, JV Heymach: Serum signature of hypoxia-regulated factors is associated with progression after induction therapy in head and neck squamous cell cancer. *Mol Cancer Ther*, 9(6), 1755-63 (2010)

120. SH Ou: Second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs): A better mousetrap? A review of the clinical evidence. *Crit Rev Oncol Hematol*, Epub ahead of print doi: 10.1016/j.critrevonc.2011.11.010 (2012)

121. KM Quesnelle, JR Grandis: Dual Kinase Inhibition of EGFR and HER2 Overcomes Resistance to Cetuximab in a Novel In Vivo Model of Acquired Cetuximab Resistance. *Clin Cancer Res*, 17(18), 5935-44 (2011)

122. V Hirsh: Afatinib (BIBW 2992) development in non-small-cell lung cancer. *Future Oncol*, 7(7), 817-25 (2011)

123. VA Miller, V Hirsh, J Cadranel, YM Chen, K Park, SW Kim, C Zhou, WC Su, M Wang, Y Sun, DS Heo, L Crino, EH Tan, TY Chao, M Shahidi, XJ Cong, RM Lorence, JC Yang: Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol*, 13(5), 528-38 (2012)

124. LL Siu, SJ Hotte, SA Laurie, S Singh, E Winquist, SKL Chia, EX Chen, KK Chan, T Wang, I Taylor, A Ruiz-Garcia, C Mormont, D Soulieres: Phase II trial of the irreversible oral pan-human EGF receptor (HER) inhibitor PF-00299804 (PF) as first-line treatment in recurrent and/or metastatic (RM) squamous cell carcinoma of the head and neck (SCCHN). In: *J Clin Oncol, 2011 ASCO Annual Meeting Proceedings*, 29(Supplement 15), American Society of Clinical Oncology abstract nr 5561 (2011)

125. DW Fry: Site-directed irreversible inhibitors of the erbB family of receptor tyrosine kinases as novel chemotherapeutic agents for cancer. *Anticancer Drug Des*, 15(1), 3-16 (2000)

126. Y Pan, Y Xu, S Feng, S Luo, R Zheng, J Yang, L Wang, L Zhong, HY Yang, BL Wang, Y Yu, J Liu, Z Cao, X Wang, P Ji, Z Wang, X Chen, S Zhang, YQ Wei, SY

Yang: SKLB1206, a novel orally available multikinase inhibitor targeting EGFR activating and T790M mutants, ErbB2, ErbB4, and VEGFR2, displays potent antitumor activity both in vitro and in vivo. *Mol Cancer Ther*, 11(4), 952-62 (2012)

127. MC Pietanza, TJ Lynch, Jr., PN Lara, Jr., J Cho, RH Yanagihara, N Vrindavanam, NM Chowhan, SM Gadgeel, NA Pennell, R Funke, B Mitchell, HA Wakelee, VA Miller: XL647-a multitargeted tyrosine kinase inhibitor: results of a phase II study in subjects with non-small cell lung cancer who have progressed after responding to treatment with either gefitinib or erlotinib. *J Thorac Oncol*, 7(1), 219-26 (2012)

128. J Chmielecki, MC Pietanza, D Aftab, R Shen, Z Zhao, X Chen, K Hutchinson, A Viale, MG Kris, T Stout, V Miller, N Rizvi, W Pao: EGFR-mutant lung adenocarcinomas treated first-line with the novel EGFR inhibitor, XL647, can subsequently retain moderate sensitivity to erlotinib. *J Thorac Oncol*, 7(2), 434-42 (2012)

129. OG Yigitbasi, MN Younes, D Doan, SA Jasser, BA Schiff, CD Bucana, BN Bekele, IJ Fidler, JN Myers: Tumor cell and endothelial cell therapy of oral cancer by dual tyrosine kinase receptor blockade. *Cancer Res*, 64(21), 7977-84 (2004)

130. JD Klein, A Christopoulos, SM Ahn, WE Gooding, JR Grandis, S Kim: Antitumor effect of vandetanib through EGFR inhibition in head and neck squamous cell carcinoma. *Head Neck*, Epub ahead of print doi: 10.1002/hed.21917 (2012)

131. D Sano, F Matsumoto, DR Valdecanas, M Zhao, DP Molkentine, Y Takahashi, EY Hanna, V Papadimitrakopoulou, J Heymach, L Milas, JN Myers: Vandetanib restores head and neck squamous cell carcinoma cells' sensitivity to cisplatin and radiation in vivo and in vitro. *Clin Cancer Res*, 17(7), 1815-27 (2011)

132. P Workman, F Burrows, L Neckers, N Rosen: Drugging the cancer chaperone HSP90: combinatorial therapeutic exploitation of oncogene addiction and tumor stress. *Ann N Y Acad Sci*, 1113, 202-16 (2007)

133. CC Chiu, CY Lin, LY Lee, YJ Chen, YC Lu, HM Wang, CT Liao, JT Chang, AJ Cheng: Molecular chaperones as a common set of proteins that regulate the invasion phenotype of head and neck cancer. *Clin Cancer Res*, 17(14), 4629-41 (2011)

134. S Sanderson, M Valenti, S Gowan, L Patterson, Z Ahmad, P Workman, SA Eccles: Benzoquinone ansamycin heat shock protein 90 inhibitors modulate multiple functions required for tumor angiogenesis. *Mol Cancer Ther*, 5(3), 522-32 (2006)

135. SA Eccles, A Massey, FI Raynaud, SY Sharp, G Box, M Valenti, L Patterson, A de Haven Brandon, S Gowan, F Boxall, W Aherne, M Rowlands, A Hayes, V Martins, F Urban, K Boxall, C Prodromou, L Pearl, K James, TP Matthews, KM Cheung, A Kalusa, K Jones, E McDonald, X Barril, PA Brough, JE Cansfield, B Dymock, MJ Drysdale, H Finch, R Howes, RE Hubbard, A Surgenor, P Webb, M Wood, L Wright, P Workman: NVP-AUY922: a novel heat shock protein 90 inhibitor active against xenograft tumor growth, angiogenesis, and metastasis. *Cancer Res*, 68(8), 2850-60 (2008)

136. S Zaidi, M McLaughlin, SA Bhide, SA Eccles, P Workman, CM Nutting, RA Huddart, KJ Harrington: The HSP90 inhibitor NVP-AUY922 radiosensitizes by abrogation of homologous recombination resulting in mitotic entry with unresolved DNA damage. *PLoS One*, 7(4), e35436 (2012)

137. P Kabolizadeh, GJ Kubicek, DE Heron, RL Ferris, MK Gibson: The role of cetuximab in the management of head and neck cancers. *Expert Opin Biol Ther*, 12(4), 517-28 (2012)

138. C Moon, YK Chae, J Lee: Targeting epidermal growth factor receptor in head and neck cancer: lessons learned from cetuximab. *Exp Biol Med (Maywood)*, 235(8), 907-20 (2010)

139. H Kimura, K Sakai, T Arao, T Shimoyama, T Tamura, K Nishio: Antibody-dependent cellular cytotoxicity of cetuximab against tumor cells with wild-type or mutant epidermal growth factor receptor. *Cancer Sci*, 98(8), 1275-80 (2007)

140. P Specenier, JB Vermorken: Cetuximab in the treatment of squamous cell carcinoma of the head and neck. *Expert Rev Anticancer Ther*, 11(4), 511-24 (2011)

141. R Mehra, IG Serebriiskii, RL Dunbrack, Jr., MK Robinson, B. Burtness, EA Golemis: Protein-intrinsic and signaling network-based sources of resistance to EGFR- and ErbB family-targeted therapies in head and neck cancer. *Drug Resist Updat*, 14(6), 260-79 (2011)

142. JA Bonner, PM Harari, J Giralt, N Azarnia, DM Shin, RB Cohen, CU Jones, R Sur, D Raben, J Jassem, R Ove, MS Kies, J Baselga, H Youssoufian, N Amellal, EK Rowinsky, KK Ang: Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*, 354(6), 567-78 (2006)

143. F Rivera, A Garcia-Castano, N Vega, ME Vega-Villegas, L Gutierrez-Sanz: Cetuximab in metastatic or recurrent head and neck cancer: the EXTREME trial. *Expert Rev Anticancer Ther*, 9(10), 1421-8 (2009)

144. DA de Andrade, JP Machiels: Treatment options for patients with recurrent or metastatic squamous cell carcinoma of the head and neck, who progress after platinum-based chemotherapy. *Curr Opin Oncol*, 24(3), 211-7 (2012)

145. JP Machiels, S Subramanian, A Ruzsa, G Repassy, I Lifirenko, A Flygare, P Sorensen, T Nielsen, S Lisby, PM Clement: Zalutumumab plus best supportive care versus

best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomised phase 3 trial. *Lancet Oncol*, 12(4), 333-43 (2011)

146. U Schick, DM Gujral, TM Richards, KJ Harrington, CM Nutting: Zalutumumab in head and neck cancer. *Expert Opin Biol Ther*, 12(1), 119-25 (2012)

147. C Berger, U Krengel, E Stang, E Moreno, IH Madshus: Nimotuzumab and cetuximab block ligand-independent EGF receptor signaling efficiently at different concentrations. *J Immunother*, 34(7), 550-5 (2011)

148. C Basavaraj, P Sierra, J Shivu, R Melarkode, E Montero, P Nair: Nimotuzumab with chemoradiation confers a survival advantage in treatment-naive head and neck tumors over expressing EGFR. *Cancer Biol Ther*, 10(7), 673-81 (2010)

149. B Kuenen, PO Witteveen, R Ruijter, G Giaccone, A Dontabhaktuni, F Fox, T Katz, H Youssoufian, J Zhu, EK Rowinsky, EE Voest: A phase I pharmacologic study of necitumumab (IMC-11F8), a fully human IgG1 monoclonal antibody directed against EGFR in patients with advanced solid malignancies. *Clin Cancer Res*, 16(6), 1915-23 (2010)

150. A Argiris, AG Duffy, S Kummar, NL Simone, Y Arai, SW Kim, SF Rudy, VR Kannabiran, X Yang, M Jang, Z Chen, N Suksta, T Cooley-Zgela, SG Ramanand, A Ahsan, MK Nyati, JJ Wright, C Van Waes: Early tumor progression associated with enhanced EGFR signaling with bortezomib, cetuximab, and radiotherapy for head and neck cancer. *Clin Cancer Res*, 17(17), 5755-64 (2011)

151. R Croasdale, K Wartha, JM Schanzer, KP Kuenkele, C Ries, K Mayer, C Gassner, M Wagner, N Dimoudis, S Herter, C Jaeger, C Ferrara, E Hoffmann, L Kling, W Lau, RF Staack, J Heinrich, W Scheuer, J Stracke, C Gerdes, U Brinkmann, P Umana, C Klein: Development of tetravalent IgG1 dual targeting IGF-1R-EGFR antibodies with potent tumor inhibition. *Arch Biochem Biophys*, Epub ahead of print doi: 10.1016/j.abb.2012.03.016 (2012)

152. D Lu, H Zhang, H Koo, J Tonra, P Balderes, M Prewett, E Corcoran, V Mangalampalli, R Bassi, D Anselma, D Patel, X Kang, DL Ludwig, DJ Hicklin, P Bohlen, L Witte, Z Zhu: A fully human recombinant IgG-like bispecific antibody to both the epidermal growth factor receptor and the insulin-like growth factor receptor for enhanced antitumor activity. *J Biol Chem*, 280(20), 19665-72 (2005)

153. AV Kamath, D Lu, P Gupta, D Jin, H. Xiang, A Wong, C Leddy, L Crocker, G Schaefer, MX Sliwkowski, LA Damico-Beyer: Preclinical pharmacokinetics of MEHD7945A, a novel EGFR/HER3 dual-action antibody, and prediction of its human pharmacokinetics and efficacious clinical dose. *Cancer Chemother Pharmacol*, 69(4), 1063-9 (2012)

154. SJ Hurwitz, H Zhang, S Yun, TD Batuwangala, M Steward, SD Holmes, D Rycroft, L Pan, M Tighiouart, HJ Shin, L Koenig, Y Wang, ZG. Chen, DM Shin: Pharmacodynamics of DT-IgG, a dual-targeting antibody against VEGF-EGFR, in tumor xenografted mice. *Cancer Chemother Pharmacol*, 69(3), 577-90 (2012)

155. RC Roovers, MJ Vosjan, T Laeremans, R El Khoulati, RC de Bruin, KM Ferguson, AJ Verkleij, GA van Dongen, PM van Bergen En Henegouwen: A biparatopic anti-EGFR nanobody efficiently inhibits solid tumour growth. *Int J Cancer*, 129(8), 2013–2024 (2011)

156. Z Liu, Y Liu, B Jia, H Zhao, X Jin, F Li, X Chen, F Wang: Epidermal growth factor receptor-targeted radioimmunotherapy of human head and neck cancer xenografts using 90Y-labeled fully human antibody panitumumab. *Mol Cancer Ther*, 9(8), 2297-308 (2010)

157. M Harris, XG Wang, Z Jiang, GL Goldberg, A Casadevall, E Dadachova: Radioimmunotherapy of experimental head and neck squamous cell carcinoma (HNSCC) with E6-specific antibody using a novel HPV-16 positive HNSCC cell line. *Head Neck Oncol*, 3(1), 9 (2011)

158. A. Sartore-Bianchi, M Moroni, S Veronese, C Carnaghi, E Bajetta, G Luppi, A Sobrero, C. Barone, S Cascinu, G Colucci, E Cortesi, M Nichelatti, M Gambacorta, S Siena: Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with panitumumab. *J Clin Oncol*, 25(22), 3238-45 (2007)

159. L Licitra, R Mesia, F Rivera, E Remenar, R Hitt, J Erfan, S Rottey, A Kawecki, D Zabolotnyy, M Benasso, S Storkel, S Senger, C Stroh, JB Vermorken: Evaluation of EGFR gene copy number as a predictive biomarker for the efficacy of cetuximab in combination with chemotherapy in the first-line treatment of recurrent and/or metastatic squamous cell carcinoma of the head and neck: EXTREME study. *Ann Oncol*, 22(5), 1078-87 (2011)

160. JC Sok, FM Coppelli, SM Thomas, MN Lango, S Xi, JL Hunt, ML Freilino, MW Graner, CJ Wikstrand, DD Bigner, WE Gooding, FB Furnari, JR Grandis: Mutant epidermal growth factor receptor (EGFRvIII) contributes to head and neck cancer growth and resistance to EGFR targeting. *Clin Cancer Res*, 12(17), 5064-73 (2006)

161. C Montagut, A Dalmases, B Bellosillo, M Crespo, S Pairet, M Iglesias, M Salido, M Gallen, S Marsters, SP Tsai, A Minoche, S Somasekar, S Serrano, H Himmelbauer, J Bellmunt, A Rovira, J Settleman, F Bosch, J Albanell: Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer. *Nat Med*, 18(2), 221-3 (2012)

162. I Tinhofer, K Klinghammer, W Weichert, M Knodler, A Stenzinger, T Gauler, V Budach, U Keilholz: Expression of amphiregulin and EGFRvIII affect outcome of patients with squamous cell carcinoma of the head and neck receiving cetuximab-docetaxel treatment. *Clin Cancer Res*, 17(15), 5197-204 (2011)

163. H Hatakeyama, H Cheng, P Wirth, A Counsell, SR Marcrom, CB Wood, PR Pohlmann, JGilbert, B Murphy,

WG Yarbrough, DL Wheeler, PM Harari, Y Guo, Y Shyr, RJ Slebos, CH Chung: Regulation of heparin-binding EGF-like growth factor by miR-212 and acquired cetuximab-resistance in head and neck squamous cell carcinoma. *PLoS One*, 5(9), e12702 (2010)

164. DL Wheeler, M Iida, TJ Kruser, MM Nechrebecki, EF Dunn, EA Armstrong, S Huang, PM Harari: Epidermal growth factor receptor cooperates with Src family kinases in acquired resistance to cetuximab. *Cancer Biol Ther*, 8(8), 696-703 (2009)

165. C Li, M Iida, EF Dunn, AJ Ghia, DL Wheeler: Nuclear EGFR contributes to acquired resistance to cetuximab. *Oncogene*, 28(43), 3801-13 (2009)

166. R Krumbach, J Schuler, M Hofmann, T Giesemann, HH Fiebig, T Beckers: Primary resistance to cetuximab in a panel of patient-derived tumour xenograft models: activation of MET as one mechanism for drug resistance. *Eur J Cancer*, 47(8), 1231-43 (2011)

167. K Yonesaka, K Zejnullahu, I Okamoto, T Satoh, F Cappuzzo, J Souglakos, D Ercan, A Rogers, M Roncalli, M Takeda, Y Fujisaka, J Philips, T Shimizu, O Maenishi, Y Cho, J Sun, A Destro, K Taira, K Takeda, T Okabe, J Swanson, H Itoh, M Takada, E Lifshits, K Okuno, JA Engelman, RA Shivdasani, K Nishio, M Fukuoka, M Varella-Garcia, K Nakagawa, PA Janne: Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. *Sci Transl Med*, 3(99), 99ra86 (2011)

168. DH Shin, HY Min, AK El-Naggar, SM Lippman, B Glisson, HY Lee: Akt/mTOR counteract the antitumor activities of cixutumumab, an anti-insulin-like growth factor I receptor monoclonal antibody. *Mol Cancer Ther*, 10(12), 2437-48 (2011)

169. A Viloria-Petit, T Crombet, S Jothy, D Hicklin, P Bohlen, JM Schlaeppi, J Rak, RS Kerbel: Acquired resistance to the antitumor effect of epidermal growth factor receptor-blocking antibodies in vivo: a role for altered tumor angiogenesis. *Cancer Res*, 61(13), 5090-101 (2001)

170. A Argiris, SC Lee, T Feinstein, S Thomas, BF Branstetter, R Seethala, L Wang, W Gooding, JR Grandis, RL Ferris: Serum biomarkers as potential predictors of antitumor activity of cetuximab-containing therapy for locally advanced head and neck cancer. *Oral Oncol*, 47(10), 961-6 (2011)

171. HD Brooks, BS Glisson, BN Bekele, LE Ginsberg, A El-Naggar, KS Culotta, N Takebe, J Wright, HT Tran, VA Papadimitrakopoulou: Phase 2 study of dasatinib in the treatment of head and neck squamous cell carcinoma. *Cancer*, 117(10), 2112-9 (2011)

172. G Martiny-Baron, P Holzer, E Billy, C Schnell, J Brueggen, M Ferretti, N Schmiedeberg, JM Wood, P Furet, P Imbach: The small molecule specific EphB4 kinase inhibitor NVP-BHG712 inhibits VEGF driven angiogenesis. *Angiogenesis*, 13(3), 259-67 (2010)

173. K Freier, C Schwaenen, C Sticht, C Flechtenmacher, J Muhling, C Hofele, B Radlwimmer, P Lichter, S Joos: Recurrent FGFR1 amplification and high FGFR1 protein expression in oral squamous cell carcinoma (OSCC). *Oral Oncol*, 43(1), 60-6 (2007)

174. Y Zhang, Y Hiraishi, H Wang, KS Sumi, Y Hayashido, S Toratani, M Kan, JD Sato, T Okamoto: Constitutive activating mutation of the FGFR3b in oral squamous cell carcinomas. *Int J Cancer*, 117(1), 166-8 (2005)

175. DT Rieke, Z Zuo, K Endhardt, M Keck, A Khattri, D Mahmutogulu, K Leung, M El Dinali, J Braegelmann, TY Seiwert,: Fibroblast growth factors in head and neck cancer: Genetic alterations and therapeutic targeting with ponatinib. In: *Proceedings of the 103rd Annual Meeting of the American Association for Cancer Research*, 2012 March 31-April 4; Chicago, Illinois. Washington,DC. Philadelphia: AACR p 7 abstract nr 2832 (2012)

176. M Resnicoff, JL Burgaud, HL Rotman, D Abraham, R Baserga: Correlation between apoptosis, tumorigenesis, and levels of insulin-like growth factor I receptors. *Cancer Res*, 55(17), 3739-41 (1995)

177. R Baserga: The insulin-like growth factor-I receptor as a target for cancer therapy. *Expert Opin Ther Targets*, 9(4), 753-68 (2005)

178. LM Knowles, LP Stabile, AM Egloff, ME Rothstein, SM Thomas, CT Gubish, EC Lerner, RR Seethala, S Suzuki, KM Quesnelle, S Morgan, RL Ferris, JR Grandis, JM Siegfried: HGF and c-Met participate in paracrine tumorigenic pathways in head and neck squamous cell cancer. *Clin Cancer Res*, 15(11), 3740-50 (2009)

179. JD Schultz, S Rotunno, F Riedel, C Anders, P Erben, RD Hofheinz, A Faber, C Thorn, JU Sommer, K Hormann, A Sauter: Synergistic effects of imatinib and carboplatin on VEGF, PDGF and PDGF-Ralpha/ss expression in squamous cell carcinoma of the head and neck in vitro. *Int J Oncol*, 38(4), 1001-12 (2011)

180. TJ Kruser, DL Wheeler, EA Armstrong, M Iida, KR Kozak, AJ van der Kogel, J Bussink, A Coxon, A Polverino, PM Harari: Augmentation of radiation response by motesanib, a multikinase inhibitor that targets vascular endothelial growth factor receptors. *Clin Cancer Res*, 16(14), 3639-47 (2010)

181. MM Cooney, KY Tserng, V Makar, RJ McPeak, ST Ingalls, A Dowlati, B Overmoyer, K McCrae, P Ksenich, P Lavertu, P Ivy, CL Hoppel, S Remick: A phase IB clinical and pharmacokinetic study of the angiogenesis inhibitor SU5416 and paclitaxel in recurrent or metastatic carcinoma of the head and neck. *Cancer Chemother Pharmacol*, 55(3), 295-300 (2005)

182. C Elser, LL Siu, E Winquist, M Agulnik, GR Pond, SF Chin, P Francis, R Cheiken, J Elting, A McNabola, D

Wilkie, O Petrenciuc, EX Chen: Phase II trial of sorafenib in patients with recurrent or metastatic squamous cell carcinoma of the head and neck or nasopharyngeal carcinoma. *J Clin Oncol*, 25(24), 3766-73 (2007)

183. G Fountzilas, A Fragkoulidi, A Kalogera-Fountzila, M Nikolaidou, M Bobos, J Calderaro, F Andreiuolo, M Marselos: A phase II study of sunitinib in patients with recurrent and/or metastatic non-nasopharyngeal head and neck cancer. *Cancer Chemother Pharmacol*, 65(4), 649-60 (2010)

184. NW Choong, M Kozloff, D Taber, HS Hu, J Wade, 3rd, P Ivy, TG Karrison, A Dekker, EE Vokes, EE Cohen: Phase II study of sunitinib malate in head and neck squamous cell carcinoma. *Invest New Drugs*, 28(5), 677-83 (2010)

185. D Soulieres, NN Senzer, EE Vokes, M Hidalgo, SS Agarwala, LL Siu: Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol*, 22(1), 77-85 (2004)

186. LL Siu, D Soulieres, EX Chen, GR Pond, SF Chin, P Francis, L Harvey, M Klein, W Zhang, J Dancey, EA Eisenhauer, E Winquist: Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital phase II consortium and National Cancer Institute of Canada Clinical Trials Group Study. *J Clin Oncol*, 25(16), 2178-83 (2007)

187. A Argiris, M Ghebremichael, J Gilbert, B Burtness, A Forastiere: A phase III randomized, placebo-controlled trial of docetaxel (D) with or without gefitinib (G) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): A trial of the Eastern Cooperative Oncology Group (ECOG). In: *J Clin Oncol, 2009 ASCO Annual Meeting Proceedings*, 27(Supplement 15), American Society of Clinical Oncology abstract nr 6011 (2009)

188. H Xu, LP Stabile, CT Gubish, WE Gooding, JR Grandis, JM Siegfried: Dual blockade of EGFR and c-Met abrogates redundant signaling and proliferation in head and neck carcinoma cells. *Clin Cancer Res*, 17(13), 4425-38 (2011)

189. F Bruzzese, A Leone, M Rocco, C Carbone, G Piro, M Caraglia, E Di Gennaro, A Budillon: HDAC inhibitor vorinostat enhances the antitumor effect of gefitinib in squamous cell carcinoma of head and neck by modulating ErbB receptor expression and reverting EMT. *J Cell Physiol*, 226(9), 2378-90 (2011)

190. V Papadimitrakopoulou, SJ Frank, GR Blumenschein, C Chen, M Kane, EE Cohen, P Langmuir, AD Krebs, SM Lipmann, D Raben: Phase I evaluation of vandetanib with radiation therapy (RT) +/– cisplatin in previously untreated advanced head and neck squamous cell carcinoma (HNSCC). In: *J Clin Oncol, 2009 ASCO Annual Meeting Proceedings*, 29(Supplement 15), American Society of Clinical Oncology abstract nr 6016 (2009)

191. T Seiwert, PM Clement, D Cupissol, J Del Campo, H de Mont-Serrat, GC Thurm, AS Blackman, EE Cohen: BIBW 2992 versus cetuximab in patients with metastatic or recurrent head and neck cancer (SCCHN) after failure of platinum-containing therapy with a cross-over period for processing patients: Preliminary results of a randomized, open-label phase II study. In: *J Clin Oncol, 2010 ASCO Annual Meeting Proceedings*, 27(Supplement 15), American Society of Clinical Oncology abstract nr 5501 (2010)

192. JA Engelman, K Zejnullahu, CM Gale, E Lifshits, AJ Gonzales, T Shimamura, F Zhao, PW Vincent, GN Naumov, JE Bradner, IW Althaus, L Gandhi, GI Shapiro, JM Nelson, JV Heymach, M Meyerson, KK Wong, PA Janne: PF00299804, an irreversible pan-ERBB inhibitor, is effective in lung cancer models with EGFR and ERBB2 mutations that are resistant to gefitinib. *Cancer Res*, 67(24), 11924-32 (2007)

193. F Tan, X Shen, D Wang, G Xie, X Zhang, L Ding, Y Hu, W He, Y Wang: Icotinib (BPI-2009H), a novel EGFR tyrosine kinase inhibitor, displays potent efficacy in preclinical studies. *Lung Cancer*, 76(2), 177-82 (2012)

194. SK Rabindran, CM Discafani, EC Rosfjord, M Baxter, MB Floyd, J Golas, WA Hallett, BD Johnson, R Nilakantan, E Overbeek, MF Reich, R Shen, X Shi, HR Tsou, YF Wang, A Wissner: Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. *Cancer Res*, 64(11), 3958-65 (2004)

195. X Cai, HX Zhai, J Wang, J Forrester, H Qu, L Yin, CJ Lai, R Bao, C Qian: Discovery of 7-(4-(3-ethynylphenylamino)-7-methoxyquinazolin-6-yloxy)-N-hydroxyheptanamide (CUDc-101) as a potent multi-acting HDAC, EGFR, and HER2 inhibitor for the treatment of cancer. *J Med Chem*, 53(5), 2000-9 (2010)

196. CJ Lai, R Bao, X Tao, J Wang, R Atoyan, H Qu, DG Wang, L Yin, M Samson, J Forrester, B Zifcak, GX Xu, S DellaRocca, HX Zhai, X Cai, WE Munger, M Keegan, CV Pepicelli, C Qian: CUDC-101, a multitargeted inhibitor of histone deacetylase, epidermal growth factor receptor, and human epidermal growth factor receptor 2, exerts potent anticancer activity. *Cancer Res*, 70(9), 3647-56 (2010)

197. T Shimizu, AW Tolcher, K Papadopoulos, A Patnaik, P LoRusso, LS Smith, M Beeram, D Rasco, G Chambers, M Keegan: The First-in-human, first-in-class study of CUDC-101, a multi-targeted inhibitor of HDAC, EGFR and HER2: A phase I study in patients with advanced cancer. In: *22nd EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics*, 2010 November 16-19; Berlin, Germany; European CanCer Organisation abstract nr 364 (2010)

198. TW Wong, FY Lee, S Emanuel, C Fairchild,. Fargnoli, B Fink, A Gavai, A Hammell, B Henley, C Hilt, JT Hunt, B Krishnan, D Kukral, A Lewin, H Malone, D

Norris, S Oppenheimer, G Vite, C Yu: Antitumor and antiangiogenic activities of BMS-690514, an inhibitor of human EGF and VEGF receptor kinase families. *Clin Cancer Res*, 17(12), 4031-41 (2011)

199. JB Vermorken, J Trigo, R Hitt, P Koralewski, E Diaz-Rubio, F Rolland, R Knecht, N Amellal, A Schueler, J Baselga: Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol*, 25(16), 2171-7 (2007)

200. JA Bonner, PM Harari, J Giralt, RB Cohen, CU Jones, RK Sur, D Raben, J Baselga, SA Spencer, J Zhu, H Youssoufian, EK Rowinsky, K K. Ang: Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol*, 11(1), 21-8 (2010)

201. B Burtness, MA Goldwasser, W Flood, B Mattar, AA Forastiere: Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin Oncol*, 23(34), 8646-54 (2005)

202. JB Vermorken, R Mesia, F Rivera, E Remenar, A Kawecki, S Rottey, J Erfan, D Zabolotnyy, HR Kienzer, D Cupissol, F Peyrade, M Benasso, I Vynnychenko, D De Raucourt, C Bokemeyer, A Schueler, N Amellal, R Hitt: Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*, 359(11), 1116-27 (2008)

203. M Merlano, E Russi, M Benasso, R Corvo, I Colantonio, R Vigna-Taglianti, V Vigo, A Bacigalupo, G Numico, N Crosetto, M Gasco, C Lo Nigro, R Vitiello, S Violante, O Garrone: Cisplatin-based chemoradiation plus cetuximab in locally advanced head and neck cancer: a phase II clinical study. *Ann Oncol*, 22(3), 712-7 (2011)

204. KK Ang, Q Zhang, DI Rosenthal, PF Nguyen-Tân, E Sherman, R Weber, J Galvin, D Schwartz, A El-Naggar, ML Gillison, R Jordan, M List, A Konski, W Thorstad, JJ Beitler, A Garden, WJ Spanos, A Trotti, SS Yom, R Axelrod: A randomized phase III trial (RTOG 0522) of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III-IV head and neck squamous cell carcinomas (HNC). In: *J Clin Oncol, 2011 ASCO Annual Meeting Proceedings*, 29(Supplement 15), American Society of Clinical Oncology abstract nr 5500 (2011)

205. MK Gibson, M Kies, S Kim, P Savvides, A Kotsakis, G Blumenschein, F Worden, H Chen, J Grandis, A Argiris: Cetuximab (C) and bevacizumab (B) in patients with recurrent or metastatic head and neck squamous cell carcinoma: An updated report. In: *J Clin Oncol, 2009 ASCO Annual Meeting Proceedings*, 27(Supplement 15), American Society of Clinical Oncology abstract nr 6049 (2009)

206. JB Vermorken, J Guigay, R Mesia, JM Trigo, U Keilholz, A Kerber, U Bethe, M Picard, TH Brummendorf: Phase I/II trial of cilengitide with cetuximab, cisplatin and 5-fluorouracil in recurrent and/or metastatic squamous cell cancer of the head and neck: findings of the phase I part. *Br J Cancer*, 104(11), 1691-6 (2011)

207. NE Bhola, SM Thomas, M Freilino, S Joyce, A Sahu, J Maxwell, A Argiris, R Seethala, JR Grandis: Targeting GPCR-mediated p70S6K activity may improve head and neck cancer response to cetuximab. *Clin Cancer Res*, 17(15), 4996-5004 (2011)

208. A Hoellein, A Pickhard, F von Keitz, S Schoeffmann, G Piontek, M Rudelius, A Baumgart, S Wagenpfeil, C Peschel, T Dechow, H Bier, U Keller: Aurora kinase inhibition overcomes cetuximab resistance in squamous cell cancer of the head and neck. *Oncotarget*, 2(8), 599-609 (2011)

209. U Vanhoefer, M Tewes, F Rojo, O Dirsch, N Schleucher, O Rosen, J Tillner, A Kovar, AH Braun, T Trarbach, S Seeber, A Harstrick, J Baselga: Phase I study of the humanized antiepidermal growth factor receptor monoclonal antibody EMD72000 in patients with advanced solid tumors that express the epidermal growth factor receptor. *J Clin Oncol*, 22(1), 175-84 (2004)

210. R Dienstmann, E Felip: Necitumumab in the treatment of advanced non-small cell lung cancer: translation from preclinical to clinical development. *Expert Opin Biol Ther*, 11(9), 1223-31 (2011)

211. MO Rodriguez, TC Rivero, R del Castillo Bahi, CR Muchuli, MA Bilbao, EN Vinageras, J Alert, JJ Galainena, E Rodriguez, E Gracias, B Mulen, B Wilkinson, EL de Armas, K Perez, I Pineda, M Frometa, I Leonard, V Mullens, C Viada, P Luaces, O Torres, N Iznaga, T Crombet: Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck. *Cancer Biol Ther*, 9(5), 343-9 (2010)

212. JB Vermorken, J Stohlmacher, I Davidenko, E Winquist, L Licitra, VR Pai, K Skladowski, CR Blajman, S Faivre, J Gansert: An analysis of safety in patients (pts) with recurrent and/or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) receiving chemotherapy (CT) with or without panitumumab (pmab) in a phase III clinical trial (SPECTRUM). In: *J Clin Oncol, 2009 ASCO Annual Meeting Proceedings*, 29(Supplement 15), American Society of Clinical Oncology abstract nr 6050 (2009)

213. H Zhang, S Yun, TD Batuwangala, M Steward, SD Holmes, L Pan, M Tighiouart, HJ Shin, L Koenig, W Park, D Rycroft, S Nannapaneni, Y Wang, ZG Chen, DM Shin: A dual-targeting antibody against EGFR-VEGF for lung and head and neck cancer treatment. *Int J Cancer*, 131(4), 956-969 (2012)

214. G Schaefer, L Haber, LM Crocker, S Shia, L Shao, D Dowbenko, K Totpal, A Wong, CV Lee, S Stawicki, R Clark, C Fields, GD L Phillips, RA Prell, DM Danilenko, Y Franke, JP Stephan, J Hwang, Y Wu, J Bostrom, MX

Sliwkowski, G Fuh,C Eigenbrot: A two-in-one antibody against HER3 and EGFR has superior inhibitory activity compared with monospecific antibodies. *Cancer Cell*, 20(4), 472-86 (2011)

Abbreviations: ADCC - antibody-dependent cellular cytotoxicity; bsAb - bispecific antibody; mAb - monoclonal antibody; HDAC – histone deacetylase; MTD - maximum tolerated dose; PET - positron emission tomography; PFS - progression-free survival; RTK – receptor tyrosine kinase, TKI - tyrosine kinase inhibitor

Key Words: Epidermal Growth Factor Receptor, Squamous Cell Carcinoma, Head and Neck, Resistance, Response, Receptor Tyrosine Kinase, Inhibitor, Antibody, Review

Send correspondence to: Suzanne A. Eccles, Tumour Biology and Metastasis Team, CR-UK Cancer Therapeutics Unit, McElwain Laboratories, The Institute of Cancer Research, Cotswold Road, Belmont, Sutton, Surrey, SM2 5NG, UK, Tel: 44-0-20-8722-4210, Fax: 44-0-20-8722-4134, E-mail: sue.eccles@icr.ac.uk