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Linifanib

Abstract

Linifanib (A 741439; A-741439; A741439; ABT-869; ABT869; RG3635) is an orally active multi-targeted receptor tyrosine kinase inhibitor for the treatment of various cancers. It was being developed by Roche but development has now reverted to Abbott. The compound is designed to inhibit vascular endothelial growth factor and platelet-derived growth factor receptors. It is in phase III development for liver cancer and phase II development for non-small cell lung cancer, breast cancer, and colorectal cancer in the US, the EU and other areas of the world. This review discusses the key development milestones and therapeutic trials of this drug.

1. Introduction

Abbott Laboratories is developing linifanib, an orally active multi-targeted receptor tyrosine kinase inhibitor, for the treatment of cancer, including non-small cell lung cancer (NSCLC), breast cancer, liver cancer, and colorectal cancer. Linifanib was being developed in collaboration with Genentech, a member of the Roche Group; however, according to Roche's 2009 results presentation, development has reverted to Abbott. The compound is designed to inhibit vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) receptors. Linifanib is hydrophobic, but is oxidized in the body to A 849529, a hydrophilic metabolite that includes both carboxyl and amino groups. Linifanib is in phase II development for breast, renal, colorectal, and NSCLC, and is being assessed in a phase III clinical trial for the treatment of liver cancer.

1.1 Company Agreements

Abbott and Genentech entered into a global research, development, and commercialization agreement for two of Abbott's investigation anticancer compounds, linifanib, and ABT 263, in June 2007. However, according to Roche's 2009 results presentation, development of the compound has reverted to Abbott, and the agreement appears to have been terminated. Under the terms of the agreement, the companies were to work together on all aspects of further development and commercialization of the compounds. Both companies would co-promote any resulting products in the US and Abbott would promote any resulting products outside of this market. Financial terms of the agreement were not disclosed.[1]

1.2 Key Development Milestones

1.2.1 Breast Cancer

In March 2010, Abbott completed a randomized phase II trial (NCT00645177) of linifanib in combination with paclitaxel as first-line therapy in patients with advanced breast cancer. The trial included an open-label lead-in portion to assess the tolerability and pharmacokinetic interactions of 0.20 mg/kg once-daily linifanib and paclitaxel

This drug profile has been extracted from Wolters Kluwer's *Adis™ R&D Insight* drug pipeline database. *R&D Insight* tracks and evaluates drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch.

(90 mg/m^2) in approximately 6–12 patients. Enrollment into the randomized portion began after the cohorts completed two cycles (8 weeks) of therapy without unacceptable toxicity. In the randomized portion, paclitaxel was given as a 1-hour infusion at 90 mg/m^2/week, every 3 out of 4 weeks. Linifanib was administered at 0.20 mg/kg/day once daily. The trial enrolled 102 patients in the US and Mexico.

Preliminary results from the non-randomized portion have been reported.[2]

1.2.2 Colorectal Cancer

Abbott has initiated a phase II study (NCT-00707889) to determine the effect of linifanib in combination with mFOLFOX6, compared with bevacizumab with mFOLFOX6, for the second-line treatment of advanced colorectal cancer. This trial will enroll approximately 147 patients in the US, the EU, Canada, South Korea, and Australia.

1.2.3 Hepatocellular Carcinoma (Liver Cancer)

Genentech and Abbott initiated a phase III clinical trial (NCT01009593) to assess the efficacy and tolerability of linifanib in patients with hepatocellular carcinoma. This trial will enroll approximately 900 subjects from the US, Australia, the EU (Belgium, Czech Republic, Denmark, France, Germany, Italy, the Netherlands, Spain), Canada, Egypt, Japan, South Korea, Malaysia, Norway, Singapore, and Taiwan. The primary endpoint will be overall survival while the secondary endpoints include time to disease progression and objective response rate.

An open-label phase II clinical trial (NCT-00517920) is taking place with linifanib in the US, Canada, Hong Kong, Singapore, and Taiwan, in 44 patients with advanced hepatocellular carcinoma. Results have been presented.[3]

1.2.4 Non-Small Cell Lung Cancer

Linifanib is in a phase II clinical trial (NCT00517790) in patients with advanced NSCLC treated with at least one, but no more than two, prior lines of systemic treatment. The trial is taking place in the US, Canada, France, Sweden, Singapore, and Taiwan and enrolled 139 patients. Results have been presented.[4,5]

Another phase II study (NCT00716534) is investigating the clinical efficacy and toxicity of linifanib in combination with carboplatin and paclitaxel as first-line therapy in approximately 120 patients with advanced or metastatic NSCLC in the US, Australia, Brazil, the Czech Republic, Russia, and Singapore.

1.2.5 Renal Cell Carcinoma (RCC)

A phase II clinical trial (NCT00486538) is underway in the US and Canada with linifanib in 53 patients with advanced RCC who have previously received treatment with sunitinib. Efficacy and safety results have been reported. In succeeding monotherapy trials, the fixed starting dose of linifanib to be used would be 17.5 mg/day.[6]

1.2.6 Solid Tumors

Abbott is conducting a phase I trial (NCT01114191) to determine the interaction of ketoconazole with linifanib in 12 subjects in the US. The company also has an ongoing pharmacokinetic phase I study (NCT00733187) evaluating effect of food and diurnal variation on linifanib in 12 patients with advanced or metastatic solid tumors in the US. A phase I study (NCT00718380) is evaluating the pharmacokinetics, safety, and tolerability of linifanib (2.5 mg or 10 mg) in 18 patients with solid tumors in Japan.

1.2.7 Acute Myeloid Leukemia

Results from preclinical trials have shown linifanib to induce apoptosis of FLT-3 ITD mutant cells both *in vitro* and *in vivo*. These studies suggest that linifanib may demonstrate potential towards the treatment of acute myeloid leukemia in patients harboring the FLT-3 ITD mutation.[7]

2. Scientific Summary

2.1 Pharmacokinetics

2.1.1 Solid Tumors

***Phase II*:** In a phase II trial in patients with refractory solid tumors who received linifanib once daily in 21-day treatment cycles, the following pharmacokinetic parameters were observed for drug doses of 0.10 mg/kg (n = 11) versus

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Table I. Features and properties

Alternate names	A 741439; A-741439; A741439; ABT-869; ABT869; RG3635
Originator	Abbott Laboratories
Highest development phase	III (Asia, Australia, Belgium, Canada, Czech Republic, Denmark, Egypt, France, Germany, Italy, Japan, the Netherlands, Norway, Spain, USA)
Active development-indications	Acute myeloid leukemia, breast cancer, colorectal cancer, liver cancer, non-small cell lung cancer, renal cancer
Class	Indazoles, phenylurea-compounds, small-molecules, urea-compounds
Mechanism of action	Protein tyrosine kinase inhibitors, proto-oncogene protein c-bcl-2 inhibitors
Chemical name	N- [4-(3-amino-1H-indazol-4-yl)phenyl] -N'-(2-fluoro-5-methylphenyl)urea
Molecular formula	C21 H18 F N5 O
CAS registry number	796967-16-3
Route of administration	IV, PO
Pharmacodynamics	Induces apoptosis of FLT-3 ITD mutant cells both *in vitro* and *in vivo;* oral preparations of linifanib in SCID mice injected with MV-4-11 induced complete tumor regression; inhibits colony-stimulating-factor-1 receptor signaling *in vitro* and *in vivo*
ATC codes	
WHO ATC code	L01 (antineoplastic agents)
EphMRA ATC code	L1 (antineoplastics)
Pharmacokinetics	
Linear kinetics	Yes
Cl (L/h)	1.5–4.1 (adult)
$t_{½\beta}$ (h)	11–23.1 (adult)
t_{max} (h) [oral]	2.7–3.5 (adult)
Adverse events	
Rare	Asthenia, erythrodysaesthesia, fatigue, hypertension, mouth disorders, muscle pain, proteinuria, skin eruptions

0.25 mg/kg (n = 12): time to maximum plasma concentration (C_{max}) 3.5 versus 2.7 h; elimination half-life 19.0 versus 18.9 h; clearance 2.3 versus 3.0 L/h; and dose-normalized steady-state exposure 0.35 versus 0.30 μg/h/mL/mg. Thirty-three patients received drug doses of 0.10–0.30 mg/kg; pharmacokinetics were dose-proportional over this dosage range and did not vary with multiple dosing over 15 days.[8] In clinical studies of linifanib, the elimination half-life of the drug ranged from 13.9 to 23.1 h.[9]

***Phase I*:** Linifanib 0.25 mg/kg exhibited area under the concentration-time curve (AUC) from time 0 to 24 hours (AUC_{24}) values, after single and multiple doses, of 6.2 ± 1.2 μg/h/mL (mean ± SD) and 10.7 ± 3.1 μg/h/mL, respectively, in preliminary results from a phase I trial. The estimated effective half-life value, based on observed accumulation, was approximately 1 day. The trial enrolled patients (n = 15) with solid tumors were assigned to four dosing cohorts (0.05, 0.10, 0.20, and 0.25 mg/kg) of linifanib given orally once daily on day 1 for 21 days.[10]

Preliminary data from a phase I open-label study in nine patients with advanced or metastatic solid tumors demonstrated a negative effect of high fat food on linifanib pharmacokinetics (a decrease of 43% in C_{max} and 20% in AUC). Morning dosing appears to result in higher exposures than afternoon dosing (an increase of 69% in C_{max} and 58% in AUC) based on data from five patients. The terminal half-life of linifanib was estimated to be approximately 1 day.[11]

In a phase I study of linifanib in patients with refractory solid malignancies, the mean (oral) plasma clearance of the drug was 2.8 L/h (SD ± 1.2 L/h), with a corresponding mean half-life of 16.9 hours (SD ± 5 hours) with minimal drug accumulation at day 15. Linifanib was administered before bedtime, except on days 1 and

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15. Six patients received a 10 mg/day dose of ABT 869, 12 patients received 0.25 mg/kg/day and 3 patients received 0.3 mg/kg/day. The target AUC (4.9 μg/h/mL) based on preclinical models was achieved with daily dosing of linifanib at 10 mg. A carboxylate derivative was identified as a major metabolite, suggesting that cytochrome P450 enzymes play a role in the metabolism of linifanib.[12,13]

2.2 Adverse Events

2.2.1 Breast Cancer

Interim data from the open-label portion of a randomized phase II trial (NCT00645177) showed that frequent linifanib dose reductions were required as a result of adverse events when the compound was given in combination with paclitaxel as first-line therapy in patients with advanced breast cancer. Paclitaxel 90 mg/m^2 was administered on days 1, 8, and 15 of every 28-day cycle and linifanib was administered once daily starting of day 3 of the first chemotherapy cycle. At the time of this interim analysis, eight patients had been enrolled, including five in the first cohort who received linifanib 0.20 mg/kg and three in the second cohort who received linifanib 0.15 mg/kg. In the first cohort, one patient withdrew due to pulmonary embolism during treatment cycle 2. Overall, the most frequently reported adverse events were neutropenia (n = 3), vomiting, increased alanine : aminotransferase levels, stomatitis, hypertension, hypokalemia, and hyperglycemia (n = 2 each). Most events were grade 1/2 in severity with the exception of neutropenia.[2]

2.2.2 Liver Cancer

In a phase II study in patients with liver cancer, the most common adverse events related to linifanib were fatigue (55%) and diarrhea (48%). Hypertension (18%) and fatigue (14%) were the most common grade 3/4 adverse events related to the drug. Dose interruptions and dose reductions due to adverse events were required in 68% and 34% of patients, respectively. As of June 2010, four patients remained on study, 27 patients discontinued due to progressive disease, eight due to adverse events unrelated to progressive disease, and five for other reasons. One death (due to intracranial hemorrhage, day 111) was reported to be possibly related to linifanib. The study enrolled 44 patients with a median age of 62 years and 84% of whom had no prior systemic therapy. Oral linifanib 0.25 mg/kg daily or every other day was administered until progressive disease or intolerable toxicity.[3]

2.2.3 Non-Small Cell Lung Cancer

The most frequently reported adverse events associated with linifanib (0.10 mg/kg/day) therapy were fatigue (35% of patients), nausea (21%), and anorexia (21%), according to interim results from a phase II trial (NCT00517790) in patients with previously treated, advanced NSCLC. Adverse events frequently associated with linifanib (0.25 mg/kg/day) therapy were hypertension (51%), fatigue (51%), diarrhea (43%), anorexia (41%), nausea (31%), proteinuria (31%), and vomiting (26%). In recipients of linifanib (0.10 mg/kg/day), the most frequently reported grade 3/4 adverse events were fatigue (7%), ascites (5%), dehydration (5%), and pleural effusion (5%). In recipients of linifanib (0.25 mg/kg/day), the most frequently reported grade 3/4 adverse events were hypertension (23%), fatigue (8%), PPE syndrome (8%), dyspnea (6%), and stomatitis (6%). The majority of adverse events were mild to moderate in severity, and were reversible with dose reductions/interruptions or discontinuation of treatment.[5] Based on updated results from the study, the most common treatment-related adverse events were fatigue (41% of patients) and hypertension (37% of patients). Hypertension was also the most common grade 3/4 adverse events (14% of patients). However, rates of hypertension, proteinuria, and fatigue were lower in patients who received low dose linifanib (0.10 mg/kg/day). Dose interruptions due to adverse events occurred in 62% of patients and dose reductions to adverse events were required in 26% of patients. As of November 2009, seven patients remained on study. Study discontinuations included 107 patients due to intolerable toxicity, 17 due to adverse events not related to intolerable toxicity and eight because of other reasons. One death occurred from cancer erosion into pulmonary

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vessels. The study enrolled 139 patients with median age of 62 years, 60% of which had two or more prior regimens and 12% had squamous cell carcinoma.[4]

2.2.4 Renal Cancer

In a phase II trial in patients with renal cell carcinoma, the most common adverse events related to linifanib were diarrhea (74%), fatigue (74%), hypertension (60%), nausea (51%), and hand-foot syndrome/skin reaction (40%). Hypertension was the most common linifanib-related grade 3/4 adverse event, occurring in 32% of patients. Dose interruptions and dose reductions due to adverse events were required in 46 patients and 36 patients, respectively. As of June 2010, 37 patients discontinued therapy due to progressive disease, eight due to adverse events unrelated to progressive disease and two for other reasons. No deaths due to linifanib adverse events were reported. In the trial, 53 patients who have undergone previous nephrectomy, have adequate organ function and have received at least two cycles of sunitinib and stopped therapy due to progressive disease within 100 days prior to screening, were administered oral linifanib 0.25 mg/kg (12.5–25.0 mg) daily.[6]

2.2.5 Solid Tumors

***Phase II*:** In a phase II trial (M04-710) in patients with refractory solid tumors who received linifanib once daily in 21-day treatment cycles, the following adverse events were observed for drug doses of 0.10 mg/kg (n = 11) versus 0.25 mg/kg (n = 12): grade 3 proteinuria (n = 2), grade 3 hypertension (n = 1) versus grade 3 proteinuria (n = 1), grade 4 proteinuria (n = 1), and grade 3 hypertension (n = 1).[8]

In two phase II trials (M06-882 and M06-879) in a total of 36 patients with solid tumors who received linifanib 0.25 mg/kg once daily in a 21-day cycle, grade 3 hypertension (n = 3), grade 3 fatigue (n = 1), and grade 2 proteinuria (n = 3) were observed. Two patients in study M06-879 had received drug treatment every other day rather than every day.[9]

***Phase I*:** Analysis of preliminary results from a phase I trial of linifanib showed that 15 patients exhibited adverse events of grade 2 or higher; hypertension (12); neutropenia (4), thrombocytopenia (3), and hand foot syndrome (2). Two patients experienced a dose limiting toxicity; one each of grade 3 ALT increase at 0.10 mg/kg and ECG T-wave inversion at 0.25 mg/kg. Patients (n = 15) with solid tumors were assigned to four dosing cohorts (0.05, 0.10, 0.20, and 0.25 mg/kg) of linifanib given orally once daily on day 1 for 21 days. Four patients had adverse events leading to dose interruptions (three patients at cycle 3 and one patient at cycle 1) and one patient had an adverse event leading to dose reduction in cycle 5. Two patients have discontinued treatment due to adverse events.[10]

Data from a phase I study of linifanib in patients with refractory solid malignancies have shown that continuous, once-daily oral dosing of the drug was tolerable in this patient population. Linifanib was administered before bedtime, except on days 1 and 15. Six patients received a 10 mg/day dose of linifanib, 12 patients received 0.25 mg/kg/day and three patients received 0.3 mg/kg/day. Adverse events associated with cycle 1 of linifanib included fatigue (grade 3 dose-limiting toxicity in one patient at 10 mg dose), asthenia, myalgia (muscle pain in table 1; grade 2 in 4 of nine patients), skin rash (maculopapular, vasculitic in one patient), hand-foot syndrome (erythrodysaesthesia in table I), hypertension, proteinuria and mouth irritation. Hypertension and proteinuria were reversible on dose interruption.[12,13]

In a phase I trial in patients who continued treatment with linifanib for >1 year, the common adverse events were myalgia and fatigue. Grade 3 adverse events related to linifanib were fatigue, abdominal pain, and palmar-plantar erythrodysesthesia. No cumulative toxicities were apparent with chronic dosing. Of 33 patients treated, four received linifanib for >12 months: one patient each alveolar soft tissue sarcoma (47+ months), renal cell carcinoma (31.1 months), colorectal cancer (19.9 months), and hepatocellular cancer (15.6 months).[14]

2.2.6 Animal Toxicology

In vivo testing revealed oral linifanib (25, 12.6, 6.25 mg/kg/day, twice daily for 21 days) to be well

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tolerated alone or in combination with cytotoxic therapy (carbotaxol, irinotecan, radiation, 5-FU/leucovorin, gemcitabine, and oxaliplatin). It also resulted in no exacerbation of cytotoxic agent toxicity. The study evaluated the activity of linifanib in xenograft models (breast, colon, head and neck squamous cell carcinoma, liver, NSCLC, small cell lung cancer, ovarian, and pancreatic cancer), alone or in combination with various cytotoxic therapies.[15]

In vitro, linifanib was found to be non-toxic to normal bone marrow progenitor cells. *In vivo*, no adverse events were observed in peripheral blood counts, bone marrow, spleens, or livers of SCID mice.[16]

2.3 Pharmacodynamics

2.3.1 Cancer

***Clinical Studies*:** Analysis of data from a phase I trial in patients who continued treatment with linifanib for >1 year showed changes in indirect vascular measurements (DCE-MRI K_{trans}/circulating endothelial cell) or physiological responses to vascular endothelial growth factor inhibition. Of 33 patients treated, four received linifanib for >12 months: one patient each alveolar soft tissue sarcoma (47+ months), renal cell carcinoma (31.1 months), colorectal cancer (19.9 months), and hepatocellular cancer (15.6 months).[14]

***Preclinical Studies*:** Oral linifanib (25, 12.6, 6.25 mg/kg/day, twice daily for 21 days) monotherapy resulted in significant tumor growth inhibition and the combination with cytotoxic therapies showed significant efficacy over linifanib or cytotoxic therapies alone. Further, lower doses of linifanib in combination with cytotoxic agents achieved similar efficacy as higher doses of linifanib alone. The *in vivo* study evaluated the activity of linifanib at clinically relevant doses in xenograft models (breast, colon, head and neck squamous cell carcinoma, liver, NSCLC, small cell lung cancer, ovarian, and pancreatic cancer), alone or in combination with various cytotoxic therapies.[15]

In vitro, linifanib inhibited the proliferation of Ba/F3 FLT-3 ITD mutant cells (concentration that produces 50% inhibition [IC_{50}] = 1 nmol/L) when compared with Ba/F3 FLT-3 D835V mutant (IC_{50} values between 1 and 10 nmol/L) and Ba/F3 FLT-3 wildtype (WT) cells (IC_{50} = 10 μmol/L). An increase in apoptosis was demonstrated in Ba/F3 FLT-3 ITD mutant cells treated with 1 μmol/L ABT 869 for 24 hours (42.8%) when compared to untreated (4.7%) or vehicle control (4.0%) cells. Ba/F3 FLT-3 D835V mutant cells lines demonstrated a 12.5% rate of apoptosis at 1 μmol/L compared to untreated (1.99%) and vehicle control (2.1%). Poly(ADP-ribose) polymerase (PARP) cleavage was observed in Ba/F3 FLT-3 ITD mutant cells following 6 hours of treatment with 1 to 100 nmol/L linifanib. No PARP cleavage was observed in linifanib treated Ba/F3 WT cells. *In vivo*, SCID mice injected with Ba/F3 FLT-3 ITD mutant cells and treated with vehicle control developed metastases had a median survival time of 2 weeks. The linifanib treated group had slower disease progression with a median survival of 6.2 weeks ($p < 0.008$). Both control and treated mice injected with Ba/F3 FLT-3 D835V mutant cell lines developed metastases and demonstrated similar survival (a median of 1.7 and 1.9 weeks, respectively). Survival times of control and treated mice injected with Ba/F3 FLT-3 WT cells were also similar (a median of 8.4 and 8.1 weeks, respectively).[7]

The combination of linifanib and suberoylanilide hydroxamic acid (SAHA) resulted in the synergistic killing of acute myeloid leukemia cells with FMS-like tyrosine kinase 3 (FLT3) mutations in conventional cell culture and human stromal cell co-culture models. A core gene signature unique to combination therapy and common to both MV4-11 and MOLM-14 cell lines was described. The core gene signature differentially induced more than 2-fold by combination therapy in both cell lines included upregulation of FRY, LM04, IFI16, ACADSB, and S100A8, and downregulation of several genes such as *PTP4A3* (*PRL-3*), *ORC1L*, *MND1*, and *ZNF85*. Overexpression of *PRL-3*, a metastasis-associated gene, has been found in different types of solid tumors and multiple myeloma. Modulation of *PRL-3* expression level using genetic approaches showed the role of *PRL-3* in the synergistic therapeutic effect of linifanib and SAHA.[17]

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Table II. History

Date	Comment
25 June 2010	Phase III clinical trials in liver cancer in Asia (PO)
25 June 2010	Phase III clinical trials in liver cancer in Australia (PO)
25 June 2010	Phase III clinical trials in liver cancer in Belgium (PO)
25 June 2010	Phase III clinical trials in liver cancer in Canada (PO)
25 June 2010	Phase III clinical trials in liver cancer in Czech Republic (PO)
25 June 2010	Phase III clinical trials in liver cancer in Denmark (PO)
25 June 2010	Phase III clinical trials in liver cancer in Egypt (PO)
25 June 2010	Phase III clinical trials in liver cancer in France (PO)
25 June 2010	Phase III clinical trials in liver cancer in Germany (PO)
25 June 2010	Phase III clinical trials in liver cancer in Italy (PO)
25 June 2010	Phase III clinical trials in liver cancer in Japan (PO)
25 June 2010	Phase III clinical trials in liver cancer in the Netherlands (PO)
25 June 2010	Phase III clinical trials in liver cancer in Norway (PO)
25 June 2010	Phase III clinical trials in liver cancer in Spain (PO)
6 June 2010	Efficacy and adverse events data from a phase II trial in non-small cell lung cancer presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2010)[4]
6 June 2010	Pharmacodynamics and adverse events data from a phase I trial in solid tumors presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2010)[14]
4 June 2010	Efficacy and adverse events data from a phase II trial in liver cancer presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2010)[3]
4 June 2010	Efficacy and adverse events data from a phase II trial in renal cancer presented at the 46th Annual Meeting of the American Society of Clinical Oncology (ASCO-2010)[6]
10 May 2010	Phase II clinical trials in colorectal cancer in South Korea (PO)
27 March 2010	Abbott completes a phase II trial in breast cancer in the US and Mexico
24 February 2010	Abbott and Genentech complete enrollment in a phase I pharmacokinetic trial in patients with advanced or metastatic solid tumors in the US
3 February 2010	Genentech terminates agreement with Abbott for development of linifanib
18 December 2009	Phase II clinical trials in colorectal cancer in Canada (PO)
18 December 2009	Phase II clinical trials in colorectal cancer in the EU (PO)
10 December 2009	Interim efficacy and adverse events data from a phase II trial in breast cancer presented at the 32nd Annual San Antonio Breast Cancer Symposium (SABCS-2010)[2]
19 November 2009	Efficacy data from pooled analysis of three phase II trials in solid tumors presented at the 21st AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2009)[21]
19 November 2009	Interim efficacy, pharmacokinetics and adverse events data from a phase I trial in solid tumors presented at the 21st AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2009)[10]
19 November 2009	Pharmacodynamics and adverse events data from a preclinical trials in solid tumors presented at the 21st AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2009)[15]
19 November 2009	Preliminary pharmacokinetics data from a phase I trial in cancer presented at the 21st AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics (AACR-NCI-EORTC-2009)[11]
14 October 2009	Phase III clinical trials in liver cancer in the US (PO)
9 June 2009	Phase II clinical trials in colorectal cancer in Australia (PO)
2 June 2009	Interim efficacy and adverse events data from a phase II trial in non-small cell lung cancer were presented at the 45th Annual Meeting of the American Society of Clinical Oncology (ASCO-2009)[5]

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Table II. Contd

Date	Comment
19 April 2009	Pharmacodynamics data from a preclinical trial in cancer presented at the 100th Annual Meeting of the American Association for Cancer Research (AACR-2009)[20]
9 December 2008	Pharmacodynamics data from preclinical trials in acute myeloid leukemia presented at the 50th Annual Meeting and Exposition of the American Society of Hematology (ASH-2008)[7,17]
9 December 2008	Preclinical trials in acute myeloid leukemia in the US (IV)
16 September 2008	Efficacy, adverse events and pharmacokinetics data from phase I and phase II trials in solid tumors presented at the 33rd Congress of the European Society for Medical Oncology (ESMO-2008)[8,9]
31 August 2008	Phase II clinical trials in colorectal cancer in the US (PO)
30 June 2008	Phase II clinical trials in non-small cell lung cancer in combination with carboplatin/paclitaxel in Russia (PO)
30 June 2008	Phase II clinical trials in non-small cell lung cancer in combination with carboplatin/paclitaxel in the Czech Republic (PO)
30 June 2008	Phase II clinical trials in non-small cell lung cancer in combination with carboplatin/paclitaxel in the US (PO)
30 June 2008	Phase II clinical trials in Non-small cell lung cancer in combination with paclitaxel/carboplatin in Brazil (PO)
30 June 2008	Phase II clinical trials in non-small cell lung cancer in combination with carboplatin/paclitaxel in Singapore (PO)
31 March 2008	Phase II clinical trials in breast cancer in Mexico (PO)
31 March 2008	Phase II clinical trials in breast cancer in the US (PO)
31 August 2007	Phase II clinical trials in Liver cancer in Canada (PO)
31 August 2007	Phase II clinical trials in liver cancer in Hong Kong (PO)
31 August 2007	Phase II clinical trials in liver cancer in Singapore (PO)
31 August 2007	Phase II clinical trials in liver cancer in Taiwan (PO)
31 August 2007	Phase II clinical trials in liver cancer in the US (PO)
31 August 2007	Phase II clinical trials in non-small cell lung cancer in Canada (PO)
31 August 2007	Phase II clinical trials in non-small cell lung cancer in France (PO)
31 August 2007	Phase II clinical trials in non-small cell lung cancer in Hong Kong (PO)
31 August 2007	Phase II clinical trials in non-small cell lung cancer in Singapore (PO)
31 August 2007	Phase II clinical trials in non-small cell lung cancer in Sweden (PO)
31 August 2007	Phase II clinical trials in non-small cell lung cancer in Taiwan (PO)
31 August 2007	Phase II clinical trials in non-small cell lung cancer in the US (PO)
31 August 2007	Phase II clinical trials in renal cancer in Canada (PO)
31 August 2007	Phase II clinical trials in renal cancer in the US (PO)
4 July 2007	Data presented at the 43rd Annual Meeting of the American Society of Clinical Oncology (ASCO-2007) added to the adverse events, pharmacokinetics, and cancer therapeutic trials sections[12]
28 June 2007	Abbott Laboratories and Genetech Inc. have entered into a collaboration for the research, development and commercialization of two of Abbott's anti-cancer candidates, including ABT 869
8 December 2006	Clinical data presented at the 18th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics (EORTC-NCI-AACR-2006) added to the adverse events, pharmacokinetics and Cancer therapeutic trials sections[13]
18 January 2006	Preclinical data presented at the 47th Annual Meeting and Exposition of the American Society of Hematology (ASH-2005) have been added to the Cancer pharmacodynamics section[16]
4 May 2005	Phase I clinical trials in cancer in the US (unspecified route)
4 May 2005	Profile created from data presented at the 96th Annual Meeting of the American Association for Cancer Research (AACR-2005)

In vitro, linifanib was shown to inhibit the phosphorylation of KDR, PDGFRβ, c-Kit, and FLT3. *In vivo*, linifanib showed pronounced regression of established xenograft tumors. It has been shown to be effective in human fibrosarcoma and human breast, colon, and small cell lung carcinoma xenograft models with dose that produces a 50% effective response (ED_{50})

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values in the range 3–10 mg/kg/day. Additionally, linifanib showed a >50% inhibition of tumor growth in orthotopic breast, prostate, and glioma models. When given in combination with other therapies, linifanib produced at least additive effects.[18,19]

Further *in vitro* studies demonstrated that linifanib at an IC_{50} of 10 nmol/L inhibited growth of MV-4-11 cells (human acute myeloid leukemia cell line that expresses FLT3-ITD) and BAF3-ITD cells (murine B-cell line stably transfected with the FLT3-ITD). The drug was also effective against D835V, another FLT3 mutation, with an IC_{50} of 100 nmol/L. Linifanib concentration-dependently inhibited phosphorylation of FLT3 and activation of STAT5 and ERK downstream signaling molecules. After 48 hours, linifanib induced apoptosis, caspase-3 activation and PARP cleavage. *In vivo*, oral preparations of linifanib, 20 and 40 mg/kg/day in SCID mice injected with MV-4-11 induced complete tumor regression.[16]

linifanib displayed potent activity against colony-stimulating factor-1 receptor (CSF-1R) signaling *in vitro* and *in vivo*. CSF-1R-dependent growth of M-NFS-60 and RAW 264.7 cells was inhibited by linifanib, with IC_{50} values of 30 and 50 nM, respectively. The compound weakly inhibited the IL-3-dependent growth of M-NFS-60 cells (IC_{50} = 4400 nM) and the CSF-1-independent growth of RAW 264.7 cells (IC_{50} = 8600 nM). Sorafenib, sunitinib, cediranib, and axitinib showed little or no separation of effects on CSF-1 and IL-3 dependent growth in M-NSF-60 cells.[20]

2.4 Therapeutic Trials

2.4.1 Cancer

Breast Cancer

Interim results from the initial open-label portion of a randomized phase II trial (NCT-00645177) demonstrated that first-line therapy with linifanib in combination with paclitaxel may have antitumor activity in patients with unresectable locally advanced or metastatic breast cancer. Paclitaxel 90 mg/m^2 was administered on days 1, 8, and 15 of every 28-day cycle and linifanib was administered once daily starting of day 3 of the first chemotherapy cycle. Of the five patients who received linifanib at 0.20 mg/kg in the first dosing cohort, two had a confirmed partial response and continued on study treatment at a reduced dose for 12 and 10 cycles, respectively, and the other three discontinued treatment due to disease progression in one, withdrawal of consent in another and an adverse event in the third. In the second dosing cohort, three patients have been dosed with linifanib 0.15 mg/kg. Two of these achieved a partial response but the other was not evaluable at the time of the interim analysis.[2]

Liver Cancer

In a phase II study in patients with liver cancer, 11 of 33 evaluable patients had decreased PIVKA (serum protein induced by vitamin K absence), which was associated with improved overall survival. The study enrolled 44 patients with a median age of 62 years and 84% of whom had no prior systemic therapy. Oral linifanib 0.25 mg/kg daily or every other day was administered until progressive disease or intolerable toxicity.[3]

Non-Small Cell Lung Cancer

In a phase II study (NCT00517790), linifanib at 0.10 mg/kg and 0.25 mg/day was effective in previously treated patients with advanced or metastatic NSCLC. Progression-free rate at 16 weeks was similar in groups who received linifanib at 0.10 and 0.25 mg/kg/day (32.3% vs 36.5% of patients, respectively). In both groups, median progression-free survival was 3.6 months, median overall response rate was 1.4% and median overall survival was 9 months. The study enrolled 139 patients with median age of 62 years, 60% of whom had at least two prior regimens and 12% had squamous cell carcinoma.[4] Interim results from this trial showed that linifanib 0.10 and 0.25 mg/kg/day were associated with 16-week progression free survival rates of 29% and 38%, respectively. The objective response rate was 0% and 7% in the linifanib (0.10 mg/kg/day) and linifanib (0.25 mg/kg/day) groups, respectively. Median time to disease progression was 110 and 19 days in the linifanib (0.10 mg/kg/day) and linifanib (0.25 mg/kg/day) groups, respectively.

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Table III. Forecasts

InThought Probability of Approval[a]			
Indication	Approval Date Estimate	inThought Approvability Index	Last Update
Breast cancer	NE	31% (NYR)	27 Jul 2009
Colorectal cancer	NE	31% (NYR)	27 Jul 2009
Liver cancer	NE	31% (NYR)	27 Jul 2009
Non-small cell lung cancer	NE	31% (NYR)	27 Jul 2009
Renal cancer	NE	31% (NYR)	27 Jul 2009

a The Wolters Kluwer Health Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with "A" indicating significantly above average/likely to progress, "C" indicating average, and "F" indicating significantly below average/unlikely to progress.'NYR' stands for 'Not Yet Rated,' indicating that the probability of approval is based on historical approval rates for similar drugs according to indication, molecule type, novelty, and phase, but without analyses of clinical data, trial design, and other factors specific to the individual agent.

NE = no estimate; **NYR** = not yet rated.

Median progression-free survival duration was 112 and 108 days in the corresponding groups.[5]

Renal Cancer

In a phase II trial of linifanib in patients with renal cell carcinoma, the overall response rate (95% CI) based on RECIST criteria was 9.4%, median progression-free survival was 5.4 months and median overall survival was 13.3 months. In the trial, 53 patients (median age of 61 years) who have undergone previous nephrectomy, have adequate organ function and have received at least two cycles of sunitinib and stopped therapy due to progressive disease within 100 days prior to screening, were administered oral linifanib 0.25 mg/kg (12.5–25.0 mg) daily. All patients had prior sunitinib and other prior treatments included cytokines (23%), sorafenib (19%), temsirolimus (4%), and bevacizumab (17%). Response rate to prior sunitinib was 13.2%. Patients who had one prior systemic therapy appeared to have similar progression-free survival and overall survival as those who had more than one prior therapy.[6]

Solid Tumors

***Phase II*:** In a phase II trial (M04-710) in 33 patients with refractory solid tumors who received linifanib 0.10–0.30 mg/kg once daily in 21-day treatment cycles, stable disease that lasted for 3 months was observed in 17 patients and a partial response in 3 patients.[8]

In three phase II trials (M06-880 [n = 42], M06-882 [n = 18], and M06-879 [n = 18]) in a total of 78 patients with solid tumors who received linifanib 0.25 mg/kg once daily in a 21-day cycle, 8 patients experienced stable disease. Some patients in study M06-880 had received a daily drug dose of 0.10 mg/kg and two patients in study M06-879 had received drug treatment every other day rather than every day.[9]

***Phase I*:** In preliminary results from a phase I trial, a partial response was observed in one breast cancer patient receiving linifanib (0.20 mg/kg) with a 32% reduction from baseline. Two patients have discontinued treatment due to radiographic progressive disease (PD), and one due to clinical PD. Patients (n = 15) with solid tumors were assigned to four dosing cohorts (0.05, 0.10, 0.20, and 0.25 mg/kg) of linifanib given orally once daily on day 1 for 21 days.[10]

In a phase I study of linifanib in 21 patients with refractory solid malignancies, two patients with NSCLC experienced partial responses and stable disease was observed in 12 patients after four treatment periods. Linifanib was administered before bedtime, except on days 1 and 15. Six patients received a 10 mg/day dose of linifanib, 12 patients received 0.25 mg/kg/day and three patients

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received 0.3 mg/kg/day. The recommended phase II dose of linifanib is 0.25 mg/kg/day.[12,13]

Pooled Analysis

***Phase II*:** The pooled analysis of three phase II trials revealed linifanib resulted in 79 of 191 evaluable patients exhibiting a maximum CT tumor volume decrease of >32%, which was associated with improved overall survival and progression-free survival ($p < 0.001$). Patients with a partial response (confirmed or unconfirmed) [n = 27] had better overall survival and progression-free survival than those without a partial response (n = 181). 117 of 236 patients had DCE-MRI scans at baseline and day 15, of these, 58% had baseline K_{trans} above the cutoff of 0.055 (established using the RATTing statistical methodology – Resampling and Aggregating Thresholds from Trees), and was associated with improved overall survival, but not progression-free survival. DCE-MRI response at 2 weeks was not associated with significant improvement in progression-free survival or overall survival. The analysis included results from trials in patients with hepatocellular, renal cell, and NSCLCs.[21]

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