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MONOGRAPH

LINIFANIB

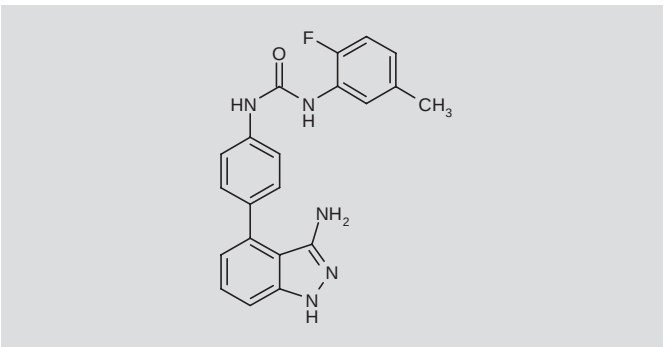
Prop INN; USAN

Receptor Tyrosine Kinase Inhibitor
Oncolytic

ABT-869
AL-39324
RG-3635

N-[4-(3-Amino-1*H*-indazol-4-yl)phenyl]-*N*'-(2-fluoro-5-methylphenyl)urea

InChI: 1S/C21H18FN5O/c1-12-5-10-16(22)18(11-12)25-21(28)24-14-8-6-13(7-9-14)15-3-2-4-17-19(15)20(23)27-26-17/h2-11H,1H3,(H3,23,26,27)(H2,24,25,28)



$C_{21}H_{18}FN_5O$
Mol wt: 375.3989
CAS: 796967-16-3
EN: 396702

SUMMARY

Angiogenesis is the physiological process by which capillary growth occurs from an existing vascular network and ensures that tissues receive sufficient vascularization during organogenesis. It is well established that aberrant angiogenesis plays a role in tumor maintenance or growth and it is therefore considered that antiangiogenic agents may prove to be a promising strategy in cancer therapy. One such antiangiogenic mechanism targets the activity of the receptor tyrosine kinase (RTK) family of proteins residing in vascular endothelium, which act as key players in the angiogenic process. Researchers at Abbott have developed a series of potent RTK inhibitors that act in the nanomolar range to inhibit the TK activity of all members of the vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) families with greater specificity than existing inhibitors. The most promising candidate among these potent inhibitors was linifanib (ABT-869). Linifanib displayed potent preclinical antitumor activity and a promising oral pharmacokinetic profile across different species, and is currently undergoing clinical trials for various malignancies, including renal, hepatic, colorectal, breast and non-small cell lung cancer, and acute myeloid leukemia.

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SYNTHESIS*

Linifanib can be synthesized as follows:

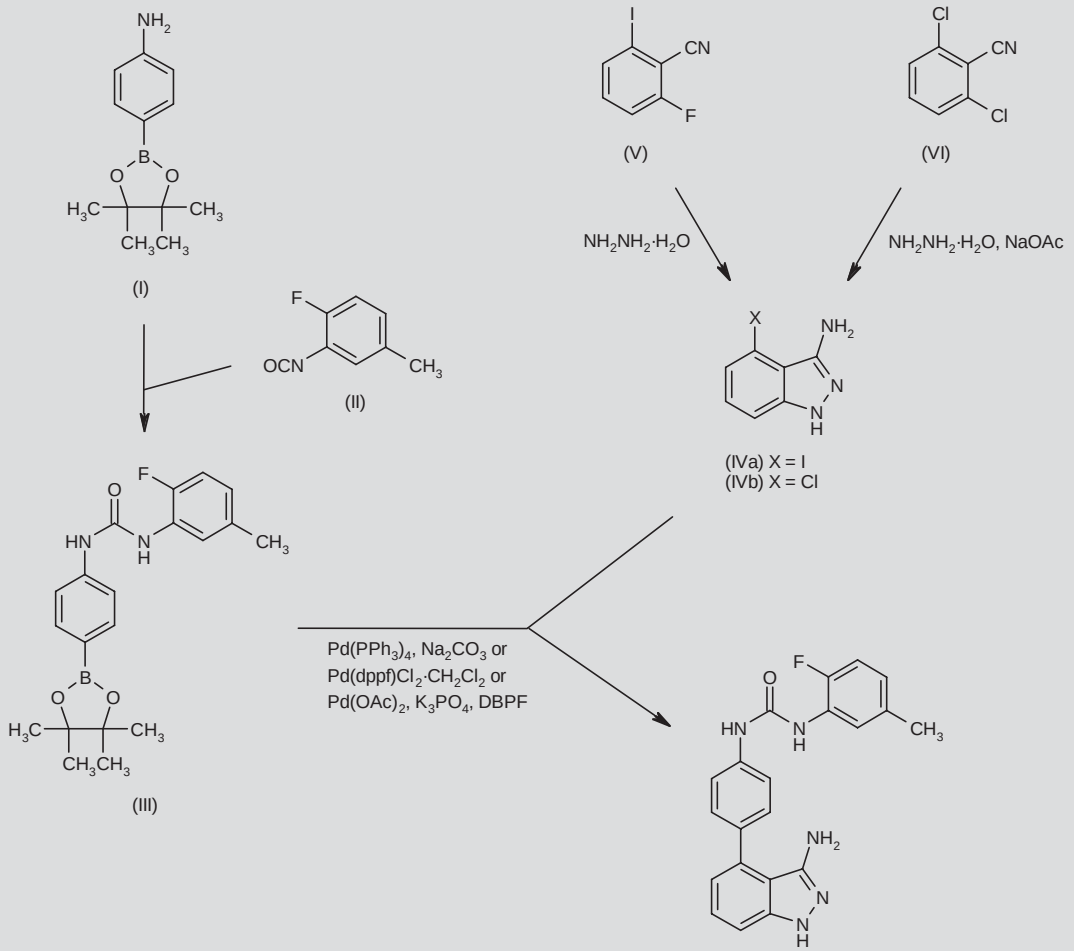
Condensation of 4-aminophenylboronic acid pinacol ester (I) with 2-fluoro-5-methylphenyl isocyanate (II) in CH_2Cl_2 provides urea (III) (1-3), which is then subjected to Suzuki coupling with either 3-amino-4-iodoindazole (IVa) (1, 2) or 3-amino-4-chloroindazole (IVb) (3) in the presence of Na_2CO_3 (1, 2) and $Pd(PPh_3)_4$ at 160 °C (1) or $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ complex (2) in dimethoxyethane/H_2O (1, 2) or K_3PO_4, $Pd(OAc)_2$ and 1,1'-bis(di-*tert*-butylphosphino)ferrocene (DBPF) in H_2O/EtOH at 55 °C (3). Scheme 1.

The aminoindazoles (IVa) and (IVb) are prepared by cyclization of 2-fluoro-6-iodobenzonitrile (V) (1, 2) or 2-chloro-6-iodobenzonitrile (VI) (3), respectively, with hydrazine hydrate (1-3) and, optionally, NaOAc (3) in boiling butanol (1, 2) or pyridine (3). Scheme 1.

BACKGROUND

In conjunction with genetic mutation, sustained angiogenesis is one of the six major cellular processes exploited in tumorigenesis (4). Changes in the microstromal environment, such as the development of hypoxia as tumor size increases, result in an ''angiogenic switch'', the mechanism by which solid tumors procure an extensive blood supply, providing nutrients and oxygen necessary for tumor maintenance, proliferation and progression to malignancy (4, 5). An angiogenic response as a consequence of development or damage includes the recruitment of a number of external signaling ligands that act at specific receptors on the vascular endothelium. Examples of such factors include fibroblast growth factor (FGF), vascular

Scheme 1. Synthesis of Linifanib



endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These ligands bind to specific subsets of the receptor tyrosine kinase (RTK) family, inducing receptor phosphorylation and initiating an intracellular signaling cascade(s) to elicit a mitogenic response, which results in cellular differentiation, proliferation and matrix remodeling (6). Tumor cells aberrantly produce these mitogenic signaling factors and release them in an autocrine fashion, leading to uncontrolled proliferation and growth (7, 8). The vascular endothelial growth factor RTK subfamily (VEGFR), consisting of FLT-1 (Fms-like tyrosine kinase 1, VEGFR-1), FLK-1 (fetal liver kinase 1, VEGFR-2) and FLT4 (VEGFR-3), and platelet derived growth factor RTK family (PDGFR), consisting of PDGF-R-α, PDGF-R-β, c-kit, CSF-1-R (macrophage colony-stimulating factor 1 receptor) and FLT3 (Fms-like tyrosine kinase 3), are also overexpressed in tumor cells. Targeting the mechanisms involved in RTK signaling to disrupt angiogenesis should prove fruitful in the search for anticancer agents, especially since a number of studies highlight VEGFR and PDGFR signaling in the progression of human breast, lung, prostate, renal, colon and liver carcinomas (2).

Several studies have already pointed to the possibility of such antiangiogenic compounds as promising candidates for eliminating tumors. Bevacizumab (Avastin®; Genentech/Roche), a monoclonal antibody against VEGFR, in conjunction with chemotherapy, is currently licensed by the FDA in the U.S. for use as an anticancer agent targeting metastatic colorectal cancer and non-small cell lung cancer (NSCLC) (2, 9). In addition, following successful clinical trials, sunitinib (Sutent®; Pfizer) and sorafenib (Nexavar®; Bayer), both dual inhibitors of VEGFR and PDGFR signaling, are currently licensed by the FDA as anticancer drugs (2, 7). When combined with chemotherapy, vatalanib (Novartis), another dual inhibitor, demonstrated remission in 5 of 17 patients with acute myeloid leukemia (AML) (10), further indication that disrupting RTK signaling could prove effective in targeting cancer.

PRECLINICAL PHARMACOLOGY

Abbott and collaborators examined the ability of several novel thienopyrimidine urea compounds to act as putative inhibitors of enzymatic tyrosine kinase phosphorylation of the VEGFR and

PDGFR family members FLK-1 (VEGFR-2), CSF-1-R, c-kit, FLT-1 (VEGFR-1), PDGF-R-β, FLT3 and FLT4 (2, 11-13). Linifanib effectively and selectively inhibited RTK phosphorylation (IC_{50} = 4, 3, 14-16, 3, 66, 4-5 and 190 nM, respectively, for FLK-1, CSF-1-R, c-kit, FLT-1, PDGF-R-α, FLT3 and FLT4). In addition, linifanib potently inhibited the formation of phosphorylated VEGFR-2 in NIH/3T3 murine fibroblast cells stably transfected with human VEGFR-2 and treated with VEGF (50 ng/mL; IC_{50} = 4 nM) and in primary human umbilical artery endothelial cells (HUAEC; IC_{50} = 2 nM). In the same cell lines modified to express human CSF-1-R, PDGF-R-α or c-kit, linifanib inhibited phosphorylation of the receptors in response to stimulation by their respective ligands M-CSF (200 ng/mL; IC_{50} = 16 nM), PDGFR-BB (50 ng/mL; IC_{50} = 2 nM) and VEGF (50 ng/mL; IC_{50} = 31 nM) (11-15). Recently, it was demonstrated for the first time in CSF-1-dependent murine M-NFS-60 cells that linifanib inhibited endogenous CSF-1 signaling with an IC_{50} value of 30 nM (15).

In a cell model of AML, MV-4-11 cells, in which an FLT3 mutation causes ligand-independent constitutive phosphorylation of the FLT3 receptor, 2-h exposure to linifanib inhibited receptor phosphorylation (IC_{50} = 1 nM), concomitant with inhibition of phosphorylation of the downstream mediators of this VEGF signaling pathway. Linifanib also inhibited phosphorylation of the downstream mediators of FLT3 signaling in MOLM-13 cells (IC_{50} = 1-10 nM), in which the FLT3 receptor contains the same mutation as in MV-4-11 cells, and it also inhibited phosphorylation of the mutant c-kit receptor and its downstream mediators in Kasumi-1 AML cells, albeit less potently (IC_{50} = 100 nM) (16). Of note is that in an in vitro model in which blood was spiked with AML cell lines to mimic the clinical setting, the IC_{50} values for inhibition of phosphorylation by linifanib increased by 100-fold. This is believed to be due to the sequestering of linifanib by serum proteins that are not present in in vitro serum-free cell culture conditions (11, 16, 17). In primary bone marrow cells from patients with AML and FLT3 mutations, linifanib inhibited colony size with an IC_{50} of 100 nM. For those patients who did not display FLT3 mutations colony size was inhibited with an IC_{50} of 1 μM (16).

In VEGF-stimulated HUAEC and MV-4-11 cells, linifanib demonstrated strong antiproliferative effects that were not observed in cells where proliferation is not mediated by VEGFR/PDGFR signaling (IC_{50} = 0.2 and 4 nM, respectively) (11, 16). The antiproliferative potency of linifanib was also demonstrated in other AML cell models, i.e., MOLM-13 (IC_{50} = 6 nM) and Kasumi-1 cells (IC_{50} = 16 nM) (16). In addition, linifanib also demonstrated apoptotic effects in a murine pro-B-lymphocytic cell line containing the FLT3 mutation (IC_{50} = 1 nM), human MV-4-11 cells (EC_{50} = 30 nM) and human MOLM-13 cells following 48-72-h exposure to the drug (11, 16-19).

Electrophysiological techniques revealed a very minimal effect of linifanib on blockade of the hERG potassium channel current in human HEK-293 cells (5.3% at 0.35 μM) and showed that it had no effect on the action potential duration in canine Purkinje fibers (5.45 μM) (2). Linifanib inhibition of the autophosphorylation activity of CSF-1-R in situ was shown to be competitive with ATP, with a K_i of 3 nmol/L (14, 15).

In an in vivo estradiol-induced mouse uterine edema model used to assess oral activity, linifanib displayed the most potent effect among the inhibitors in reducing edema (ED_{50} = 0.5 mg/kg) (2, 11). Oral administration of linifanib (0.3 mg/kg) also resulted in complete inhibition of VEGFR-2 phosphorylation in murine lung tissue as soon as 1 h after dosing. However, for time periods over 3.5 h the effective dose for complete inhibition increased to 3 mg/kg (11). In an in vivo murine model of angiogenesis, increases in the vascular permeability and density of corneal vessels, seen as a result of VEGF signaling, were significantly inhibited by linifanib (7.5 and 15 mg/kg).

Various tumor xenograft models have been employed to examine the potential of linifanib to reduce tumor volume. In an in vivo murine human fibrosarcoma HT-1080 xenograft model, linifanib when given twice daily significantly inhibited tumor growth by about 70% (ED_{75} = 7.5 mg/kg) (2, 11). Moreover, rapid and dose-dependent tumor regression was achieved in similar models utilizing grafted human MV-4-11 leukemia cells, human A-431 epidermoid carcinoma cells or cells with mutated human FLT3 (11, 16-18).

Strikingly, pretreatment with linifanib prevented the formation of tumors in the MV-4-11 xenograft model and severely restricted tumor formation in a similar MOLM-13 model (16). Linifanib when given twice daily demonstrated potent inhibition of tumor growth (> 70% inhibition) in a DLD-1 colon carcinoma model (ED_{75} = 4.5 mg/kg), an MX-1 breast carcinoma model (ED_{75} = 6 mg/kg) and an NCI-H526 small cell lung carcinoma model (ED_{75} = 12 mg/kg). In a murine orthotopic model in which the human breast cancer cell lines MDA-MB-231 and MDA-MB-435LM were implanted in immunodeficient mice, linifanib displayed similar potency, inhibiting tumor growth to the same degree as in the MX-1 xenograft model (11). In a murine AML engraftment model in which MV-4-11 cells were inoculated into mice that had had their bone marrow artificially ablated, treatment with linifanib significantly enhanced survival outcome in a dose-dependent manner (3 weeks at 1 mg/kg/day and 20 weeks at 10 mg/kg/day) (16). Further analysis confirmed a decrease in phosphorylation of the downstream mediators of RTK signaling in these animals. When immunodeficient mice were injected with a murine pro-B-lymphocytic cell line containing the FLT3 mutation, tumor formation and subsequent death occurred within 2 weeks; however, when compared to controls, survival outcome was much improved in mice treated with linifanib (median survival of 6.2 weeks; $P < 0.008$) (18, 19). Finally, dose-dependent inhibition of tumor growth following treatment with linifanib was also observed in a rat brain tumor model (> 65% inhibition) (11).

When used in combination with paclitaxel, linifanib potently inhibited tumor growth in xenograft models of human breast cancer by > 20% and 50% compared to monotherapy (linifanib and paclitaxel, respectively) (20, 21). Suberoylanilide hydroxamic acid (SAHA, vorinostat), a small-molecule histone deacetylase inhibitor, demonstrated potential for treating solid tumors and was shown to act synergistically with linifanib to increase cell death in the AML cell lines MV-4-11 and MOLM-14 (22). In combination with rapamycin, linifanib synergistically reduced tumor volume in hepatocellular carcinoma (HCC) xenograft models when compared to either treatment alone (23). In an AML cell line and in primary bone marrow blasts from AML patients, linifanib demonstrated an additive or mildly synergistic antiproliferative effect when used at low concentrations following pretreatment with a chemotherapeutic agent (cytosine arabinoside 100 mg/mL or doxorubicin 2 mg/mL). In addition, when used in combination with short hairpin RNAs targeting cell cycle and MAP kinase signaling components (BCL-1 and c-mos), linifanib treatment

potently increased apoptosis in AML cell lines in a similar manner to that observed for other chemotherapeutic agents (24).

PHARMACOKINETICS AND METABOLISM

Linifanib has a high lipophilicity (logD) of 4.2 at pH 7.4 and a low aqueous solubility at room temperature of 27 ng/mL at pH 7. When administered i.p. or p.o. to rats, monkeys and dogs, linifanib (5 mg/kg in rats and 2.5 mg/kg in other species) exhibited a moderate volume of distribution (Vd = 1.0, 1.2 and 2.2 L/kg, respectively), low plasma clearance (Cl = 3.3, 8.2 and 7.2 mL/min/kg, respectively) and a plasma half-life of 3.6, 3.1 and 2.0 h, respectively (6). The plasma elimination half-life in humans diagnosed with various cancers ranged from 13.9 to 23.1 h (25). The oral bioavailability of linifanib was 27%, 10% and 47%, respectively, and it was found to exhibit extensive plasma protein binding (99.0% in humans, 96.8% in monkeys, 98.2% in mice and 99.1% in rats). The AUC on this dosing regimen was determined to be 6.0, 0.6 and 1.5 µg.h/mL, respectively, for rats, monkeys and dogs. The in vitro metabolic turnover of linifanib was minimal in mouse, dog, monkey and human hepatocytes, with 8-9% metabolized during a 6-h incubation period.

In a mixed-population pharmacokinetic analysis of 181 patients enrolled in 5 clinical trials for multiple types of cancer, where 90% of patients received linifanib based on body weight dosing (average weight of 71 kg), it was determined that race and impaired renal function do not change the pharmacokinetic profile of linifanib. However, patients with HCC displayed an approximate 40% decrease in clearance and oral availability values compared to those with other cancers, suggesting that a lower dose may be appropriate for HCC patients (26).

SAFETY

Mild adverse events (AEs) and dose-limiting toxicities (DLTs) associated with daily linifanib administration include fatigue, asthenia, myalgia, skin rash, hand–foot syndrome, reversible hypertension, reversible proteinuria and mouth irritation, all of which are attenuated following withdrawal of treatment or a decrease in dose. When given daily the drug plasma accumulation levels of the drug and its metabolites were low, with an acceptable plasma half-life and clearance. Following the discovery of a lower plasma clearance rate in HCC patients (26), a mixed-population study of linifanib pharmacokinetics was expanded to assess the safe drug dose in these patients. Among the 224 patients in the analysis, 45% were Asian, 47% Caucasian and 8% other races; mean body weight was 72 kg (range: 35-177 kg). The significant side effects associated with the treatment included increased hypertension and skin toxicity (P = 0.05). These effects were dose-dependent, with those patients receiving a higher dose being more severely affected. Switching from weight-based dosing to a fixed daily dose of 17.5 mg showed that the predicted hypertension rate remains similar (33%) for patients with averaged body weight, but in those whose weight fluctuates from the mean the hypertension rate range is tighter for the fixed dose (30-36%) as compared to the weight-based dose (23-44%). A similar trend was observed for skin toxicity. This study concluded that a fixed 17.5-mg dose of linifanib is recommended for HCC patients (27). All studies to date have concluded that linifanib is safe and effective in ablating tumor growth.

CLINICAL STUDIES

There have been a number of proposed clinical trials for linifanib in the treatment of cancer. The majority of these clinical trials are sponsored by Abbott and collaborator Genentech. An ongoing, open-label phase I study to determine the maximum tolerated dose (MTD; dose at which two of six patients experienced DLT) and assess the pharmacokinetic/pharmacodynamic profile of linifanib in a Japanese population of patients with refractory solid malignancies is being sponsored by Abbott and Abbott Japan (28) and began in Tokyo in September 2008. Eighteen patients have been recruited to this study, with inclusion criteria of adequate bone marrow, renal and hepatic function and a solid tumor refractory to standard therapies. The estimated primary completion date for this trial is March 2010. Linifanib was administered orally once daily for 21 days (single treatment period). CT scans were performed every 6 weeks to assess tumor status. DCE-MRI was performed prior to treatment and at days 3 and 14 of the first cycle. Doses were weight-adjusted, six patients receiving a dose of 10 mg and three a dose of 0.25 mg/kg. Nine patients with solid malignancies (4 male, 5 female; median age of 55 years [range: 29-73 years]) received 34 treatment periods. Cycle 1 DLTs were mild and included fatigue, asthenia, myalgia, skin rash, hand–foot syndrome, reversible hypertension, reversible proteinuria and mouth irritation. No significant drug accumulation was observed and plasma clearance was 2.8 ± 1.2 L/h, while mean plasma half-life was 16.9 ± 5.0 h. The desired AUC (4.9 µg.h/mL) for activity based on preclinical models was reached with 10 mg/day (mean 4.1 ± 2.2 µg.h/mL). Of those subjects receiving a dose of 10 mg/day, five of six had stable disease, presenting signs of tumor necrosis and reduced vascular permeability, leakage and blood flow (29).

The second stage of this study was extended to include 21 patients (11 male, 10 female; median age of 58 years [range: 29-76 years]) who received a daily dose of linifanib (6 at 10 mg, 12 at 0.25 mg/kg and 3 at 0.3 mg/kg). Cycle 1 DLTs were similar to those in the previous study, with the exception that two patients developed a pneumothorax related to cavitating lung nodule. Two partial responses (PR) were seen in NSCLC patients and stable disease was observed in 12 patients following more than 4 treatment periods, with evidence of cavitation of pulmonary disease and reduced microcirculatory-related tumor parameters. Mean peak plasma VEGF levels were significantly increased (P = 0.031) and circulating endothelial cells (CECs) and their progenitors (CEPs) were reduced, demonstrating antiangiogenic activity. The most recent output from this trial was conducted on 33 patients who were given doses of 10 mg/day, 0.1 mg/kg/day, 0.25 mg/kg/day and 0.3 mg/kg/day. No significant plasma drug accumulation was observed at day 15 and both clearance and half-life measurements were similar to those previously observed (2.7 ± 1.2 L/h and 18.4 ± 5.7 h, respectively). Two patients with NSCLC and a patient with colorectal cancer achieved PR, and 48% of patients demonstrated stable disease for more than four treatment cycles. By day 15, DCE-MRI showed a dose-dependent reduction in tumor vascular permeability, with concomitant changes in biomarkers of antiangiogenesis, increased plasma VEGF levels (P = 0.004) and reduced CECs (P = 0.007). The conclusion of these studies was that the recommended effective dose of linifanib for phase II studies should be 0.25 mg/kg/day or less and that such a dose demonstrated promising antiangiogenic potential for clinical use (30-32).

An ongoing international, open-label, randomized phase II trial is assessing the antitumor efficacy and toxicity of linifanib in patients with advanced or metastatic NSCLC (33). The study began in August 2007 across the U.S., Canada, France, Sweden, Singapore and Taiwan. The estimated primary completion date was December 2009. The study included 139 patients and interim data were collected from 94 patients (43 from arm A [median age: 64 years] and 51 from arm B [median age: 62 years]). For inclusion patients had to have at least one lesion measurable by CT scan as defined by RECIST and at least one systemic treatment. Two cohorts were given a daily dose of linifanib (0.10 mg/kg [arm A] or 0.25 mg/kg [arm B]). Twenty-four patients were selected from each arm for interim analysis of the primary endpoint at 16 weeks, and 7 patients in arm A and 9 in arm B were progression-free. Secondary endpoints included the objective response rate (ORR; 0% [30 patients in arm A] and 7.3% [41 patients in arm B]), the average time to progression (TTP; 110 and 109 days, respectively, in arms A and B) and median progression-free survival (PFS; 112 and 108 days, respectively, in arms A and B). Mild and reversible AEs included fatigue (35%), nausea (21%) and anorexia (21%) in arm A and hypertension (51%), fatigue (51%), diarrhea (43%), anorexia (41%), nausea (31%), proteinuria (31%) and vomiting (26%) in arm B. Common grade 3/4 toxicities included fatigue (7%), ascites (5%), dehydration (5%) and pleural effusion (5%) in arm A and hypertension (23%), fatigue (8%), plantar–palmar erythrodysesthesia (PPE) syndrome (8%), dyspnea (6%) and stomatitis (6%) in arm B. The interim results concluded that linifanib demonstrated an acceptable safety profile and was active in patients with NSCLC (34).

An open-label, nonrandomized phase II efficacy and tolerability study of linifanib in advanced renal cell carcinoma (RCC) in patients previously treated with sunitinib is also ongoing in the U.S. and Canada (35). The study began in August 2007 and the estimated primary completion date was December 2009. Eligibility criteria included subjects who had received at least 2 cycles (12 weeks) of treatment with sunitinib for RCC and who had stopped therapy due to progressive disease within 100 days prior to screening, those with prior nephrectomy and those with adequate organ function. The study enrolled 53 patients (median age: 61 years [range: 40-80 years]). A number of these had received additional prior treatments (median: 2 [range: 1-4]), including cytokines (23%), sorafenib (19%), temsirolimus (4%) and bevacizumab (17%). For 53 patients the primary endpoint of ORR was 9.4%. The secondary endpoints of PFS and TTP were 5.4 months, while overall survival (OS) was 11.6 months. The most common AEs were diarrhea (72%), fatigue (72%), hypertension (57%), nausea (53%) and anorexia (40%). Grade 3/4 toxicities included hypertension (28%), fatigue (19%), diarrhea (17%) and hand–foot syndrome (17%). AEs were reversed in 31 subjects following dose reductions. Thirty patients were discontinued due to progressive disease, 7 due to AEs not related to progressive disease and 1 for other reasons. Fifteen patients remained on study at the time of the analysis. The interim results concluded that linifanib demonstrated antitumor activity in RCC following sunitinib failure but that dosing required further optimization (36, 37).

An ongoing, multicenter, nonrandomized, open-label phase II trial to determine the efficacy, safety and tolerability profile of linifanib in subjects with advanced HCC began in August 2007 in the U.S., Canada, Singapore and Taiwan, and was due for completion in December 2009 (38). Inclusion criteria included that subjects should have unresectable or metastatic HCC, must have a measurable lesion by RECIST and could have received a single systemic treatment prior to inclusion. Forty-four subjects (median age: 62 years [range: 20-81 years]) were enrolled and treated with the recommended effective dose as previously determined (0.25 mg/kg). Two arms were determined by HCC type (Child-Pugh A [CP-A; n = 38] or Child-Pugh B [CP-B; n = 6]). PFS was measured at 16 weeks as the primary outcome measure (34.2% and 16.0%, respectively, for CP-A and CP-B). Secondary outcomes included ORR (7.9% and 0%, respectively, for CP-A and CP-B), median TTP (5.4 and 3.7 months, respectively), median PFS (5.4 and 1.3 months, respectively) and median OS (9.7 and 2.5 months, respectively). Median OS was found to be significantly influenced by CP type and gender. AEs included fatigue (57%), diarrhea (43%), hypertension and rash (39% each), and peripheral edema (25%). Thirty percent of subjects had dose reductions, while 61% had dose interruptions due to reversible AEs. A number of patients discontinued due to progressive disease (21 patients), while 10 patients (CP-A) remained on study at the time of the analysis. One CP-B patient died during the study, possibly in relation to linifanib treatment. It was, however, concluded that linifanib displayed an acceptable safety profile and was clinically active in advanced HCC (39, 40).

An investigation into the best predictors of disease progression, including dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI), fluorodeoxyglucose [^{18}F]-positron emission tomography (FDG-PET) and computerized tomography (CT), was performed, with 235 patients currently enrolled in 3 clinical trials for various cancers. Imaging data were collected from 188 patients, 17 of whom were assessed with all 3 analyses. For 14 of these patients there was a significant positive correlation between DCE-MRI (at 2 weeks) and FDG-PET (at 8 weeks). In 41 patients with NSCLC a positive correlation was observed between decreased K_{trans} levels and a decrease in tumor volume, as measured by DCE-MRI and CT. Fifty percent of patients with a decrease in K_{trans} of < 40% showed a reduction in tumor volume, whereas 83% of those with a > 40% decrease in K_{trans} showed a reduction in tumor volume. The study concluded that the relationship between DCE-MRI and FDG-PET, and that between decreased K_{trans} and tumor volume, can be used to predict metabolic activity in solid tumors (41). An earlier analysis in five patients with NSCLC did not find a correlation between K_{trans} and tumor volume, although this might be explained by the small sample size. This study did report that blood flow and permeability–surface area product were associated with tumor response, although eventually all patients were withdrawn from analysis due to DLT (42).

Biomarkers such as serum VEGF, placenta growth factor (PlGF), soluble FLT-1 (sFLT-1) and CECs were measured in a time sequence from patients with advanced solid tumors during daily treatment with linifanib (0.1 mg/kg [n = 12], 10 mg [about 0.2 mg/kg; n = 6], 0.25 mg/kg [n = 12] and 0.3 mg/kg [n = 3]). At 6 h after the initial dose the serum level of sFLT-1 was reduced concomitant with an increase in PlGF that was maintained throughout the treatment. By day 15, VEGF and PlGF levels and the percentage of apoptotic CECs were significantly increased (P = 0.02, P = 0.017 and P = 0.027, respectively), while sFLT-1 levels and the percentage of activated CECs were significantly reduced (P = 0.023

and $P = 0.027$, respectively). These changes in serum biomarker levels occurred in a dose-dependent fashion but displayed limited value in predicting drug safety due to a lack of correlation between biomarkers and DLT (43).

Additional clinical trials are in the recruitment phase, including a pharmacokinetic study to evaluate the effect of food and diurnal variation on linifanib (phase I, 2008-2009) (44) and the efficacy and tolerability of linifanib versus sorafenib in advanced HCC (phase III, 2009-2012) (45).

A phase II study to assess carboplatin/paclitaxel in combination with linifanib in subjects with advanced or metastatic NSCLC suggested that linifanib can potentiate the activity of carboplatin/paclitaxel (46). Treatment cycles were every 21 days for carboplatin (AUC 6 mg/mL/min) and paclitaxel (200 mg/m^2) administered on the first day of each cycle and linifanib 0.2 mg/kg given once daily beginning on the third day of each cycle. There were no AEs associated with linifanib, although mild AEs were associated with carboplatin/paclitaxel dosing. Of the six NSCLC patients enrolled in the study 60% showed PR (47).

A drug interaction investigation on the use of linifanib in combination with mFOLFOX6 versus bevacizumab in combination with mFOLFOX6 to treat advanced colorectal cancer is ongoing (phase II, 2008-2011) (48).

SOURCES

Abbott Laboratories (US); licensed to Genentech, Ltd. (a member of the Roche Group) (US).

DISCLOSURES

The author states no conflicts of interest.

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