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MONOGRAPH

MM-121

Human Anti-erbB-3 IgG_2 MAb
Oncolytic

SAR-256212

Human monoclonal IgG_2 antibody against erbB-3

EN: 367364

SUMMARY

The role of tyrosine kinase-dependent epidermal growth factor receptor (EGFR) signaling in the progression of cancer is well documented and occurs in diverse cancer types, including breast, lung, ovarian, pancreatic and prostate cancer. Signaling via these receptors is ligand- and dimer-specific, producing a complex signaling system. Receptor mutations, amplifications and upregulation of growth factor ligand can all act to promote tumor growth. Current therapies targeting this system include tyrosine kinase inhibitors and monoclonal antibodies (MAbs) against the receptors. These therapies are effective in some cancer types, but not in others. The majority used to date have focused on two receptors, EGFR (receptor tyrosine-protein kinase erbB-1, HER1) and receptor tyrosine-protein kinase erbB-2 (HER2/Neu); however, a third receptor, receptor tyrosine-protein kinase erbB-3 (HER3), whose activation leads to the induction of phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K)/Akt signaling, has generated interest, because this has been shown to be a major pathway in promoting tumor growth. MM-121 is a human anti-erbB-3 MAb. Preclinical assessment in in vitro and in vivo cancer models has demonstrated the efficacy of MM-121 in inhibiting erbB-3 activation, PI3K/Akt phosphorylation and tumor growth. MM-121 is being clinically evaluated as a therapeutic agent in patients with solid tumors and non-small cell lung cancer as both a single agent and in combination with existing therapies.

Key words: Anti-erbB-3 monoclonal antibody – Cancer – MM-121 – SAR-256212

BACKGROUND

Epidermal growth factor receptor (EGFR) signal transduction pathways are one of the major tyrosine kinase signaling networks involved in mediating cell survival, differentiation and proliferation. Activating mutations and overexpression of the EGFR family, as well as aberrant ligand signaling, are well documented in a wide range of epithelial cancers and are associated with a poor prognosis. In malignant cells, excessive EGFR activation reduces apoptosis, while increasing cellular proliferation, motility, invasion and metastasis, making aberrant EGFR signaling an attractive target for therapeutic intervention.

The human EGFR family is comprised of four members, receptor tyrosine-protein kinase erbB-1 (HER1), receptor tyrosine-protein kinase erbB-2 (HER2/Neu), receptor tyrosine-protein kinase erbB-3 (HER3) and receptor tyrosine-protein kinase erbB-4 (HER4). These cell surface receptors are composed of a cytoplasmic tyrosine kinase domain, a single transmembrane domain and an extracellular domain that is involved in ligand binding and receptor dimerization. EGFR family members form homo- and heterodimers with one another and differ in their tissue distribution, ligand binding profiles and tyrosine kinase activity (1).

The erbB-1 receptor specifically binds epidermal growth factor (EGF), transforming growth factor α (TGF-α) and amphiregulin, as well as interacting with ligands that will also activate the erbB-4 receptor, such as probetacellulin (BTC), heparin-binding EGF and epiregulin. The erbB-2 receptor is unable to bind any ligands and therefore frequently forms a heterodimer with the other receptors. Specific ligand binding for the erbB-3 and erbB-4 receptors comes in the form of neureregulins. ErbB-3 demonstrates specific binding for pro-neureregulin-1 and -2 (NRG1/NRG2) isoforms, while erbB-4 receptors can bind pro-neureregulin-1 to -4 (NRG1-4) isoforms (1, 2).

Ligand binding to the EGFR family members elicits activation of dimer-specific downstream signaling cascades by autophosphorylation of receptor tyrosine residues and depends upon the dimer formed. These cascades include: the Ras/extracellular signal regulated kinase (ERK) pathway, the phosphatidylinositol 4,5-bisphosphate 3-kinase (PI3K)/Akt pathway and the tyrosine-protein kinase JAK/signal transducer and activator of transcription (JAK/STAT) pathway, all of which can promote cell growth and survival. Termination of the signaling cascade is also dimer-specific and is mediated by receptor internalization, degradation and recycling (3).

Mutations in erbB family members that lead to constitutive activation of the receptors or gain of function are apparent in a number of cancers, in particular, *ERBB1* and *ERBB2* mutations. *ERBB1* mutations occur in up to 13% of American and European populations, but can be as high as 50% in Asian populations (4). Furthermore, mutations in *ERBB2*, leading to upregulation of the receptor, have been identified in up to 25% of breast cancers (4-6).

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Many of the currently existing therapies target the erbB-1 and erbB-2 receptors and include small-molecule tyrosine kinase inhibitors (TKIs) or monoclonal antibodies (MAbs) that promote receptor internalization or obscure ligand binding domains. For example, the MAb trastuzumab and the dual erbB-1/erbB-2 TKI lapatinib have both demonstrated efficacy in treating erbB-2-amplified tumors (7, 8). Erlotinib and gefitinib, both erbB-1-targeting TKIs, have shown promise in the treatment of patients with non-small cell lung cancer (NSCLC), increasing initial response rates and progression-free survival (PFS) compared to standard chemotherapy (4). However, the success of many of these FDA-approved therapies varies between cancer types, and although TKIs have proven effective in treating NSCLC, the development of drug resistance is a major obstacle for many patients. Such resistance is known to be due to mutations in *ERBB1* that interfere with TKI actions, or due to the development of amplification of mesenchymal-epithelial transition (MET) factor, which has been noted in > 20% of NSCLC tumors following TKI treatment (9). However, resistance may also occur as a result of the complexity of erbB signaling, in particular, dimer formation and differing degrees of receptor and ligand expression, which may lead to the activation of more than one signal transduction pathway. Additionally, not all EGFR-related cancers are solely mediated by mutation-dependent overactivation or receptor amplification, but could be dependent on hyperactivity of a specific subunit due to an increased abundance of ligands as a result of changes in the tumor microenvironment and related changes in paracrine/autocrine signaling.

Therapeutic targeting of the erbB-3 receptor has been somewhat neglected because of a suspected lack of kinase activity, although recently this has been contested, with some reports of erbB-3 demonstrating autophosphorylation upon NRG1 binding; however, this is still a matter of debate (10). In addition, the heterodimerization of erbB-2 with erbB-3 has long been thought to be advantageous, because erbB-2 cannot bind ligands. Furthermore, in patients with *MET* gene amplification, tumor growth is stimulated via erbB-3 activation (11). Existing therapies that target upregulation of the erbB-1 receptor, such as cetuximab and gefitinib for lung cancer (11) and erlotinib for pancreatic cancer (12), have been shown to lack efficacy due to simultaneous ligand-mediated hyperactivity of the erbB-3 receptor as a result of increased growth factor expression in the tumor microenvironment. It is now well established that erbB-3 is the major mechanism of PI3K/Akt activation in both erbB-1- and erbB-2-driven cancers, suggesting that erbB-3 could be a potential therapeutic target for a number of cancers (13).

A systematic approach using computational network modeling and simulation demonstrated an important role for erbB-3-mediated PI3K/Akt activation in response to the growth factors probetacellulin (BTC) and NRG1 beta, and led to the development of MM-121 (SAR-256212), a fully human IgG_2 MAb designed to block signaling of the erbB-3 receptor by inhibiting the binding of NRG1 beta ligand. MM-121 is currently in early clinical development at Merrimack Pharmaceuticals and Sanofi for the treatment of advanced solid tumors, including breast cancer, as well as NSCLC (14, 15). In addition, preclinical data have demonstrated that MM-121 has an impact on multiple cancer models, including lung, ovarian, breast, prostate and renal cancers, and as a combination agent in pancreatic cancer when used with drugs targeting erbB-1 (12).

PRECLINICAL PHARMACOLOGY

The computational systems approach used in the development of MM-121 was used to identify biomarkers based on the five most critical proteins required for erbB-3/PI3K activation in order to predict patient response to treatment with MM-121 (17). These proteins included the erbB-1, erbB-2 and erbB-3 receptors, and the ligands NRG1 and BTC. The system was also used to compare the simulated IC_{50} values with previously determined experimental IC_{50} values for the existing erbB-1 inhibitors lapatinib, cetuximab and pertuzumab in blocking erbB-1 and erbB-2 activation in response to the ligands NRG1 beta and BTC. These were then used to predict IC_{50} values for MM-121. Experimental determination of the IC_{50} of MM-121 was subsequently assessed in adriamycin-resistant ovarian cancer cell lines and found to fit the stimulated model (16, 17).

Experimental stimulation of a panel of cell lines representing breast, colon, melanoma, prostate and renal cancers with NRG1 beta or BTC demonstrated a major role for erbB-3 in eliciting phosphorylation and activation of the Akt pathway, whereas central nervous system cancers responded only to BTC stimulation, indicating a major role for erbB-1. Furthermore, analysis of primary tissue from tumors indicated that these ligands are abundant in many cancer types. Specifically, NRG1 beta was found in all cell lines, but was particularly highly expressed in cervical, ovarian, breast and skin tumors, indicating that erbB-3 hyperactivity may be important in these types of cancer (16).

Further predictions made from the computational network model suggested that activation of erbB-3 by either ligand was a particularly sensitive point in signaling. The inclusion of a virtual MAb that would prevent dimerization of erbB-3 with either erbB-1 or erbB-2 and that would block ligand binding to erbB-3 indicated that this could be a potent inhibitor of PI3K/Akt initiation via NRG1 beta/BTC binding to erbB-3, a property that could significantly prevent cell proliferation and tumor growth.

Based on these findings, MM-121 was developed as an MAb that would bind to erbB-3 with low-nanomolar affinity to block NRG1 beta binding and BTC-induced erbB-3 phosphorylation. The experimental validity of MM-121 as an antagonist of erbB-3 was determined in adriamycin-resistant ovarian cancer cells. MM-121 effectively inhibited NRG1 beta-induced erbB-2–erbB-3 dimer formation. In addition, kinase assays revealed that MM-121 (7.6 pM-2 μM) inhibited the phosphorylation of erbB-3 by either NRG1 beta (IC_{50} = 2.4 nM) or BTC (IC_{50} = 5.8 nM) in a concentration-dependent manner. MM-121 also inhibited Akt phosphorylation by NRG1 beta (IC_{50} = 6.2 nM) and BTC (IC_{50} = 4.9 nM) (16, 17). Similar simulations and experimental dose–response testing was performed in the human ovarian adenocarcinoma cell line OVCAR-8 and the prostate carcinoma cell line DU 145. These experiments also confirmed the validity of the computational model and the efficacy of MM-121 as an inhibitor of NRG1 beta- or BTC-mediated activation of the erbB-3 receptor. At 100 nM, MM-121 significantly inhibited in vitro the proliferation of spheroids derived from ovarian cancer cell lines compared to those treated with an isotype control (16).

In pancreatic ductal adenocarcinoma (PDAC), stromal–epithelial interactions were determined to play a role in erbB-1 resistance to treatment with the TKI erlotinib. PDAC tumors highly express erbB-1

and possess erbB-1–erbB-3 heterodimers. However, within the tumor stromal environment there is an abundance of cancer-associated fibroblasts (CAFs) that secrete elevated levels of NRG1, the favored erbB-3 receptor ligand, suggesting that this could account for erbB-1-based drug resistance. Therefore, the impact of MM-121 on overcoming this resistance as a single agent or in combination with erbB-1 inhibitors was assessed in several PDAC cell lines (12).

In the pancreatic adenocarcinoma AsPC-1 cell line, which highly expresses erbB-3, application of conditioned media from primary cultured CAFs, which contained secreted NRG1, resulted in phosphorylation of erbB-3/Akt and induced cellular proliferation. These actions were reversed by blocking the binding of NRG1 to erbB-3 or removal of NRG1 from the conditioned media, suggesting that in this type of cancer a paracrine action of NRG1 from CAFs could be responsible for blocking the tumor-inhibiting properties of erbB-1-targeting inhibitors. Similarly, exogenous application of NRG1 beta (0.22 µg/mL) to PDAC cells that highly express erbB-3 (S2-013, Capan-1, HPAF-II and AsPC-1) prevented the modest inhibition of cell growth obtained with the erbB-1-targeting inhibitor (5 µM). In the same cell lines, the application of CAF-conditioned media completely blocked the inhibitory effect of erlotinib (5 µM) (12).

The effect of NRG1 on proliferation was completely abolished when AsPC-1 cells were pretreated with MM-121 (250 µg/mL), and more importantly, the effect of NRG1 on preventing erlotinib-mediated inhibition of cell growth was completely abolished in the presence of MM-121, confirming that in these cells hyperactivity of erbB-3 receptor signaling is responsible for the poor response to erbB-1 inhibitors, and that a combination of erbB-1 and erbB-3 inhibition could provide the most effective treatment regimen, especially in cancers in which the stromal environment provides an enrichment of paracrine acting growth factors. This was further confirmed by a synergistic effect of erlotinib and MM-121 on decreasing cellular proliferation in vitro (12).

One study has assessed the impact of MM-121 on the ability to affect erbB-3 phosphorylation and expression in cancer cell lines that demonstrate different sensitivities to treatment. In the renal adenocarcinoma cell line ACHN (sensitive), erbB-3 phosphorylation was inhibited and a subsequent decrease in receptor expression was observed. In contrast, in the gastric carcinoma cell line NCI-N87 (moderately sensitive), there was a simultaneous decrease in erbB-3 phosphorylation and receptor expression. MM-121 had little effect on erbB-3 phosphorylation or expression in the human breast ductal carcinoma cell line BT-474 (resistant), likely due to those cells being characterized by erbB-2 overexpression and displaying ligand-independent activation of erbB-3. This study concluded that those cancers presenting erbB-2-driven erbB-3 phosphorylation in a ligand-dependent manner are likely to be most sensitive to MM-121 as a single agent (13).

Estrogen receptor-positive (ER^+) breast cancers account for up to 80% of breast cancers. Conventional treatment regimens involve the use of hormone replacement therapy, although the disease often becomes resistant to such therapies. In a breast cancer cell line, MM-121 was shown to inhibit NRG1-induced activation of erbB-3 and to prevent its phosphorylation (18).

In tumor xenograft models of mice implanted with human renal adenocarcinoma ACHN tumors, MM-121 (100 µg) administered every third day for 45 days delayed tumor growth compared to untreated controls. Increasing the dose to 300 µg resulted in complete inhibition of tumor growth over the same time period. If the dose was given on a weekly basis, complete inhibition was only observed at 2500 µg (16).

In tumor xenograft models of mice implanted with human lung carcinoma A459 tumors, MM-121 effectively retarded tumor growth compared with untreated controls (16, 19).

In AsPC-1 subcutaneous xenograft tumor models of PDAC in mice, MM-121-mediated inhibition of erbB-3 activation and Akt phosphorylation prevented tumor growth in a dose-dependent manner (70-600 mg/kg) (12).

The regular administration of MM-121 in tumor xenograft models of human prostate cancer reduced tumor size in a dose-dependent manner by inhibiting erbB-3 activation, and such inhibition was correlated with efficacy (14, 15, 20).

Preclinical studies suggest that MM-121 could be beneficial for the treatment of drug- or hormone-resistant breast cancers. In xenograft models of ER^+ human breast cancer, MM-121 was demonstrated to be effective in combination with chemotherapeutic agents or hormone therapy. When MM-121 was used as a single agent in a triple-negative human breast cancer xenograft model (ER^-, progesterone receptor negative [PR^-] and low erbB-2 expression), tumor growth was suppressed (18).

The computational model developed to model EGFR-related cancers has also been used to predict MM-121 response in 11 different xenograft models that express the 5 identified biomarkers –erbB-1-3, NRG1 and BTC– to differing degrees. For example, human colorectal carcinoma HCT 116 and HT-29, and NSCLC adenocarcinoma NCI-H1975 cancer cells were predicted to be nonresponders and gastric carcinoma NCI-N87 cells were predicted to be partial responders. The effect of MM-121 in these in vivo models mostly corresponded to those seen in vitro in the corresponding cell lines, although there were exceptions. MM-121 elicited substantial tumor growth arrest in DU 145, OVCAR-8 and ACHN cancer models, modest tumor growth delay in NCI-N87 and human ovary adenocarcinoma SK-OV-3 cancer models, and no significant antitumor activity in NCI-ADRr (once thought to be breast but most likely ovarian in origin), BT-474, ovarian cancer IGROV-1 and melanoma Malme-3M cancer models. The presence of exceptions could be due to effects of other growth factors in vivo that induce alternative pathways which are not present in in vitro environments (13). To date, the computational model has correctly predicted tumor response to MM-121 in all of these models (17).

PHARMACOKINETICS AND METABOLISM

Studies are ongoing to establish the pharmacokinetics (PK) and metabolism of MM-121.

SAFETY

Studies are ongoing to establish the safety and tolerability of MM-121. Initial data have been presented at a recent conference from one study in patients with NSCLC. The most frequent adverse events (AEs) in these patients (N = 33) receiving MM-121 in combination

with erlotinib were rash, diarrhea, nausea and fatigue. As of July 2011, 16 patients remain on the study (21, 22).

CLINICAL STUDIES

Six phase I clinical trials are recruiting patients, three of which are evaluating the safety and tolerability of MM-121.

The first is a nonrandomized, interventional study to investigate MM-121 when used as a combination agent with cetuximab and irinotecan in patients with advanced solid tumors (23). The study is expected to enroll 45 patients with various solid tumors, including breast, NSCLC, colorectal and head and neck cancer. The primary outcome measure is the number of dose-limiting toxicity (DLT) events in response to treatment. The second is an interventional, open-label, dose-escalation study to examine MM-121 in combination with paclitaxel in patients with advanced gynecological and breast cancers. The estimated enrollment is 24 patients and the primary outcome measure will examine the severity of AEs. Secondary endpoints include assessment of the objective response rate (ORR) and clinical benefits of the treatment and the PK of the combination therapy (24). The third safety study is a nonrandomized, open-label, dose-escalation study to evaluate MM-121 used in combination with gemcitabine, carboplatin, pemetrexed or cabazitaxel in patients with advanced solid tumors. The estimated enrolment is 48 patients and the primary endpoint measurement will be the number of DLT events in response to treatment (25).

A pharmacological, open-label, dose-escalation phase I investigation is being conducted to examine the safety and tolerability of MM-121 in treating patients with advanced solid tumors who are resistant to current therapies. The estimated enrolment is 40 patients and the primary outcome measure will be to determine the phase II dose based on the maximum tolerated dose (MTD) or the maximum dose of 20 mg/kg and ORR based on RECIST. Secondary outcome measures will include AEs, PK and pharmacodynamic (PD) data (26).

An interventional, nonrandomized, open-label phase Ib trial is being carried out to determine the MTD and recommended phase II dose of SAR-245408 administered in combination with MM-121 in adult patients with locally advanced or metastatic solid tumors. The study is expected to enroll 56 patients and the primary outcome measure will be to determine the MTD. Secondary endpoints include AEs, ORR, immunogenic response and determination of PD data based on erbB-3 receptor expression and activation of the PI3K pathway components (27).

The last is a phase I/II study to investigate the efficacy of MM-121 as a combination therapy in patients with advanced NSCLC (N = 33; median age = 64 years). MM-121 is being administered weekly and erlotinib is being administered daily in this dose-escalation study to determine the MTD, AEs and PK data (21, 22, 28).

Four phase II studies are currently recruiting.

The first is part of the phase I study of MM-121 as a combination therapy in patients with advanced NSCLC. This study is expect to enroll patients who will be placed in one of three cohorts: 1) patients with no *ERBB1* mutations who are TKI-naive and have received at least one line of prior chemotherapy, to assess whether MM-121 enhances intrinsic sensitivity of tumors to erlotinib; 2) patients with *ERBB1* mutations who are TKI-naive, to assess whether MM-121 delays or prevents acquired resistance or enhances intrinsic sensitivity to erlotinib; and 3) patients with *ERBB1* mutations who have developed acquired resistance to TKI, to assess whether MM-121 can reverse acquired resistance. The MTD, as determined in the phase I study, will be used to determine the primary endpoint of PFS in each group and the secondary endpoints of overall survival (OS) and ORR of MM-121 and erlotinib in combination. In addition, AEs, PK parameters, immunogenicity and biomarker profiles will be determined for each patient (21, 28).

The second is a global, double-blind, randomized trial of exemestane (25 mg/day p.o.) in combination with MM-121 (20 mg/kg/week i.v.) in postmenopausal women (N = 130) with locally advanced or metastatic ER^+ and/or PR^+, erbB-2-negative breast cancer whose disease has failed to respond to hormone treatment. The primary objective of the study is to determine whether the combination of MM-121 plus exemestane is more effective than exemestane alone based on PFS. Secondary objectives will include OS, ORR and clinical benefit rate (29, 30).

The third phase II study is an interventional, randomized, open-label trial of preoperative MM-121 with paclitaxel in erbB-2-negative breast cancer and is expected to enroll 200 patients. Primary outcome measures will be to determine the complete response rate following weekly treatment with MM-121 plus paclitaxel followed by the combination treatment of doxorubicin plus cyclophosphamide compared to that in which MM-121 is omitted (31).

The fourth phase II study is an interventional, randomized, open-label trial that will investigate the application of MM-121 in combination with paclitaxel in patients with platinum-resistant/refractory advanced ovarian cancer. The study is expected to enroll 210 patients and will measure the PFS at 38 months as the primary endpoint (32).

DRUG INTERACTIONS

In preclinical assessments, MM-121 was shown to act synergistically with erlotinib and cetuximab, both erbB-1 activation inhibitors, to prevent erbB-3 activation and Akt phosphorylation in various cancer cell lines and tumor xenograft models. The clinical assessment of interactions with existing therapies is ongoing. Drug interactions of a clinical nature are yet to be determined.

SOURCES

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