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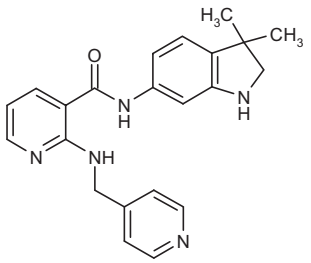
AMG-706

Oncolytic
Antiangiogenic Agent
Multikinase Inhibitor

N-(3,3-Dimethyl-2,3-dihydro-1*H*-indol-6-yl)-2-(pyridin-4-ylmethylamino)pyridine-3-carboxamide



$C_{22}H_{23}N_5O$
Mol wt: 373.4511

CAS: 453562-69-1

CAS: 857876-30-3 (phosphate salt)

EN: 365085

Abstract

Tumor progression requires angiogenesis and cancers are believed to lie dormant until a disruption in the balance between the production of angiogenesis-stimulatory and -inhibitory factors occurs, causing an angiogenic switch. Vascular endothelial growth factor (VEGF) in particular is an important proangiogenic mediator. Binding of VEGF to its receptors (VEGFRs) results in intracellular autophosphorylation of the receptor kinase domain and a subsequent cascade of signal transmission that eventually leads to the growth message in the cell nucleus. Interference with the VEGF/VEGFR system therefore represents an attractive strategy in cancer research. One orally active multikinase inhibitor to emerge is AMG-706. The agent targets VEGFR-1, VEGFR-2, VEGR-3 and platelet-derived growth factor (PDGFR), and also inhibits Kit receptors, thereby directly interfering with signal transduction of the tumor cell. AMG-706 was shown to exert potent antiangiogenic actions, as well as direct cytotoxic antitumor activity, in preclinical models. Moreover, the clinical safety and efficacy of the agent both as monotherapy and in combination with other chemotherapeutics have been demonstrated in patients with advanced solid malignancies.

Synthesis

AMG-706 is synthesized as follows:

1-Acetyl-3,3-dimethyl-6-nitroindoline (I) is reduced by catalytic hydrogenation over Pd/C, giving the aminoindoline (II), which is then coupled with 2-chloronicotinoyl chloride (III) in the presence of DIEA to yield the corresponding nicotinamide (IV). Subsequent condensation of (IV) with neat 4-(aminomethyl)pyridine (V) at 120 °C affords the 2-aminonicotinamide derivative (VI). The *N*-acetyl group of (VI) is finally removed by acidic hydrolysis to furnish the title compound (1, 2). Scheme 1.

Background

Angiogenesis is a complex process defined as the formation of new blood vessels from pre-existing vessels. It is essential for the progression of solid tumor growth to more than 1-2 mm^3. Mediators of this process include the proangiogenic cytokines vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), which stimulate endothelial cells to secrete proteases and plasminogen activators. These in turn cause degradation of the vessel basement membrane, allowing cells to invade the surrounding matrix. Cells will then migrate, proliferate and eventually differentiate to form a new lumen-containing vessel. The endothelial cells subsequently deposit a new basement membrane and also secrete growth factors (*e.g.*, platelet-derived growth factor, or PDGF) that attract supporting cells, which, together with angiopoietins and ephrins, ensure and regulate stability of the new vessel (3-6).

The driving force behind angiogenesis is an imbalance between the production of angiogenesis-stimulatory (*e.g.*, VEGF, FGF, PDGF) and -inhibitory (*e.g.*, thrombospondins) factors, causing an angiogenic switch. Tumor cell lines secrete VEGF *in vitro* and VEGF mRNA is increased in most human tumors, while mRNA for VEGF receptors (VEGFRs) is upregulated in endothelial cells associated with tumors. Moreover, elevated serum

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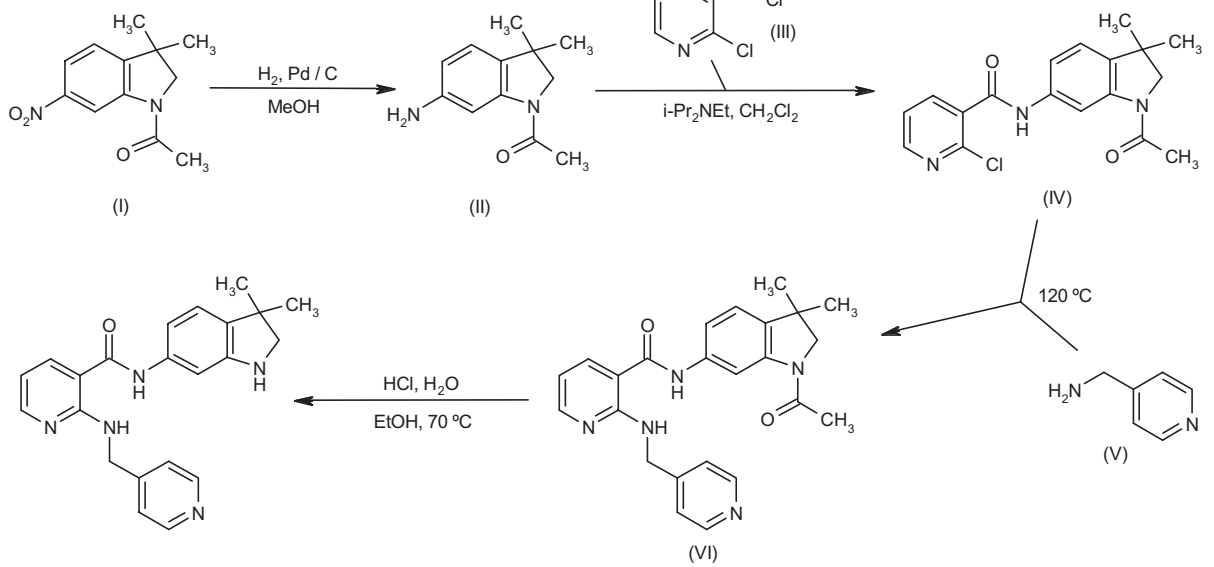
Scheme 1: Synthesis of AMG-706



levels of VEGF and basic FGF (bFGF or FGF-2) have been detected in individuals with several tumor types. Thus, interference with the VEGF/VEGFR system represents an attractive target for inhibition of angiogenesis in cancer (4-9).

Targeting angiogenesis and VEGF in particular was validated with the 2004 approval of the first angiogenic agent, bevacizumab (Avastin™; Genentech, Roche), an anti-VEGF monoclonal antibody approved for the treatment of metastatic colon cancer (10). Other antiangiogenic strategies for the treatment of malignancies have emerged and include blocking matrix degradation (*i.e.*, matrix metalloproteinase [MMP] inhibitors), blocking VEGF, FGF and PDGF receptor signaling, inhibiting normal endothelial cells and antagonizing integrin. Because VEGF is a key mediator of neovascularization, research has intensely focused on interfering with the VEGF/VEGFR system in order to modulate angiogenesis. The activity of VEGFs is mediated through binding to specific cell-surface receptors: VEGFR-1 (Flt-1), VEGFR-2 (KDR or Flt-2) and VEGFR-3 (Flt-4). VEGFR-1 and VEGFR-2 are expressed predominantly on vascular endothelial cells, while VEGFR-3 is expressed on lymphatic endothelium and is not as important for tumorigenesis. VEGF binding to its receptors induces homo- or heterodimerization of the ligand, which subsequently triggers intracellular autophosphorylation in their kinase domain. A cascade of signal transmission eventually leads to the growth message in the cell nucleus (Fig. 1) (4, 11-13).

AMG-706 is an orally active, small-molecule, ATP-competitive multikinase inhibitor that targets VEGFR-1, VEGFR-2, VEGFR-3 and PDGFR. In addition, it also inhibits the stem cell factor (SCF) receptor Kit (CD117). SCF is a cytokine that stimulates cell growth and differentiation. The c-kit proto-oncogene encodes this type III transmembrane receptor kinase, which is expressed on mast cells, melanocytes and some hematopoietic stem cells and has been linked to several types of cancer, including gastrointestinal stromal tumors (GISTs), melanoma, small cell lung cancer (SCLC), ovarian cancer and breast cancer (14). Thus, AMG-706 not only possesses potent antiangiogenic actions but also direct cytotoxic antitumor activity through blockade of Kit. AMG-706 was selected for further development as monotherapy and in combination with other chemotherapeutics in the treatment of breast, bladder, colorectal, lung, thyroid and ovarian cancers (15).

Preclinical Pharmacology

AMG-706 potently inhibited recombinant human VEGFR-1 (IC_{50} = 2 ± 0.7 nM), VEGFR-2 (IC_{50} = 3 ± 0.5 nM), VEGFR-3 (IC_{50} = 6 ± 4 nM), Kit (IC_{50} = 8 ± 2 nM), Ret (IC_{50} = 59 ± 4 nM), PDGFR (IC_{50} = 84 ± 33 nM) and murine VEGFR-2 (IC_{50} = 6 ± 2 nM) *in vitro*, but it had little effect on approximately 47 other kinases, including FGF receptor (FGFR; IC_{50} > 2800 nM), epidermal growth factor receptor (EGFR), Src and p38 (IC_{50} > 3000 nM). Studies performed *in vitro* using human umbilical vein endothelial cells (HUVECs) showed that pretreatment with AMG-706 (for up to 2 h) markedly inhibited VEGF- and PDGF-induced proliferation (IC_{50} = 10 and 207 nM, respectively) and c-Kit phosphorylation (IC_{50} = 37 nM), but was ineffective against bFGF-induced proliferation (IC_{50} > 3000 nM) and EGF-induced EGFR phosphorylation in human epidermoid carcinoma A-431 cells (IC_{50} > 25 μM) (15, 16).

The antiangiogenic effects of AMG-706 were demonstrated in a number of studies *in vivo*. AMG-706 (100 mg/kg for 2, 4, 16, 18 and 24 h) time-dependently inhibit-

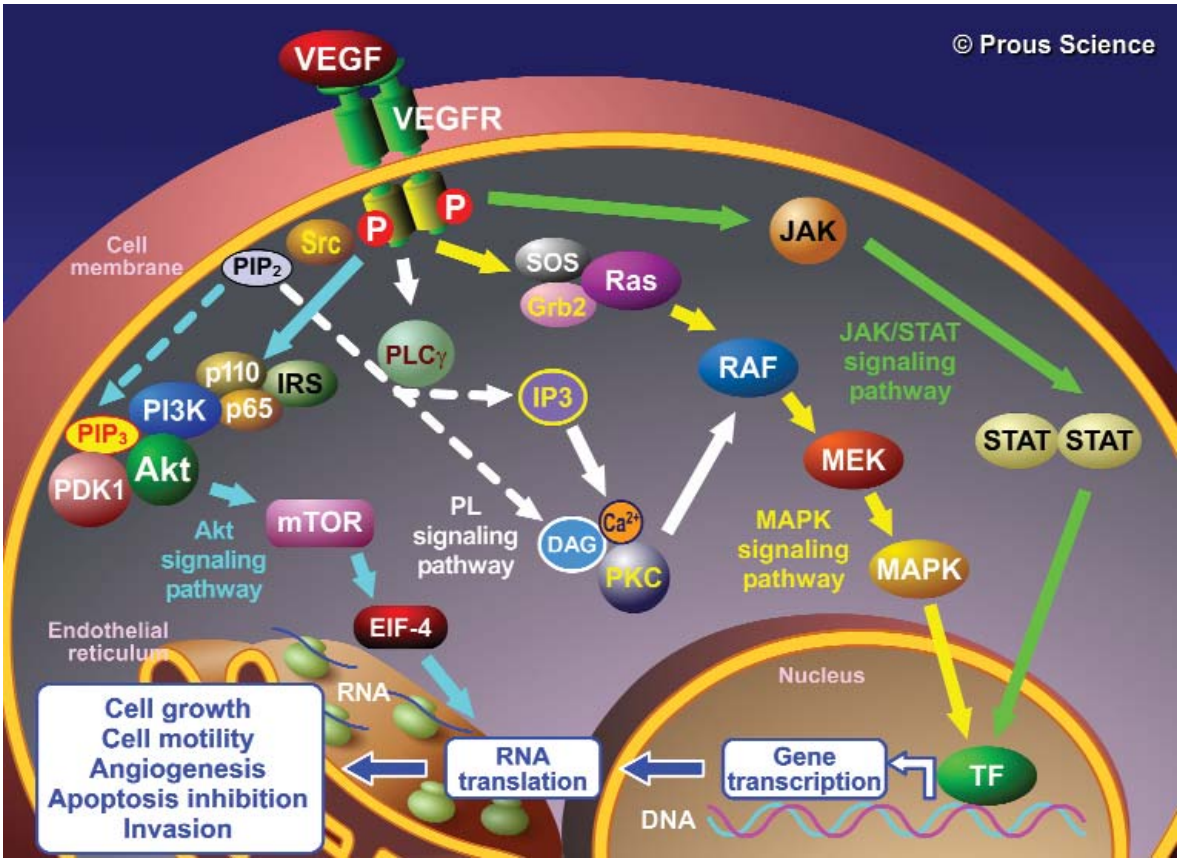


Fig. 1. VEGFR signaling pathways.

ed VEGF-induced vascular permeability in athymic nude mice injected s.c. on the ventral surface with murine VEGF-expressing HEK93 cells; significant inhibition was observed with 4-h exposure. In addition, AMG-706 dose-dependently reduced VEGF-induced corneal angiogenesis in a rat model; significant reductions in the number of blood vessels and in blood vessel area were observed at doses of 1, 3, 5 and 10 mg/kg b.i.d. administered for 7 days (ED_{50} = 2.1 mg/kg b.i.d.). Once-daily dosing with the agent for 7 days also significantly inhibited angiogenesis in this model (ED_{50} = 4.9 mg/kg/day) (15, 16).

AMG-706 potently inhibited the growth of several human tumor xenografts in athymic nude mice. AMG-706 was well tolerated and provided dose-dependent inhibition of A-431 and human colon carcinoma (HT-29) tumor growth at all doses examined (10, 30 and 100 mg/kg p.o. b.i.d. starting 10 days postinoculation when tumors reached about 125 mm^3). Significant tumor regression was observed after only 7 days of treatment with 100 mg/kg in the A-431 model; similar effects were observed in animals bearing HT-29 tumors, although significant regression was not observed until 18 days. Moreover, experiments evaluating initiation of treatment (75 mg/kg b.i.d.) when A-431 tumors were established demonstrated that tumor regression was associated with a rapid and marked loss of tumor-associated vasculature, followed by increased tumor cell apoptosis (15-18).

Further analysis of the effects of AMG-706 in the A-431 xenograft model using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) was performed to determine the effects on vascular permeability and blood flow. Treatment at doses of 10 and 75 mg/kg when tumors reached 300 mm^3 significantly decreased tumor blood flow and vascular blood flow as early as 24 h post-dosing. Results indicated that the antitumor effect of AMG-706 is due to destruction of tumor blood vessels (19).

AMG-706 was also shown to be effective in combination with panitumumab, a fully human IgG_2 antibody that targets human EGFR, in A-431, HT-29 and non-small cell lung cancer (NSCLC) Calu-6 xenograft models in athymic nude mice. Combination treatment including AMG-706 (10-75 mg/kg starting when tumors reached about 200-800 mm^3) and panitumumab (20-500 μg/mouse twice weekly) resulted in significantly greater antitumor activity than that observed with either agent alone in all three models. No adverse drug interactions were observed (20).

Results from experiments using the HT-29 and Calu-6 xenograft models in athymic nude mice demonstrated the efficacy of AMG-706 alone (37.5 or 75 mg/kg once daily starting when tumors reached about 350-500 mm^3) and in combination with irinotecan (50 mg/kg i.v. every 4-5 days), 5-fluorouracil (40 mg/kg i.p.) or cisplatin (5 mg/kg i.p. once weekly). AMG-706 alone or in combination with the other chemotherapeutic agents was well tolerated.

While treatment with AMG-706 alone caused regression of HT-29 tumors, combination treatment including CPT-11 or 5-fluorouracil resulted in a significantly greater inhibition of tumor growth. Similarly, AMG-706 alone delayed Calu-6 tumor growth, but combination treatment including cisplatin resulted in significant tumor regression. The HT-29 model was more responsive to AMG-706 monotherapy than the Calu-6 model (21).

Pharmacokinetics and Metabolism

The pharmacokinetics of a tablet formulation of AMG-706 (100 mg/tablet or 25 mg/tablet x 4) were compared to those of the original capsule formulation (100 mg) in beagle dogs and in a cohort of 12 patients with advanced solid tumors. Comparable pharmacokinetics were obtained in dogs and humans for the two formulations in the three single-dose regimens. Mean plasma AUC ratios in dogs were 1.11 and 1.12 for tablet and capsule formulations, respectively. In humans, the point estimates of the geometric ratios (tablet/capsule) for AUC and C_{max} were 1.02 and 1.23, respectively. Thus, the new tablet formulation produces circulating levels of the agent comparable to the original capsule formulation (22, 23).

The safety and pharmacokinetics of AMG-706 (50, 100, 125 or 150 mg p.o. once daily on days 1 and 3-21 in cycle 1, followed by 1 week off and daily dosing in 28-day cycles) were investigated in 15 Japanese patients with advanced solid tumors. Data were reported from 9 evaluable patients (sarcoma, cholangiocarcinoma, NSCLC, SCLC or colorectal, bile duct or stomach cancers). The mean C_{max} and $AUC_{0-\infty}$ values for the 50, 100 and 125 mg cohorts on day 1 were 493 ng/ml and 1.63 μg.h/ml, 562 ng/ml and 3.64 μg.h/ml, and 1040 ng/ml and 3.62 μg.h/ml, respectively; $t_{1/2}$ values on day 1 were 5.7, 7.6 and 6.7 h, respectively. Slightly lower exposure was observed on day 21, such that mean C_{max} values for the respective doses were 499, 459 and 694 ng/ml and $AUC_{0-\infty}$ values were 1.22, 2.79 and 3.19 μg.h/ml, respectively. Mean plasma concentrations at 24 h after dosing on day 21 were well above the IC_{50} value. The agent was generally well tolerated, with no dose-limiting toxicity (DLT) reported; the maximum tolerated dose (MTD) was not reached. Six patients who had received 2 cycles or more had stable disease, but no objective tumor responses were seen (24).

An open-label phase I trial including 71 patients with advanced solid tumors examined the pharmacokinetics, safety and pharmacodynamics of once-daily oral AMG-706. AMG-706 was generally well tolerated up to 125 mg once daily. The most common adverse events reported were fatigue (37%), hypertension (34%), diarrhea (27%) and headache (24%). The agent was readily absorbed. Pharmacokinetic parameters were approximately dose-proportional between the 50- and 175-mg doses and parameters were similar on days 1 and 21, indicating no accumulation. The overall mean t_{max} and mean $t_{1/2}$ values after a single dose were 0.5-1.5 and 6.3-7.5 h, respectively. A dose of 125 mg once daily achieved and maintained plasma concentrations (25-29 ng/ml) at levels estimated to be therapeutic from preclinical models (C_{min} > 18 ng/ml) (25).

Clinical Studies

The safety and efficacy of oral AMG-706 (50, 100, 125 or 175 once daily for 21 days of a 28-day cycle) were examined in an ongoing, open-label, dose-escalation study in 31 patients with advanced solid tumors. The agent was generally well tolerated at doses up to 125 mg once daily. The majority of adverse events reported were reversible and mild to moderate. Of the 9 patients treated at 125 mg, all remained on study up to day 50, including 2 patients who developed grade 3 hypertension and grade 3 creatinine elevation/grade 4 hyponatremia. Of the 26 patients evaluable for response at day 50, 1 patient with leiomyosarcoma had a partial response and 3 patients with GIST, thyroid and carcinoid tumors had minor responses. Of the 9 patients who had stable disease, 3 patients maintained it for at least 218 days. Bioavailability was favorable and a $t_{1/2}$ of about 7 h was seen at all doses. No significant accumulation was detected during the first 3 weeks of dosing (26).

The safety and efficacy of AMG-706 (125 mg p.o. once daily for 21 or 28 days of a 28-day cycle) were examined in an open-label phase I study in 65 patients with advanced solid tumors. The agent was well tolerated when given on both intermittent and continuous dosing schedules, and 3 patients continued on the study for more than 1 year. The majority of the adverse events reported were reversible and mild to moderate, the most common being hypertension (31%), fatigue (29%) and headache (25%). Of 56 evaluable patients, 2 had partial responses and 34 experienced disease stabilization. Examination of tumor vascular permeability in 18 patients using DCE-MRI revealed reductions of up to 37% and 61% in AUC on treatment days 3 and 21, respectively (27).

The above-mentioned phase I study in 71 patients with advanced malignancies (11 sarcoma, 10 gastrointestinal, 9 genitourinary, 7 thyroid, 6 GIST, 6 NSCLC, and others) also examined the safety and efficacy of oral AMG-706 (25 mg b.i.d. or 50, 100, 125 or 175 mg once daily on 28-day cycles). AMG-706 was well tolerated at doses up to 125 mg once daily. Sixty-six patients were evaluable for response at day 50, 3 of whom had partial responses, 40 stable disease and 23 progressive disease. Examination of serum levels of placental growth factor (PlGF) and soluble VEGFR-2 revealed that while PlGF increased (peak on day 2 and sustained through day 22) with increasing AMG-706 exposure, soluble VEGFR-2 decreased. These changes were shown to significantly correlate with tumor response to AMG-706. Serum levels of VEGF, soluble Kit-1, bFGF and soluble VEGFR-1 did not correlate with tumor response. Results suggest that PlGF and VEGFR-2 may be used as biomarkers for AMG-706-induced tumor response (25, 28). The results and/or aims of this and several of the following studies are summarized in Table I.

Further analysis of a subset of 7 patients with stage IV thyroid cancer treated with AMG-706 (median time on treatment = 141 days) in the above study (25, 28) was performed and demonstrated the efficacy of AMG-706. The MTD was 125 mg once daily and responses included 3 partial responses and 3 cases of stable disease. The partial responses, 2 of which were not confirmed, were observed in patients with medullary, papillary and follicular thyroid cancers. These 3 patients were treated for 338, 366 and 564 days, respectively, and the time to response was 210, 217 and 304 days, respectively. Two patients continue on AMG-706 (29).

AMG-706 is currently undergoing phase I and II development for the treatment of metastatic colorectal, lung, bladder, breast, ovarian and thyroid cancers and GIST (30-34).

Table I: Clinical studies of AMG-706 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Cancer	Open	AMG-706, 25 mg p.o. b.i.d. (n=7) AMG-706, 50 mg p.o. o.d. (n=3) AMG-706, 100 mg p.o. o.d. (n=6) AMG-706, 125 mg p.o. o.d. (n=49) AMG-706, 175 mg p.o. o.d. (n=6)	71	AMG-706 was well tolerated at up to 125 mg/day, and was associated with antitumor activity in patients with advanced cancer, with a tumor control rate of 61%	26
Cancer, thyroid	Open	AMG-706, 25 mg p.o. b.i.d. AMG-706, 50 mg p.o. o.d. AMG-706, 100 mg p.o. o.d. AMG-706, 125 mg p.o. o.d. AMG-706, 175 mg p.o. o.d.	7	AMG-706 was relatively well tolerated and showed promising antitumor activity in some patients with thyroid cancer	27
Cancer, colorectal metastatic	Open Multicenter	AMG-706 + Panitumumab + Chemotherapy		This phase I study, which began in December 2004, will provide data on the safety profile of AMG-706 plus panitumumab plus chemotherapy in patients with metastatic colorectal cancer	28
Cancer, lung (non-small cell)	Open Multicenter	AMG-706 + Carboplatin + Paclitaxel AMG-706 + Panitumumab AMG-706 + Carboplatin + Paclitaxel + Panitumumab		This phase I/II study will evaluate the safety profile and pharmacokinetics of AMG-706 with carboplatin and paclitaxel, panitumumab or all three drugs in patients with advanced non-small cell lung cancer	29
Cancer	Open Multicenter	AMG-706 + Panitumumab + Gemcitabine + Cisplatin		Started in January 2005, this phase Ib study will determine the tolerability of adding AMG-706 and panitumumab to gemcitabine plus cisplatin therapy in patients with advanced cancer	30
Cancer, thyroid	Open Multicenter	AMG-706		The antitumor effect of AMG-706 in patients with locally advanced or metastatic thyroid cancer will be assessed in this phase II study which began in July 2003	31
Cancer, gastrointestinal (stromal)	Open	AMG-706	35	The antitumor effect of AMG-706 in Japanese patients with advanced gastrointestinal stromal cancer will be evaluated in this phase I clinical study initiated in November 2005	32
Cancer, lung (non-small cell)	Open Multicenter	AMG-706, 50 mg p.o. o.d. + Panitumumab, 9 mg/kg 1x/3 wks AMG-706, 50 mg p.o. o.d. + Carboplatin, AUC = 6 mg/ml.min + Paclitaxel, 200 mg/m^2 1x/3 wks AMG-706, 125 mg p.o. o.d. + Panitumumab, 9 mg/kg 1x/3 wks AMG-706, 125 mg p.o. o.d. + Carboplatin, AUC = 6 mg/ml.min + Paclitaxel, 200 mg/m^2 1x/3 wks	22	AMG-706 was safely combined with panitumumab or carboplatin/paclitaxel in patients with advanced non-small cell lung cancer, and no pharmacokinetic interactions were observed	34
Cancer	Open Multicenter	AMG-706, 50 mg o.d. + Panitumumab, 9 mg/kg i.v. on d 1 + Cisplatin, 75 mg/m^2 i.v. on d 1 + Gemcitabine, 1250 mg/m^2 on d 1 & 8 1x/3 wks (n=8) Panitumumab, 9 mg/kg i.v. on d 1 + Cisplatin, 75 mg/m^2 i.v. on d 1 + Gemcitabine, 1250 mg/m^2 on d 1 & 8 1x/3 wks (n=7)	15	AMG-706 was safely combined with panitumumab, cisplatin and gemcitabine, with no pharmacokinetic interactions	35

Drug Interactions

In vitro studies have shown that AMG-706 inhibits cytochrome P-450 isozymes CYP3A4, CYP2D6, CYP2C9 and CYPC19 (IC_{50} = 2, 2.8, 2.1 and 11.7 μM, respectively). An open-label, fixed-dose, sequential substudy (see 20) in 12 patients with advanced solid tumors examined the effects of AMG-706 (125 mg p.o. daily for at least 14 days) on CYP3A using an oral midazolam probe (2 mg alone followed by daily dosing after the AMG-706 dose for at least 14 days). Systemic exposure to midazolam increased only slightly with concomitant AMG-706 administration. Results suggest that AMG-706 is a weak inhibitor of CYP3A in humans. Thus, AMG-706 has little propensity to interact with other agents that are CYP3A substrates (23, 35).

Preliminary results were reported from an ongoing, multicenter, dose-finding phase Ib trial in 22 patients with stage IIIB/IV NSCLC (ECOG score = 0.1) examining the safety and pharmacokinetics of oral AMG-706 (50 or 125 mg once daily or 75 mg b.i.d. dosed continually in 21-day cycles) in combination with panitumumab (9 mg/kg every 3 weeks) and/or carboplatin/paclitaxel (AUC = 6 mg/ml.min/200 mg/m^2). Treatment was well tolerated. One patient receiving 125 mg AMG-706 combined with panitumumab developed grade 5 pneumonia. The most common grade 3 and 4 adverse events were fatigue and hypertension seen in 3 and 6 of the 22 patients, respectively. Results suggest that the pharmacokinetic profile of AMG-706 was similar regardless of whether it was administered with carboplatin/paclitaxel 30 min or 48 min apart. In addition, analysis of the 50-mg cohort showed that AMG-706 had no effect on the pharmacokinetics of panitumumab (36).

A multicenter, dose-finding study in 15 patients with advanced malignancies (NSCLC, pancreatic, esophageal, ovarian and others) showed that AMG-706 (50, 75, 100 and 125 mg once daily) can be safely combined with panitumumab (9 mg/kg i.v. on day 1) and gemcitabine (1250 mg/m^2 i.v. on days 1 and 8 every 3 weeks)/cisplatin (75 mg/m^2 i.v. on day 1 every 3 weeks). No pharmacokinetic interactions were detected among the agents (37).

Source

Amgen, Inc. (US).

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