10.5005/jp-journals-10001-1058

REVIEW ARTICLE

Therapeutic Monoclonal Antibodies: Current Perspectives and Applications for the Treatment of Head and Neck Cancer

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ABSTRACT

Over the past two decades, monoclonal antibodies have emerged as a versatile class of therapeutics with unique properties. More than 30 therapeutic antibodies are now approved in the United States and European Union, with numerous candidates filling the preclinical and clinical pipeline of every major pharmaceutical companies and biotechnology firms. Monoclonal antibodies have the advantage over traditional medicines in that they are able to specifically bind to the desired targets with little to no associated toxicity. In the recent years, monoclonal antibodies approved for oncology treatments have gained in notoriety and are now used as adjuvants or neo-adjuvants to radiotherapy, chemotherapy and surgery. In the field of head and neck cancer, the anti-EGF receptor antibody Erbitux has paved the way for new targeted treatments to SCCHN. This review introduces some basic concepts and recent perspectives on monoclonal antibodies with a focus on head and neck cancer treatments.

Keywords: Antibodies, Monoclonal, Therapy, SCCHN, Carcinoma, Squamous cell, Immunotherapy, Combined chemotherapy, Combined radiation therapy, Head and neck cancer, Neoplasms.

INTRODUCTION

The immune system functions by distinguishing self from non-self and has evolved a number of mechanisms related to removing non-self or foreign elements. Non-self is usually defined as invasive pathogenic organisms, such as bacteria, fungi, protozoa and viruses, but can also be considered as altered-self, such as virally-infected cells or the aberrant growth of cells, such as seen with cancer. The components of the immune system are many and varied with many pathways of stimulation, maintenance and function, but the system designed to detect and remove predominantly extracellular targets or antigens are the antibodies.

Antibodies are a family of glycoproteins with exquisitely specific binding properties that have evolved to become a major protective mechanism in neutralizing potentially harmful pathogens and molecules.[1] Their unique binding properties come from a configuration of target-binding sequences found within variable regions at the antigen-binding ends of the molecules. Antibodies also have effector mechanisms located in constant regions that act by specifically activating other host immune responses.

The basic structure of a single antibody or immunoglobulin can be considered as a "Y" shape[2] (Fig. 1). The molecule is a homodimer of two chains, one light and one heavy. The two heavy chains dimerise to form the base of the "Y" with overlapping ends forming the inside of the arms of the "Y" which pair to the light chains. Both the light and heavy chains are comprised of variable sequences which are unique to an antibody and constant regions which remain conserved among different antibody subclasses or isotypes. In the early analyses of antibodies, it was found that the enzyme papain could digest the immunoglobulin "Y" into three fragments; two "fragment antigen binding" (Fab) portions, located at the two arms of the "Y", and the "fragment crystallisable or constant" (Fc) region located at the bottom of the "Y". The Fabs bind to the antigen and the Fc binds to specific Fc receptors on different cell surfaces and are associated with effector mechanisms.[3,4]

Immunoglobulins can either be secreted or cell surface bound.[5] When expressed on the cell surface they become part of the specific receptor of the cell that produces and secretes antibody, the B cell or B lymphocyte. The "B" comes from the fact that B cells were first identified in the bursal sac of chickens and were subsequently found to originate from precursor cells in the bone marrow of mammals. B cells have the only purpose of producing and secreting antibodies. In the cycle of activation, maturation and antibody secretion, the B cell undergoes a number of morphological changes to eventually become an antibody-secreting cell or plasma cell. Plasma cells are generally short-lived but can be very long-lived, if they migrate to the bone marrow, where they become a source of serum antibodies.

As mentioned earlier, antibodies have evolved to become the major component of the immune system responsible for the detection and removal of extracellular pathogens and molecules. They do this by a number of mechanisms related

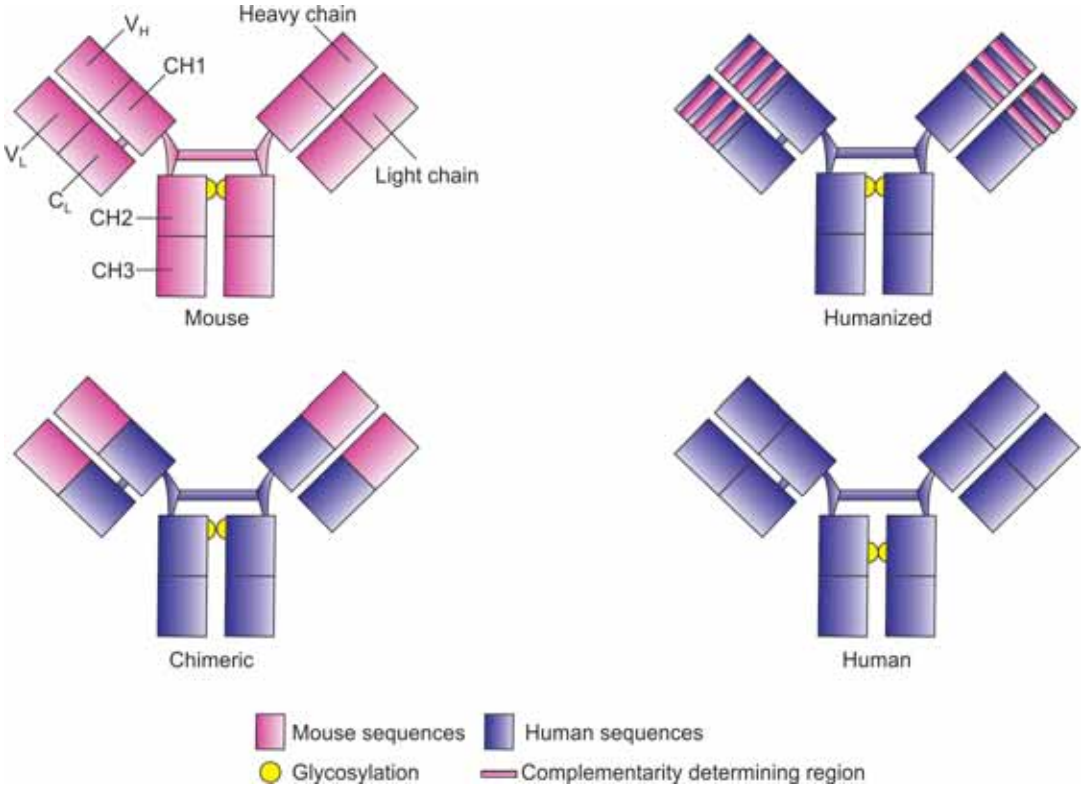

Fig. 1: Chimeric, humanized and fully human monoclonal antibodies

to their Fc region. The Fc region confers the isotype or subclass of the antibody, namely IgD, IgM, IgG1, IgG2, IgG3, IgG4, IgA1, IgA2 or IgE.[6] Subtypes also exist within specific isotypes and minute differences in sequences can also be found within isotypes within different human populations and these have been termed allotypes. The effector mechanisms produced by specific antibody isotypes are related to the specific proteins and/or Fc receptors that they bind to IgM and IgA isotopes generally do not bind to any effector Fc receptors and hence do not normally activate other immune mechanisms. These two isotypes function by blocking and/or neutralizing the target organism(s). IgGs on the other hand can stimulate a number of cellular or humoral (soluble) immune responses with different isotypes in different species having similar functions. For example, human IgG1 and IgG3 and mouse IgG2 (subtypes a and b) all bind to complement protein C1q which can then trigger a cascade of other complement molecules to eventually lead to the formation of a MAC (membrane attack complex) which leads to the lysis of the target cell or organism.[7,8] This mechanism is termed complement dependent cytotoxicity or CDC. The same isotypes can also bind to a number of Fc receptors on NK (natural killer) cells, neutrophils and/or macrophages that can lead to target cell death by a number of cellular mechanisms or antibody dependent cellular (or cell-mediated) cytotoxicity or ADCC.[9]

As already described, one of the advantages that antibodies have over small molecule drugs is the fine specificity and strong binding abilities to their targets, thus allowing for less chance of (cross) reactivity to closely related targets, which can lead to toxicity. Antibodies also have effector functions related to properties associated with their Fc regions which small molecules do not have. Another advantage that antibodies possess is a much longer half-life again related to residues within their Fc regions. Antibodies can bind to a salvaging receptor called FcRn (Fc receptor neonatal) which can allow for the recycling of antibodies. This receptor plays a role in adult salvage of IgG through its occurrence in the pathway of endocytosis in endothelial cells. FcRn receptors in endosomes bind to IgG internalized through pinocytosis, recycling the antibodies to the cell surface and preventing them from undergoing lysosomal degradation.[10] The recycled antibodies are then released back into the circulation thus extending their half-life.

Scientists have been able to harness the binding properties and effector functions of the antibody to produce modern drugs of very high specificity and function.

The normal antibody response generated by a host against an antigen has many specificities and binding properties recognizing a number of different regions or epitopes on the target. A number of different isotypes will also develop as the antibody response matures. This normal type of response is termed a polyclonal response and the extent of the response is proportional to the numbers of B cells that respond. However, each responding B cell produces a single clone or antibody molecule and it is this property that has been manipulated to produce monoclonal or single specificity, single isotype antibodies.

It was Kohler and Milstein who first identified the possibility of producing monoclonal antibodies (mAbs) by hybridoma technology.[11] The simple fusion of an antibody secreting B or plasma cell with a tumour myeloma cell line resulting in a continuously growing, long-lived, continuously secreting cell line producing antibodies of single specificity or clones, has revolutionized the clinical fields of diagnostics, detection, isolation, identification and treatment.

The original method of monoclonal antibody production using hybridomas was developed in mice and this has remained virtually unchanged since discovery. The basis of this method is the immunization of mice with the antigen of

Table 1: Therapeutic mAbs and Fab fragments approved in the United States and European Union

Name	*INN name*	*Type*	*mAb format*	*Antigen*	*Indication*	*Company*	*Approval*
Orthoclone	Muromonab	Mouse	IgG2a	CD3	Transplantation	J and J	1986
ReoPro	Abciximab	Chimeric	FAB fragment	GPIIb/IIIa	Thrombosis	Lilly/Centocor	1994
Zenapax	Daclizumab	Humanized	IgG1	CD25 (IL-2R)	Transplantation	Roche	1997
Rituxan	Rituximab	Chimeric	IgG1	CD20	NHL/RA	Roche/Genentech/IDEC	1997
Remicade	Infliximab	Chimera	IgG1	TNF	Inflammation	Schering-Plough/Centocor	1998
Simulect	Basiliximab	Chimeric	IgG1	CD25	Transplantation	Novartis	1998
Herceptin	Trastuzumab	Humanized	IgG1	Her2/neu	Breast cancer	Roche/Genentech	1998
Synagis	Palivizumab	Humanized	IgG1	RSV	Viral infection	Abbott	1998
Mylotarg	Gemtuzumab ozogamicin	Humanized	IgG4	CD33	AML	Celltech/AHP	2000
Campath	Alemtuzumab	Humanized	IgG1	CD52	CLL	ScheringAG/Millenium/ILEX	2001
Zevalin	Ibritumomab tiuxetan	Mouse	IgG1	CD20	NHL	ScheringAG/IDEC	2002
Bexxar	^{131}I-tositumomab	Mouse	IgG2a	CD20	NHL	Corixa/GSB	2003
Erbitux	Cetuximab	Chimeric	IgG1	EGFR	CRC/HNC	Imclone/BMS/Merck	2003
Xolair	Omalizumab	Humanized	IgG1	IgE	Asthma	Novartis/Genentech	2003
Raptiva	Efalizumab	Humanized	IgG1	CD11a	Psoriasis	Xoma/Genentech	2003 (withdrawn)
Humira	Adalimumab	Human	IgG1	TNF	Inflammation	Abbott/CAT	2003
Avastin	Bevacizumab	Humanized	IgG1	VEGF	CRC	Genentech/Roche	2004
Tysabri	Natalizumab	Humanized	IgG4	VLA4	Multiple sclerosis	Elan	2006
Vectibix	Panitumumab	Human	IgG2	EGFR	mCRC	Abgenix/Amgen	2006
Lucentis	Ranibizumab	Humanized	IgG1 Fab	VEGF	Macular degeneration	Genentech/Roche	2006
Soliris	Eculizumab	Humanized	IgG2/4	C5	Paroxysmal nocturnal hemoglobinuria	Alexion pharmaceuticals	2007
Cimzia	Certolizumab pegol	Humanized	Fab, pegylated	TNF	Crohn disease	UBC-Celltech	2008
Arzerra	Ofatumumab	Human	IgG1	CD20	B-CLL	Genmab/GSK	2009
Stelara	Ustekinumab	Human	IgG1	IL12/23	Plaque psoriasis	Centocor	2009
Ilaris	Canakinumab	Human	IgG1	IL1β	Muckle-Wells syndrome	Novartis	2009
Simponi	Golimumab	Human	IgG1	TNF	RA, PA, AS	Centocor	2009
Removab	Catumaxomab	Rat-mouse hybrid	Mouse IgG2a /rat IgG2b	CD3 and EpCAM	Malignant ascites in patients with EpCAM-positive cancer	Fresenius Biotech/Trion pharma	2009 (EMA)
Actemra	Tocilizumab	Humanized	IgG1	IL6R	RA	Roche/Chugai	2010
Prolia	Denosumab	Human	IgG2	RANK-L	Bone loss	Amgen	2010
Yervoy	Ipilimumab	Human	IgG1	CTLA-4	Late-stage melanoma	Medarex/BMS	2011
Benlysta	Belimumab	Human	IgG1	BLyS	SLE	Human genome sciences/GSK	2011

AML: Acute myeloid leukemia; AS: Ankylosing spondylitis; B-CLL: B-cell chronic lymphocytic leukemia; CRC: Colorectal cancer; HNC: Head and neck cancer; mCRC: Metastatic colorectal cancer; NHL: Non-Hodgkin lymphoma; PA: Psoriatic arthritis; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus.

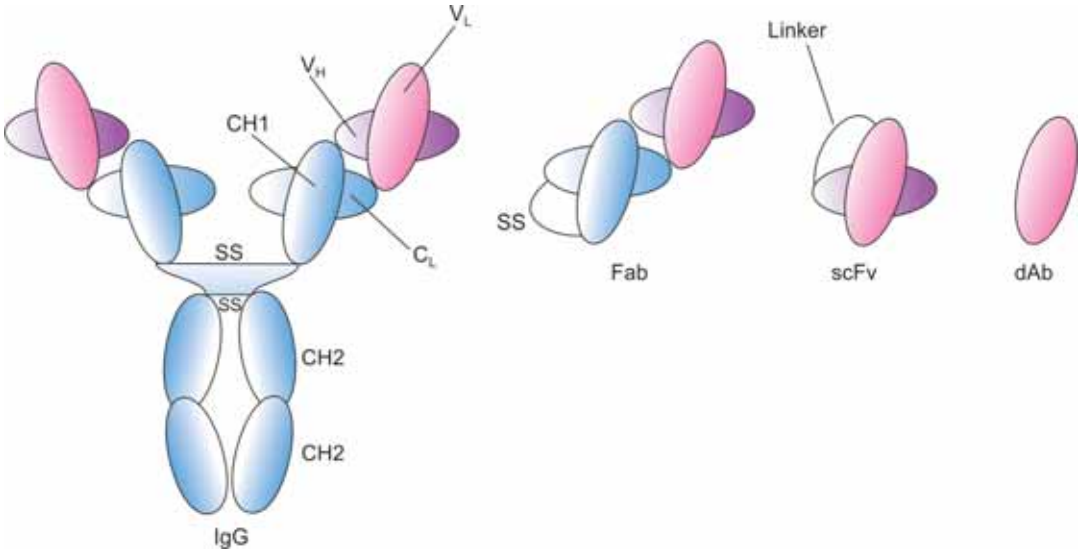

Fig. 2: Antibody, Fab, scFv and domain antibody (dAb) formats

choice and when a desired high concentration or titer of antigen-specific antibody has been detected in the serum from these mice, cell suspensions are made from the lymph nodes or spleens which contain the highest populations of B cells and these cell suspensions are fused with a myeloma cell line. The fused cells or hybridomas are then grown in selective media that will only allow the survival of the fused cells. The result is a collection of individual clones secreting a number of different antibodies. Selection then takes place usually using limiting dilution whereby several rounds of plating out of the antigen-specific cell lines occur based on the dilution of the cell concentrations so that only one cell is plated out per well, allowing for the growth of only one clone per well.

The vast majority of the monoclonal antibodies in the clinic today originate in mice using hybridoma technology (Table 1). The problem is that if these antibodies are used for treatment and are introduced into a human patient then human anti-mouse antibody (HAMA) responses can be generated as the mouse antibody is "foreign". This effectively neutralizes the benefits of the monoclonal antibody treatment. The HAMA effect has largely been circumvented by molecular biological methods producing several degrees of "humanization" of the mouse antibody (Fig. 1), starting with basic chimera molecules having complete mouse variable domains and culminating in fully human monoclonal antibodies that are less likely to stimulate immune responses.[12]

Conversely a number of methods have also been developed to produce fully human antibodies without first producing a mouse antibody. Phage display and transgenic mouse technologies have allowed the engineering of therapeutic antibodies with genuine human variable domains.[13]

With phage display, the variable fragments which make an antigen-binding site are displayed at the surface of a filamentous phage, a bacteriophage that lives on *Escherichia coli*. Phages are viruses that infect bacteria and essentially consist of an outer protein capsid enclosing genetic material. By building libraries containing billions of different recombinant bacteriophages, a mimic of the human immune system is reconstituted *in vitro*. The built-in connection between the genotype of a recombinant bacteriophage and its antigen-binding site phenotype allows the selection of specific antigen-binding site sequences through the panning of large recombinant bacteriophage libraries against an immobilized antigen.

Other antibody companies have developed transgenic mice capable of producing human antibodies partially or in full.[14] This was respectively achieved by either disrupting the endogenous mouse immunoglobulin (Ig) genes and introducing either yeast artificial chromosomes bearing a portion of the nonrearranged human Ig heavy and kappa light chain loci (Medarex and Abgenix), or chromosomal fragments bearing the intact human Ig loci (Kirin).

The first antibodies derived from these two fully human methods are now in the clinic, and a true differentiation from the first humanized antibodies remains unproven. More recently, display technologies have allowed the development of non-antibody scaffolds and opened new avenues for protein-based therapeutics.[15]

Along with traditional "Y" shaped antibodies, several new formats of antibody-like structures are being tested in the clinic (Fig. 2), small antibody fragments are usually being tested for enhanced tumor penetration in oncology, but often lack the long half-life of the traditional antibodies. To date, only two Fab fragments have been approved by the US FDA, one of which has been grafted with a long poly-ethylene chain to enhance its half-life (Cimzia).

The most successful therapeutic areas for mAbs have been inflammation and oncology. Anti-TNF antibodies have been particularly useful in the treatment of rheumatoid

arthritis, and anti-B cell antibodies targeting the CD20 antigen are now the standard of care in several lymphoma indications. These successes have encouraged further research into these two therapeutic areas and several new mAbs for these two indications have been approved in recent years. Although mAbs can be used as single agent therapies, they are often used in conjunction with chemotherapy. For example, the treatment for non-Hodgkin lymphoma called R-CHOP consists of rituximab (a monoclonal antibody), cyclophosphamide (chemotherapy drug), hydroxy-daunorubicin (chemotherapy drug), Oncovin (chemotherapy drug) and prednisolone (a steroid).

An insight into the future of mAb-based therapies is found in the pipeline and R&D activities from leaders in the field. Three lines of research can clearly be identified: (i) Making mAbs with enhanced killing properties in oncology, either by enhancing the natural effector mechanisms of the Fc fragment[16,17] or by means of a grafted toxic payload.[18] (ii) Creating mAbs with more than one specificity, this is important since many challenging indications are pleiotropic diseases. The focus here is on bispecific antibodies,[19] where the dual targeting approach has at least an additive effect, and more preferably a synergistic one. To date, only one bispecific mAb is commercially available, however its dual targeting property is really used for redirected T-cell killing.[20] (iii) Enhancing mAb delivery by either enabling the delivery of larger quantities and/or enabling a local delivery (pulmonary and ocular deliveries).[21-23]

HEAD AND NECK CANCER

Head and neck cancer usually refers to a group of biologically similar tumors originating from the upper aerodigestive tract, including the oral cavity, paranasal sinuses and nasal cavity, pharynx, larynx and salivary glands. Excluding non melanoma skin cancers that arise in these anatomical areas, head and neck cancers account for approximately 6% of all cancers worldwide (http://globocan.iarc.fr/,Globocan 2002). More than 90% of diagnosed head and neck cancers are of the squamous cell histology (www.cancer.gov), referred to as squamous cell carcinomas (SCCHN).[24] Despite its relatively low incidence in comparison to other types of cancer, the mortality rate from head and neck cancer is fairly high. As early detection strategies have not been successful, most patients with head and neck cancer present advanced disease (stages III and IV), and currently available therapies induce only modest response rates. Overall these factors result in a poor prognosis and low survival rates. The major advances in the field have come from the integration of targeted therapeutics into treatment regimens. The current treatment for SCCHN mainly consists of a combination of surgery and radiation, or combined radiation and chemotherapy depending on the site and stage of the disease and patient's health status. The success of conventional therapies is limited, in part, by the resistance to chemotherapy. Attempts to overcome resistance with higher doses of chemotherapies are inevitably met with a high degree of toxicity and damages to normal tissues. The malignant progression of SCCHN is linked to the over-expression and/or amplification of oncogenes, mutations and deletions leading to inactivated tumor suppressor genes. Numerous preclinical and clinical studies have identified the epidermal growth factor receptor (EGFR) as the most important target for new therapeutic strategies. In 80 to 90% of SCCHNs, EGFR is over-expressed but not mutated.[24] Furthermore, EGFR over-expression has been found to correlate with a more aggressive disease, resistance to both radiotherapy and chemotherapy, and a poor prognosis.

Erbitux (INN-cetuximab; IMC-C225; ImClone/Bristol-Myers Squib/Merck Serono) was the first approved monoclonal antibody for head and neck cancer—the first new therapy for this indication in almost half a century.[25,26]

In 2006, the FDA and EMEA granted regulatory approval for Erbitux in combination with radiotherapy for the treatment of locally advanced squamous cell carcinoma of the head and neck and as a single agent for patients with recurrent or metastatic squamous cell carcinoma following failure of prior platinum-based therapy.

To date, only Erbitux has been approved by the US FDA in head and neck cancer as a radiation-sensitizing agent for patients undergoing primary radiation-based therapies, and for patients with recurrent or metastatic disease.

Erbitux is a chimeric (mouse/human) monoclonal antibody that targets the epidermal growth factor receptor (EGFR; ErbB-1; HER1 in humans), a cell-surface receptor for members of the epidermal growth factor family (EGF-family) of extracellular protein ligands.[26] EGFR is a transmembrane receptor belonging to a family of four related proteins (EGFR, ERBB2, ERBB3 and ERBB4).[27] Ten different ligands can selectively bind to each receptor, excepting for the ERBB2 receptor which has no ligand. After a ligand binds to a single EGFR, the receptor forms a homodimer or heterodimer that signals within the cell by activating receptor autophosphorylation through tyrosine kinase activity. Autophosphorylation triggers a series of intracellular pathways that result in cancer-cell proliferation, blocking apoptosis, activating invasion, metastasis and stimulating tumor-induced neovascularization.

Anti-EGFR monoclonal antibodies (Table 2), such as Erbitux, bind to the extracellular domain of EGFR when it is in the inactive configuration, compete for receptor binding by occluding the ligand-binding region, and thereby block ligand-induced EGFR tyrosine kinase activation.[28] In addition to ligand blocking, ADCC and receptor internalization/down-regulation enhance receptor degradation and make a contribution to antitumor activity.

EGFR is also important for proliferation and differentiation of the human epidermis and hair follicles. As a consequence, cutaneous side effects are frequently observed

during cancer therapy with EGFR inhibitors. Other reported side effects encompass infusion-related hypersensitivity (with severe cases) and cardiopulmonary toxicity.

The success of Erbitux in SCCHN has prompted exploration into other cancer types, more particularly in colorectal cancers where cancer cells have also been shown to over-express EGFR. However, in this type of cancer, the use of Erbitux has been limited. Only patients whose tumors harbor the wild-type KRAS allele have benefited from anti-EGFR therapies.[29,30] KRAS is one of the down-stream signaling molecules found in pathways which are blocked by anti-EFGR drugs. When mutated, KRAS is locked into an active conformation regardless of whether the EGFR is blocked. The success of anti-EGFR therapies in SCCHN is indeed related to the extremely low incidence of KRAS mutations in head and neck cancer— in the order of 5%.

Vectibix (INN-panitumumab) is a fully human anti-EGFR monoclonal antibody developed by Amgen, that may eventually compete against Erbitux.[31] It has been approved by the US FDA as a single agent for the treatment of metastatic colorectal cancer, and its activity was found to be limited to patients whose tumors expressed the wild-type KRAS. Erbitux is an IgG1 chimeric monoclonal antibody, and Vectibix, a fully human IgG2 antibody derived from transgenic mice. Preclinical data suggest a similar mode of action for these two drugs with the difference that Vectibix does not induce antibody-dependent cellular cytotoxicity.[32] The fully human nature of the antibody may explain why Vectibix has a lower incidence of hypersensitivity.

Amgen has initiated a phase II trial in first-line locally advanced SCCHN (cisplatin and radiation ± Vectibix)[33,34] and a phase III trial in first-line recurrent or metastatic SCCHN (cisplatin ± Vectibix).[35] Data from this study are expected in 2011. Consultants expect that Vectibix will demonstrate efficacy similar to Erbitux, but has advantages in safety (fewer hypersensitivity reactions). Although consultants expect very little initial off label use for Vectibix in SCCHN, they believe these benefits could eventually allow Vectibix to capture significant market share versus Erbitux.

HuMax-EGFr (INN-zalutumumab) is another fully human anti-EGFR antibody for head and neck solid tumors[36] developed by Genmab. HuMax-EGFr (INN-zalutumumab) is a human IgG1κ monoclonal antibody targeting the EGFR. In preclinical models, HuMax-EGFr potently inhibits tumor growth through a reduction in receptor phosphorylation and antibody-dependent cellular cytotoxicity.[37]

The company began phase III trials in refractory head and neck cancer versus best supportive care in September 2006. Enrollment of 286 patients in the study was completed in June 2009. Data from this study were recently released,[38] although HuMax-EGFr did not increase overall survival, progression-free survival was extended in patients with recurrent squamous-cell carcinoma of the head and neck who had failed platinum-based chemotherapy. HuMax-EGFr dose titration on the basis of rash was safe.

h-R3 (INN-nimotuzumab) is a humanized anti-EGFR monoclonal antibody developed at the Center of Molecular Immunology in Havana (Cuba).[39] This humanized antibody is of the IgG1 subclass and targets the same domain of EGFR as the Erbitux antibody. However, in the clinic, h-R3 has shown a surprisingly low degree of dermatological toxicity. This improvement in side effect profile appears to be related to h-R3's unique binding affinity and receptor density dependence, as a lower affinity between h-R3 and EGFR allows for an optimal dose of the drug that is below the toxic dose. Another explanation for lower unwanted toxicities is that EGFR expression is too low in normal cells to cause a bivalent binding, hence limiting h-R3's potency. h-R3 is approved in many countries for either head and neck cancer or glioma or both, but has yet to be approved in the United States, Europe or Japan. Clinical trials in these regions are on-going.

Table 2: Current anti-EGFr monoclonal antibodies[39]

Product	*Erbitux(IMC-C225)*	*Vectibix*	*HuMax-EGFr*	*h-R3*	*EMD 72000*
INN name	Cetuximab	Panitumumab	Zalutumumab	Nimotuzumab	Matuzumab
Company	ImClone Merck BMS	Abgenix Amgen	Genmab	CIMYM Oncoscience Biocon IGK Kunhill BPL	Merck KGaA Takeda
Type of mAb	Chimeric	Fully human	Fully human	Humanized	Humanized
Affinity (M)	10^{-10}	10^{-11}	$7x10^{-9}$ (EC_{50})	4.5×10^{-8}	10^{-9}
Ig subclass	IgG1	IgG2	IgG1	IgG1	IgG1
Clinical status	marketed	Marketed phase II-III	Phase III	Phase III or marketed*	Phase II (discontinued)
Indications	HNC mCRC	mCRC HNC	HNC	Glioma HNC	NSCLC gastric cancer

*Outside Europe, US and Japan; HNC: Head and neck cancer; mCRC: Metastatic colorectal cancer; NSCLC: Non-small cell lung cancer.

EMD 72000 (INN-matuzumab) is another humanized monoclonal antibody of the IgG1 subclass that binds selectively to the EGFR, competing with both EGF and TGF-α for binding.[40] In contrast to the chimeric antibody Erbitux, EMD 72000 has a prolonged half-life, approximately 6 to 7 days, allowing a less frequent dosing schedule. Initial clinical investigations focus on advanced non-small-cellular lung carcinoma and advanced adenocarcinomas of stomach and esophagus.[41,42] Developed by Merck Serono in cooperation with Takeda Pharmaceutical, matuzumab has been investigated in phase II clinical trials in indications, such as metastatic colorectal cancer (mCRC), gastric cancer and non-small cell lung cancer (NSCLC), where it did not meet its predefined clinical endpoints of activity. In February 2008, EMD 72000 development was halted because of disappointing study results.

The Future of Head and Neck Cancer Therapies

The concomitant use of Erbitux and radiotherapy has led to a gain in survival in locally advanced SCCHN. However, Erbitux efficacy is not clearly established, in particular in the metastatic form of the disease where the benefit is minimal.

For patients with head and neck cancer, tumor hypoxia is a potent predictor of adverse outcomes.[43] Hypoxia stimulates angiogenesis through upregulation of the hypoxia-inducible factor 1 alpha (HIF1-α)/vascular endothelial growth factor receptor (VEGFR) pathway. Head and neck cancer that is both hypoxic and highly angiogenic has a poor prognosis even after chemotherapy and radiation therapy, and patients with substantial over-expression of VEGF (also referred to as VEGF-A, a major ligand of the VEGFR family) have two-times increased risk of dying.

EGFR signaling stimulates angiogenesis via mechanisms independent of hypoxia and HIF1-α, and there is a redundancy of angiogenic pathways where the inhibition of one pathway (e.g. EGFR) probably upregulates the signaling of alternative pathways (e.g. VEGF). Simultaneous blockage of VEGFR and EGFR pathways is therefore a logical concept which was recently tested in a phase I/II study involving patients with recurrent and metastatic SCCHN.[44] In this trial, the EGFR small-molecule tyrosine kinase inhibitor erlotinib was administrated concurrently or in combination with the anti-VEGF-A monoclonal antibody Avastin (INN-bevacizumab, Roche/Genentech), a humanized monoclonal antibody that binds to VEGF-A. In spite of inadequate criteria to determine efficacy, the trial showed a small subset of patients having a prolonged benefit from the combination. This study highlights the on-going efforts in developing future treatments based on multiagent targeted therapies. In this regard, new monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors show considerable promise in treating the severe forms of the disease, either alone or in combination, with or without radiation and chemotherapy.

Another focus of improvement is the need to reduce side effects. Regarding cutaneous adverse effects, some of the new anti-EGFR monoclonal antibodies have already shown reduced skin toxicity, which may be linked to the subtle differences in their binding mode on the EGFR molecule. Presently, the infusion-related hypersensitivity is still the most challenging problem. Solutions to the hypersensitivity problem will help community oncologists to include anti-EGFR monoclonal antibodies in therapeutic regimens more widely. Finally, the poor correlation between EGFR expression and clinical response prompt to broaden our understanding of the EGFR *in vivo*.[45]

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