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Matuzumab

Prop INN

Solid Tumor Therapy
Humanized Anti-EGFR Monoclonal Antibody

EMD-72000

Immunoglobulin G_1, anti-(human epidermal growth factor receptor) (humanized MAb 425 γ_1-chain), disulfide with humanized MAb 425 κ-chain, dimer

CAS: 339186-68-4

EN: 306297

Abstract

Membrane tyrosine kinase receptors in cancer cells are a particularly attractive therapeutic target. The epidermal growth factor (EGF) family of membrane receptors, and the epidermal growth factor receptor (EGFR) in particular, has emerged as one of the most promising targets. Ligand binding to the EGFR initiates multiple growth-regulatory signaling pathways, including the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/Akt pathways which regulate cellular gene transcription/proliferation and prosurvival signaling, respectively. One possible strategy to pharmacologically target EGFR is the use of anti-EGFR monoclonal antibodies (MAbs) to compete with activating EGFR ligands for binding to the extracellular domain. Matuzumab (EMD-72000) is a humanized IgG_1 MAb that not only binds with high specificity and affinity to EGFR, but also modulates antibody-dependent cellular cytotoxicity (ADCC). It has shown excellent antitumor activity against several human tumor types, including head and neck, lung, gastric and pancreatic cancers, and was chosen for further development. The efficacy, safety and pharmacokinetics of matuzumab as a single agent or in combination with other chemotherapeutics have been reported in several clinical trials. Matuzumab is presently undergoing phase II development for the treatment of solid tumors, including cervical, gastric, ovarian and non-small cell lung cancer (NSCLC).

Introduction

Disruption of signal transduction pathways through pharmacological targeting of relevant components within these pathways has become an effective therapeutic option to treat various types of cancer. Membrane tyrosine kinase receptors in cancer cells are a particularly attractive target, with the epidermal growth factor (EGF) family of membrane receptors emerging as one of the most promising. The EGF family consists of the epidermal growth factor receptor (EGFR, ErbB1, HER1), HER2 (ErbB2, Neu), HER3 (ErbB3) and HER4 (ErbB4). Structurally, EGF receptors all contain: 1) an amino-terminal extracellular domain comprised of 621 amino acid residues, which includes the ligand-binding domain; 2) a single 23-amino-acid transmembrane-anchoring region which may contribute to stability; and 3) a 542-amino-acid carboxyl-terminal intracellular domain which possesses tyrosine kinase activity that activates cytoplasmic targets. Alterations in the function of receptors from the EGF family, especially dysregulation of EGFR, have been shown to be associated with autonomous cell growth, invasion, angiogenic potential and the development of metastases (1-7).

Ligands such as EGF-like growth factors activate EGFR through binding to the extracellular domain, which initiates multiple growth-regulatory signaling pathways. The two most relevant pathways are the MAPK (mitogen-activated protein kinase, also known as extracellular signal-regulated kinase [ERK]) mitogenic pathway and the phosphatidylinositol 3-kinase (PI3K)/Akt (also known as protein kinase B [PKB]) pathway. The MAPK pathway regulates gene transcription and proliferation through activation of numerous substrate molecules in the cytosol, nucleus and plasma membrane. The PI3K/Akt signaling pathway mediates cell survival in that recruitment of Akt to the plasma membrane results in prosurvival signaling due to increased expression of antiapoptotic signals, decreased expression of proapoptotic signals and activation of mRNA translation (8-16) (Fig. 1).

Oncogenic transformation due to aberrant EGFR signaling can be a consequence of several different mechanisms, including receptor overexpression; activating

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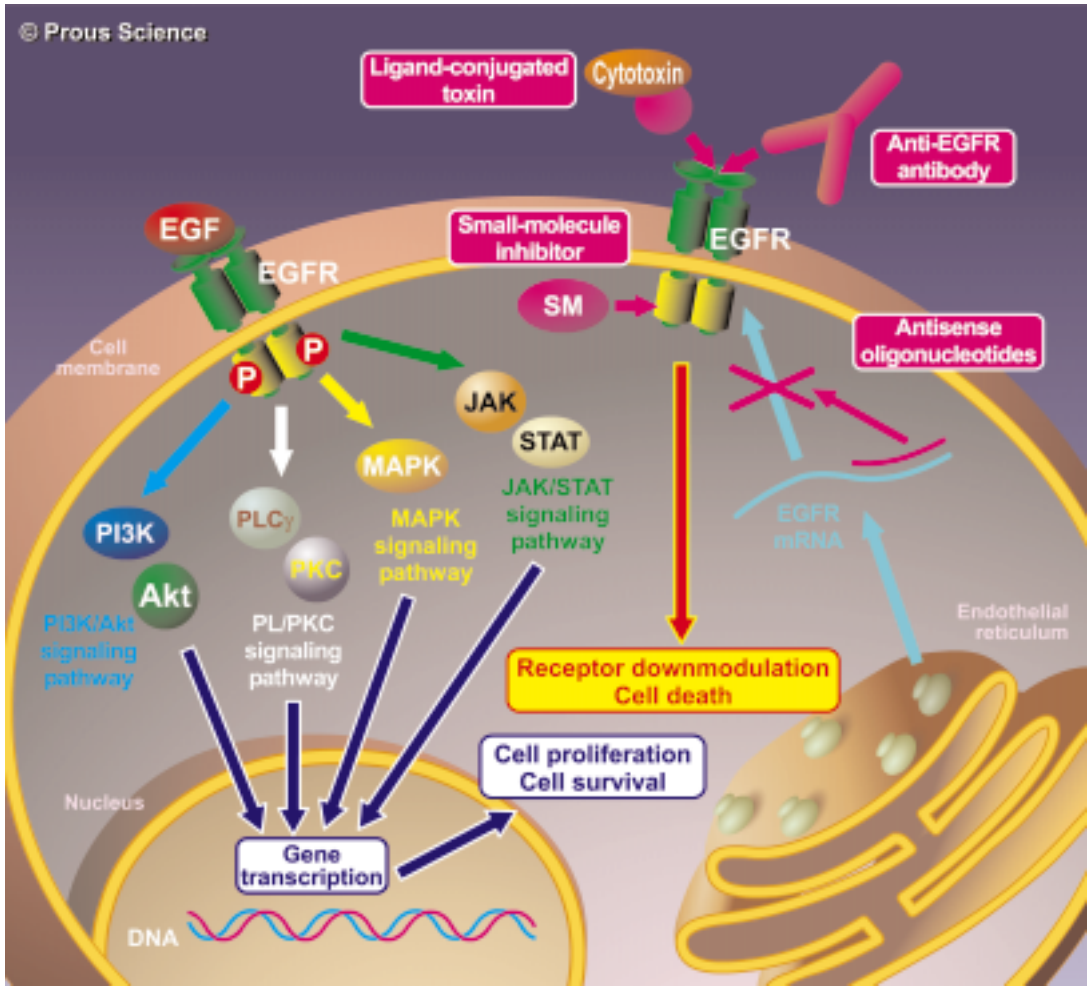

Fig. 1. EGF signaling pathways and strategies to pharmacologically target the EGFR.

mutations; alterations in the dimerization process required to induce conformational changes in EGFR that activate the intracellular tyrosine kinase moiety and receptor autophosphorylation; activation of the autocrine growth factor loop; and deficiencies in specific phosphatases. One of the most frequently seen is gene overexpression without gene amplification. This is associated with activation by TGF-α in an autocrine loop. Variant EGFR forms carrying mutations in the extracellular domain have been identified and the EGFR variant III (EGFRvIII) is associated with several types of cancer (17-20).

There are several possible strategies to pharmacologically target EGFR, including monoclonal antibodies (MAbs) to compete with activating EGFR ligands for binding to the extracellular domain; small-molecule inhibitors of the intracellular tyrosine kinase domain of the receptor; EGFR ligand-conjugated toxins to deliver toxins into tumor cells; antisense oligonucleotides to reduce EGFR levels; and inhibitors of downstream effectors of EGFR signaling pathways.

The first strategy used clinically to target aberrant EGFR signaling in malignant cells was the use of MAbs. Anti-EGFR antibodies not only disrupt receptor/ligand interactions, blocking aberrant signaling and thus tumor cell proliferation and growth, but they may also modulate antitumor effectors via antibody-dependent cellular cytotoxicity (ADCC). Natural killer (NK) cells mediate ADCC by recognizing the carboxyl-terminal ends of antibody molecules via the low-affinity receptor for IgG, FcγRIIIA/CD16. NK cells therefore can closely interact with antibody-coated tumor cells and destroy cells via necrosis and apoptosis (21-23). The first murine anti-EGFR MAbs developed showed good antitumor activity in animal models. However, their clinical use was limited due to the high incidence of human antimurine antibodies in patients, resulting in reduced efficacy (24). In response to this disadvantage, researchers developed chimeric and humanized forms of anti-EGFR MAbs. Cetuximab (IMC-C225, Erbitux®; ImClone Systems), a chimeric anti-EGFR MAb, was the first antibody of this type that successfully completed clinical trials and was launched in

Table I: Anti-EGFR monoclonal antibodies under active development for cancer (from Prous Science Integrity®).

Name	Source	Phase
Panitumumab	Abgenix; Amgen	III
Matuzumab	EMD Pharmaceuticals; Merck KGaA	II
Nimotuzumab (TheraCIM h-R3; Theraloc)	YM BioSciences; Center of Molecular Immunology; Oncoscience; Biocon Biopharmaceuticals	II
HuMax™-EGFr	Genmab	I/II
IMC-11F8	ImClone	I
RadioTheraCIM	YM BioSciences; Center of Molecular Immunology	I

2003 as a treatment for several cancers. There are a number of other anti-EGFR antibodies under active clinical development for the treatment of cancer, as shown in Table I.

Matuzumab (EMD-72000) is a humanized IgG_1 MAb that binds with high specificity and affinity to EGFR. It has been shown in animal tumor xenograft models to have potent inhibitory activity against human cancers, including head and neck, gastric, pancreatic and lung cancers. Matuzumab was shown to block EGF binding to EGFR, thereby inhibiting downstream signaling pathways, and it may also act via ADCC through FcR binding on immune cells. Matuzumab was selected for further development as a treatment for cancer.

Pharmacological Actions

A study was conducted using 1,060 xenotransplants in NMRI-*nu/nu* mice derived from human epidermoid carcinoma A-431 and human pharynx carcinoma Detroit 562 and clinical specimens from patients with head and neck or gynecological tumors (larynx, pharynx, mammary gland, uterine cervix and vulva) to examine the antitumor activity of matuzumab (40 μg/g i.p. on days 1 and 7, starting when tumors reached 25 mm^3). The MAb was only effective in significantly reducing tumor size in those carcinomas with an EGFR protein content of at least 70 fmol/mg protein, and tumor regression induced by matuzumab correlated with tumor EGFR concentrations. The antitumor activity of matuzumab was enhanced up to complete eradication in mice also treated with TNF-α (0.5 μg/g once daily on days 2-6). Moreover, carcinomas with an EGFR protein content of < 70 fmol/mg protein that were initially insensitive to matuzumab became susceptible in mice treated with TNF-α, such that significant reductions in tumors were observed in these animals (25).

Matuzumab (0.4, 4 or 40 mg/kg twice weekly for 2 weeks) showed dose-dependent efficacy against human pancreatic cancer in a study in nude rats bearing orthotopic L3.6pl tumors. Mean tumor weights for the 3 dose groups were 0.85 ± 0.52, 0.65 ± 0.4 and 0.21 ± 0.25 g, respectively, *versus* 1.4 ± 0.2 g in untreated controls. Although lymph node metastases developed in animals treated with the 0.4 and 4 mg/kg, none were observed in animals treated with the highest dose. Contrast-enhanced magnetic resonance imaging (MRI) analysis of animals performed *in vivo* 6 days after the end of treatment revealed that the dose of 40 mg/kg markedly decreased vascular permeability in primary pancreatic tumors as compared to untreated controls or animals treated with the lowest matuzumab dose (26).

Matuzumab exhibited antitumor activity against surgical specimens of EGFR-expressing human lung (LXFA629) and gastric (GXF251) adenocarcinomas and pancreas adenosquamous carcinoma (PAXF546) that were insensitive to chemotherapeutic drugs (bleomycin, cisplatin, vindesine, paclitaxel, ifosfamide) and implanted s.c. in nude mice. Treatment with matuzumab (0.5 or 0.5 mg/mouse i.p. once weekly for 2 weeks starting when tumors reached 70-120 mm^3) was well tolerated and effective against all 3 tumor types. Complete remissions were observed in 83% and 87%, respectively, of animals bearing gastric and lung carcinomas treated with the higher dose. Marked reductions in pancreatic tumors were observed, such that a mean tumor volume of 31% compared to controls was obtained (27).

The antitumor efficacy of matuzumab (40 mg/kg biweekly) in mice bearing orthotopic human L3.6pl pancreatic tumors was shown to be enhanced by simultaneous treatment with gemcitabine (100 mg/kg biweekly). Treatment with either agent alone caused a reduction in tumor size and lymph node and liver metastases. These effects were markedly enhanced by combination treatment. Treatment with matuzumab alone or in combination with gemcitabine also significantly decreased microvessel density and proliferative indices. Treatment was most effective when administered early after tumor cell injection (28).

Results from *in vitro* and *in vivo* studies suggest that the antitumor effects of matuzumab involve ADCC. Experiments using established squamous cell carcinoma of the head and neck cell lines (UM-SCC 11B, 14C and 22B, 8029A NA) which had an EGFR protein content of 170-8100 fmol/mg protein examined the antitumor activity of peripheral blood mononuclear cells (PBMCs) combined with matuzumab; the EGFR-negative MCF7 breast cancer cell line was used as a negative control. Addition of matuzumab enhanced the already marked antitumor activity of PBMCs. Higher EGFR protein content appeared to correlate with greater susceptibility to PBMC cytotoxicity. When PBMC subpopulations were tested, the antitumor effects appeared to be due to NK cell-

mediated ADCC. Matuzumab had no effect on MCF7 cells (29).

An ADCC effector function was also shown to be involved in the antitumor efficacy of matuzumab in SCID mice bearing established s.c. human epidermoid A-431 tumors (about 120 mm^3). Matuzumab was enzymatically deglycosylated so that EGFR signaling remained intact but FcR binding and ADCC activity were abrogated. Studies conducted *in vitro* using A-431 cells expressing high levels of EGFR confirmed that deglycosylated matuzumab lacked ADCC activity but continued to inhibit the growth and VEGF production of cells. Treatment of SCID mice bearing A-431 tumors with either intact or deglycosylated MAb (50 μg i.p. once weekly for 3 weeks) resulted in differential antitumor activity, with intact MAb exhibiting greater effects. Results suggest that ADCC and/or FcR binding contribute to the antitumor effects of matuzumab (30).

Toxicity

The toxicity of multiple-dose matuzumab administered as a weekly 1-h i.v. infusion (10, 33 and 100 mg/kg) was assessed in cynomolgus monkeys. The agent was well tolerated. The only adverse events were emesis and reduced activity in 1 animal each administered the highest dose. No skin reactions or adverse organ alterations were seen. Minor pathological organ lesions were observed in all groups, including the control. Menstrual cycles in 1 and 2 females receiving doses of 33 and 100 mg/kg, respectively, appeared to be arrested. The pharmacokinetic parameters obtained for animals administered 10 mg/kg corresponded with pharmacokinetics obtained for humans administered a weekly 800-mg dose of matuzumab, and systemic exposure in animals receiving 100 mg/kg was about 8 times that observed in humans given 800 mg, suggesting an adequate safety profile in humans (31).

Pharmacokinetics

The pharmacokinetics of single- and multiple-dose matuzumab obtained from several phase I clinical trials have been summarized. The agent was administered as a 1-h i.v. infusion every 1, 2 or 3 weeks at doses ranging from 50 to 2000 mg, and serum samples were obtained at baseline and up to 168 h after the first infusion and during week 4 or thereafter. Although analysis of data was hindered by short sampling periods in some studies, the pharmacokinetics obtained from the different studies were consistent. Dose-limiting toxicities (DLTs) were reported in 2 of the 3 patients receiving the highest dose and they required dose reductions to 1600 mg from week 2 on. The C_{max} and AUC values were found to be dose-proportional after single and multiple dosing and terminal half-life values increased with the lower doses and plateaued at the higher doses of 400-2000 mg. This suggests parallel elimination pathways, including capacity-limited and first-order elimination processes. A small (about 4 l) volume of distribution was obtained which was dose-independent. One multiple-dose study included in this analysis involved administration of loading/maintenance doses which were concluded to be unnecessary. Body surface area and body weight did not appear to influence the parameters examined and the pharmacokinetics described were similar to those obtained for other MAbs. Because of the insufficient sampling interval in some studies, it was noted that the $t_{1/2}$ values may be underestimated. A $t_{1/2}$ value of 180 h was obtained for multiple dosing every 3 weeks (32-37) (Table II).

Clinical Studies

An open, uncontrolled, dose-escalating phase I study conducted in 9 patients with stage III and IV squamous cell carcinoma of the larynx and hypopharynx examined the safety and tolerability of matuzumab (100, 200 and 400 mg by 1-h i.v. infusion as a loading dose followed by 4 weekly maintenance doses of 50, 100 and 200 mg, respectively). Matuzumab was very well tolerated. A total of 102 adverse events were reported. All grade 3 toxicities were concluded to be unrelated or only remotely related to matuzumab treatment. Fever and transient elevation of liver enzymes were the most common side effects (33). The results from this and several of the studies discussed below are depicted in Table III.

An uncontrolled, open-label study involving 14 subjects with EGFR-positive stage III or IV head and neck squamous cell carcinoma examined tumor uptake of a single dose of matuzumab (group A: 198 mg unlabeled + 2 mg [^{123}I]-labeled MAb by 1-h i.v. infusion; group B: 198 mg unlabeled MAb by 1-h i.v. infusion followed by i.v. injection of 2 mg of labeled MAb 24 h later). [^{123}I]-Matuzumab was well tolerated. No grade 3 or higher adverse events were reported. A total of 5 and 2 adverse events were experienced by 3 and 2 subjects in groups A and B, respectively. These included elevation of liver enzymes and fever, which were possibly related to treatment, and hypokalemia and tachycardia unrelated to matuzumab. A minimum 1.5-fold accumulation of matuzumab was observed in tumor tissue as compared to surrounding tumor-free tissue for both groups. The 200-mg dose was not enough to saturate all EGFRs present within the tumor. Accumulation of matuzumab in liver was slightly but not significantly lower in group B. However, at 48 h postadministration, planar whole-body accumulation of matuzumab was significantly less in group A (84% *vs.* 94%) (34).

Results from a dose-escalating phase I study conducted in 22 patients with measurable metastatic or advanced solid malignancies expressing EGFR examined the safety and tolerability of matuzumab (400, 800, 600, 1200 and 2000 mg by 1-h i.v. infusion weekly until disease progression or unacceptable toxicity developed). DLTs of grade 3 headache and fever were seen after the

Table II: Pharmacokinetics of matuzumab in humans after single and repeated i.v. administration (from Prous Science Integrity®).

Dose (mg)	AUC (g·h/l)	C_{max} (mg/l)	Cl (ml/h)	$t_{1/2}$ (h	t_{max} (h)	V_d (l)
Single dose						
100	2.3	19	95	55	1.6	4.3
200	5.8	57	35	57	1.5	2.6
400	15.7	105	28	105	1.8	3.2
800	35.4	276	26	115	1.3	3.9
1200	70.4	424	20	163	2.0	3.9
1600	73.3	625	23	94	2.8	3.0
2000	141	659	21	157	4.0	3.4
Multiple doses: o.w. 4.w.						
50	0.4	13.2	146	22	-	4.3
100	4.3	59.2	31	53	-	2.6
200	9.1	79.1	29	87	-	3.2
400	54.7	259	15	160	1.7	5.2
800	117	363	18	253	1.6	9.1
1200	132	543	20	180	5.6	5.2
1600	193	879	23	165	2.4	4.4
2000	175	852	19	152	1.4	4.1

AUC, area under the concentration-time curve from 0 to infinity; C_{max}, peak plasma concentration; Cl, plasma clearance; $t_{1/2}$, elimination half-life; t_{max}, time to reach peak plasma concentration; V_d, volume of distribution. Data taken from Refs. 32, 33 and 37.

Table III: Clinical studies of matuzumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Cancer, larynx, Cancer, hypopharynx	Open Multicenter	Matuzumab, 100 mg i.v. over 1 h on wk 1 → 50 mg i.v. over 1 h 1x/wk x 4 wks (n=3) Matuzumab, 200 mg i.v. over 1 h on wk 1 → 100 mg i.v. over 1 h 1x/wk x 4 wks (n=4) Matuzumab, 400 mg i.v. over 1 h on wk 1 → 200 mg i.v. over 1 h 1x/wk x 4 wks (n=3)	10	Matuzumab was very well tolerated in advanced squamous cell carcinoma of the larynx and hypopharynx	33
Cancer		Matuzumab, 400 mg i.v. over 1 h 1x/wk x 10 [median] wks (n=3) Matuzumab, 800 mg i.v. over 1 h 1x/wk x 10 [median] wks (n=3) Matuzumab, 1200 mg i.v. over 1 h 1x/wk x 10 [median] wks (n=6) Matuzumab, 1600 mg i.v. over 1 h 1x/wk x 10 [median] wks (n=7) Matuzumab, 2000 mg i.v. over 1 h 1x/wk x 10 [median] wks (n=3)	22	Matuzumab induced partial response and stable disease in 23% and 27%, respectively, of patients with tumors expressing the EGFR. Matuzumab was generally well tolerated and the maximum tolerated dose was established at 1600 mg once weekly, with severe headache and fever being dose-limiting at higher doses. This drug showed promising efficacy as asingle agent	35
Cancer, gastrointestinal	Randomized	Matuzumab, 100 mg i.v. over 1 h 1x/wk x 4 wks → 400 mg i.v. over 1 h 1x/wk [until disease progression] (n=7) Matuzumab, 200 mg i.v. over 1 h 1x/wk x 4 wks → 400 mg i.v. over 1 h 1x/wk [until disease progression] (n=6) Matuzumab, 400 mg i.v. over 1 h 1x/wk x 4 wks → 400 mg i.v. over 1 h 1x/wk [until disease progression] (n=6) Matuzumab, 800 mg i.v. over 1 h 1x/wk x 4 wks → 400 mg i.v. over 1 h 1x/wk [until disease progression] (n=6)	25	Matuzumab was well tolerated and induced disease stabilization in 15 of 20 evaluable patients with progressive gastrointestinal cancer expressing the EGFR. The median time to progression was 9.7 weeks	36
Cancer, lung (non-small cell)		Matuzumab, 100 mg 1x/wk + Paclitaxel, 175 mg/m^2 1x/28 d x 3 [median] cycles (n=3) Matuzumab, 200 mg 1x/wk + Paclitaxel, 175 mg/m^2 1x/28 d x 3 [median] cycles (n=3) Matuzumab, 400 mg 1x/wk + Paclitaxel, 175 mg/m^2 1x/28 d x 3 [median] cycles (n=4) Matuzumab, 800 mg 1x/wk + Paclitaxel, 175 mg/m^2 1x/28 d x 3 [median] cycles (n=7)	17	Matuzumab at doses up to 800 mg/week and combined with paclitaxel was generally well tolerated and induced a response rate of 44% in patients with advanced non-small cell lung cancer	38

first infusion of 200 mg and the maximum tolerated dose (MTD) was 1600 mg/week. No serious adverse events, allergic reactions or diarrhea were reported. The most common adverse event was mild grade 1 (50%) and 2 (14%) acneiform skin reaction. Analysis of defined punch skin biopsies before the first infusion and at about day 28 revealed that treatment with matuzumab abrogated EGFR signaling. There was a reduction in phosphorylation of EGFR and MAPK, with no changes in total EGFR protein. Objective responses (23%) and disease stabilization (27%) were reported at all doses. Treatment was continued in those patients who responded for up to 18 months with no cumulative toxicity (35).

The efficacy, safety and tolerability of matuzumab (100, 200, 400 or 800 mg/week by 1-h i.v. infusion for 4 weeks without premedication, followed by 400 mg/week until disease progression) were examined in a double-blind, randomized phase I trial conducted in 25 heavily pretreated patients with EGFR-positive gastrointestinal tumors and metastases (liver, lung, lymph nodes, peritoneum, bone) who were refractory to standard treatment (median of 4 prior chemotherapy regimens). Matuzumab was well tolerated, with no grade 3 or 4 toxicities reported. Grade 1 (n=7) and 2 (n=11) acneiform rash was the most common adverse drug-related event. The median time to progression was 9.7 weeks. Best confirmed responses in the intent-to-treat population were 1 (4%) complete response and 9 (36%) disease stabilizations. Responses determined at 4 weeks using dual-modality PET/CT imaging included: a complete metabolic response with disease stabilization for 13 months in 1 patient receiving 800 mg; partial responses in 1, 1, 2 and 2 patients, respectively, receiving 100, 200, 400 and 800 mg; and stable disease in 2, 4, 2 and 2 patients, respectively, receiving 100, 200, 400 and 800 mg (36).

The safety, tolerability and efficacy of matuzumab (100, 200, 400 and 800 mg/week) in combination with paclitaxel (175 mg/m^2 every 3 weeks) were demonstrated in a dose-escalating phase I trial in 17 patients with EGFR-positive advanced NSCLC (3 squamous cell and 10 adenocarcinoma), of whom 7 were previously treated (median of 2 chemotherapy regimens which included gemcitabine; 5 also received prior cisplatin or carboplatin). Combination treatment was well tolerated up to 800 mg/week; the MTD was not reached in this study. Skin-related toxicities were observed, although they did not exceed grade 2. Grade 1 flushing and grade 2 bronchospasm were experienced by 1 patient after the third matuzumab infusion, which did not recur after re-exposure to matuzumab. Grade 1, 2 and 3 allergic reactions were reported in 3, 1 and 1 patients, respectively, requiring postponement of paclitaxel dosing in 2 patients and withdrawal of 3 patients. The pharmacokinetics of matuzumab were comparable to the pharmacokinetics of the agent administered as monotherapy. In the 16 evaluable patients, an overall response rate of 44% was achieved. Responses included 1 complete response, 6 partial responses (3 pretreated and 3 chemotherapy-naïve patients) and 5 disease stabilizations (38).

An open-label, nonrandomized, dose-escalating phase I trial in 17 patients with advanced pancreatic tumors (16 confirmed to be EGFR-positive) examined the safety, tolerability and efficacy of combination treatment including matuzumab (400 or 800 mg/week or 800 mg every 2 weeks by 1-h i.v. infusion) and gemcitabine (1000 mg/m^2 every week). Treatment was administered for two 4-week cycles, after which those patients with stable or responding disease continued treatment. Combination treatment was well tolerated, with no serious drug-related adverse events. Toxicities (grade 3 or less) observed included skin toxicity (n=9), fever (n=4), neutropenia (n=3), cholangitis (n=2), hypokalemia (n= 2) and elevated liver enzymes (n=11). Grade 4 toxicities reported were unrelated to treatment except for 1 case of grade 4 Guillain-Barré syndrome in a quadriplegic patient administered 800 mg/week which could have been related to treatment. One death occurred due to respiratory failure unrelated to treatment. The pharmacokinetics obtained were similar to those reported for matuzumab monotherapy. Stable disease was obtained in 3 of 5 patients receiving 400 mg/week, 3 of 4 patients receiving 800 mg/week and 5 of 8 patients receiving 800 mg every 2 weeks with continuous treatment up to 50 weeks. Analysis of skin biopsies after the first treatment cycle at 4 weeks revealed that treatment with all regimens of matuzumab inhibited EGFR activation and affected receptor-dependent signaling, as indicated by reductions in phosphorylated MAPK and Ki67 and increases in p27 and CK-1 (39).

Matuzumab has entered early phase II development for the treatment of non-small cell lung, cervical, ovarian and gastric cancers (40, 41).

Sources

EMD Pharmaceuticals, Inc. (US); Merck KGaA (DE).

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