

Expert Opinion

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Nimotuzumab: a novel anti-EGFR monoclonal antibody that retains anti-EGFR activity while minimizing skin toxicity

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Due to the broad importance of EGFR to tumorigenesis, targeted therapy against it has rapidly developed into a novel paradigm for cancer treatment. Two promising classes of drugs are now in use and undergoing development that target this receptor: tyrosine kinase inhibitors (TKIs) and mAbs that inhibit EGFR's extracellular domain. Nimotuzumab, a humanized murine mAb created in Cuba, has demonstrated antitumor activity similar to that of other anti-EGFR mAbs and shows promise as a single agent and as an adjunct to radiation in Phase I and II clinical trials. Surprisingly, the typical severe dermatological toxicities thus far associated with anti-EGFR therapy have not been described with nimotuzumab. Here we summarize the background, development and characteristics of this new drug while reviewing the latest preclinical and clinical trial data that underpin its gradual adoption into clinical practice.

Keywords: acneiform rash, EGFR, h-r3, monoclonal antibody, nimotuzumab, targeted therapy

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1. Background

Our understanding of EGFR's role in cancer has grown immensely over the past 30 years. It is now known that its overexpression is not only present in a majority of carcinomas, including 80 – 100% of head and neck squamous cell carcinomas (HNSCCs), 70 – 90% of colorectal cancers (CRC) and 40 – 60% of non-small cell lung carcinomas (NSCLC) cases, but that corrupted EGFR signaling pathways contribute to a number of tumorigenic processes such as tumor proliferation, apoptosis resistance, angiogenesis, invasion, and metastasis [1-4]. Furthermore, in the clinical setting, EGFR overexpression has been linked to a worse patient prognosis as well as radio and chemotherapy resistance [5,6]. Because of the potential treatment benefit from inhibiting this receptor, research and development into therapeutic drugs that specifically target EGFR has been aggressively pursued.

While a number of tyrosine kinase inhibitors (TKIs) that interfere with EGFR's intracellular domain have already been developed and found a role in cancer management (especially in NSCLC characterized by an increase in EGFR gene copy number or specific activating mutations [7-9]), they have yet to show effective synergy with chemotherapy [10]. Meanwhile, several anti-EGFR mAbs, which target the extracellular domain, display marked results in combination with both chemotherapy and radiation. These mAbs, summarised in Table 1 and currently in varying states of pre-clinical/clinical use and approval, are cetuximab, panitumumab, zalutumumab, matuzumab and nimotuzumab (Box 1). Each binds to an EGFR extracellular epitope and inhibits downstream oncogenic signaling pathways. For this to happen, they must either block EGFR agonists from binding to the EGF binding site, competitively inhibiting ligand activity, or attach in such a way as to sterically hinder the optimal dimerization conformation necessary for signal transduction [11].

Table 1. Current anti-EGFR monoclonal antibodies.

Product	Cetuximab (Erbix, C225)	Nimotuzumab (h-R3)	Matuzumab (EMD 72000)	Panitumumab (Vectibix)	Zalutumumab (HuMax-EGFr)
Company	ImClone/ Merck/BMS	CIMYM/ Oncoscience Biocon IGK Kunhill BPL	Merck KGaA Takeda	Abgenix/ Amgen	Genmab
Type of molecule	Chimeric mAb	Humanized mAb	Humanized mAb	Fully human mAb	Fully human mAb
Affinity (M)*	10 ⁻¹⁰	4.5 × 10 ⁻⁸	10 ⁻⁹	10 ⁻¹¹	7 × 10 ⁻⁹ (EC ₅₀)
Ig Subclass	IgG1	IgG1	IgG1	IgG2	IgG1
Clinical status	Marketed	Phase III /Marketed	Phase II	Marketed	Phase III
Initial indications	Head and neck mCRC	Glioma Head and Neck	NSCLC Gastric	mCRC	Head and neck

*Affinity values are reported as dissociation constants (K_d) for cetuximab, nimotuzumab, matuzumab and panatinumab. For zalutumumab, the affinity value is reported as EC₅₀.

mCRC: Metastatic colorectal carcinoma; NSCLC: Non-small cell lung carcinoma.

Box 1. Drug summary.

Drug name	Nimotuzumab
Phase	Phase III
Indication	Cancer: HNSCC, Glioma and NSCLC
Pharmacology description	EGFR monoclonal antibody
Route of administration	Parenteral, intravenous; Parenteral, general
Pivotal trial(s)	[30,32,49]

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HNSCC: Head and neck squamous cell carcinomas;

NSCLC: Non-small cell lung carcinoma.

The most developed of these anti-EGFR mAbs thus far is cetuximab (or C225), which in 2004, became the first mAb against EGFR approved for cancer treatment by the FDA. Originally indicated in metastatic CRC, cetuximab is now accepted by several agencies, including the FDA and the European Medicines Agency (EMA), to additionally treat HNSCC when used as a single-agent post-primary chemotherapy or in combination with radiation. Moreover, it has recently shown efficacy for those with advanced NSCLC in a large Phase III trial as a concurrent treatment to chemotherapy [12].

The only other EGFR-mAb with approval from the FDA and EMA presently is panitumumab. Both these mAbs have exhibited a dependence on wild-type *K-ras* expression for clinically beneficial results [13,14], which is so strongly predictive of response in CRC and HNSCC, that the EMA has tied a normal genotype to approved use. However, it is interesting to note that in NSCLC *K-ras* mutations may not

preclude a clinical benefit [15]. Other biological markers that show promise as predictors of a positive outcome are higher fluorescence *in situ* hybridization (FISH)-determined EGFR gene copy numbers, active phosphatase and tensin homolog (PTEN) expression, and elevated tumor levels of epiregulin and amphiregulin mRNA, while mutations in EGFR, v-raf murine sarcoma viral oncogene homolog B1 (B-RAF) and PI3K seem to have less significance [16].

Despite the initial clinical successes, most anti-EGFR mAbs are responsible for a typical skin toxicity that develops in up to 90% of mAb-treated patients [17], a phenomenon that has prompted a revision of the cutaneous severe adverse events (SAE) toxicity scale. Often described as an acneiform rash, these dermatological toxicities can present as a grade 3 or 4 adverse reaction in as many as 38% of patients and significantly impinge on their quality of life [18]. Curiously, increased severity of the rashes has been linked to a greater effectiveness of the mAbs and as a result a skin-rash-determined dose regimen has been proposed [4,19,20]. In contrast, nimotuzumab, in clinical trials to date, is not associated with any severe cutaneous toxicity [21-32].

2. Preclinical data

Nimotuzumab, also known as h-R3, is an anti-EGFR mAb developed at the Center of Molecular Immunology in Havana, Cuba. Originally isolated as a mouse IgG2a antibody known as R₃, the mAb was humanized to reduce its immunogenicity and to slow clearance from the body by grafting the complementarity-determining regions (CDRs) of R₃ to a human IgG1 gene [33]. In the process, the antibody's variable fraction was further modified by recreating three specific murine amino acids (Ser 75, Thr 76, Thr 93) in order to preserve the new mAb's anti-EGFR activity [33]. The resulting humanized R₃ (h-R3) inhibits EGFR by binding

to domain III of the receptor's extracellular region with a dissociation constant (K_d) of 4.51×10^{-8} M [34], partially blocking the EGF binding site, as well as stabilizing a receptor protein conformation unfavorable to dimer formation [35]. As a consequence of diminished EGFR phosphorylation and the ensuing decrease in growth and cell division commands, nimotuzumab is reported to reduce proliferation of *in vitro* A431 cells (a vulvar epidermoid cell line with a characteristically high expression of EGFR) by up to 40%, while displaying only a weak apoptotic effect [36].

In vivo, however, in addition to repressed tumor proliferation, the mAb has exhibited a fivefold increase in apoptosis of xenographic A431 SCID mice tumors [36]. It has been suggested that nimotuzumab's *in vivo* cytotoxic effect is mainly mediated by a decrease in VEGF production, a maximum 56% when measured by VEGF mRNA [36], causing apoptosis in those cells isolated from the necessary blood supply [36]. This hypothesis is supported by the lack of an antineoplastic response *in vitro* [36] and by the presence of constitutively upregulated VEGF in nimotuzumab-resistant tumors [37]. However, due to the difficulty of *in vivo* testing, VEGF-dependent apoptosis has yet to be conclusively proven, and there exists a complex interaction of many downstream EGFR signals that likely also contribute to some *in vivo* tumor cell death including other PI3K, MAPK, signal transducer and activator of transcription (STAT) and hypoxia inducible factor (HIF)-1 α signaling products [38,39]. Furthermore, nimotuzumab promotes an *in vivo* antineoplastic effect not dependent on inactivating EGFR because it can stimulate the cell- and complement-mediated cytotoxic immune response to attack the tumor cells to which it is bound [40,41]. As a consequence, further study is warranted to determine exactly which cellular pathways or immunological responses control nimotuzumab's mechanism of action and more importantly, since there are probably multiple simultaneous effects, to what extent each plays a role.

In vitro and *in vivo* pre-clinical studies have also compared nimotuzumab with the more established mAb, cetuximab, which at a K_d of 1×10^{-10} M has a significantly more robust affinity for EGFR. These experiments, using A431 cells, reveal that nimotuzumab reaches maximal inhibition at four times the concentration of cetuximab (2 μ g/ml with nimotuzumab versus 0.5 μ g/ml for cetuximab), and that while cetuximab results in the complete abrogation of EGF-induced phosphorylation, nimotuzumab allows for a very low level of EGFR to remain activated [41]. However, they also make evident that at their most effective doses, cetuximab and nimotuzumab exhibit equivalent levels of pro-apoptotic and antiproliferative activity in A431 colonies, despite their differing affinities towards EGFR [36,37,41]. This anticancer activity has likewise been demonstrated in other tumor cell lines, where nimotuzumab is found to be most effective as a monotherapy and as a radiosensitizing agent against cells with medium to high expression of the receptor [5]. The correlation between EGFR expression on the cell surface and an advantageous response differentiates

nimotuzumab from the other mAbs (mainly cetuximab and panitumumab), which do not show this relationship when analyzed by immunohistochemistry (IHC) [42]. It is currently believed that nimotuzumab's lower monovalent (single-arm) binding affinity is complemented by an appreciably increased bivalent (two-arm) binding avidity, meaning that the higher the density of EGFR on the cell membrane, the stronger the bond of the receptor–mAb complex [43]. A density-selective model of nimotuzumab binding is important from several clinical perspectives: i) Since ionizing radiation is known to up-regulate EGFR, it would thus be expected to greatly enhance nimotuzumab's antitumor effect [5]; ii) nimotuzumab's response could potentially be predicted by IHC of EGFR expression (unlike the other mAbs); and iii) it could yield a substantially more tolerable side effect profile, as discussed later.

3. Clinical data

Clinical data on nimotuzumab is derived from over 30 clinical trials incorporating 10 tumor types, mainly Phase I and II trials that have focused on head and neck and brain malignancies. When special access programs, compassionate use cases and commercial sales are included, nimotuzumab has been administered to over 4000 patients.

The first Phase I trial for nimotuzumab [21] enrolled 12 Cuban patients with advanced epithelial tumors (four ovarian adenocarcinomas, four breast, two lung, one stomach, and one renal carcinoma), and administered a one-time dose of 50, 100, 200 or 400 mg nimotuzumab. Of the 12 participants 7 developed mild or moderate adverse reactions but, surprisingly, no acneiform rash was found.

Several subsequent studies focused on head and neck cancers and confirmed nimotuzumab's tolerable side effects while establishing its clinical efficacy. In one [22], a Canadian trial, 17 HNSCC patients were enrolled to receive 100 or 200 mg of nimotuzumab with radiotherapy (RT), it was reported that out of 8 evaluable patients, 7 had a complete response (CR) and 1 displayed progressive disease (PD). A follow-up Phase I/II study from Cuba [23] tabulated the response of 22 HNSCC patients who received either 50, 100, 200 or 400 mg nimotuzumab per week for 6 weeks concurrent with RT. Within the cohort receiving 50 or 100 mg nimotuzumab, 2 out of 6 had a CR while 14 out of 16 receiving 200 or 400 mg achieved an objective response, 9 of which responded with complete tumor remission. The median survival of patients administered 50 or 100 mg nimotuzumab was 8.6 months versus 44.3 months for those receiving 200 or 400 mg, indicating that the response may be dose-dependent. The encouraging response rates under nimotuzumab were echoed in a single-center Phase I Spanish study where Rojo *et al.* [24] treated 10 advanced HNSCC patients for 8 weeks with the mAb (200 mg and 400 mg doses) as well as RT and documented an objective response rate (ORR) of 80% (two CR and six partial responses (PR)). Meanwhile, Reddy *et al.* [25] treated 17 stage III or IV-A

HNSCC patients with RT and nimotuzumab (200mg/week for 6 weeks) within a multicenter Phase II 4-arm trial in an effort to compare these promising results with controls. They found an ORR of 76% in nimotuzumab receiving participants, which compared well with an ORR of 40% in the RT control arm.

At the same time as it was being investigated in HNSCC, clinical trials were being conducted on patients with brain cancers. Nimotuzumab was first extended to this population in a Phase I/II study of Cubans with high-grade gliomas. Ramos *et al.* [28] reported on 29 patients from multiple medical centers – 16 glioblastomas (GB), 12 anaplastic astrocytomas (AA) and 1 anaplastic oligodendroglioma – who were given six weekly infusions of 200 mg nimotuzumab with radiation (50 – 60 Gy). They displayed an ORR of 37.9% (17.2% CR and 20.7% PR) while 41.4% exhibited stable disease (SD) and only 20.7% progressed. For glioblastoma subjects, the median survival time (MST) with nimotuzumab was 22.2 months versus 17.5 months in standard treated patients. A follow up Phase II/III study [29], also done in Cuba, randomized 30 GB and 35 AA patients to receive nimotuzumab and RT (60 Gy) or only RT as primary treatment. Mean and median survival for GB was 13.9 and 8.4 months with nimotuzumab and 9.3 and 7.9 months without, respectively. At the same time, the nimotuzumab-infused AA patients had a mean survival time 76.2% greater than those administered a placebo. The GB disease control rate (CR + PR + SD) was 33.3% without nimotuzumab and 53.8% with the mAb, while AA's control rate was 83.3% with and 66.7% without.

In children, a multi-center German study [30] with 46 pre-treated (second-line) pediatric brain cancer patients (13 GB, 11 AA, and 22 pontine glioma) found clinical benefit in 14 of 46 (4 PR and 10 SD) given the mAb. The most promising results were those of the pontine glioma patients who showed a 45.5% disease control rate. Overall responsive patients had MST of 10 months compared with 4 for non-responsive ones. A subsequent German Phase III trial [31] has enrolled 42 children with pontine gliomas for first line nimotuzumab treatment and preliminary results seem to reflect these Phase II impressions.

Two other Phase I studies conducted by teams in Canada have expanded nimotuzumab testing to CRC and NSCLC. Brade *et al.* [26] treated 16 advanced refractory tumors (13 colorectal) with single-agent nimotuzumab at four dose levels: 100, 200, 400 and 800 mg. Stable disease was recorded in six patients and one had a PR, additionally, no SAEs were reported for doses up to 800 mg, except for one grade 3 fatigue at the 100 mg level. A palliative NSCLC trial, in which Bebb *et al.* [27] treated patients with nimotuzumab (100 mg, 200 mg or 400 mg) for eight weeks with concurrent RT (30 Gy) found a best response of 12 PR. For all three doses, median progression free survival (PFS) was 16 weeks, and median overall survival was 60 weeks, comparing favorably with those of historical controls [44]. A similar

study performed in South Korea has generated almost identical results (Hye Jin Choi *et al.* 2009; personal communication) and is now being followed by a randomized Phase II study in that population.

Currently the role of nimotuzumab is being explored in brain metastasis. Early results from a Phase II study [32] in Cuba document a disease control rate of 91.6% (11 SD and 1 PD) in NSCLC patients with unresectable brain metastases given nimotuzumab (200 mg) and RT (40 Gy). Mean and median survival, respectively, was 7.3 and 7.0 months with nimotuzumab and 3.0 and 2.5 with only RT. Based on these positive results in a poor prognostic patient group, confirmatory studies have since been initiated in a North American setting.

In addition to the above mentioned trials of nimotuzumab with RT, several studies of nimotuzumab with chemotherapy or chemoradiation have been launched. Phase I data indicates nimotuzumab continues to be tolerated well with these treatments [45,46]. A Phase II study [47] of nimotuzumab with or without irinotecan in refractory CRC was recently conducted in Canada, and although response rates were lower, overall disease control rates (50%) and overall survival (9.3 months) were similar to results from studies of other EGFR mAbs in this setting. Furthermore, of the 61 patients enrolled, *K-ras* analysis was performed on 17 of them. *K-ras*-mutant tumors, found in 30% of patients, corresponded with a PFS of 12 weeks, whereas patients expressing wild-type *K-ras* had a PFS of 18 weeks; although the study was too small to be statistically significant, these results do correlate with expectations. More encouraging results were established in the previously noted 4-arm Reddy *et al.* study [25], which also included a nimotuzumab, cisplatin and RT arm with 20 evaluable members. After 24 weeks on treatment, 100% of the HNSCC patients showed response (90% CR and 10% PR), in contrast, the chemoradiation control arm ORR was 70% [48]. Not only was the 30 month post-RT survival rate increased from 21.7% to 69.5% but PFS was raised from 21.7% to 56.5% in those receiving nimotuzumab plus standard chemoradiotherapy [49]. Presently, another Phase II trial investigating combined modality chemoradiation with or without nimotuzumab is planned, this one in locally advanced NSCLC.

4. Side effect profile: Why no rash?

In clinical trials completed to date, SAEs remain extremely rare with nimotuzumab [23,28], most notably, the grade 3 and 4 acneiform rash commonly associated with other anti-EGFR mAbs is surprisingly absent [50]. In fact, when nimotuzumab was tested for toxicity in a large mammal model, *Cercopithecus aethiops sabaues* (Green Monkeys), it was found to not display any dermatological side effects, even at doses 10 times the amount recommended for human use [34]. The benign side effect profile of nimotuzumab is not limited to a minimal skin toxicity as it additionally

includes the absence of severe hypomagnesemia, a condition derived from a compromised renal magnesium retention system, and the lack of grade 3 or 4 gastro-intestinal side effects [51], both events encountered with other mAbs of EGFR [52,53].

The lessened side effects of this mAb are probably related to its unique binding affinity and density dependence. A lower affinity between nimotuzumab and EGFR allows for an optimal dose of the drug that is below the toxic dose. Mathematical models predict that the binding affinity (K_d) for anti-EGFR mAbs should be in the range of 10^{-8} M – 10^{-9} M to maximize tumor cell targeting while minimizing normal cell toxicity [23]. Although nimotuzumab is within this range, cetuximab and panitumumab have binding affinities more than 10-fold stronger. The more recently proposed receptor density model, in which nimotuzumab is described as being transiently bound monovalently and strongly bound bivalently to EGFR epitopes [43], further explains nimotuzumab's diminished adverse events. In normal cells (e.g., skin epithelial cells) EGFR expression is too low to cause nimotuzumab bivalent binding, thus limiting the mAb's potency, and avoiding unwanted toxicities. Overexpressing tumor cells, on the other hand, have enough receptor density for nimotuzumab to bind bivalently and robustly inhibit the receptor. This theory is supported by comparative dose binding curves of nimotuzumab and cetuximab on normal skin and kidney cells where nimotuzumab displays significantly less binding than cetuximab [51].

5. Summary

Nimotuzumab is a novel EGFR-targeting mAb that has the potential to be used as a single agent or as a radio- and chemotherapy sensitizer for the treatment of a diverse group of EGFR-expressing carcinomas. It appears to affect tumors by inhibiting cell division commands and decreasing VEGF

expression through inactivation of EGFR signaling, in addition to inciting an antineoplastic cell- and complement-mediated cytotoxic immune response. Experience to date from Phase I and II clinical trials conducted in Cuba, Canada, Germany, India, Spain and South Korea has shown it to be well tolerated in both adult and pediatric populations, with and without radiation or chemotherapy. Most conspicuously, it has not displayed any grade 3 or 4 skin toxicities common to other anti-EGFR mAbs. This lack of cutaneous manifestation is thought to be due to nimotuzumab's unique EGFR binding affinity and density selectivity.

6. Expert opinion

If nimotuzumab is shown to be clinically useful in ongoing and upcoming Phase II and III trials, its benign side effect profile will make it an attractive therapeutic option when compared with other anti-EGFR mAbs. Once completed, these Phase III trials will help to delineate exactly in which clinical situation nimotuzumab should be used and whether it works best as a single agent or as an adjunct with radiation and/or chemotherapy. Future trials should also reveal to what capacity, if any, nimotuzumab and TKIs (such as Gefitinib and Erlotinib) will work together to inhibit EGFR synergistically. The final research goal will be to identify molecular markers (EGFR expression, EGFR mutations, EGFR gene amplification or *K-ras* gene status) that best predict response. These can ultimately be used to correlate nimotuzumab treatment to specific tumor genotypes or phenotypes in order to maximize patient benefit.

Declaration of interest

G Bebb was the principal investigator for a Phase I study and is for a Phase II study of nimotuzumab.

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